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Annual Meeting of the American Epilepsy Society

December 5, 2004
Investigators' Workshop
8:30 a.m.–5:30 p.m.

IW.01
MODELS OF EPILEPSY IN AGING

[1]Eric M. Blalock, [2]Peter R. Patrylo, and [3]Kevin M. Kelly ([1]Molecular and Biomedical Pharmacology, University of Kentucky Medical Center, Lexington, KY; [2]Physiology, Southern Illinois University School of Medicine, Carbondale, IL; and [3]Neurology, Drexel University College of Medicine, Allegheny-Singer Research Institute, Pittsburgh, PA)

New onset epilepsy in the elderly is a significant clinical problem yet there has been little animal modeling of the pathologies relevant to this population. This workshop will review: 1) concepts and methods used within the field of aging research; 2) application of old and new animal models of epilepsy to aged rodents - where they are and where they need to go; and 3) resources available to investigators from the National Institute on Aging. Eric Blalock will discuss the 'calcium hypothesis of aging', i.e., the aging-related alteration of Ca2+ homeostasis that contributes to certain neurophysiological changes during aging. Although several studies indicate that Ca2+ signaling is altered in animal models of epilepsy, little information is available on the potential interplay between aging- and epilepsy-related alterations in Ca2+ homeostasis. The application of 'zipper' slice technology to delineate neuron-specific alterations in L-type Ca2+ channel activity in animal models of both aging and kindling will be reviewed. The development of strategies for the amplification/microarray-based detection of zipper slice single cell mRNA, and the potential application of this technology to studies designed to examine the interplay between aging and epilepsy will be explored. Peter Patrylo will discuss aging-related changes in the dentate gyrus - alterations that could affect granule cell activity/output and thus the role of the dentate in "gating" activity into the hippocampus. Electrophysiological data will detail how local dentate circuit activity is modified during aging and an overview of in vivo studies of kainic acid-induced seizures and status epilepticus in adult and aged rats will be presented. Kevin Kelly will discuss the use of the middle cerebral artery occlusion and photothrombosis models of cerebral infarction in aged rats, explore the challenges of long-term video-EEG data collection and interpretation, and review resources for aging research made available to investigators by the NIA.

IW.02
PLASTICITY OF CHLORIDE TRANSPORT AND GABA SIGNALING

[1,2,3]Massimo Avoli, [4]Francisco Alvarez-Leefmans, [5]Richard Miles, and [6]Melanie Woodin [[1]Neurology & Neurosurgery and Physiology, McGill University, Montreal, QC, Canada; [2]Dept of Physiology, Universita "La Sapienza," Rome, Italy; [3]Dept of Physiology, IRCCS Neuromed, Pozzilli (IS), Italy; [4]Dept. of Physiology, Instituto Politecnico Nacional, Mexico City, Mexico; [5]EMI 0224/CHU Pitié-Salpêtrière, Université Paris VI, Paris, France; and [6]Dept. of Zoology, University of Toronto, Toronto, ON, Canada]

Inhibition, which is mediated by $GABA_A$ and $GABA_B$ receptors, controls CNS excitability, and represents the target of several antiepileptic drugs. Long-term changes in the reversal potential of $GABA_A$ receptor-mediated, Cl^- outward currents toward less negative values have been reported to occur in animal models of epilepsy as well as in human epileptic tissue. Indeed, such an "excitatory shift" in the reversal potential of $GABA_A$ recep-tor-mediated currents may represent a mechanism of disinhibition contributing to the gen-eration and/or propagation of seizures. In this workshop we will focus on the role of K^+/Cl^- cotransport in epilepsy. First, Dr. Alvarez-Leefmans will describe how changes in K^+/Cl^- cotransport can alter the reversal potential of $GABA_A$ receptor-mediated currents. Next, Dr. Woodin will identify the long-term, activity-dependent changes in Cl^- reversal potential in hippocampal neurons. Finally, Dr. Miles will discuss the involvement of changes in Cl^- homeostasis in the generation of interictal spikes recorded in the human epileptic subiculum as well as the relevance of these findings for seizure generation and epileptogenesis. In summary, this workshop will present a novel mechanism that may play a prominent role in epileptiform synchronization and epileptogenesis. (Supported by CIHR, INSERM, MIUR, NIH MH54671, and NSERC.)

IW.03
ASSESSING COGNITIVE EFFECT AND OUTCOMES OF AEDs

David W. Loring (Department of Neurology, University of Florida, Gainesville, FL)

When to initiate antiepileptic drug (AED) therapy and selection of specific AED depends on well established factors including seizure type and epilepsy syndrome, and the primary aim is successful seizure control. Within these broad categories, however, AED selection is often based upon clinical experience and individual physician preference rather than evidence-based medicine because long-term randomized monotherapy studies comparing the cognitive and behavioral outcomes have been limited. In the absence efficacy differences, AEDs should be selected based upon their safety, tolerability, and side effect profiles including cognition and behavior. Unfortunately, when studies have been conducted, they have been limited by methodological issues including absence of random assignment, non-equivalent representation of different seizure types, absence of appropriate longitudinal controls, and a variety of cognitive and behavioral measures, some of which may not be sensitive to subtle change and others that may unduly influenced by practice effects with repeated testing. In addition, a serious limitation has been the absence of long-term follow-up assessment, and this limitation is more significant in pediatric epilepsy since cognitive and behavioral AED effects occur against the backdrop of normal maturation and development. This workshop will discuss issues of study design, practical and administrative limitations in performing large randomized AED studies, and provide direction for the design of future studies using cognition and behavior as the primary outcome variables. In the absence of differences in efficacy, AEDs should be selected based upon their safety, tolerability, and side effect profiles including cognition and behavior. These effects, however, have been insufficiently studied. This workshop will discuss issues of study design, practical and administrative limitations in performing large randomized AED studies, and provide direction for the design of future studies using cognition and behavior as the primary outcome variables.

IW.04
ORIGIN AND MIGRATION OF CORTICAL NEURONS

[1]Arnold R. Kriegstein, [2]Joseph Loturco, [3]Stewart A. Anderson, and [1]Samuel J. Pleasure ([1]Neurology, UCSF, San Francisco, CA; [2]Physiology and Neurobiology, University of Connecticut, Storrs, CT; [3]Psychiatry, Neurology and Neuroscience, Weill Med College of Cornell, New York, NY)

Precise patterns of cell division and migration are crucial to transform the neuroepithelium of the embryonic forebrain into the adult cerebral cortex. Dr. Kriegstein will present data that neurons are generated in two proliferative zones by distinct patterns of division. Furthermore, newborn neurons do not migrate directly to the cortex but instead exhibit four distinct phases of migration, including a phase of retrograde movement toward the ventricle before migration to the cortical plate. These findings provide a new view of the dynamics of cortical neurogenesis and

migration and may have clinical significance in relation to neuronal migration disorders. Neuronal migration is controlled by a growing number of different proteins. The current challenge is to define the specific roles played by these proteins in the formation of neocortical layers. Dr. LoTurco will describe some of the new migration mechanisms and pathways that have been discovered using the novel methods of Intracerebral RNAi and in utero electroporation. GABAergic interneurons perform important roles in cortical development and are critical regulators of cortical excitability and epilepsy. However, little is known about the molecular mechanisms that underlie interneuron fate determination. Dr. Anderson will discuss the molecular signals that specify interneurons within the medial ganglionic eminence (MGE). Since mutations in some of these signaling genes have been linked to forebrain malformations in humans, identifying the molecular code for interneuron specification should enhance our understanding and treatment of disorders associated with epilepsy. Cajal-Retzius cells are among the earliest born cortical neurons and are required for normal cortical development. However their embryonic origin has been controversial. Dr. Pleasure will present evidence that all Cajal-Retzius cells originate from the cortical hem, a small region of caudo-medial neuroepithelium, and subsequently migrate to cover the whole cortical surface. The findings summarized in these presentations are helping to transform our understanding of the patterns of cell origin and migration in the developing cortex. (Supported by grants from the NIH.)

IW.05
KETONE BODIES AND NEURONAL EXCITABILITY

[1]W. McIntyre Burnham, [2]Gary Yellen, and [3]Jong M. Rho ([1]Bloorview Epilepsy Research Program, Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada; [2]Department of Neurobiology, Harvard Medical School, Boston, Massachusetts; [3]Barrow Neurological Institute and St. Joseph's Hospital & Medical Center, Phoenix, Arizona).

One of the hallmark biochemical features associated with fasting and ketogenic diet (KD) therapy is the production of ketone bodies (i.e., beta-hydroxybutyrate, acetoacetate and acetone). Investigators have previously demonstrated that ketone bodies, when injected intraperitoneally in rodents, exhibit dose-dependent anticonvulsant effects. In contrast, in vitro experiments have failed thus far to confirm any significant effects of ketones on glutamate or GABA receptors, or on standard parameters of synaptic transmission in brain slices. Whether ketone bodies exert direct effects on neuronal excitability, or whether they represent an epiphenomenon remains an unresolved question for those studying mechanisms of KD action. In this workshop, Dr. Mac Burnham will review data supporting the broad-spectrum in vivo anticonvulsant activity exhibited by acetone - the byproduct of spontaneous decarboxylation of acetoacetate. Acetone is highly effective in blocking seizures induced by maximal electroshock, pentylenetetrazole, AY-9944 (which induces atypical absence seizures), and even after amygdala kindling. Next, Dr. Gary Yellen will then present a series of intriguing experiments conducted in the substantia nigra, highlighting a potential molecular target of ketone bodies, namely, adenosine triphosphate (ATP)-sensitive potassium (KATP) channels. KATP channels, when activated, causes membrane hyperpolarization and may play an important role in neuroprotection following ischemic brain injury. Finally, Dr. Jong Rho will review the electrophysiological effects of ketones bodies on rat neocortical neurons, and potential neuroprotective effects in an in vitro model of oxidative stress. Taken together, recent experimental data support more firmly the direct anticonvulsant, and potential neuroprotective, properties of ketone bodies.

IW.06
MEG AND EEG: ADVANCES AND CONTROVERSIES IN SOURCE LOCALIZATION AND CLINICAL UTILIZATION

[1]Paul A. Garcia, [2]John S. Ebersole, and [3]William Sutherling ([1]Neurology, University of California, San Francisco, San Francisco, CA; [2]Neurology, University of Chicago, Chicago, IL; and [3]Epilepsy and Brain Mapping Center, Pasadena, CA)

EEG has traditionally been the gold standard for guiding epilepsy surgery. It is practical for obtaining ictal recordings and provides excellent temporal resolution of ongoing electrocerebral activity. In recent years, MEG has been used increasingly as a pre-surgical tool at many centers. It shares many of EEG's characteristics but it also has inherent advantages that often allow for more accurate source analysis.

In this session, lecturers will outline recent advances in the field of EEG and MEG source localization. The optimum use of both modalities will be considered. The contribution of MEG to the traditional pre-surgical evaluation will also be discussed.

IW.07
CREATING NEW ANIMAL MODELS OF THE CHILDHOOD EPILEPSIES

[1]Margaret P. Jacobs, [2]Solomon L. Moshé, [3]Astrid Nehlig, [4]Philip A. Schwartzkroin, and [5]John W. Swann ([1]National Institute of Neurological Disorders & Stroke, NIH-DHHS, Bethesda, MD; [2]Dept of Neurology, Albert Einstein College of Medicine, Bronx, NY; [3]Faculte de Medecine, University L. Pasteur Inserm, Strasbourg, Cedex, France; [4]Dept of Neurological Surgery, University of California-Davis, Davis, CA; and [5]Dept of Pediatrics, Baylor College of Medicine, Houston, TX)

The childhood epilepsies are among the most common epileptic syndromes. They are often unresponsive to conventional treatments and can have devastating developmental consequences. The causes of pediatric epilepsy are likely to be multi-factorial, and result from a combination of genetic and environmental insults. Currently, progress is being made in understanding the basic mechanisms underlying epilepsy in the mature nervous system, in part due to the existence of relevant animal models. However, the study of epileptogenesis in the developing brain lags far behind. The dearth of developmental animal models is one important contributing factor that slows progress. The questions posed by the pediatric epilepsies differ markedly from those of adulthood due to the unique interplay of genetic mutations, brain malformations, brain injuries and seizures with the rapidly growing brain of infants and children.

The purpose of this workshop is to expand upon an NIH/NINDS meeting that took place in May 2004, and discuss potential guidelines for creating animal models of the early-onset epilepsies. Topics include:1) Models of childhood epilepsy – where we are now; 2) Which disorders need to be modeled; 3) Strategies for model development - I : Intractable Complex Partial Epilepsy; 4) Strategies for model development II : Infantile Spasms; 5) How new models will be used.

IW.08
THE ROLE OF KAINATE RECEPTORS IN EPILEPSY

[1]Yesekiel Ben-Ari, [2]Anis Contractor, [3]John J. Hablitz, and [4]Michael A. Rogawski ([1]INMED, INSERM U29, Marseille, France; [2]Dept.of Physiology, Northwestern University School of Medicine, Chicago, IL; [3]Dept. of Neurobiology, University of Alabama at Birmingham, Birmingham, AL; and [4]Epilepsy Research Section, NINDS, Washington, DC)

Kainate receptors (KARs) are a family of ionotropic glutamate receptors comprised of combinations of GluR5-7 and KA1-2 subunits. Development of pharmacological tools discriminating KARs from other ionotropic glutamate receptors has increased our knowledge of KAR function. It is now clear that KARs are located both pre- and postsynaptically where they exert a complex influence on neuronal excitability. Studies in animal models have shown that KAR antagonists have anticonvulsant properties and KAR expression can be altered by seizures. The speakers in this symposium will present information from basic studies of KAR structure and function, their physiological role in modulating synaptic transmission and effects on epileptiform discharges. In this session, Anis Contractor will review the classification and molecular biology of KARs and present information on their role in synaptic plasticity in the hippocampus. Michael Rogawski will provide information amygdala KARs; results of research on KAR-mediated heterosynaptic facilitation and antagonism of KAR mediated synaptic currents by Topiramate will be discussed. The role of KARs in influencing excitability of hippocampal interneurons and implications for epileptogenesis will be discussed by Yehezkel Ben-Ari. The participants will consider the relevance of KAR-dependent mechanisms for epileptogenesis and possible future research directions.

IW.09
FLUMAZENIL PET IN HUMAN EPILEPSY

William D. Gaillard and [2]Csaba Juhasz ([1]Children's National Medical Center, George Washington University School of Medicine, Washington, DC; and [2]Detroit Children's Hospital, Wayne State School of Medicine, Detroit, MI)

This workshop will provide a critical overview of the role of ^{11}C-Flumazenil (FMZ) in PET studies of human epilepsy with an emphasis on investigating the pathophysiology of localization related epilepsy and pre-surgical localization. FMZ ($t_{1/2}$ = 20 min) is a selective benzodiazepine antagonist of the $GABA_A$ receptor that serves as probe for inhibitory receptor systems implicated in both seizure generation and control. The kinetics of FMZ will be reviewed. Dr Juhasz will present experience with FMZ in pediatric epilepsy with a focus on pre-operative evaluation of non-lesional epilepsy. He will discuss the identification of FMZ abnormalities in relation to FDG-PET findings. FMZ abnormalities in relation to electrophysiological findings regarding the primary seizure focus and propagation will also be discussed. Multi-modal image co-registration techniques will be reviewed as well as approaches for objective determination of FMZ binding abnormalities. Dr Hammers will present data on FMZ in adult populations, focusing on non-lesional epilepsy and cortical dysplasia. He will discuss methods of partial volume correction and voxelwise analysis. He will also present pathophysiological correlations to FMZ Findings: Increased FMZ binding in white matter derives from ectopic neurons; in general cortical dysplsias express decreased FMZ binding. FMZ has proved useful in preoperative planning in 25% of patients. Challenges of providing correlations and outcome in patient populations will also be considered. The presentation is designed to highlight methodological issues in evaluating the utility of a new ligand in the pre-surgical evaluation of patients with epilepsy and the role–strengths and shortcomings–of FMZ-PET.

IW.10
NONSYNAPTIC SEIZURE MECHANISMS
[1]Peter L. Carlen, [2]John G. Jefferys, [3]Dominique Durand, [4]Ante L. Padjen, and [5]Renato Rozental ([1]Medicine and Physiology, Toronto Western Research Institute and U. of Toronto, Toronto, ON, Canada; [2]Dept. Neurophysiology, University of Birmingham, Birmingham, England; [3]Dept. Biomedical Engineering, Case Western Reserve University, Cleveland, OH; [4]Dept. Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada; and [5]Cell Biology and Anatomy, New York Medical College, Valhalla, NY)

Gap junctional communication and field effects are still relatively unappreciated as being major factors underlying the genesis and modulation of seizures. In addition, changes in the extracellular ionic environment and metabolism can have profound effects on neuronal and aggregate excitability. Finally modulation of axonal conduction is almost completely ignored as a major mechanism for spreading seizure activity throughout the brain. The suggested speakers have in vitro and in vivo expertise related to the importance of these various nonsynaptic mechanisms of seizure development and spread.

With the active help of the audience, the following issues will be discussed and debated:

–the role of gap junctional communication in seizure development, spread, and spreading depression. The questions as to the critical location of the these junctions, be it between specific neuronal types, between dendrites and/or between axons, or importantly in glia, will be addressed.
–electrical fields as both initiators and followers of seizure activity; their origin be it dendrites or glia?
–high potassium, low calcium, low magnesium, high pH, metabolic influences; cause or effect?
–the role of axons in seizures; more than conduits, axonal spikes, retrograde axonal conduction, transmission at bifurcations?

We hope to stimulate heated discussions focussed on the important issues of non-synaptic seizure mechanisms, which to date have been mainly ignored as potential therapeutic targets.

IW.11
NEUROTROPHINS AND EPILEPTOGENESIS
James O. McNamara, Samuel S. Newton, and Helen E. Scharfman (Duke University School of Medicine, Durham, North Carolina; Yale University School of Medicine, New Haven, Connecticut; Helen Hayes Hospital, Columbia University School of Medicine, New York, New York).

Increasing evidence implicates a critical role for neurotrophins and their receptors in epileptogenesis, the process by which a normal brain becomes epileptic. Among the neurotrophins, the most extensive evidence implicates BDNF and its cognate receptor, TrkB. Samuel Newton will present recent studies of the role of BDNF in dentate granule cell neurogenesis. Helen Scharfman will present electrophysiological analyses of BDNF regulation of neuronal excitability, including recent evidence suggesting a role for BDNF in catamenial epilepsy. Jim McNamara will present studies of conditional mutants of BDNF and TrkB which demonstrate that TrkB is required for limbic epileptogenesis in the kindling model.

IW.12
MECHANISMS OF PHARMACORESISTANCE IN EPILEPSY
[1]Terence J. O'Brien, [2]H. Steve White, [3]Heinz Beck, and [4]Nicole Soranzo ([1]The Department of Medicine, RMH, The University of Melbourne, Parkville, Victoria, Australia; [2]Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT; [3]Department of Epileptology, University of Bonn Medical Center, Bonn, Germany; and [4]University College London, London, England)

Current anti-epileptic drugs (AEDs) do not adequately control seizures in 20-40% of patients, with significant consequences for the quality of life and safety of these individuals with pharmacoresistant epilepsy. Even though many new AEDs have been marketed over the last 10-15 years, the proportion of patients with pharmacoresistant epilepsy has decreased very little. Patients who are refractory to one type of AED tend to be refractory to all other AEDs. Despite the clinical importance of drug resistance, the underlying cellular and molecular mechanisms have remained elusive. New treatments that modify pharmacoresistance are essential to improving the medical management of patients with epilepsy. This Investigator Workshop will discuss current research relating to pharmacoresistant epilepsy, focusing on neurobiological mechanisms and the identification of targets and strategies to overcome this important clinical problem.

H.S. White will discuss animal models of pharamcoresistance. The use of traditional animal models of seizures and epilepsy have been largely unsuccessful in identifying compounds that are effective in patients with pharmacoresistant epilepsy. Strategies will be discussed for the development of new models to be utilised to the understanding of the neurobiology of pharmacoresistance, and for designing and testing novel therapies.

H. Beck will discuss cellular drug target mechanisms that may cause drug resistance, in particular the reduced sensitivity of receptors or ion channels to AEDs. Altered expression of specific ion channels may not only lead to altered excitability, but could also cause resistance to drugs. The presentation will summarise the current state of knowledge regarding changes in drug targets. It will also describe some recent studies that have started to dissect the molecular underpinnings of target-mediated mechanisms of pharmacoresistance in human and experimental epilepsy. An emerging understanding of these underlying molecular and cellular mechanisms is likely to provide important impetus for the development of new pharmacological treatment strategies.

N. Soranzo will discuss human pharmacogenetic studies of both efficacy and dosing of AEDs. First, a detailed survey of variation in the ABCB1 drug transporter gene will be described, which aims to identify causal variants responsible for altered activity that may predispose to refractory epilepsy. Second, a newly identified polymorphism in the drug target SCN1A is reported that is associated with dosing of both phenytoin and carbamazepine. This study provides a rare example of a haplotype tagging strategy that has led to the identification of a previously unknown functional variant associated with drug response.

December 5, 2004
Basic Scientists' Poster Sessions
12:00 noon–2:00 p.m.

3.001
ATYPICAL HYPERTHERMIC SEIZURES IN RATS WITH FOCAL CORTICAL DYSPLASIA LEADS TO SPONTANEOUS RECURRENT SEIZURES AND IMPAIRED LEARNING AND MEMORY
Morris H. Scantlebury, Steve A. Gibbs, Caterina Psarropoulou, and Lionel Carmant (Pediatrics, Div. Neurology, Saint Justine Hospital, Montreal, QC, Canada)

Rationale: The reported association between atypical febrile seizures and temporal lobe epilepsy (TLE) is controversial and thus far has not been supported by cohort or experimental studies. We have recently demonstrated that focal cortical dysplasia resulted in atypical hyperthermic seizures (HS). The purpose of this study is to determine whether HS in lesioned rats will result in subsequent spontaneous recurrent seizures along with visuo-spatial learning and memory deficits paralleling that seen in patients with TLE.

Methods: Freeze lesions (focal microgyri) were induced in the right fronto-parietal cortex of rats on postnatal day (P) 1, followed by HS at P10. To evaluate for spontaneous recurrent seizures, male rats > P 60 were video monitored for 5 hours/day for 10 days. In a subgroup of animals, EEGs were then recorded 20 minutes/day for 5 days from the amygdala ipsilateral to the lesion. Prior to the EEG study visuo-spatial learning and memory were evaluated using the Morris water maze test. Controls were sham-operated and naïve rats with and without hyperthermic seizures (non-lesioned controls) and rats that received the lesion alone (lesioned controls).

Results: Recurrent behavioural seizures were observed in 4/11 (36%) of lesioned rats with HS and were characterized by freezing in association with head nodding and less frequently jaw-myoclonus. This activity was often preceded or followed by wet dog shakes. Of this group spontaneous electrographic seizures were recorded in 6/7 (86%) of rats and were characterized by runs of epileptic spikes and/or rhythmic slow (1–2HZ) spike or polyspikes and wave activity. EEG seizures were associated with behavioural manifestations similar to that observed on video-monitoring. Behavioural seizures were also seen in (1/7) 14% of the sham-operated rats with HS and electrographic seizure activity were recorded in 4/6 (66%). Behaviour or electrographic seizures were not observed in the other control groups. Regarding the Morris water maze testing there were no differences in the mean search difference score (MSD) between the non-lesioned control groups therefore their results were pooled. The MSD in lesioned rats with HS (Mean $\pm$ SD; 25.6 $\pm$ 12.8, n = 13) was significantly lower than in non-lesioned controls (34.7 $\pm$ 10.3, n = 20; $p < 0.05$). The MSD in lesioned controls was in between that of lesioned rats with HS and that of non-lesioned controls, but did not statistically differ from the two groups.

Conclusions: This study demonstrates a link between the atypical febrile seizure and the development of TLE as well as learning and memory deficits; supporting a complicating role for cortical dysplasia and possibly significant neonatal stress for the development of these conditions, following febrile seizures. (Supported by Saint Justine Research Foundation, Epilepsy Canada/CIHR, Hospital for Sick Children Foundation.)

3.002
REDUCING TrkB LEVELS PROTECTS HIPPOCAMPAL NEURONS FROM SEIZURE-INDUCED CELL DEATH

[1]Steve C. Danzer, [1]Maya Hughes, [1]Robert J. Kotloski, [4]Serge Nef, [4]Luis F. Parada, and [1,2,3]James O. McNamara ([1]Neurobiology, [2]Medicine, and [3]Pharmacology and Molecular Cancer Biology, Duke University, Durham, NC; and [4]Ctr Developmental Biology, University of Texas, Southwestern, Dallas, TX)

Rationale: The hallmark pathology of human temporal lobe epilepsy is hippocampal sclerosis, a condition characterized by extensive neuronal loss and glial scaring. Tyrosine kinase B (TrkB), and its ligand BDNF, are potent survival factors for hippocampal neurons *in vitro*. Whether TrkB regulates the development of hippocampal sclerosis, however, has not been established. To address this question, conditional TrkB null mice were treated with pilocarpine, a drug that produces status epilepticus-induced hippocampal sclerosis.

Methods: In TrkB null mice, the first coding exon of the TrkB gene is flanked by lox P sites and TrkB expression is eliminated from neurons expressing synapsin 1 promoter-driven Cre recombinase. TrkB expression in these animals is eliminated from the majority of dentate granule and CA3 pyramidal cells, and a subset of cortical, thalamic and amygdala neurons. To induce hippocampal sclerosis, 4 TrkB null and 6 wildtype littermates were treated with 340 mg/kg pilocarpine, allowed to seize for 3 hours, and killed 48 hours later. Cell death was assessed by Nissl staining and Fluorojade B staining, the latter labeling dead and dying neurons.

Results: Pilocarpine-treatment produced status epilepticus in both wildtype and TrkB null mice. Surprisingly, despite qualitatively similar seizures, dentate hilar cell loss was profoundly *reduced* in TrkB nulls relative to wildtype mice (wildtype, 52 $\pm$ 11 Fluorojade B positive neurons/hemisection; null, 8 $\pm$ 6; $P < 0.01$). Even more surprising, neurons in other regions, including cortex, amygdala and thalamus, were not protected in TrkB nulls (e.g., cingulate cortex; wildtype, 43 $\pm$ 21; null, 91 $\pm$ 29). Nissl staining of adjacent sections confirmed the presence of healthy hilar neurons in wildtype control, TrkB null control and TrkB null pilocarpine-treated animals. Consistent with the Fluorojade B findings, significant cell loss in the hilus was only observed in pilocarpine-treated wildtype mice with Nissl staining.

Conclusions: Dentate hilar neurons are extremely sensitive to seizure-induced cell death, and the preservation of these neurons in the context of extensive cell death in other regions of the brain is striking. Studies are underway to determine whether this finding reflects reduced invasion of seizure activity into the hippocampus, or whether hippocampal seizure activity is equivalent in these animals and neuroprotection is due to a reduction in toxic effects of TrkB activation. In summary, the present findings indicate that TrkB, either directly or indirectly, may exacerbate hippocampal sclerosis. (Supported by NIH grants NS07370, NS32334 and NINDS grant NS17771, the Epilepsy Foundation, and the Ruth K. Broad Foundation.)

3.003
ACUTE CHANGES IN GENE EXPRESSION OF GABA RECEPTOR SUBUNITS IN DENTATE GYRUS AFTER PROLONGED SEIZURES ARE AGE DEPENDENT

[1]Guojun Zhang, [1]YogendraSinh H. Raol, and [1,2]Amy R. Brooks-Kayal ([1]Neurology, Children's Hospital of Philadelphia; and [2]Pediatrics and Neurology, University of Pennsylvania, Philadelphia, PA)

Rationale: $GABA_A$ receptors are the most abundant inhibitory neurotransmitter receptors in forebrain, and many studies indicated that alterations in these receptor may play a important role in epileptogenesis. Previous studies from our laboratory suggest that long-term alterations in GABA receptor function and gene expression in hippocampal dentate granule neurons (DGNs) during epileptogenesis differ between immature and mature rats. For example, a decrease in a1-mRNA levels were found in the rats that had experienced SE in adulthood, whereas, adult rats that had experienced SE at 20 days postnatal age (P20) had higher a1 levels in single DGNs. In the present study we determined the acute effect of SE at P20 and adult on GABAR expression in the whole dentate gyrus.

Methods: P20 and adult rats were subjected to pilocarpine induced status epilepticus (SE). The antisense RNA amplification (aRNA) technique was used to examine the expression of 16 GABAAR and two GABABR subunits mRNA in acutely dissected dentate gyrus 24 hours and 7 days after SE.

Results: 24 hours after SE, total GABAAR subunit mRNA expression was decreased in both P20 and adult rats; Both α1 and α2 subunit mRNA expression were decreased significantly in adult rats; whereas, there were no changes after SE in P20 rats. 7 days after SE, total GABAAR subunits mRNA expression was decreased 1.5 fold in adult rats and increased 3 fold in P20 rats; α1 subunit mRNA expression was decreased 2 fold in adult rats and increased 3 fold in P20 rats; α2 subunit mRNA expression was decreased 1.5 fold in adult rats and increased 2.5 fold in P20 rats; and α5 subunit mRNA expression was decreased 1.5 fold in adult rats and increased 3 fold in P20 rats. GABAB receptor subunits R1 mRNA expression was decreased 2 fold in adult rats and increased 2.5 fold in P20 rats at 7 days after SE.

Conclusions: Prolonged seizures at P20 and in adulthood lead to differential alterations in GABAAR and GABABR subunits mRNA expression. These findings suggest that GABA receptor subunit mRNA changes after SE are dependent on the age at which SE occurs. (Supported by NIH NS38595 to A.B.K.)

3.004
KCNQ/M-CHANNEL DEFICIENCY DURING POSTNATAL DEVELOPMENT CAUSES PROGRESSIVE HIPPOCAMPAL NEURODEGENERATION AND EPILEPSY IN TRANSGENIC MICE

[1]Christian Peters, [2]Huah Hu, [3]Edward C. Cooper, [1]Axel Neu, [2]Johan F. Storm, [1]Olaf Pongs, and [1]Dirk Isbrandt ([1]Institute for Neural Signal Transduction, Center for Molecular Neurobiology Hamburg, Hamburg,

Germany; [2]Institute of Physiology and Centre for Molecular Biology and Neuroscience, University of Oslo, Oslo, Norway; and [3]Department of Neurology, University of Pennsylvania, Philadelphia, PA)

Rationale: In certain neurons, stimulation of muscarinergic receptors attenuates a repolarizing potassium current, the M-current. This leads to increase in action-potential firing frequencies and neuronal electrical activity. M-currents are mediated by voltage-gated potassium channels of the KCNQ family. Mutations in the genes coding for KCNQ2 and KCNQ3 subunits are associated with inherited forms of generalized epilepsy and myokymia.

Methods: In order to investigate the physiological role of M-channels in neurons of the central nervous system of mice, we have generated transgenic mouse lines, which specifically express dominant-negative KCNQ2 subunits in brain. This strategy was chosen to avoid lethal phenotypes associated with a general loss of KCNQ2 gene function. Also, the expected assembly of dominant-negative KCNQ2 subunits with wild-type KCNQ2 and/or KCNQ3 subunits was supposed to inactivate M-currents mediated by respective homo- or heteromultimeric KCNQ channels.

Results: CA1 neurons in acute slice preparations of mutant brains, which expressed the dominant negative KCNQ2 transgene, showed attenuated M-current amplitudes, reduced mAHP amplitude, increased excitability, and altered subthreshold resonance behavior. Mutant mice exhibit behavioural hyperactivity and spontaneous epileptic seizures. Here, we show that suppression of M-currents during postnatal development induced progressive morphological changes in hippocampus, which were most pronounced in the CA1 field and dentate gyrus (DG). Both structures are known to express KCNQ2/3 subunits. The changes included loss of neurons and degeneration of mossy fibres. Electron microscopy revealed the presence of inclusion bodies in CA1 and DG neurons as early as in seven-days-old mice. Postnatal suppression of transgene expression during the first two weeks of life prevented the neurodegenerative alterations.

Conclusions: These data indicate that M-channel activity plays an important role in the developing brain of newborn and adolescent mice. (Supported by German Genome Research Net.)

3.005
ALTERED SYNAPTIC INHIBITION IN AN ANIMAL MODEL FOR CORTICAL MALFORMATION

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Rationale: Cortical malformations are a common cause of epilepsy, although the mechanism behind this association remains poorly understood. As such, several animal models have been developed to explore this association. A genetic model, the Tish rat, displays bilateral subcortical band heterotopia and recurrent spontaneous seizure activity. Previous work has demonstrated altered GABA-mediated synaptic inhibition, and in the work presented here, we focused on determining potential mechanisms for this alteration.

Methods: Whole-cell voltage clamp recordings from brain slices obtained from 15 day old heterozygotic and homozygotic rats were performed using standard techniques to study GABA-mediated IPSCs. Layer V pyramidal neurons from heterozygous (control cells) and homozygous cortices (normotopic cells) were selected. The heterotopia in homozygotes is not layered, so large pyramidal cells were selected for recording (heterotopic cells). Excitatory glutamatergic activity was blocked to facilitate recording of multi-synaptic spontaneous IPSCs (sIPSCs) followed by addition of TTX thus permitting recording single vesicle-mediated miniature IPSCs. Immunohistochemistry was done to indicate the relative distribution of inhibitory interneurons by labeling GAD-67.

Results: Amplitude: sIPSC amplitude in normotopic cells (52.7 $\pm$ 1.9 pA) was reduced comared to control (58.0 $\pm$ 2.8 pA) and heterotopic (58.4 $\pm$ 3.4 pA) cells. In contrast, mIPSC amplitude of heterotopic cells (40.8 $\pm$ 1.5 pA) was significantly smaller than control (49.2 +/− 2.2 pA) and normotopic (48.7 $\pm$ 2.6 pA) cells ($p = 0.3$, One-way ANOVA).

Frequency: sIPSC frequency recorded from control cells (4.3 $\pm$ 0.8 Hz) was higher than that recorded from heterotopic (3.4 $\pm$ 0.5 Hz) and normotopic (2.1 $\pm$ 0.7 $\pm$ Hz) cells. Similarly, mIPSCs frequency recorded from control cells (2.0 $\pm$ 0.3 Hz) was significatly higher than heterotopic (1.1 $\pm$ 0.3 Hz) and normotopic (1.2 $\pm$ 0.2 Hz) cells ($p = 0.04$, One-way ANOVA).

Immunohistochemistry: The heterotopia showed enhanced labeling of GAD-67 compared to control and normotopic cells. Moreover, normotopic cortex showed reduced labeling of GAD-67 compared to control.

Conclusions: Heterotopic cells of the Tish brain showed postsynaptic alterations. Smaller mIPSC amplitude but not sIPSC amplitude suggest an alteration of the $GABA_A$ receptor, possibly from altered subunit expression. These cells also showed a change in the presynaptic properties, as mIPSC frequency was reduced when compared to control. Futhermore, normotopic cells of the Tish brain show presynaptic alterations: reduced sIPSC amplitude but not mIPSC amplitude, lower mIPSC frequency, and reduced GAD-67 labeling when compared to control. Overall, these results reveal mechanisms of altered synaptic inhibition in the Tish rat cortex, and may have implications for strategies to treat human epilepsy associated with cortical malformation. (Supported by NIH:NS34124, RO1:NS040281, NARSAD Foundation.)

3.006
$GABA_A$ RECEPTOR INTERNALIZATION DURING STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) is a progressive condition in which a reduction in GABA-mediated inhibition facilitates the self-sustaining nature of the seizure. An activity-dependent increase in the rate of internalization of postsynaptic $GABA_A$ receptors (GABARs) is an attractive mechanism to explain the reduction. However, it is not known whether the rate of GABAR internalization is activity-dependent. Electrophysiological and immunocytochemical techniques were used to examine the effect of SE on GABAergic synaptic transmission and the internalization of GABARs in a network of cultured hippocampal neurons.

Methods: Hippocampal pyramidal neurons were cultured per the methods of Goslin and Banker. Removing $MgCl_2$ from the extracellular media results in sustained epileptiform bursting (*in vitro* SE). Electrophysiology: Miniature inhibitory postsynaptic currents (mIPSCs) and whole-cell GABA currents were recorded using standard whole-cell patch clamp techniques. Internalization assay: The GABARs on living cultured neurons were tagged with an antibody directed against the GABAR $\beta 2/3$ subunit. After tagging, the neurons were incubated in an antibody-free external media at 37C allowing antibody-tagged receptors to undergo endocytosis. Following fixation, the neurons were exposed to secondary antibodies before and after permeabilization permitting antibody-tagged surface and internalized receptors to be independently identified. The surface and internalized immunoreactivity was measured and used to determine the percentage of internalized tagged-receptors.

Results: Synaptic transmission: Compared to controls, *in vitro* SE of >2 hours resulted in a 30% reduction in mIPSC amplitude (53.8 $\pm$ 1.6 vs. 36.2 $\pm$ 1.5 pA) and an 80% reduction in the maximal whole-cell GABA current (3897 $\pm$ 364 vs. 685 $\pm$ 48 pA). Rate of internalization: The rate of GABAR internalization was assessed under the following conditions: (1) control external media, (2) neuronal activity inhibited with TTX, and (3) *in vitro* SE. Under all conditions, surface immunoreactivity diminished and internalized immunoreactivity increased with time. At 30 minutes, in control external media, approximately 50% of the receptors were internalized. This fraction remained stable over the next 30 minutes. When neuronal activity was inhibited, the percentage of internalized receptors at all time points (10, 20, 30, and 60 minutes) was reduced reaching a plateau of 35%. In contrast, during *in vitro* SE, the percentage of internalized receptors was increased at all time points, with a plateau of 60% internalization.

Conclusions: A reduction in GABA-mediated inhibition occurs during *in vitro* SE. A concurrent, activity-dependent increase in the rate of GABAR internalization likely contributes to this reduction in GABA-mediated inhibition. Further studies are required to better define the mechanisms involved in the activity-dependent internalization of GABARs. (Supported by NINDS.)

3.007

REDUCED INHIBITION AND EPILEPSY IN DLX1$^{-/-}$ MICE

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Rationale: GABA-mediated synaptic inhibition is the most targeted pathway among known inherited epilepsies in humans. Recent progress has been made in identifying molecules that control the development of cortical GABAergic neurons. For example, the Dlx family of transcription factors is essential for differentiation of GABAergic neurons in the embryonic ganglionic eminences, and for tangential migration of GABAergic interneurons into cerebral cortex and hippocampus. Here, we use morphological and electrophysiological approaches to study alterations in GABA-mediated inhibition in mice lacking Dlx1 and its implications for hyperexcitability.

Methods: For immunohistochemistry, staining was performed on 10-40μm brain sections using antibodies against GABA, somatostatin, parvalbumin, calretinin, calbindin and NPY. For electrophysiology, IR-DIC visualized whole-cell voltage-clamp technique was used to record spontaneous and evoked inhibitory postsynaptic currents (sIPSCs-eIPSCs) from neocortical and CA3 pyramidal cells in brain slices from Dlx1$^{-/-}$and Dlx$^{+/}$(control) at 2 different ages (1 and 2 m.o). To isolate GABAergic synaptic currents, slices were perfused with nACSF containing CNQX and APV. IPSCs were recorded at h.p. of 0 mV and evoked at 0.1 Hz using a concentric bipolar electrode. IPSCs were abolished by 10 μM bicuculline.

Results: In Dlx1$^{-/-}$mice, the number of GABAergic neurons (primarily those immunoreactive for GABA, NPY and calretinin) gradually decreased in all cortical and hippocampal regions starting at 1 month of age. At 2 months of age, an approximately 30% decrease in the number of GABA-IR was noted. Analysis of sIPSC kinetics in Dlx1$^{-/-}$mice (1 m.o) revealed a small decrease in frequency and amplitude when compared with controls ($n = 10$). At 2 m.o., decreases in sIPSC frequency and amplitude reached statistical significance ($n = 20$; $p < 0.05$). No significant changes in IPSC decay time constant or 10–90% rise time were observed at either timepoint. Coincident with the loss of GABA interneurons and reductions in synaptic inhibition, seizures were observed in 14 out of 19 Dlx1$^{-/-}$mice video monitored at 2 m.o.

Conclusions: Adult Dlx1$^{-/-}$mice display a time-specific loss of cortical and hippocampal GABAergic interneurons. This reduction in interneuron density leads to impairment of the inhibitory network in regions linked to epileptogenesis (e.g., neocortex and hippocampus) and spontaneous seizures. To our knowledge, this is the first evidence of a requirement for Dlx transcription factor expression in the proper function of cortical interneurons in adult brain. Thus, Dlx mutants may serve as an important new model to study epileptogenesis in an animal with "programmed" loss of interneurons. [Supported by NARSAD (National Alliance for Research on Schizophrenia and Depression) to J.L.R. and CURE (Citizens United for Research in Epilepsy) to S.C.B.]

3.008

PROLONGED EXPERIMENTAL FEBRILE SEIZURES IN IMMATURE RAT CAUSE SPONTANEOUS BEHAVIORAL AND ELECTROPHYSIOLOGICAL SEIZURES DURING ADULTHOOD

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Rationale: Experimental prolonged febrile seizures lead to structural and molecular changes that promote hippocampal hyperexcitability and reduce the threshold to further convulsants. However, whether these early-life 'prolonged febrile' seizures lead to spontaneous seizures (epilepsy) later in life has remained unclear. Previously, daytime video-EEG monitoring did not reveal spontaneous seizures in adult rats subjected to experimental prolonged febrile seizures during infancy. Because limbic seizures may vary diurnally and may be behaviorally subtle, we determined here the presence of *nocturnal* spontaneous limbic seizures, using chronic nocturnal hippocampal EEGs combined with videos.

Methods: Experimental prolonged febrile seizures were induced on postnatal day (P)10. Digital video EEG monitoring was performed chronically at night in control (n = 9) and experimental (n = 17) rats carrying unilateral bipolar hippocampal and cortical electrodes. Starting on P70, each rat was recorded for a total of 6 nights over 3 months. EEGs were analyzed blindly for the presence of limbic seizures, and correlated with concurrent videotaped behavior.

Results: EEGs were normal in all control rats, and none developed spontaneous seizures. Spontaneous behavioral and EEG seizures were found in 31% of experimental rats, and seizures averaged 7.1 $\pm$ 0.8 seconds. An additional 9 rats (56%) did not become epileptic but demonstrated abnormalities on nocturnal EEGs, consisting interictal bursts of spikes. Three experimental rats (13%) had no evidence of EEG or behavioral abnormalities.

Conclusions: Prolonged experimental febrile seizures in immature rats result in spontaneous seizures (limbic epilepsy) later in life in a significant proportion of subjects, and to abnormal EEGs in the majority. Understanding how these experimental febrile seizures lead to epilepsy, i.e., the mechanisms of this epileptogenic process, should yield molecular targets for epilepsy prevention. [Supported by an NIH grant 35439 (T.Z.B.) and by an Epilepsy Foundation of America postdoctoral research fellowship (C.D.).]

3.009

MIDDLE CEREBRAL ARTERY OCCLUSION: A CLINICALLY RELEVANT ANIMAL MODEL OF POSTSTROKE EPILEPSY

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Rationale: Middle cerebral artery occlusion (MCAO) is a well-established model of stroke, yet no study using MCAO has demonstrated the development of poststroke epilepsy. We assessed the MCAO model for its potential to generate epileptogenesis by testing both young adult and aged rats to determine whether age was a critical variable.

Methods: Six 2.5 mo old Long Evans rats were lesioned by transient (3 hour) unilateral occlusion of the left middle cerebral and common carotid arteries (MCA/CCAO), and five animals were sham-operated. Animals were implanted with six skull screw electrodes, and were entered into a rotating weekly schedule of video-EEG monitoring for 6 months following lesioning. Additionally, four 4 mo old and five 20 mo old Fischer 344 rats were subjected to the same procedures.

Results: Our initial study using young adult Long Evans animals showed similarities, but also significant differences between lesioned and control EEG recordings. Both cohorts demonstrated brief, focal, 1–3 sec 7-Hz spike-wave discharges originating independently or synchronously from bilateral hemispheres without any observable change in normal behavior. More prolonged, generalized 7-Hz spike-wave discharges with prominent motor arrest were frequent in all five control animals (100%), but present in only two (33%) of the six lesioned animals. These discharges in lesioned animals were shorter in duration and decreased in frequency of occurrence compared to those of the control group. However, no lesion-associated epileptic seizure was recorded during the six-month monitoring period. Preliminary studies of four 4 mo old F344 lesioned animals have not demonstrated any evidence of convulsive seizure activity. In contrast, 5/5 (100%) 20 mo old animals have demonstrated spontaneous, recurrent convulsive seizures within the first month following lesioning. Seizures were characterized by ictal EEG patterns associated with Racine grade 4–5 convulsions. Interictal EEG records and animal behavior was otherwise normal.

Conclusions: These results indicate the ability of transient unilateral MCA/CCAO to generate poststroke epilepsy characterized by recurrent convulsive seizures when used in aged animals. These findings suggest a physiologically relevant animal model of poststroke epilepsy in the elderly and establish the groundwork for a working model of poststroke epileptogenesis so that translational studies can shift from the control of symptoms to potential prevention and cure. (Supported by an NIH-NIA pilot study award, and Pennsylvania Department of Health RFA 01-07-26 awarded to K.M.K.)

3.010

CHANGES IN KAINATE RECEPTOR SUBUNIT EXPRESSION AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: Kainate receptors have been implicated in the pathogenesis of epilepsy and contribute to seizures in hippocampal area CA3. The epileptogenic effect of these receptors may result from their ability to both reduce GABAergic inhibition and directly excite principal cells. Kainate receptors are comprised of a family of subunits, including GluR5-7 and KA1 and KA2, the combination of which determines the pharmacological and physiological properties of the receptor. The KA1 and KA2 subunits do not form functional channels by themselves but modify the properties of the channel-forming subunits. Recent work has indicated that kainate receptors containing KA subunits serve distinct functional roles in hippocampal circuits. Furthermore, these subunits confer upon kainate receptors a greatly heightened sensitivity to inhibition by zinc. Changes in the expression of kainate receptor subunits following pilocarpine-induced status epilepticus may contribute to the development of epilepsy.

Methods: Microdissected tissue from the principal cell layers of the dentate gyrus, area CA3 and area CA1 was obtained from young adult rats 3 days after pilocarpine-induced status epilepticus or sham treatment. Real time RT-PCR using selective primers was used to quantify the level of mRNA for each kainate receptor subunit in the different hippocampal subregions. The RNA level of each kainate receptor subunit was normalized relative to that of neuron specific enolase. The normalized mRNA levels in pilocarpine treated rats were then expressed relative to that in sham treated animals. Field potential recordings from area CA3 of pilocarpine and sham treated rats were then used to determine whether changes in RNA levels of the kainate receptor subunits altered the function of synaptic kainate receptors. CA3 responses were evoked by mossy fiber stimulation.

Results: KA1 mRNA expression increased by 17 and 3 fold in the dentate and area CA3 respectively, following pilocarpine-induced status epilepticus. In contrast, KA2 mRNA levels in the dentate and CA3 decreased, being only 0.4 and 0.8 fold, respectively of control levels following pilocarpine treatment. KA2 mRNA levels in CA1 remained unchanged. GluR6 mRNA level in area CA3 doubled following pilocarpine treatment. In field potential recordings from hippocampal slices of pilocarpine-treated rats, the zinc sensitivity of the synaptic kainate response in CA3 was markedly reduced, as expected if the KA2 subunit confers high zinc sensitivity upon these receptors.

Conclusions: These findings indicate dynamic changes in kainate receptor subunit expression during the period of epileptogenesis and suggest that decreases in the expression of the KA2 subunit might contribute to the seizure-induced loss of zinc sensitivity of kainate receptors in the mossy fiber pathway. Loss of this zinc-mediated inhibitory control following pilocarpine treatment could enhance excitability of neurons in area CA3. [Supported by NINDS (D.M., R.D.) and NARSAD (D.M.).]

3.011
EXCITOTOXIC LESION-INDUCED EPILEPTOGENESIS IN IMMATURE RATS

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Rationale: The aim of this study was to test weather or not unilateral excitotoxic hippocampal lesion in immature rats could induce epileptogenesis.

Methods: Experiments were performed in 12-day-old Wistar rats (P12; n = 49). NMDA in doses of 50, 75 and/or 90 nmol (pH 7.4) was injected in a volume of 0.5 μl into the dorsal hippocampus under halothane anesthesia. Controls received the same volume of solvent. Pattern and duration of NMDA-induced convulsions was registered. Registration electrodes were implanted into the dorsal hippocampus and the sensorimotor cortex four months after NMDA application. Animals were video/EEG monitored for one week to detect seizures, then they were given an overdose of urethane and the brains were prepared for histology. Severity and extension of damage was evaluated from Nissl-stained sections. Timm staining was used to evaluate mossy fiber sprouting and the density of sprouting was scored from 0 (no sprouting) to 5 (confluent dense band of sprouting covering the entire inner molecular layer).

Results: All three doses of NMDA immediately induced motor status epilepticus lasting approximately 4 h. No dose-related differences were found in intensity or pattern of convulsions. There was also no difference in mortality between controls and experimental groups (<10% rats died in every group). Four months after SE, EEG analysis demonstrated presence of epileptiform graphoelements consisting of spikes or sharp waves in all animals receiving NMDA. Nonconvulsive seizures were formed by series of spikes in both hippocampi with a moderate spread to the neocortex. They were accompanied by behavioral arrest or automatisms were also recorded. Percentage of animals exhibiting seizures increased from 43% to 75% in a dose-dependent manner. Morphological evaluation revealed extensive unilateral lesions and gliosis on the site of injection. In addition to the hippocampus the thalamus was also involved. Extension of lesion was clearly related to the dose of NMDA. Mossy fiber sprouting was present in all experimental animals and it was significantly more intense on the side of injection ($1.8 + 0.2$, $2.6 + 0.3$ and $3.0 + 0.1$, respectively, for the three doses of NMDA) than contralaterally ($1.0 + 0.1$, $1.1 + 0.2$ and $1.2 + 0.1$, respectively). There was no significant difference among these individual doses in intensity of sprouting. Intrahippocampal injection of solvent never resulted in an increase of sprouting density ($0.6 + 0.1$ and $0.7 + 0.1$ for the side of injection and contralateral hippocampus, respectively).

Conclusions: Excitotoxic damage combined with status epilepticus early in development resulted in morphological damage, mossy fiber sprouting and development of epilepsy later in the development. (Supported by a Center for Neuropsychiatric Studies, project No.LN00B122.)

3.012
KAINATE MODULATION OF EPSCS AND EPILEPTIFORM ACTIVITY IN RAT NEOCORTEX

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Rationale: Activation of kainate receptors (KARs) has been shown to modulate excitatory and inhibitory synaptic transmission. Kainate has a dose-dependent biphasic effect on excitatory postsynaptic currents (EPSCs) in hippocampus. Although kainate receptors are expressed in the prefrontal cortex, the effects of kainate on EPSCs in layer II/III pyramidal cells have not been studied. In addition, the role of presynaptic KARs in modulation of epileptiform activity has not been examined. This study has examined the effect of bath application of kainate on EPSCs, mEPSC, and epileptiform discharges in neocortex.

Methods: Neocortical brain slices were prepared from rats 18-23 days of age. Whole cell patch clamp recordings were obtained from layer II/III of prefrontal cortex. EPSCs were evoked by subthreshold stimulation in deeper cortical layers in the presence of bath-applied bicuculline. Epileptiform discharges were evoked by stronger stimulation. mEPSCs were recorded in presence of TTX. Kainate (50 nM–3 μM) was bath applied.

Results: In the presence of bicuculline, low concentrations of KA (50–500 nM) increased the amplitude of evoked EPSCs, while higher concentration (1–3 μM) cause a depression. Kainate had a biphasic effect on the probability of evoking epileptiform discharges, causing an increase at lower concentration and a decrease at higher concentration. At 250 and 500 nM, kainate application increased the amplitude and area of epileptiform discharges. Application of kainate at a higher concentration (3 μM) caused a transient increase in both the amplitude and response area of epileptiform discharges followed by a sustained decrease below control levels. Miniature EPSC frequency but not amplitude was also increased by kainate (250 nM).

Conclusions: Our results show that presynaptic facilitatory KARs are present on layer II/III pyramidal cells where they modulate excitatory transmission and epileptiform discharges in a dose-dependent manner. Activation of these receptors by synaptically released glutamate is proconvulsant and may underlie the convulsant action of kainate. (Supported by NS22373.)

3.013
STATUS EPILEPTICUS ALTERS AMPA AND KAINATE GLUTAMATE RECEPTOR mRNA LEVELS IN MATURE BUT NOT IMMATURE DENTATE GRANULE NEURONS

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Rationale: There is an increase in the birth of dentate granule neurons (DGNs) after status epilepticus (SE) and concurrent alterations in DGN neurotransmitter receptors that may contribute to the development of spontaneous seizures. In this study, we identify which populations of DGN's: immature, mature or both, undergo changes in their glutamate receptor (AMPA and Kainate) subunit expression following SE.

Methods: Rats at postnatal day 19–20 (P19–20) were injected with lithium and pilocarpine to induce a prolonged episode of SE. Fourteen days later (P34) animals were sacrificed and perfused with 4% paraformaldehyde for immunohistochemistry. Individual immature, PSA-NCAM expressing, or mature, NeuN expressing DGNs were dissected from antibody labeled sections. Single cell RNA amplification was performed and a reverse northern was probed for neurotransmitter receptor subunits, AMPA (gluR1, 2, 3, 4) and kainate (gluR5, 6, 7, KA2).

Results: In control animals only a single difference in AMPA (glu R1) subunit mRNA levels was identified between the immature and mature DGN and no diffference in the kainate receptor subunit mRNA levels. Mature DGN after SE had multiple alterations in their AMPA (glu R1↓, R2↑, R3↓, and R4↓), and kainate (glu R5↑, R6↓, R7↓, and KA2↑) receptor subunit mRNA levels. After SE mature DGN had a 50% overall reduction in total AMPA receptor mRNA levels (sum of gluR1,2,3 and 4), and no change in the total kainate receptor subunit (sum glu R5,6,7 and KA2) levels. In contrast, SE had little impact on immature DGN. A decreased expression of the glu R6 subunit was the only difference in immature DGN AMPA and kainate receptor mRNA levels, after SE.

Conclusions: Alterations in glutamate receptor transcription after SE are predominantly in the mature population of DGN, those neurons present at the time of SE. Mature DGN had alterations in all AMPA and kainate receptor subunit mRNA levels measured. Specific changes include increases in GluR2 and decreases in GluR1, 3, and 4 suggesting a shift to a Ca ion impermeable AMPA receptor and an overall 50% reduction in AMPA receptor mRNA levels. SE has distinct effects on transcriptional regulation of neurotransmitter receptors in immature and mature population of DGN. Thus, each population of DGN may differentially contribute to DGN physiology during the latent period and to the eventual development of epilepsy. (Supported by NINDS K08 grant to B.E.P. and Child Neurology Foundation grant to A.B.K.)

3.014
A NOVEL GEFS+ MUTATION IN THE SODIUM CHANNEL SCN1A IDENTIFIES A CYTOPLASMIC DOMAIN FOR β SUBUNIT INTERACTION

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Rationale: A mutation in the sodium channel SCN1A was identified in a small Italian family with dominantly inherited Generalized Epilepsy with Febrile Seizures Plus (GEFS+). The mutation alters an evolutionarily conserved aspartate residue in the C-terminal cytoplasmic domain of the sodium channel α subunit. Characterization of this disease allele of SCN1A can contribute to our understanding of how changes in sodium channel function can cause spontaneous seizures and epilepsy.

Methods: The electrophysiological properties of the mutant channel were determined in the absence and presence of the β1 subunit in *Xenopus* oocytes using the cut-open oocyte voltage clamp. Molecular interactions between the α subunit C-terminal domain and the β1 subunit were identified using yeast two hybrid and co-immunoprecipitation assays. Finally, a computational model was used to analyze how the biophysical effects of the mutation on sodium channel function might alter action potential generation in a model neuron.

Results: The β1 subunit causes a negative shift in the voltage-dependence of inactivation for the wild-type channel. There is less of a shift with the mutant channel, resulting in a 10 mV difference between the wild-type and mutant channels in the presence of β1. Computational analysis suggests that neurons expressing the mutant channels will fire an action potential with a shorter onset delay in response to a threshold current injection, and multiple action potentials with a shorter spike to spike interval at higher stimulus. Direct interaction between the cytoplasmic C-terminal domains of the wild-type α subunit with β1 or β3 subunits was demonstrated by yeast two-hybrid analysis. Coimmunoprecipiation analysis showed that the C-terminal domains of $Na_v1.1$ and β1 interact and that the strength of this interaction is decreased for the mutant α subunit.

Conclusions: Biophysical and computational analyses suggest a causal relationship between a positive shift in sodium channel inactivation and spontaneous seizure activity. This is further supported by the findings that the mutation reduces interaction with the β1 subunit, a novel molecular mechanism leading to seizure susceptibility. [Supported by NIH grants NS34509 (M.H.M.), NS26729 (A.L.G.), NS48336 (A.L.G.), MH59980 (L.L.I.), NS38580 (I.S.), and McKnight Award 34653 (A.L.G.). D. McEwen was supported by NRSA NS43067 and the U. Michigan Pharmacological Science Training Program (NIH GM07767). S. Levin was supported by the Michigan Program in Biomedical Research Training for Veterinary Scientists (NIH T32 RR07008).]

3.015
SODIUM CHANNEL ALPHA SUBUNIT TYPE I (SCN 1A) GENE MUTATION IN GEFS+ IN INFANTS AND CHILDREN

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Rationale: Mutations on SCN1A, the gene encoding the brain voltage-gated sodium channel alpha 1 subunit, are associated with epilepsy in infants and children. So we conducted the SCN1A genetic study in Taiwanese's patients for further understanding the role of these mutations in the epileptic syndromes.

Methods: Total 21 patients had been enrolled in this study, who were consented to receive genetic study by their parents and had permitted by institutional review board (IRB). Among them, one intractable childhood epilepsy with GTC (ICEGTC), eight severe myoclonic epilepsy in infants (SMEI, Dravet syndrome) and twelve generalized epilepsy with febrile seizure plus (GEFS+) were classified based on Seino & Higashi (1979), ILAE (1989) and Scheffer & Berkovic (1997), respectively. We had also done hot water bath test with temperature between 38°C and 40°C for the patients with permission by their parents. We used ABI 3100 for molecular analysis.

Results: Total nine gene mutations of SCN1A were found, including two nonsense mutations, one deletion, and six missence mutations, which were located in four different domains. Among ten cases who had done hot water bath test, nine cases had electroencephalographic seizure pattern during the test. 8 out of 9 had gene mutations and all were SMEI.

Conclusions: Most of the SCN1A gene mutations were discovered in patients with SMEI in our study group. But the genetic studies of those parents revealed normal results. These findings are indicated of de novo gene mutations in their children. In addition, we find all 8 SMEI patients could be induced electroencephalographic seizure pattern by hot water bath test. Hot water bath test might be helpful as a screening method for choosing the candidate to perform SCN1A genetic study, especially in patient suspicious with SMEI.

3.016
GENETIC INTERACTION BETWEEN *SCN2A* AND *KCNQ2* EXACERBATES EPILEPSY IN *Q54-SZT1* DOUBLE MUTANT MICE

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Rationale: A dominant, gain-of-function mutation in the voltage-gated sodium channel *Scn2a* results in epilepsy in *Q54* transgenic mice. The mice have adult-onset, progressive epilepsy beginning with short duration partial seizures that originate in the hippocampus (Kearney et al. Neuroscience 2001;102:307). The hippocampus shows pathologic features of mesial temporal lobe epilepsy including mossy fiber sprouting and extensive loss of CA1, CA3 and hilar neurons. M current (I_{KM}) is thought to play a critical role in controlling the excitability and limiting repetitive firing of hippocampal neurons (Cooper et al. *J Neurosci* 2001;21:9529). *Szt1* mice have a spontaneous C-terminal deletion of the voltage-gated potassium channel *Kcnq2* which underlies M current in neurons. Heterozygous *Szt1*/+ mice have lowered threshold to seizures

induced by trans-corneal stimulation or PTZ, although they do not have spontaneous seizures. *Kcnq2* transcript is reduced in *Szt1*/+ brain and lowered seizure threshold is thought to result from reduction of M current (Yang et al. *Hum Mol Genet* 2003;12:975). We examined the effect of reduced M-current function on the epilepsy phenotype of *Q54* mice by analysis of *Q54-Szt1* double mutants.

Methods: C57BL/6J.*Q54* mice were crossed with C57BL/6J.*Szt1*/+ mice to generate *Q54-Szt1* double mutants. Mice were genotyped at 12 days of age and monitored for visible seizures and survival.

Results: Single mutant *Q54* and *Szt1*/+ mice do not exhibit spontaneous seizures or lethality during the first three weeks of life. In contrast, *Q54-Szt1* double mutant mice have a severe, early-onset epilepsy with prolonged generalized tonic-clonic seizures beginning in the 3rd week of life. Most double mutants do not survive beyond 3 weeks of age.

Conclusions: The short duration, partial seizures in *Q54* mice begin in adulthood and result from an *Scn2a* mutation with increased persistent sodium current. The phenotype of double mutant *Q54-Szt1* mice is much more severe, with very early onset of prolonged generalized seizures. These results suggest that M current is important for preventing seizure initiation and spreading in Q54 mice. The genetic interaction between *Scn2a* and *Kcnq2* suggests that interaction between mild alleles of known monogenic epilepsy genes may contribute to the complex inheritance of human epilepsy. [Supported by NIH R21 NS046315 (J.A.K.).]

3.017
THE KETOGENIC DIET IS NEUROPROTECTIVE AGAINST KAINATE-INDUCED STATUS EPILEPTICUS IN JUVENILE MICE

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Rationale: Previous reports have suggested that the ketogenic diet (KD) may exert neuroprotective actions. We asked whether the KD reduces neuronal cell death in the CA3/hilar region of the hippocampus after kainic acid-induced status epilepticus, independent of effects on seizure severity.

Methods: C3HeB/FeJ mice were fed either the Bio-Serv F3666 diet (6:1 ratio of [fats:carbohydrate + protein]; N = 14) or normal rodent chow (N = 7) for 10-14 days beginning at P21-23. Blood D-β-hydroxybutyrate (BHB) levels were measured using a commercially available reflectance meter. After dietary treatment, each mouse was injected with 20 mg/kg SC kainic acid (KA), and behavioral seizure scores (using a modified Racine scale) were given each minute for 2 hours. Three days after KA injection, mice were sacrificed for histochemistry with Fuoro-Jade B (FJ) and cell counts were conducted of FJ-positive neurons in the CA3/hilar region of the hippocampus.

Results: BHB levels 1 day prior to sacrifice were significantly higher for KD-treated vs. control diet-fed mice, respectively ($P < 0.05$). Cumulative seizure scores were 326 ± 9 and 336 ± 4 ($P = NS$) in KD- and SD-groups, respectively. There were significantly less FJ-positive CA3/hilar neurons in KD-fed animals versus controls (left hippocampus: 81 ± 11 vs. 265 ± 84, $P < 0.05$).

Conclusions: A ketogenic diet is neuroprotective against kainic acid-induced status epilepticus in juvenile mouse hippocampus. This protective effect does not appear to be a consequence of the KD reducing the severity of status epilepticus. [Supported by NIH K02 NS 044846 (J.M.R.).]

3.018
INITIATION AND PROPAGATION OF SPONTANEOUS EPILEPTIFORM ACTIVITY IN HIPPOCAMPAL SLICES CONTAINING MAM-INDUCED HETEROTOPIA

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Rationale: Methylazoxymethanol (MAM) injection in rats produces a model of cortical dysplasia consisting of intrahippocampal and/or periventricular heterotopia. Previously we showed that CA1 heterotopic cells are integrated into hippocampal and cortical circuits. In the present study, we have compared heterotopic and normal CA1 hippocampus with respect to initiation and propagation of epileptiform discharges. We hypothesized that the heterotopia would be the site of discharge initiation when the slice was challenged with an epileptogenic agent.

Methods: Pregnant female Spargue-Dawley rats were injected with MAM (25 mg/kg, i.p.) at E15. Acute hippocampal brain slices were obtained from MAM-exposed offspring at P21–P35. Simultaneous field recordings were obtained from the CA1 heterotopia and the neighboring normal CA1 subfield. Spontaneous activity was elicited by adding the $GABA_A$-receptor antagonist, bicuculline methiodide (50 μM), and elevating the K^+-concentration (from 3 to 5 mM) in the bathing solution. A bipolar electrode was placed in the stratum radiatum near CA3 to stimulate Schaffer collaterals.

Results: A single MAM injection consistently produced hippocampal (CA1) heterotopia in the exposed offspring. Bicuculline application with K^+-concentration elevation led to spontaneous synchronized epileptiform events (multiple population spikes) in the heteropia and neighboring CA1. Onset of spontaneous events, relative to the time of bicuculline introduction, was indistinguishable between CA1 and the heterotopia. Epileptiform bursts were often followed by large negative shifts, with or without after-discharge; after-discharge spikes could occur in the heterotopia electrode without concurrent spiking in normal CA1. In most cases, spontaneous events in CA1 preceded the discharges in the heterotopia (independent of the location of the heterotopia within the CA1 subfield). When responses were evoked by the stimulating electrode, however, the recording electrode closer to the stimulus site (whether in normal CA1 or in the heterotopia) showed the earlier onset of discharge.

Conclusions: Our data suggest that: 1) spontaneous epileptiform events arise in the hippocampus, not the heterotopia; 2) the heterotopia is capable of independent epileptiform spiking; and 3) there is a powerful synaptic input from the normal hippocampus to the heterotopia that usually drives epileptiform discharges in the heterotopia. [Supported by NIH grant NS18895 (P.A.S.).]

3.019
ANALYSIS OF PTEN AND Akt IN EPILEPSY-ASSOCIATED FOCAL CORTICAL DYSPLASIAS WITH TAYLOR-TYPE BALLOON CELLS

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Rationale: Focal cortical dysplasia with Taylor type balloon cells (FCDIIb) constitutes a frequent and histopathologically distinct finding in patients with pharmacoresistant focal epilepsies. Recent data indicate a pathogenetic role of TSC1, known to be mutated in Tuberous Sclerosis (TSC), for FCDIIb. TSC1 represents a key factor in the phosphatidylinositol 3-kinase (PI3K) pathway. In order to further elucidate the molecular pathology of FCDIIb, we have analyzed two additional major components of the PI3K-cascade in FCDIIb, i.e. PTEN and Akt which operate upstream of TSC1.

Methods: Mutational screening of PTEN was performed by single-strand conformation polymorphism analysis (SSCP) in 37 FCDIIb compared to 100 controls. Immunohistochemistry with antibodies against phospho-Akt (Ser473) was carried out in FCDIIb ($n = 37$).

Results: We found several silent polymorphisms of PTEN in exon 2 ($n = 3$) and exon 8 ($n = 1$) as well as an amino-acid exchange at position 279 (exon 8) with replacement of phenylalanine by leucine (F279L) in one patient. Using laser assisted microdissected cell samples, this alteration was only found in FCDIIb components but not in adjacent CNS tissue. We demonstrated an increased immunoreactivity for phospho-Akt in balloon cells and dysplastic neurons but not in adjacent normal CNS tissue.

Conclusions: These data demonstrate alterations of the PI3K pathway components PTEN and Akt in FCDIIb. This is in line with the hypothetical role of the PI3K cascade in focal cortical dysplasias with Taylor type balloon cells. [Supported by DFG (SFB TR3) and BONFOR.]

3.020

DYSPLASTIC ASTROCYTES IN TUBEROUS SCLEROSIS CORTICAL LESIONS EXPRESS ABNORMAL GLUTAMATE RECEPTOR SUBUNITS

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Rationale: Tuberous Sclerosis Complex (TSC) represents an autosomal dominant disorder characterized by the presence of hamartomas in multiple organs, including the brain. The cortical hamartomas, called tubers, are highly epileptogenic lesions, containing abnormal large cells with neuronal or glial characteristics. We showed previously that the dysplastic neurons express selective alterations of glutamate receptor (GluR) subunits, which may enhance network excitability, contributing to the highly epileptogenicity of the tubers [*Epilepsia* 2003;44(S9):36]. As the GluRs critically regulate gap junction-mediated glia-glia signaling, we hypothesized that abnormal astrocytes in the tuber also express GluRs with altered subunit composition.

Methods: Cortical tubers from 6 patients ages 4–8 years were obtained during epilepsy surgery, in accordance with the Clinical Research Committee at Children's Hospital, Boston. All patients met clinical criteria for TSC with neuropathologic confirmation of the diagnosis. Tissue was fixed in 4% paraformaldehyde, cut at 50 μm and immunocytochemically double labeled with neuronal and glial cell markers, in combination with the TSC mutation marker pS6 and antibodies against AMPAR subunits GluR1-4, NMDAR subunits NR2A and NR2B, as well as the gap junction protein connexin 43 (Cx43).

Results: Two types of abnormal glial cells were identified within the tuber, based on their immunoreactivity for cell specific markers and the mutation marker pS6. Dysplastic astrocytes, localized predominantly around the blood vessels, were consistently immunopositive for vimentin and pS6, but only occasionally for GFAP. They showed intense GluR4 and GluR3 immunoreactivity, while GluR2, GluR1, NR2A and NR2B subunits were expressed only at low levels. In contrast, reactive astrocytes were distributed more uniformly throughout the cortex and labeled with both vimentin and GFAP, but not with pS6. Reactive astrocytes were strongly immunopositive for GluR1-4, as well as NR2A subunits. Both cell types showed intense Cx43 immunoreactivity, suggesting capacity for intercellular coupling.

Conclusions: Dysplastic astrocytes appear to express AMPA receptor subunits consistent with a pattern of calcium permeability (low GluR2 expression) and Cx43, which may augment cell-cell signaling in this abnormal cell population. 2. Reactive astrocytes display GluR and Cx expression patterns, similar to that reported in other pathologic states. 3. Taken together, these results suggest that dysplastic astrocytes in TSC lesions may be unique in their properties and future studies are necessary to examine their potential role in epileptogenesis of TSC lesions. [Supported by Boston Neurosurgical Fdn (D.M.T., P.M.B.) and NS31718 (F.E.J.).]

3.021

NEURONAL NITRIC OXIDE SYNTHASE (nNOS) EXPRESSION IN DYSPLASTIC HUMAN NEOCORTEX

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Rationale: Nitric oxide (NO) has been proposed as an agent involved in epileptogenesis, and increased expression of neuronal nitric oxide synthase (nNOS) has been demonstrated in post-mortem cortical samples from epileptic patients. Cortical dysplasia (CD) is a frequent cause of pharmacoresistent epilepsy. Previous studies have shown increased expression of the N-Methyl-D-Aspartate (NMDA) receptor NR2B subunit in epileptic dysplastic human neocortex. In normal rodent cortex, NR2B and nNOS are physically linked to the same scaffolding protein (PSD-95). In this study we investigate whether (1) nNOS is increasingly expressed in focal-epileptic, compared to extrafocal neocortex from patients with epileptic cortical dysplasia, and whether (2) increase in nNOS expression is correlated with increase in NR2B.

Methods: Ten patients with medically intractable epilepsy due to CD and 2 patients with mesial temporal sclerosis (controls) were submitted to pre and/or intra-operative invasive monitoring evaluation in order to define epileptogenic and non-epileptogenic cortical areas. During the surgical resection, cortical samples from epileptogenic and non-epileptogenic areas were collected from each patient. The matched samples were processed for CV staining, immunocytochemistry for nNOS, NeuN and NR2B and immunoflurescence analyses in order to evaluate co-localized immunoreactivity between nNOS and NR2B.

Results: Different degrees of CD were noted in all epileptogenic samples. In non-epileptogenic samples, CV staining revealed normal cortical architecture in 3 samples but mild degree of CD in 6 patients. The histological analysis of lateral temporal lobe from patients with mesial temporal sclerosis was normal. We identified nNOS expressing neurons in both epileptogenic and non-epileptogenic samples. The density and intensity of nNOS stained neurons was remarkably increased in the epileptogenic samples. Two types of nNOS stained neurons were identified: type 1, expressing strong nNOS immunoreactivity in larger neurons, and type 2, expressing weak nNOS immunoreactivity in slightly smaller neurons. Differently from type 1 neurons, type 2 nNOS stained neurons revealed immunoreactivity co-localization with NR2B antibody.

Conclusions: The overexpression of nNOS in the epileptogenic samples and the immunoreactivity co-localization between nNOS and NR2B may suggest a possible role of nNOS and NO in the mechanisms related to in situ epileptogenicity. NO and nNOS may constitute a target for improvement of diagnostic tools and new pharmacotherapeutic approaches for epilepsy. [Supported by NINDS for Imad M Najm (K08NS02046 and 1R21 NS42354).]

3.022

MODULATION OF HIPPOCAMPAL NF-κB TRANSCRIPTIONAL ACTIVITY IN THE KAINATE MODEL OF EPILEPSY

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Rationale: Nuclear-factor kappa B (NF-κB) has been well characterized in the immune system as a transcriptional regulator of inflammatory responsive genes. More recently, NF-κB activation has been implicated in neuronal plasticity and in disorders of the CNS. Gene expression profiles are altered in epilepsy but the transcription factors regulating these changes are not defined. NF-κB has been identified as a potential key regulator of gene responses in epilepsy. In these studies we characterized activation of NF-κB in the kainate (KA)-seizure model *in vivo*. We also investigated whether KA-induced NF-κB activation couples to specific gene expression changes in hippocampus.

Methods: For these studies, we evaluated NF-κB activation in hippocampus following KA (15 mg/kg IP) administration in male rats. KA-mediated NF-κB activation was determined by western blotting using phospho-selective antibodies and through assessment of DNA binding activity by electrophoretic mobility shift assay analysis. Using RT-PCR, we determined whether NF-κB activation coupled to hippocampal gene changes following KA-induced status epilepticus using an inhibitor of NF-κB, diethyldithiocarbamate (DDTC).

Results: Immunoblot analysis of hippocampal whole cell extracts from animals with KA-induced status epilepticus (SE) showed increased levels of phospho-NF-κB in area CA3 ($p < 0.05$). We observed no significant change in phospho-NF-κB levels in whole cell extracts from area CA1 and dentate gyrus. In parallel, NF-κB DNA binding activity increased in area CA3 ($p < 0.05$) following SE. NF-κB-mediated gene expression changes in area CA3 of hippocampus included increases in IκBα (NF-κB autoregulatory loop), BDNF, and *bcl-2* following SE compared to controls. Preliminary inhibitor studies using DDTC suggest that NF-κB activation may be necessary for the KA-induced activation of BDNF gene expression in area CA3. Similar DDTC inhibitor studies are currently underway for assessment of IκBα and *bcl-2* genes.

Conclusions: In summary, we have shown modulated NF-κB activation in hippocampal area CA3 following KA-induced SE. Furthermore, we have pilot data suggesting that at this early time point following KA-induced seizures there is evidence of altered NF-κB gene regulation. These findings suggest that NF-κB is a candidate transcriptional regulator of gene expression changes in the KA model of epilepsy. (Supported by NIH/NINDS, Epilepsy Foundation Awards, and SFN Travel Fellowships.)

3.023

LONG-LASTING CHANGES IN INTRINSIC PROPERTIES OF SURVIVING MOSSY CELLS AFTER HEAD INJURY

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Rationale: After fluid percussion injury (FPI), a large number of mossy cells in the dentate gyrus die. However, the loss of mossy cells does not lead directly to hyperexcitability of dentate granule cells (Ratzliff et al., J Neurosci. 2004;24:2259–69). The "irritable mossy cell hypothesis" proposes that the surviving mossy cells themselves are either hyperexcitable or spread hyperexcitability, thereby contributing to the hyperexcitability of dentate granule cells (Santhakumar et al, J Physiol. 2000 524:117–34; Ratzliff et al., Trends Neurosci. 2002;25:140–42). In this study, we tested this hypothesis by examining the intrinsic properties of surviving mossy cells.

Methods: Whole-cell recordings were made from prelabeled mossy cells (Ratzliff et al., 2004) in 350 μm horizontal hippocampal slices at 32°C. Slices were obtained from P20-P23 rats 5–8 days after fluid percussion injury or sham injury. The intracellular solution contained (in mM): 140 K Gluconate, 2 $MgCl_2$, and 10 mM N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES). The bath was perfused with ACSF containing 5 μM NBQX and 10 μM AP-5. Statistics were performed using Student's t-test, with significance set at $p < 0.05$.

Results: The resting membrane potential of mossy cells after FPI was significantly depolarized compared to controls (FPI: −63.12 +/− 0.84 mV, Control: −66.56 +/− 1.35 mV). Intrinsic properties of mossy cells were measured in current clamp configuration using 500 ms using current steps from −320 to +440 pA, incrementing by 40 pA, from a holding potential of −60 mV. The amplitude of the depolarizing sag in response to hyperpolarizing current pulses was significantly increased at current pulses between −40 and −280 pA (at −200 pA steps, FPI: 8.1 +/− 1.1 mV, CON: 5.6 +/− 0.7 mV). In addition, the afterdepolarization seen after the termination of hyperpolarization was significantly increased at negative current steps between −40 and −320 pA (at −200 pA steps, FPI: 4.9 +/− 0.7 mV, CON: 2.5 +/− 0.7 mV).

Conclusions: Mossy cells which survive head injury exhibit long-lasting changes in their intrinsic properties following the insult. The changes seen, an increased resting membrane potential, increased depolarizing sag, and increased afterdepolarization, are all consistent with an increased expression of I_h. Increase in I_h can modulate increased neuronal excitability in complex ways. (Chen et al. *Trends Pharmacol Sci* 2002;23:552–7). The changes seen here could be expected to have large downstream effects since mossy cells are uniquely positioned to spread excitability through the hippocampus due to their long-ranging associational and commissural projections. [Supported by NIH (NS35915) to I.S.]

3.024

SUSCEPTIBILITY GENES OF $GABA_A$ RECEPTOR δ SUBUNIT FOR HUMAN GENERALIZED EPILEPSIES HAVE DEFECTIVE CHANNEL GATING

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Rationale: Mutations in $GABA_A$ receptor $\gamma 2$ and $\alpha 1$ subunits have been linked to human generalized epilepsies. However, these monogenic mutations only account for a minority of the generalized epilepsies, suggesting that most of the generalized epilepsies are polygenic. Recently a rare variant of $GABA_A$ receptor δ subunit (E177A) was found in a small family heterozygously associated with generalized epilepsy with febrile seizures plus (GEFS+), and a polymorphic allele (R220H) was present in a family with juvenile myoclonic epilepsy as well as in general population. Recombinant h$\alpha 1\beta 2S\delta$ receptors containing heterozygous and homozygous δE177A or δR220H subunit variants had significantly reduced $GABA_A$ receptor currents. The variants E177A and R220H were proposed to be susceptibility genes for the generalized epilepsies (Dibbens et al. *Hum Mol Genet*, in press). Studies found that the δ subunit preferably coassembles with the $\alpha 4$ subunit. The function and gating properties of $\alpha 4\beta 2S\delta$ receptors containing E177A or R220H variant are unknown.

Methods: HEK 293T cells were transfected with human $\alpha 4$, $\beta 2S$ and wild type as well as variant δ subunit cDNAs and the expressed receptors were studied using the whole cell and single channel patch clamp technique.

Results: Compared to wild type $\alpha 4\beta 2S\delta$ receptor whole cell currents, saturating GABA-evoked currents were significantly smaller for heterozygous or homozygous $\alpha 4\beta 2S\delta$(E177A) receptors as well as for heterozygous or homozygous $\alpha 4\beta 2S\delta$(R220H) receptors. No significant changes in kinetic properties were observed with $\alpha 4\beta 2S\delta$(R220H) receptors. However, desensitization was significantly decreased for heterozygous and homozygous $\alpha 4\beta 2S\delta$(E177A) receptors, and deactivation was significantly prolonged for homozygous $\alpha 4\beta 2S\delta$(E177A) receptors. The mean open durations of both homozygous $\alpha 4\beta 2S\delta$(E177A) (1.3 $\pm$ 0.2 ms) and $\alpha 4\beta 2S\delta$(R220H) (1.6 $\pm$ 0.1 ms) receptor single channel currents were significantly decreased as compared to wild type $\alpha 4\beta 2S\delta$ receptors (2.6 $\pm$ 0.2 ms).

Conclusions: These data suggest that these δ subunit variants may decrease surface receptor expression and produce defective channel gating, resulting in $GABA_A$ receptor current reduction. (Supported by NIH NS 33300 to R.L.M. and an Epilepsy Foundation postdoctorate fellowship to H.J.F.)

3.025

EPILEPTOGENESIS INDUCES ACUTE AND CHRONIC INCREASES IN $GABA_A$ RECEPTOR ENDOCYTOSIS AND DECREASED RECEPTOR FUNCTION: IMPLICATIONS FOR THE ROLE OF $GABA_A$ RECEPTOR RECYCLING IN THE INDUCTION AND MAINTENANCE OF SEIZURE DISCHARGES IN EPILEPSY

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Rationale: Studies have shown that $GABA_A$ receptor ($GABA_AR$) function is decreased immediately following SE and in association with epilepsy. One mechanism whereby neurons regulate receptor function and overall synaptic efficacy is by internalization and recycling of neurotransmitter receptors at the plasma membrane. This study was initiated to investigate the contribution of altered $GABA_AR$ endocytosis towards both the decrease in receptor function and induction and maintenance of seizure discharges associated with SE and epilepsy.

Methods: SE was induced in hippocampal cultures by exposure to low Mg^{++} media, and spontaneous recurrent epileptiform discharges (SREDs) were produced for the life of the neurons in culture by 3 hours of SE. Electrophysiological analysis of SE and SRED activity was obtained with whole-cell current-clamp recordings. GABA concentration/response curves were generated using the whole-cell voltage-clamp technique. Immunohistochemical detection of membrane $GABA_AR$ was carried out using a monoclonal antibody to the $\beta 2/3$ receptor subunits and analyzed by laser scanning confocal microscopy. $GABA_AR$ endocytosis was inhibited in hippocampal cultures with either GDP-βS (600 uM) or a peptide that specifically blocks the dynamin-amphiphysin association step in clathrin-mediated receptor endocytosis. An additional study involved confocal microscopic analysis of membrane $GABA_AR$ $\beta 2/3$ staining on hippocampal sections from the rat pilocarpine model of acquired epilepsy.

Results: Low Mg^{++} treatment of hippocampal cultures resulted in SE and the development of SREDs following 3 hr of SE. A 50% reduction in GABA response was observed with the induction of the "epileptic" condition in this model. Confocal analysis of $GABA_AR$ $\beta 2/3$ immunostaining revealed a significant reduction in $GABA_AR$ membrane levels in both acute (SE) and "epileptic" hippocampal cultures when compared to control. Inhibition of $GABA_AR$ endocytosis in "epileptic" cultures resulted in both the total blockade of SREDs and a recovery of $GABA_AR$ $\beta 2/3$ membrane staining back to control levels. Further studies in the pilocarpine model of acquired epilepsy demonstrated decreased hippocampal $GABA_AR$ membrane staining in epileptic compared to control animals one year after the onset of epilepsy. No changes in hippocampal synaptophysin membrane staining were observed between epileptic and control animals.

Conclusions: Increased $GABA_AR$ endocytosis may contribute to decreased receptor function and the induction and maintenance of seizure

discharges observed in both SE and "epileptic" neuronal cultures and in the intact pilocarpine model of acquired epilepsy. The findings of this study suggest a role for altered $GABA_AR$ membrane recycling in the pathophysiology of SE and epilepsy. (Supported by NINDS RO1-NS23350 and P50-NS25630 to R.J.D.)

3.026
KAINATE-INDUCED STATUS EPILEPTICUS UPREGULATES KCC2 mRNA EXPRESSION IN THE SUBSTANTIA NIGRA OF IMMATURE RATS

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Rationale: We have previously shown that in the substantia nigra reticulata (SNR) of both male and female neonatal rats, GABA(A) receptor activation causes neuronal depolarization. The switch of GABA(A) receptors from depolarizing to hyperpolarizing occurs earlier in female SNR neurons (around postnatal days 10–12 (PN10-12)) compared to male (still depolarizing at PN17). Three episodes of kainate (KA)—induced status epilepticus (SE) at PN4, PN5, and PN6 accelerate the switch of GABA(A) receptors from depolarizing to hyperpolarizing in the rat SNR of both sexes. It is also known that one of the factors that regulate the functional maturation of GABA(A) receptors is the level of expression of the neuronal-specific potassium chloride cotransporter KCC2. We tested therefore the effect of KA-induced SE at PN4-6 on the level of KCC2 mRNA expression in the SNR of PN10 male and female rats.

Methods: Sprague-Dawley male and female rats were subjected to 3 episodes of KA-induced status epilepticus (SE) at PN4 (KA 1.5 mg/kg intraperitoneally (ip)), PN5 (KA 2 mg/kg ip) and PN6 (KA 2.5 mg/kg ip). Controls received saline injections and were kept separated from their dams for the same period as the pups subjected to SE (6–7 hours). Rats were sacrificed at PN10 and brains were processed with a KCC2-specific in situ hybridization. KCC2 cellular mRNA expression was compared semi-quantitatively with signal densitometry.

Results: Saline-injected female PN10 pups had increased levels of KCC2 mRNA in the SNR compared with saline-injected male PN10 pups. In both sexes, KA-induced SE (PN4-6) further increased KCC2 mRNA expression in PN10 SNR neurons, compared to same-sex rats.

Conclusions: (1) KCC2 mRNA expression in female PN10 rat SNR is higher than in male and correlates therefore with the earlier time of switch of GABA(A) receptors to hyperpolarizing in female SNR neurons. (2) KA-induced seizures in early postnatal life increase KCC2 mRNA expression in the SNR in both sexes. These changes in KCC2 expression may explain the acceleration in the functional maturation of the GABA(A) receptors in the SNR of rats that experienced early life seizures. By altering KCC2 expression and the function of GABA(A) receptors, early life SE may therefore alter the phenotype and function of the SNR in seizure control. (Supported by NIH NINDS NS 45243 and NS 20253 grants.)

3.027
CARBAMAZEPINE, BUT NOT VALPROATE, DISPLAYS PHARMACORESISTANCE IN LAMOTRIGINE-RESISTANT AMYGDALA-KINDLED RATS

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Rationale: Pharmaco-resistance is a common clinical problem for approximately 25–40% of the patients with partial epilepsy. Lamotrigine (LTG), administered prior to amygdala or pentylenetetrazol (PTZ) kindling, leads to the subsequent development of LTG resistance (Postma et al. *Epilepsia* 2000;41(12):1514–21; Srivastava et al. *Epilepsia* 2003; 44(42)). However the mechanism underlying this resistance is unclear.

The present study aimed to (1): assess whether LTG-resistant amygdala-kindled rats display subsequent resistance to carbamazepine (CBZ) and sodium valproate(VPA), and (2): to assess whether pharmacokinetics underlie the subsequent resistance to LTG.

Methods: Two groups of male Sprague Dawley rats were amygdala kindled according to method described by Postma et al. (2000). One hour before each kindling stimulation, rats in the control group received 0.5% methylcellulose and rats in the experimental group received LTG(5mg/kg, i.p.). Treatments were stopped once the control group were fully kindled. One day later, both groups were challenged with a higher dose of LTG (15 mg/kg, i.p.) to verify LTG resistance in the experimental group (i.e., LTG- pretreated rats). The efficacy of CBZ and VPA was then evaluated in both the groups. In a separate set of identical experiments, animals from both vehicle- and LTG-treated groups were sacrificed at one hour and plasma LTG levels determined by high performance liquid chromatography (HPLC).

Results: A stable kindled state was established in both vehicle- and LTG-treated animals. Upon subsequent challenge with a higher dose of LTG, the fully kindled seizure of the vehicle-treated rats, but not the LTG-treated rats, was blocked by LTG. HPLC study demonstrated that the observed pharmaco-resistance to LTG could not be accounted for by any depression in plasma LTG level following 15mg/kg dose. Interestingly, CBZ (10, 20, and 40 mg/kg) displayed a dose-dependent anticonvulsant effect in the vehicle kindled group but, was ineffective in the LTG-treated animals. In contrast, VPA (300 mg/kg) effectively blocked the behavioral seizure and decreased the afterdischarge duration in both the groups.

Conclusions: The present findings with amygdala kindling confirm our previous findings in the PTZ kindled rats and demonstrate that LTG, when administered at low doses during kindling acquisition, does not prevent the development of kindling but leads to the subsequent development of pharmaco-resistance to LTG and are in agreement with findings of Postma et al. (2000). In addition, LTG-resistant rats displayed a pharmaco-resistance to CBZ but not to VPA. These findings suggest that the LTG-resistant, amygdala -kindled rat may represent a novel model of pharmaco-resistant epilepsy. Ongoing studies continue to evaluate the mechanism underlying the development of pharmaco-resistance to LTG and CBZ. (Supported by NINDS contract NO1-NS-9-2313.)

3.028
INDUCTION OF MULTIDRUG TRANSPORTER AND DRUG METABOLISM mRNAs IN RAT LIVER BY KAINIC ACID–INDUCED SEIZURES: IMPLICATIONS FOR THERAPY-RESISTANT EPILEPSY

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Rationale: Antiepileptic drugs are usually taken orally and drug availability may therefore be markedly influenced by "first-pass" metabolism/elimination in the liver. An increase in the expression of multidrug transporters (MDTs), including multidrug resistant 2 (MDR2) and multidrug resistance related protein 2 (MRP2 or cMoat) in the liver have been proposed as a possible factor responsible for therapy resistant seizures. Hepatic expression of enzymes involved in drug metabolism, exemplified here by glutathione S-transferase A2 (GSTA2) and NAD(P)H:quinone oxidoreductase (QOR or DT-diphorase) have also been implicated in therapy resistance in epilepsy. Kainic acid (KA) is used in animals to model human temporal lobe epilepsy. We examined the effect of prolonged KA-induced seizure activity ($\geq$3.5 hours) on the expression of MDR2, MRP2, GSTA2 and QOR mRNAs in rat liver.

Methods: KA-induced seizures were achieved by the method of Hellier et. al. (1998). Animals were given a 5 mg/kg intra-peritoneal injection every hour until marked, repeated stage 4/5 (Racine, 1972) seizures were achieved. Saline-treated animals were used as controls. Total RNA was isolated from liver tissue and the level of MRP2, GSTA2, and QOR mRNA assessed by Northern blot analysis at 24 hours and ten weeks after KA-induced seizure activity. The level of MDR2 mRNA was assessed by real-time PCR at 24 hours and ten weeks after KA-induced seizure activity using a Roche lightcycler.

Results: Significant elevations of MRP2, MDR2, GSTA2 and QOR mRNAs were detected in the liver ten weeks after kainic acid induced seizure activity. 24 hours after KA-induced seizure activity only QOR mRNA was significantly increased.

Conclusions: KA-induced seizure activity has been reported to cause induction of MDR2, MRP2, and QOR mRNA in the brain. Our results indicate that KA-induced seizure activity also causes increased expression of these mRNAs in the liver. The increase in the liver was detected ten weeks after KA treatment, suggesting that it might be the seizures themselves causing mRNA induction. The multidrug transporter mRNAs examined in this study are all involved in the elimination of antiepileptic drugs. The fact that these genes have human homologues and that the mRNA induction occurs in the liver, a major organ in drug metabolism, has implications for therapy resistance. (Supported by NS-42311.)

December 6, 2004
Poster Session 1
8:00 a.m.–5:00 p.m.

Translational Research: Basic Mechanisms 1

1.001
THE ROLE OF BCL-2 FAMILY OF GENES DURING MURINE MODEL OF EPILEPTOGENESIS, KINDLING

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Rationale: Several experimental models of human temporal lobe epilepsy have shown that apoptotic death of neurons is an important part of this degenerative disease. However, the role of apoptotic regulators is not clear during the epileptogenesis. Therefore, we investigated the expression pattern of *bcl-2* family of genes during the formation of kindling model of epilepsy in rats.

Methods: We examined the expression pattern of *bax, bcl-2, bcl-x_L, mtd* and *bcl-w* both at mRNA and protein level in the brain tissues during the formation of epilepsy with kindling model in adult rats, which has been the most acceptable form of experimental model of human epilepsy. We also assessed the onset of DNA fragmentation by using TUNEL assay.

Results: Animals have started to have epileptic discharges after the 10th day of kindling model. Recurrent subthreshold electrical stimuli induced not only epileptic foci but also the expression of *bax*, an inducer of apoptosis, in this time period. On the other hand, *bcl-x_L*, which is an inhibitor of apoptosis, had an opposite pattern of expression both at mRNA and protein level during the formation of epilepsy. We did not observe DNA fragmentation by TUNEL staining.

Conclusions: Our study shows differential expression of Bax and Bcl-x_L at the CA1 region during the formation of hippocampal kindling model. The absence of DNA fragmentation during this period suggests that epileptic changes in neurons has the potential to induce DNA fragmentation by altering the expression levels of Bax and Bcl-x_L. [Supported by Bilkent University Research Grant, Bilkent University Faculty Development Grant, Ege University and Tubitak (SBAG-2239).]

1.002
COMPARISON OF SEIZURE ONSET IN THE INTRAHIPPOCAMPAL KAINATE AND PILOCARPINE RAT MODELS OF CHRONIC EPILEPSY

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Rationale: There exists a general consensus that the variety of seizure types in TLE patients can be classified into two groups: hypersynchronous onset (HYP) and low voltage fast onset (LVF). Currently, it is not clear if corresponding seizure onset types exist in animal models of temporal lobe epilepsy. In this study, we compared seizure onsets in two rodent models of chronic epilepsy to determine the morphology of seizure onset.

Methods: Kainic acid (0.4 μg/0.22μl) was injected in the right CA3 area of posterior hippocampus of adult Wistar rats. Pilocarpine (25–30 mg/kg) was injected subcutaneously in a second group of rats. After the development of spontaneous seizures, microelectrodes (tungsten, 50 μm) were implanted bilaterally in the hippocampus and entorhinal cortex for wide-band *in vivo* EEG recording (0.1 Hz–1kHz). Seizures were classified on the basis of morphological onset pattern, signal averaging and power spectral analysis.

Results: Seizures in the kainic acid group (n = 86, in 10 rats) were classified as either LVF (25%) or HYP (71%), with the remaining seizures (4%) falling into a third category, named "Gradual" because of their slower development. Signal averaging within each onset type revealed the presence of an Initial Slow Wave at onset in the LVF, but not at HYP, seizures. Of all HYP seizures, most (82.6%) were local and did not spread to other brain areas, while the remaining (17.4%) seizures generalized to both sides of the brain.

Seizures in the pilocarpine group (n = 151, 4 animals) were classified visually as LVF (51%) or HYP (3.3%) onsets. Distinct from LVF and HYP, the remaining seizures (45.7%), exhibited high voltage fast activity (HVF) at onset. Signal averaging within each onset type revealed the presence of an Initial Slow Wave at onset in the LVF and HVF, but not at HYP, seizures. All seizures in the pilocarpine group generalized to both sides of the brain.

Conclusions: These data indicate that two rodent models of chronic epilepsy exhibit seizures morphologically similar to those recorded patients with temporal lobe epilepsy. HVF and LVF seizures that exhibited a slow wave at onset were dominant in the pilocarpine model, while HYP onsets lacking a slow wave onset were more frequent in the KA rodent. The differences of seizure type ratio between may indicate that each model lends itself to the study of a particular onset pattern. Additionally, a useful relationship between the initial chemical insult, mechanism of seizure generation and morphological type of onset may exist. (Supported by NSF IGERT Neuroengineering Training Grant DGE-9972802; NIH grants NS-02808 and NS-33310.)

1.003
TIME COURSE OF SEIZURE-INDUCED CHANGES OF HCN CHANNEL ISOFORM EXPRESSION

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Rationale: Experimental prolonged febrile (and kainate-evoked) seizures alter the expression of HCN channels in the hippocampus: one week after the seizures, reduction of HCN1 and enhancement of HCN2 in the hippocampal CA1 and CA3 has been found (Brewster et al., 2002). This regulation of HCN channel expression could be a direct, activity-dependent effect of seizures, or secondary to 'compensatory' phenomena, including increased activation of these hyperpolarization-triggered channels by enhanced GABAergic inhibition (Chen et al., 1999). Because increased IPSC frequency was present at 1 week after seizures but not at 24 hours, we set out to determine the time course of seizure-evoked alteration of HCN expression levels.

Methods: Seizures were induced *in vivo* (prolonged experimental febrile seizures) and *in vitro* (low [Mg^{2+}] in organotypic hippocampal slice cultures). HCN1 and HCN2 mRNA expression levels were determined at 24,48 and 72 hours after both *in vivo* and *in vitro* seizures, using semi-quantitative *in situ* hybridization (Brewster et al., J Neurosci, 2002; Bender et al., J Neurosci, 2003) and aRNA single cell analysis.

Results: The enduring alterations of HCN1 and HCN2 expression that were found at 1–12 weeks after developmental seizures, were not evident at 24 hours after induction of experimental febrile seizures *in vivo*. This is consistent with the lack of HCN1 and HCN2 changes at the 24 hour point after *in vitro* seizures, where the divergence of HCN1 and HCN2 expression was found by 48 hours. Because these time-course data do not conclusively determine the relationship of enhanced hyperpolarizing drive and HCN channel expression, *in vitro* manipulations of GABA levels and GABAergic activity are currently under way.

Conclusions: Changes in HCN channel expression are not present at 24 hours after *in vivo* or *in vitro* seizures, but are found by 48 hours. Whether slow mRNA turnover, or indirect (or compensatory) effects

of the seizures underlie these findings is currently under investigation. (Supported by NIH NS 35439; 28912 EFA.)

1.004
EXPRESSION OF POTASSIUM ION CHANNEL KIR4.1 (KCNJ10) IN BRAINS OF C57BL6/J AND DBA2/J MICE
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Rationale: Our previous studies utilized quantitative trait loci mapping in seizure resistant C57BL/6 (B6) and seizure sensitive DBA/2 (D2) mice to document linkage to a gene(s) on mouse chr 1 with a large effect on seizure susceptibility. We identified the inward rectifying potassium ion channel gene Kcnj10 as our primary candidate based on its function and location. In addition we demonstrated a Kcnj10 coding region variation that differentiates B6 from D2 (Ferraro et al., Mam Gen 2004;15:239–251) and a coding region variation in the human KCNJ10 that is associated with epilepsy (Buono et al., Epi Res 2004;58:175–183). Since the coding region variations alter the amino acid sequence of the Kir4.1 protein in mice (T262S) and humans (R271C), we hypothesize that altered protein function is related to seizure susceptibility. However, no detailed studies of Kir4.1 expression in the brain have been reported. Since differences in expression could underlie the seizure sensitivity difference in the inbred strains, we used immuno-histochemistry and image analyses to localize the Kir4.1 protein in the brains of B6 and D2 mice and to compare expression levels between the two strains.

Methods: Six male mice of each strain were used. Brains were fixed by perfusion and immersion, paraffin embedded, sectioned in the sagital plane and stained with anti Kir4.1 (Alamone Labs Inc.). Antibody was visualized with Vecatstain reagents, photographed and analyzed (Image-Pro Plus, v 4.0).

Results: Our results demonstrate that the Kir4.1 staining was prominent in tectum, tegmentum, olfactory bulb, hypothalamus, thalamus, fornix, septum, and brainstem with weaker staining in hippocampus, cortex and cerebellum. In contrast to all previous reports of Kir4.1 localization being restricted to glial cells, we find clear evidence of immunoreactivity in cortical pyramidal neurons and Purkinje cells. Image analyses comparing intensity of stain between B6 ($n = 6$) and D2 ($n = 6$) mice was performed. Six regions were systematically scanned (brainstem, cerebellum, olfactory bulb, hippocampus, thalamus, hypothalamus, frontal cortex) and showed no statistically significant differences between B6 and D2 mice.

Conclusions: We conclude that Kir4.1 is expressed in both neurons and glial cells and that brain expression levels are not different between B6 and D2 mice. (Supported by grants R01NS40396 to R.J.B. and R01NS40554 to T.N.F.)

1.005
THE THRESHOLD FOR JNK ACTIVATION DECREASES DURING KINDLING EPILEPTOGENESIS
Kasie K. Cole-Edwards, Alberto E. Musto, and Nicolas G. Bazan (The Neuroscience Center of Excellence, Louisiana State University Health Science Center, New Orleans, LA)

Rationale: In kindling epileptogenesis, a model of mesial temporal lobe epilepsy, repetitive stimulation of the perforant path leads to increased after-discharges as measured by EEG and an enduring seizure-prone state. Stimulus-induced glutamate release is thought to participate in rearrangements of neuronal circuitry favoring a permanent hyperexcitable state, often associated with mossy fiber sprouting. But the molecular mechanisms by which repetitive stimuli evoke these long-lasting changes in synaptic strength are unknown. We hypothesize that during seizures, glutamate-receptor activation turns on protein signaling cascades, possible via 1-*O*-alkyl-2-acetyl-glycero-3-phosphocholine (PAF), which lead to long-term changes in neuronal circuitry through alterations in gene transcription. In the current study, we set out to determine the role of the stress-activated MAPK, c-jun N-terminal kinase (JNK) and the newly-discovered JNK scaffold-regulating proteins in kindling.

Methods: Adult, male Wistar rats were stereotaxically implanted in the right ventral hippocampus with stimulatory and recording electrodes and underwent a rapid kindling protocol. The progression of kindling was verfied behaviorally, by scoring seizures according to Racine's scale and electrophysiologically, by recording after-discharges. Immunoblot analysis of Thr183/Tyr185-phosphorylated JNK-1, −2, and −3 was employed as indication of the JNK activation state in the dentate gyrus, CA3, and CA1 sub-regions of the hippocampus as well as in the cortex. Immunofluorescent analysis was performed to confirm this region-specific localization of phosphorylated JNK and to examine the distribution of the JIP proteins in kindled animals. Finally, brain sections from fully kindled animals were processed with a Nissl stain to assess the distribution of neuronal injury.

Results: Preliminary results indicate that kindled animals experiencing severe stimulus-induced seizures (stage 5 on Racine's scale) not only exhibit an increased mean number of spikes on EEG recordings but also display marked JNK phosphorylation in the hippocampus and the cortex compared to their naïve counterparts. Immunofluorescence analysis of phosphorylated JNK confirms this region-specific pattern of JNK activation in the cortex and the hippocampus. In addition, JNK activation, which has been implicated in neuronal death under many pathological conditions in the CNS, coincides with neuronal damage as seen with Nissl stain.

Conclusions: These data suggest that decreasing thresholds for JNK activation may play a critical role in the progression of kindling by promoting death of neurons, possibly inhibitory interneurons, and/or by phosphorylating substrates which may act to modulate synaptic strength during kindling epileptogenesis. (Supported by NIH NS 23002.)

1.006
DO SEIZURES ACT AS A DETERRENT TO CELL PROLIFERATION?
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Rationale: Historically, it has always been assumed that brain tumors (BT) are a frequent cause of epileptic seizures. Seizures occur in 50% of patients with intracranial brain tumors and AED therapy is prophylactically administered to most brain tumor patients. Chronic epilepsy can be the only symptom of low grade brain tumors. There is a significant overlap between genes that are associated with genetic forms of epilepsy and alterations in tumor suppressor genes. It is however not clear if a cause-effect relationship exists between epileptogenesis and tumorigenesis. Chronic epilepsy prolongs survival of patients with low-grade gliomas that present with seizures (1). We hypothesized that two factors associated with chronic epilepsy, abnormal electrical activity and elevated [K]out can act as anti-proliferative agents.

Methods: We used normal human astrocytes, epileptic glia and C6 rat glioma cells in multi-well Petri dishes equipped with an array of stainless steel electrodes connected to a PC via an I/O board. The electrodes were connected to a pulse generator interfaced with a computer. Cells were exposed to different electrical parameters of stimulation (current intensity 7.5 μA) for three to five days.

Results: Cells exposed to10 Hz stimulation grew at a rate comparable to control ($p < 0.05$). Stimulation at 25–100 Hz caused a pronounced decrease in the number of cells as early as three days after stimulation. The effects persisted and grew larger with prolonged exposure to electric pulses. We hypothesized that decreased cell proliferation rather than cell death were responsible for the decreased number of cells in stimulated wells. We confirmed that stimulation at 50 Hz decreased cell number by a direct effect on cell cycle and not by triggering cell death by measuring incorporation of BrdU and release of adenylate kinase, markers of cell division and cellular damage respectively. Applying current intensities higher 8.5 uA caused cellular damage as reveled by a statistical significant increase of AK release. Proteomic analysis demonstrated that the decreased propensity to cell proliferation was accompanied by an increased expression of a specific member of the KIR family, GIRK2 (Kir3.2). Blockade of KIR by cesium or barium abolished the effects

of electrical stimulation. However, since blockade of KIR results in depolarization, we also tested whether changes in membrane potential per se may affect proliferation. This was achieved by exposing unstimulated astrocytes to increasing concentrations of KCl; manipulations of extracellular sodium were entirely ineffective. External potassium acted as deterrent for cell division at concentrations >4 mM suggesting that depolarization was not crucial.

Conclusions: Our results suggest that 1) High frequency epileptic activity acts a deterrent to cell division; 2) This effect appears to involve potassium coundactances, specifically Kir3.2.

REFERENCE

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(Supported by NIH NINDS, NHLBI.)

1.007
POSTTRANSLATIONAL MODIFICATIONS OF NMDA RECEPTORS FOLLOWING PERINATAL HYPOXIA-INDUCED SEIZURES

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Rationale: We have previously shown that seizures in the immature brain, and this is associated with immediate (<1h post seizure) increases in hippocampal hyperexcitability and long term seizure susceptibility (*J Neurophysiol* 1998;79:73–81). Epileptogenic sequela of seizures in the immature brain (P10 rat) are likely to be due to alterations in multiple neurotransmitter systems. AMPA receptor current activity is increased within 1 h after seizures. AMPA mediated activation of calcineurin within 1 h after seizures leads to a decrease in GABAergic inhibition. We have recently reported a seizure induced downregulation of the NR2B subunit at 24 h following seizures at P10 (*Epilepsia* 2003;44:18–9). In the present study, we examined the time course of alterations in NMDAR function and expression.

Methods: Postnatal day (P) 10 rats were placed to 4–7% of O_2(15 min). Whole-cell recordings were made in pyramidal cells of hippocampal slices removed 1h after hypoxia or from control rats. Single stimulus shocks were delivered through a bipolar electrode to evoke NMDAR-mediated EPSCs (eEPSCs). We used the NR2B specific antagonist Ro25–6981 to evaluate NR2B mediated currents. NR2B expression levels as well as phosphorylation state of the serine (pSer) residue were analyzed by Western blot with anti-pSer or anti-NR2B antibodies.

Results: We have previously shown that NMDA responses were negatively regulated by Ro25–6981 (1 μM) in control rats but not at 24h post hypoxia-induced seizures in P10 rats (*Epilepsia* 2003;44:18–9). In contrast, at 1 h after hypoxia-induced seizures, there were no differences in NMDA (200 μM) induced responses in CA1 pyramidal neurons from slices from hypoxic vs control P10 rats. Furthermore, NMDA responses were significantly inhibited by Ro25–6981 in both groups (70% decrease in control rats vs 77% in hypoxic rats). In addition, Ro25–6981 showed similar inhibition of the eEPSCs mediated by NMDARs, suggesting only synaptic NMDARs are involved in this study (65% decrease in control rats). Unlike 24h post hypoxic seizures, NR2B expression was not altered at 1 h compared to control rats. However, there was a significant decrease (23% of control, $p < 0.05$) in NR2B phosphorylation as measured by pSer labeling.

Conclusions: Our data indicate that seizure induced alterations of overall levels of NR2B subunit in the P10 rat brain are not immediate and become apparent by 24h. However, NR2B phosphorylation does change as early as 1h, indicating that seizure-induced receptor dephosphorylation may precede membrane protein decreases. Future studies are required to determine the specific NR2B site involved or whether NR2B subunit dephosphorylation results in subunit removal from the membrane. Furthermore, it is not yet clear whether the seizure-induced decreases in NR2B represent a compensatory response to suppress excitability or in fact contribute to epileptogenesis in this model of neonatal seizures. [Supported by EF/AES fellowship (W.D.); NS31718 (F.E.J.).]

1.008
MICRO-PET DURING VAGUS NERVE STIMULATION IN RATS: A PILOT STUDY

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Rationale: Vagus nerve stimulation (VNS) is a neurophysiological adjunctive treatment for refractory epilepsy. A positive effect of VNS has been shown in a great number of human and animal studies, however the precise mechanism of action is not known. Through diffuse projections of the vagus nerve in the nervous system, VNS can have a broad effect on neuronal excitability. Micro-PET (positron emission tomography) is used for quantitative determination of the location of positron emitting isotopes in the tissue of small animals. This technique permits the monitoring of biochemical processes over time both during a scan and across multiple scans of the same subject. The aim of this study was to explore the effect of acute and chronic VNS on glucose metabolism in Wistar rats, using 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) as a tracer.

Methods: Male Wistar rats (300–350g) were implanted with a cuff-electrode around the left vagus nerve. During a 2-week period three scans were taken 45 min after [^{18}F]-FDG (0.2 mCi, i.v.) injection. During the baseline period (day 1–7), the animals (n = 8) were not stimulated and a baseline scan was taken on day 7. In the second week (day 8–14), five animals were stimulated 24 hours-a-day with the following stimulation parameters: output current: 1.5 mA, frequency: 30 Hz, pulse width: 500 μs, on/off time: 60 s/12 s. Three control animals were not stimulated. To investigate the acute effect, a scan of the control group (n = 3) and VNS group (n = 4) was taken on day 8, when VNS was activated. As to the chronic effect, a scan was taken after one week of stimulation on day 14 in both control (n = 3) and VNS group (n = 3). MRI-data of the rat brain were used to assign regions of interest (ROI): cortex, limbic structures, cerebellum and brainstem. After acquisition, the images of the PET and MRI-scan were manually fused. Left/right ratios of the ROI were compared between the control and VNS group and between the different points of time (day 7, 8 and 14).

Results: There was no change in left/right ratio in the different brain regions after acute VNS. A trend towards an increase in left/right ratio in the limbic structures after chronic VNS was found.

Conclusions: Limbic structures play an important role in epilepsy and also human imaging studies show evidence of the involvement of the limbic system in the action of VNS. This study shows a trend towards an increased left/right ratio in the limbic structures of the rat brain due to chronic VNS, but this study still needs to be refined and extended. (Supported by BOF grants 011D9601 and 011105399, FWO grants 1.5236.99 and 6.0324.02, and by the Clinical Epilepsy Grant Ghent University Hospital 2000–2004.)

1.009
MOLECULAR REGULATION OF GLUTAMATE AND GABA TRANSPORTER PROTEINS BY CLOBAZAM DURING EPILEPTOGENESIS IN FE+++-INDUCED EPILEPTIC RATS

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Rationale: To assess the molecular effects of the antiepileptic drug clobazam (CLB, 1, 5-benzodiazepiene) which was shown to be superior to other benzodiazepines in the management of epilepsy, we performed a series of experiments using rats with chronic, spontaneous recurrent seizures induced by amygdalar injection of FeCl3 that were treated for 14 days with CLB. We then measured the expression of glutamate and GABA transporter proteins and evaluated the changes that occurred in these proteins using both experimental epilepsy model and control animals.

Methods: Experimental animals, male Wistar rats were grouped by amygdalar injectate, either FeCl3 or acidified saline, and then

randomized for 14 days of treatment to either intraperitoneal (i.p.) injection of muddled 10 mg/kg CLB or with an equal volume of 0.5% methyl cellulose solution. Groups used in this experiment were as follows; Group S-V (n = 6), amygdalar saline-injection followed by methyl cellulose solution treatment; Group S-CLB (n = 7), amygdalar saline-injection followed by CLB treatment; Group F-V (n = 8), amygdalar FeCl3-injection followed by CLB treatment; Group F-CLB (n = 7), amygdalar FeCl3-injection followed by saline treatment. Animals were sacrificed on the 14th day of treatment just after the last injection of CLB or methyl cellulose solution. Both hippocampi and frontal cortexes were removed. We used western blots to measure levels of glutamate transporters (EAAC1, GLT1, GLAST) and GABA transporters (GAT1, GAT3) with each antibody.

Results: GLAST protein immunoreactivity in the right hippocampus of F-V animals was statistically reduced by 30% of S-V group. And CLB treatment was associated with an increase in the production of GLT1 in the left hippocampus of F-CLB group. CLB treatment caused marked up-regulation of the GABA transporters GAT3 in the left hippocampus of animals receiving amygdalar FeCl3.

Conclusions: From the previous experiments, we concluded that chronic epileptogenesis might be associated with down- regulation of the production of glial excitatory amino acid transporters, GLAST and GLT1, proteins that cause increase in the basal extracellular concentrations of glutamate. Elevated GABA transporters expression resulted in the increase of reverse transport of GABA to the extracellular space during periods of intense excitation. From these reasons, in addition to allosteric activation of GABAA receptor, CLB might exhibit its anti-epileptic action by increasing GLT1 expression and GAT3 in the hippocampus of rats with epileptogenesis. [Supported by a Grant-in-Aid for Encouragement of Young Scientists (15790629) from the Ministry of Education, Science, Sport and Culture, Japan (to T.D.).]

1.010
ALTERED MAGNETIC RESONANCE IMAGING (MRI) T_2 SIGNAL AFTER EXPERIMENTAL PROLONGED FEBRILE SEIZURES DOES NOT SIGNIFY NEURONAL DEATH

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Rationale: Whereas most febrile seizures carry a benign outcome, a subpopulation of individuals with prolonged febrile seizures are at risk for later temporal lobe epilepsy. Signal changes on MRI may provide early markers for changes in neuronal integrity that promote epileptogenesis in such individuals. Serial MRIs were obtained before and following experimental prolonged febrile seizures in immature rat, to determine the prevalence and distribution of T2 weighted signal changes, and to determine their pathological substrate.

Methods: T2 weighted coronal images were acquired using fast spin echo, on a 4 Tesla scanner (Picker console, Philips Medical Inc.). Initial scans were performed on day 10 of life (P10; n = 5 controls and 8 experimentals). Seizures were evoked in the experimental group on P11, and all animals were imaged on P12 (24 hours after the seizures in the experimental group), and 7 days later. Neuronal injury was assessed using the Fluoro-Jade method.

Results: 75% of immature rats with experimental prolonged febrile seizures had abnormal T2 signal enhancement at 24 hours, and 87.5% at 8 days after the seizures. While abnormal signals involved the amygdala (87.5%), dorsal hippocampus (75%) and piriform cortex (87.5%), these changes were not accompanied by evidence of neuronal death in these regions.

Conclusions: Experimental prolonged febrile seizures lead to relatively frequent abnormal MRI signal in 'temporal lobe' structures. While these changes do not indicate cell death, they may signify pathological cellular processes that promote epileptogenesis. (Supported by an NIH grant 35439 and by a research initiative award from the AES.)

1.011
THE ROLE OF pH, PURINES, AND ECTO-ATPASES IN MODULATING INTERICTAL ACTIVITY IN THE HIPPOCAMPUS

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Rationale: Lowering brain carbon dioxide (CO_2) levels is used clinically to lower seizure threshold and to induce *absence* seizures. Increasing CO_2 levels has profound effects on respiration, memory, and consciousness. We have used hippocampal slices to investigate how CO_2 alters pH, extracellular adenosine concentration, and neuronal excitability. We examined how, via alteration of purine metabolism, CO_2 levels affect a model of interictal activity.

Methods: Rat hippocampal slices were cut from 4–8 week old male Sprague-Dawley rats as described in Dunwiddie & Hoffer, Br. J. Pharmacol. 69, 59–68. fEPSPs were recorded from area CA1 and epileptiform activity was induced in area CA3 by LTP of the recurrent collateral pathway (Stasheff et al., *Brain Res* 344:296–302). Extracellular adenosine levels were monitored with an enzymatic adenosine sensor (Dale, *J Physiol* 511:265–72) while electrophysiological recordings were made. Intracellular pH was measured using 2-photon imaging of CA1 pyramidal cells loaded with BCECF.

Results: Hypercapnic acidosis (20% CO_2) caused a $48.8 \pm 2.4\%$ decrease in fEPSP amplitude in area CA1; extracellular adenosine rose by 1.2 ± 0.2 μM which contributed significantly to this inhibition ($19.9 \pm 3.6\%$). Mild Hypercapnic acidosis (10%CO_2) also caused adenosine release which was shown to be pH-dependent. Hypercapnic acidosis attenuated epileptiform activity in area CA3 (6 out of 6 trials) by causing adenosine release. Hypocapnic alkalosis (2% CO_2) increased CA1 fEPSP amplitude by $22.1 \pm 3.6\%$ and decreased extracellular adenosine concentration by 0.5 ± 0.1 μM. This also increased the frequency of epileptiform activity in area CA3 from 0.06 ± 0.01 Hz to 0.11 ± 0.02. The increase in CA1 excitability due to hypocapnic alkalosis was significantly attenuated by blockade of adenosine A_1 receptors and purinergic P_2 receptors. Inhibition of ecto-ATPases had no effect on inhibition caused by hypercapnic alkalosis.

Conclusions: Based on our studies, we conclude that changes in pH caused by alterations in brain CO_2 levels alter extracellular adenosine concentration. This in turn modulates excitability. During hypocapnia, decreased adenosine levels cause increased excitability, due to both increased activation of P_2receptors and decreased activation of A_1 receptors, suggesting that ecto-APTases mediate this effect. Decreased effects of adenosine increase the rate of epileptiform activity and thus are likely to contribute to hypocapnia-induced lowering of seizure threshold. During hypercapnia sufficient adenosine is released to attenuate epileptiform activity. This increase in extracellular adenosine does not depend on ecto-ATPases suggesting that there may be multiple pathways contributing to pH modulation of extracellular adenosine concentration. (Supported by the Epilepsy Foundation, American Epilepsy Society, and the NIH.)

1.012
THE KETOGENIC DIET DOES NOT ALTER IEG EXPRESSION FOLLOWING MES SEIZURES IN RATS

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Rationale: Furothyl-induced seizures have been shown to increase Immediate Early Gene (IEG) expression (c-fos, c-jun) in mice and valproic acid (VPA), but not lamotrigine, has been shown to prevent seizure-dependent c-fos expression. The ketogenic diet (KD) is effective against many types of epilepsy in children and adolescents and against a variety of acute seizures induced in experimental animals. The KD has also been shown to be as effective as high-dose VPA in suppression of pentylenetetrazole-induced seizures. Valproic acid and the KD differ with respect to MES seizures: VPA reduces seizure severity but the KD makes such seizures more severe. We wished to detemine whether the increased severity of MES seizures in KD-fed rats would either elevate, or decrease, IEG expression compared to those fed a control diet.

Methods: Half of a cohort of male Harlan Sprague-Dawley rats were switched from a rodent chow diet (Purina 5001) fed ad libitum to a ketogenic diet (BioServe F3666) fed at 100% of caloric daily requirement, calculated on the basis of body weight, at the time they began the diet (age P47) and this amount was kept constant until seizure testing at age

P67. Tail vein blood was obtained at the time of seizure testing and levels of β-hydroxybutyrate (Stat-Site, Stanbio, Boerne, TX) and glucose (PrecisionXtra, Abbott, Chicago, IL) were measured just prior to seizure testing. Maximal electroshock seizures were induced by means of ear clip electrodes delivering a constant-current pulse (99 mA, 299 Hz, 9 ms. pulse duration; Ugo Basile ECT Unite 7801). Seizure severity was taken as the extension/flexion (E/F) ratio. Twenty-micrometer coronal serial sections were taken at the levels of the locus coeruleus and hippocampus. In situ hybridization with an oligonucleotide probe complementary to c-fos mRNA was performed. c-fos mRNA expression was measured in the cortex, septum, locus coeruleus, ventromedial hypothalamus, dentate gyrus, CA3 and CA1.

Results: At the time of seizure testing KD-fed rats showed elevated blood levels of β-hydroxybutyrate, lowered blood glucose levels and increased seizure severity compared to chow-fed controls. There were no differences in c-fos mRNA expression in KD-fed vs. control rats in any brain area examined. Consistent with observations in other laboratories, however, c-fos mRNA was highest in VMH in response to MES in both control and KD-fed rats.

Conclusions: The KD is not protective against MES seizures and actually makes them more severe. It has no effect upon c-fos mRNA expression, however. This finding may suggest that the KD, while not protective, does not lead to increased IEG expression despite elevation in seizure severity. The uniquely elevated expression in VMH serves as a positive control, indicating that the IEG assay was fully functional. (Supported by Department of Biology, Georgetown University, and VAMC, Seattle WA)

1.013

POSTICTAL $GABA_B$ RECEPTOR ACTIVATION WORSENS SUBSEQUENT SEIZURES

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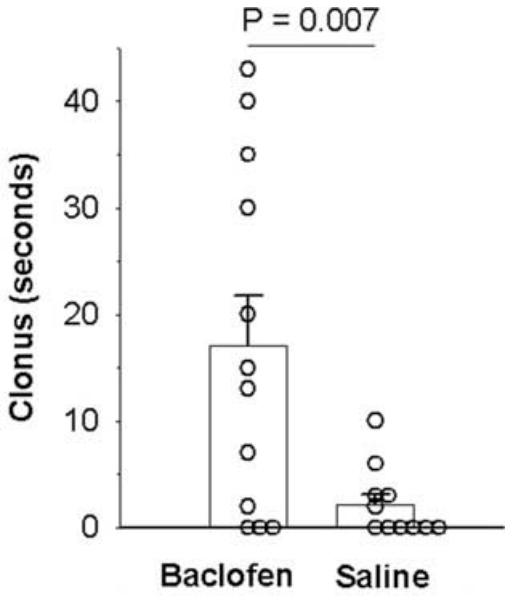
Rationale: The GABAB receptor agonist baclofen is used clinically for spasticity. Acutely, it causes neuronal inhibition through postsynaptic hyperpolarization and presynaptic inhibition of neurotransmitter release. Baclofen acutely inhibits seizures in animal models, but is not useful as an antiepileptic in humans. Baclofen withdrawal in humans can have marked proconvulsant actions, through unknown mechanisms that do not involve GABAB receptor transcription or translation (Lehmann et al. *Neurochem Res* 2002;28:387–93). To further investigate baclofen's proconvulsant actions, we studied the effects of baclofen on audiogenic seizures (AGS) in genetically epilepsy-prone rats (GEPR).

Methods: In one experiment, baclofen (6 mg/kg intraperitoneal) or saline was injected immediately after AGS in GEPR (GEPR-9, severe-seizure strain). After one AGS and injection, the effect on an AGS one day later was assessed. AGS were recorded on videotape, and AGS score, latency to onset, and duration of wild running, tonus, and post-tonic clonus were measured. In a second experiment, 12 daily repeated AGS with injection of baclofen or vehicle, were given. In a third experiment, baclofen or vehicle alone was given daily for 1 or 3 days, without seizures, and the effect on the animal's first seizure was assessed 24 hours after the last dose.

Results: The duration of a second seizure elicited 24 hours later was markedly longer if baclofen was given immediately after the first seizure. There was a dramatic increase in the duration of the last phase of the seizure, post-tonic clonus (Figure 1; N = 12 baclofen, 11 saline, P value is for two-tailed t test). Repeated seizures (12 consecutive once-daily AGS) caused a gradual increase in the duration of post-tonic clonus. When baclofen was given after AGS, there was a marked increase in the duration of post-tonic clonus in early seizures, but the baclofen-treated group was similar to saline after 5 seizures. In contrast, baclofen caused a significant reduction in the latency to seizure onset that persisted throughout 12 seizures. Baclofen given without seizure, in one dose, had no effect on a subsequent test seizure. However, baclofen given in three consecutive once-daily doses significantly reduced the duration of post-tonic clonus compared to saline-treated rats.

Conclusions: The $GABA_B$ receptor agonist baclofen has significant pro-epileptic effects that are unmasked only in the presence of repeated seizures.



(Supported by SIU Epilepsy Research Fund.)

1.014

AGE- AND TIME-DEPENDENT EFFECTS OF STATUS EPILEPTICUS ON HIPPOCAMPAL NEUROGENESIS

Linda K. Friedman, Magrys W. Bonaventure, and Keesey L. Robert (Neuroscience, NJ Neuroscience Institute/Seton Hall University, South Orange, NJ)

Rationale: In rat pups neurogenesis of the dentate gyrus is constrained by seizures where in adult rats it is provoked. To determine long-term effects of a single episode of status epilepticus on the developing hippocampus we examined neurogenesis after kainate (KA) administration in pups on postnatal (P) day 13 and then let them grow to adults. To determine whether neurogenesis is affected just by the seizure itself and or by cell death, neurogenesis was also examined in adult rats after KA-induced status epilepticus with and without a delay of bromodeoxyuridine (BrdU) injection.

Methods: KA was administered on P13 (2 mg/kg, i.p.) and animals were sacrificed on P62. BrdU was injected at the time of KA injection. P60 rats were injected with KA (12 mg/kg) and sacrificed at 48 and 96 hrs. BrdU was injected at the time of KA injection and after a 48 delay when neurodegeneration is near maximal. Brains were processed for BrdU immunohistochemistry and sections were co-labeled with GFAP.

Results: In control P60 rats, BrdU positive nuclei lined the hilar border of the dentate gyrus (DG) and they were few in number (approx. 18). Within molecular layers of the DG additional BrdU-positive cells were observed. A few cells were also detected throughout the rest of the hippocampal layers (approx. 15). In contrast, adult rats injected with KA and BrdU on P13, had BrdU-labeled nuclei deep within the granule cell layers but they were also few in number. The pattern of BrdU-labeled nuclei observed throughout the hippocampus was different from control P60 adults. In adults without delay of BrdU injection and 48 hrs after KA, there was a small increase in the number of BrdU-labeled nuclei within the hilus as reported after pilocarpine seizures, but marked increases were observed in the CA3, particularly the CA3a, highly sensitive to neurodegeneration. In contrast to our expectation, co-labeling with GFAP was minimal. Numbers of BrdU labeled nuclei were elevated further with delayed BrdU injection; the CA1 and ventricular zone were robustly labeled as well as CA3/hilus.

Conclusions: Although the number of BrdU-labeled cells did not appear to increase when adults had an early seizure, the altered pattern suggests that one early life seizure could lead to permanently altered hippocampal circuitry in adulthood. The marked increases observed in the CA3/hilus without BrdU delay were not due to proliferating astrocytes. Enhanced elevation of BrdU-labeled cells with BrdU delay suggests that neurodegenerative process also contribute to

neurogenesis following status epilepticus. (Supported by NJ Neuroscience Institute.)

1.015
$GABA_A$ RECEPTOR α5 SUBUNIT DEFICIENT MICE SHOW REDUCED TONIC INHIBITION AND EPILEPTIFORM ACTIVITY IN CA1 AND CA3 REGIONS OF THE HIPPOCAMPUS

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Rationale: GABAergic circuits control the level of excitation in the hippocampus, and their disruption can induce epileptic activity. $GABA_A$ receptors mediating tonic inhibition are assembled from different subunits than receptors responsible for phasic inhibition. The α5 subunit is thought to mediate tonic inhibition in the CA1 and CA3 areas of mice. Here, we report a significant reduction in the inhibitory tonic current of CA1 and CA3 pyramidal neurons leading to epileptiform hyperexcitability in hippocampal slices of mice lacking the α5 subunit.

Methods: Horizontal and coronal brain slices (350 μm thick) were prepared from C57BL/6, α5 wild-type littermates (wt) and α5 KO male mice ($\sim$2 months old). Slices were continually perfused ($\sim$2.0 ml/min) with bubbled aCSF with 3 mM kynurenic acid and 5 μM GABA at 33–35°C. Whole cell recordings were obtained from visually identified CA1 - CA3 pyramidal neurons. Tonic current was measured by calculating the net mean holding baseline current before and after application of bicuculline methiodide (BMI $>$100 μM final concentration).

Results: In contrast to a previous report (Caraiscos et al., *Proc Natl Acad Sci USA* 2004;101:3662), CA1 and CA3 pyramidal neurons from α5 KO mice did not show a complete loss of tonic inhibition. A residual tonic current (50% of that found in wt) was present in hippocampal pyramidal cells. The tonic current in the KO, but not in the wt, was sensitive to THDOC, a neurosteroid known to increase $GABA_A$ conductance only when the δ subunits are present. Although phasic inhibition was similar between α5 KO and wt animals, there was an increased epileptiform excitability in field recordings from α5 KO.

Conclusions: Our results demonstrate that mice lacking α5 subunits show a residual tonic current in CA1 and CA3 pyramidal neurons that is in part due to the upregulation of δ subunits. This compensatory change can only restore the tonic inhibition to half of its original value resulting in the hyperexcitability of pyramidal neurons. Thus tonic inhibition is an important factor in maintaining the hippocampal excitatory-inhibitory balance. (Supported by NS02808 to I.M.)

1.016
VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IMMUNOREACTIVITY IS EXPRESSED IN CORTICAL NEURONS AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS IN THE RAT

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Rationale: VEGF, a growth factor normally expressed in glial and endothelial cells, promotes angiogenesis and has been demonstrated to be neuroprotective in experimental models of ischemia and epilepsy when exogenously applied to the hippocampus. Recently it has been observed that status epilepticus (SE) can induce the neuronal expression of VEGF in hippocampal and hypothalamic neurons. The neuronal expression of VEGF may contribute to its neuroprotective action. To further characterize the neuronal expression of VEGF after SE, we examined VEGF-immunroreactivity (IR) in the cortex of the rat after pilocarpine-induced SE.

Methods: Pilocarpine (380 mg/kg, s.c.) was injected into adult, male Sprague-Dawley rats 30 min after pretreatment with atropine methylbromide (1 mg/kg, s.c.). One hr after the onset of SE each animal received diazepam (5 mg/kg, i.p.). Control animals (n = 5) were treated in a similar fashion except saline was substituted for pilocarpine. All animals were perfusion-fixed with 4% paraformaldehyde 24 hr (n = 10) or 1 week (n = 4) after SE. The brains were removed and cut on a vibratome. Free-floating sections (50 μ) were incubated in antisera against VEGF (goat polyclonal, 1:500 dilution, R&D Sys.) or Heat Shock Protein (HSP70, mouse monoclonal, 1:1000 dilution, Stressgen). Additional sections were slide mounted and processed for Fluorojade B or silver degeneration stain.

Results: VEGF-IR was observed in select neuronal populations within the cortex 24 hr SE. Neurons in the middle layers of the sensory, and motor cortices stained positively for VEGF. In the cingulate, perirhinal, piriform and entorhinal cortices VEGF-IR was expressed in layer 2 and 4/5 neurons. The same neuronal populations that expressed VEGF-IR also expressed HSP-IR and stained positively for Fluorojade B 24 hr after SE. One week after SE, VEGF-IR was still present in some cells but greatly diminished. There was no VEGF-IR in the cortical neurons of control animals.

Conclusions: These results demonstrate that VEGF, a growth factor not normally expressed in neurons, can be induced in select populations of cortical neurons after SE. The observation that these neurons also express HSP and and stained positively for Fluorojade suggests that these neurons were stressed or injured. It is unclear whether the neuronal expression of VEGF contributes to its neuroprotective action observed after ischemia and seizures. It remains to be determined whether the neuroprotective action of VEGF is mediated through an activation of the Akt survival pathway. (Supported by The CURE Foundation, the New York State Department of Health, and the Helen Hayes Hospital Foundation and NS37562.)

1.017
EFFECTS OF PREVENTIVE TREATMENT ON NARP EXPRESSION IN POSTTRAUMATIC EPILEPTOGENESIS

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Rationale: Severe penetrating head injury often results in posttraumatic epilepsy, frequently with seizures beginning after a latent period. In the rodent undercut model of neocortical posttraumatic epileptogenesis, hyperexcitability occurs in brain slices in vitro after a latent period, but not acutely following injury. Prior investigations have suggested the presence of increased synaptogenesis in pyramidal neurons of this model. Localized treatment of the injured area with tetrodotoxin (TTX) during a critical period of three days post injury prevents the development of posttraumatic hyperexcitability. We have previously used Affymetrix GeneChips to help identify potential genes that may play a role in the antiepileptogenic effect of TTX-treatment. One candidate target sequence identified represents Narp (neuronal activity-regulated pentraxin, also known as neuronal pentraxin 2), an immediate early gene product that plays a role in excitatory synaptogenesis. We performed follow-up studies of Narp protein to confirm these findings.

Methods: Partially isolated islands of sensorimotor neocortex were made in P28–30 male Sprague-Dawley rats, and thin sheets of sustained release polymer either containing TTX or control polymer placed subdurally over the lesioned areas. During the critical period of three days post injury, TTX-treated and control animals were euthanized and undercut and control cortices dissected for protein studies using polyclonal antibody against Narp. Other animals were perfused for immunohistochemical analysis.

Results: Western blotting and immunocytochemical staining for Narp was increased in undercut versus naïve control cortex 3 days post injury. However, TTX-treatment reduced Narp immunoreactivity assessed with these techniques, as it had in gene expression studies.

Conclusions: An increase of Narp protein in neocortical lesions is correlated with epileptogenesis, and a treatment-induced reduction correlated with antiepileptogenesis, although a causal relationship has not yet been clearly established in this model. Results suggest that 1) further studies of the role of Narp in epileptogenesis are warranted, and 2) that targeted molecular approaches might lead to effective prophylaxis for posttraumatic epileptogenesis. (Supported by NIH grants NS02167, NS12151, and the Phil N. Allen Trust.)

1.018

ANTIEPILEPTIC EFFECT OF CHEMICAL SUPPRESSION OF THE SUBTHALAMUS

Kiyotaka Hashizume, and Tatsuya Tanaka (Neurosurgery, Asahikawa Medical College, Asahikawa, Hokkaido, Japan)

Rationale: High-frequency electrical stimulation (HFS) suppressed the neuronal activity of the subthalamus (STN), and HFS-STN is effective to control epilepsy. Chemical suppression of STN also suppressed seizures. We have reported that both electrical and chemical suppression of unilateral STN reduced focal neocortical seizures in rats. To clarify the antiepileptic mechanism of STN suppression, we studied changes in cerebral glucose metabolism and benzodiazepine-receptor binding after chemical suppression of STN.

Methods: A guide cannula was stereotactically implanted into the left sensorimotor cortex and STN of male Wistar rats. Focal cortical seizures were induced by an injection of kainic acid into the left sensorimotor cortex. Using this focal seizure model, 200 ng of muscimol was injected into the left (focus side) STN during seizure status. Sixty minutes later of the muscimol injection, 14C-deoxyglucose was intravenously injected, and local cerebral glucose metabolism was measured with the autoradiographic technique. Change in benzodiazepine-receptor binding was also studied by 125I-iomazenil autoradiography. The data was compared with control group and analyzed statistically.

Results: An intracortical injection of kainic acid was induced focal and secondarily generalized seizures in all animals. When the unilateral STN was suppressed by the muscimol injection, seizure status was terminated. Local glucose metabolism was increased in the superior colliculus and interpeduncular nucleus compared with control. The benzodiazepine-receptor binding tended to increase in the ipsilateral cerebral cortex.

Conclusions: Chemical suppression of STN lead to hypermetabolism in the superior colliculus, which supported that antilepileptic mechanism of HFS-STN may be activation of the dorsal midbrain region. Furthermore, increase in benzodiazepine-receptor binding of the ipsilateral cerebral cortex is an important result to consider the mechanism of HFS-STN.

1.019

INCREASED EXPRESSION OF THE δ SUBUNIT OF THE $GABA_A$ RECEPTOR IN HIPPOCAMPAL INTERNEURONS DURING POSTNATAL DEVELOPMENT

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Rationale: The δ subunit of the $GABA_A$ receptor is distributed diffusely throughout the molecular layer of the dentate gyrus and is also present in some GABAergic interneurons within the hippocampal formation. Many of these interneurons are only lightly labeled in normal adult mice. However, in a pilocarpine mouse model of recurrent seizures, the δ subunit labeling of some interneurons increases substantially. These changes are of particular interest because they could be associated with increased tonic inhibition of some GABAergic interneurons and, thus, less effective inhibition of the principal cells. To further characterize these interneurons in normal animals, δ subunit expression was studied during the first few weeks of postnatal life. The goal was to determine if all subpopulations of GABAergic interneurons express the δ subunit of the $GABA_A$ receptor during normal development.

Methods: C57BL/6 mice were prepared for histological study at regular intervals from 5 to 35 postnatal days. Sections were processed for immunohistochemical localization of the δ subunit of the $GABA_A$ receptor with a subunit-specific antiserum, and labeled neurons were mapped within the hippocampal formation at each age.

Results: During the second and third postnatal weeks, δ subunit labeling of interneurons was higher than in adult mice. Within the dentate gyrus, strongly labeled interneurons were present along the inner border of the granule cell layer and within the molecular layer. However, few δ subunit-labeled interneurons were evident in the hilus. Within the hippocampal formation, many δ subunit-labeled interneurons were present in the pyramidal cell layer of CA1-CA2. Numerous labeled interneurons with fine dendritic processes were also observed in stratum lacunosum-moleculare. In contrast, relatively few δ subunit-labeled interneurons were found in these regions of CA3. By four to five postnatal weeks, δ subunit labeling had decreased in many interneurons. As a result, only small numbers of labeled interneurons were evident in strata pyramidale and lacunosum moleculare of CA1, and labeled interneurons were sparse in the molecular layer of the dentate gyrus of mature mice. The patterns of labeling throughout the postnatal period suggest that somatostatin neurons in the hilus do not contain the δ subunit.

Conclusions: : These findings demonstrate that many, but not all, groups of GABA neurons transiently express the δ subunit of the $GABA_A$ receptor during early postnatal development. The normal lack of δ subunit labeling in subgroups of GABAergic interneurons, such as those in the hilus and many in CA3, suggests that δ subunit-mediated tonic inhibition may be limited in these interneurons. (Supported by NIH grant NS35985 and VA Medical Research Funds.)

1.020

MRI AND FDG-PET SHOW PROGRESSIVE HIPPOCAMPAL CHANGES DURING EPILEPTOGENESIS IN THE AMYGDALA KINDLING RAT MODEL OF TLE

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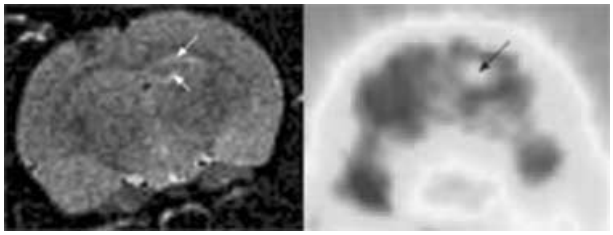
Rationale: Patients with non-lesional temporal lobe epilepsy (NL-TLE) commonly show prominent imaging abnormalities on magnetic resonance imaging (MRI) and flurodeoxyglycose positron emission tomography (FDG-PET) in the ipsilateral temporal lobe in the absence of hippocampal atrophy. The rat amygdala electrical kindling model shows many of the characteristics of NLTLE, including a relative lack of cell loss in the hippocampus. It is unknown if the imaging changes seen in NLTLE also are present in this model. The present study aimed to determine whether imaging changes seen on MRI and FDG-PET in NL-TLE are also detectable in the hippocampus in the rat amygdala kindling model, and then utilise this model to investigate the pathophysiological processes underlying these changes.

Methods: MRI compatible stimulating, ground and reference electrodes were developed to enable imaging without the induction of 'artefacts' created by magnetic components within the magnetic field. Surgeries were performed according to well established methods. Following one week of recovery, FDG-PET and T_2 weighted images were acquired every two weeks for six weeks on dedicated small animal imaging scanners. Electrical stimulations were started the day following the first imaging session and continued six days a week for four weeks.

Results: MRI demonstrated the development of focal regions of hyper intense T_2signal in the rostral hippocampus during kindling ($n = 4/5$) both ipsilaterally ($n = 3$) and bilaterally ($n = 1$) specifically in CA1 and dentate gyrus. FDG-PET demonstrated progressive development of hypometabolism ($n = 4/4$) compared with control animals (median change in ipsilateral/contralateral ratios from pre-kindling to fully kindled: 5.6% vs. -1.6%, $p < 0.05$) (Figs. 1 and 2).



Conclusions: We have developed a method for acquiring high quality serial MR and FDG-PET images in amygdala kindled rats. Results demoonstrate that amygdala kindling produces progressive changes in

T_2 MRI and FDG-PET images similar to those seen in NLTLE. This model will provide a powerful tool to investigate the pathophysiological basis of the imaging changes and epileptogenesis in this common form of epilepsy.

1.021
IDENTIFICATION OF POTENTIAL NEUROPROTECTIVE GENES INVOLVED IN SEIZURE PRECONDITIONING IN THE HIPPOCAMPUS
Borges Karin, Shaw Renee, and Dingledine Raymond (Pharmacology, Emory University, Atlanta, GA)

Rationale: Rodents experience severe hippocampal damage after a kainate-induced status epilepticus (SE). However, if rats are preconditioned by a short duration of kainate-induced seizures (20 min.) one and two days before a prolonged SE, neuronal damage can be prevented (Zhang et al. *J Neurosci* 2002;22:6052–61). The goal of this study is to identify genes that are specifically expressed after preconditioning and might protect neurons from injury.

Methods: For preconditioning rats were injected on day −2 and −1 with kainate (12–15 mg/kg i.p.) and after 20 min. of seizure activity pentobarbital (40 mg/kg i.p.) was injected to stop seizures. To confirm the neuroprotective effect of preconditioning, some rats were injected with kainate on day 0 and status epilepticus was induced. These rats were sacrificed 3 d after SE and neuronal damage was evaluated by Fluoro-Jade staining. We compared the mRNA expression profiles of 3 different hippocampal cell populations from 8 preconditioned and 8 control (non-preconditioned) rats, using Affymetrix 230A microarrays. RNA was extracted and amplified from cells one day after the second preconditioning seizure harvested by laser capture microscopy from the dentate granule cell layer, the CA3 and the CA1 pyramidal cell layer.

Results: Hippocampal neuronal damage was observed by Fluoro-Jade labeling 3 days after kainate-induced SE (N = 3 rats). In contrast, in rats that were preconditioned prior to SE (N = 3) Fluoro-Jade-labeled cells were found in several brain areas but not the hippocampus, confirming that preconditioning is neuroprotective in the hippocampus. Microarray analysis revealed that more genes were significantly changed after preconditioning in the dentate granule cell layer (1231 genes), than in the CA1 (116) and CA3 (48) pyramidal cell layer (fig 1, false discovery rate 5%). Eleven genes were found to be significantly changed in all 3 cell populations, including neuropeptide Y (NPY), which is known to be upregulated by seizures.

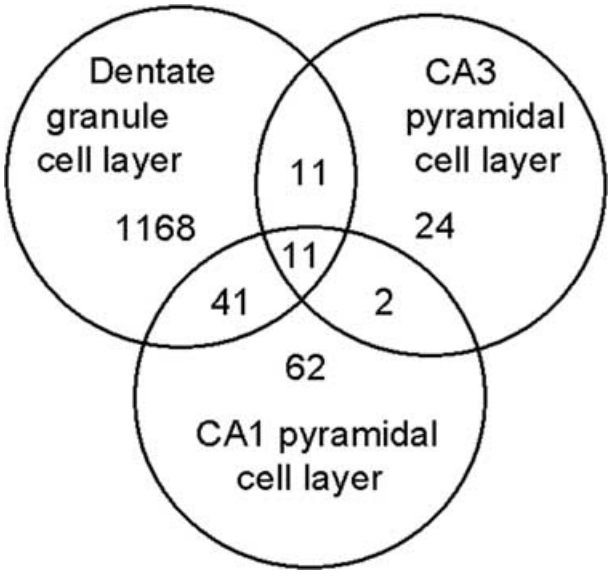


Fig. 1 shows the number of commonly changed genes after preconditioning in the 3 areas examined.

Conclusions: Although CA3 and CA1 pyramidal cells are protected by brief preconditioning seizures, by far the most extensive changes in gene expression occurred in dentate granule cells, indicating that the dentate gyrus may be most critical in the neuroprotective effect of preconditioning. Among the genes changed after preconditioning in all 3 main hippocampal neuronal cell layers NPY is likely to play a role in preconditioning due to its anticonvulsant properties. Other promising genes will be validated and evaluated for their neuroprotective potential. [Supported by CURE (K.B.), NINDS (R.D.)]

1.022
THE $GABA_A$ RECEPTOR α SUBUNIT SUBTYPE DETERMINES THE RECEPTOR'S KINETIC PROPERTIES
Andre H. Lagrange and Robert L. Macdonald (Neurology, Vanderbilt University, Nashville, TN)

Rationale: GABAA receptors (GABAAR) are pentameric ion channels usually formed from combinations of the six α, three β, three γ and/or one δ subunit isoforms. Although many combinations are possible, relatively few are actually found in the central nervous system. Each combination has a specific pattern of expression that varies among brain regions, cell types and even synaptic versus extrasynaptic locations. The expression of these isoforms is altered in certain pathological states and may play a role in the pathogenesis of diseases, such as epilepsy.

The subunit composition of individual GABAARs determines much of their pharmacologic properties. However, because GABAARs rapidly activate and desensitize (<10–100 ms), less is known about the role of subunit composition in determining receptor kinetics. We characterized the current kinetics of GABAARs containing α1, 3, 4 or 5 with β3 and γ2L using an ultrafast GABA perfusion.

Methods: 4 μg each of cDNA for β3 and γ2L and one of the α subunits, with 2 μg of pHook were transfected into HEK 293T cells with a calcium phosphate co-precipitation technique. The next day, transfected cells were selected using a magnetic immuno-bead approach. Whole cell voltage clamp was performed the next day, and kinetic properties were determined using lifted cells exposed to 1 mM GABA using an ultrafast drug application system (exchange times $\approx$ 500 μs).

Results: As shown in Table 1, α1 and α4 GABAARs activate and desensitize quickly. In contrast, α3 and α5 GABAAR have very little fast desensitization. Furthermore, α3 containing GABARs are unique in that their activation is an order of magnitude more slowly than the others.

Conclusions: These studies demonstrate that the α subunit subtype is critical in determining kinetics GABAAR currents. Further studies will explore the response of these receptors to different types of GABA application, including paired pulse, repetitive stimulation and determining the concentration dependence of these receptors. (Supported by R01 NS33300–10.)

1.023
COMPUTATIONAL MODELING AND DECONVOLUTION ANALYSIS COMPLIMENT WHOLE-CELL STUDIES OF HILAR MOSSY CELLS
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Rationale: We present initial results of a combined experimental and computational modeling study of how the anatomical and biophysical properties of mossy cells (MCs) and their synaptic inputs may affect their function in temporal lobe epilepsy (TLE) and learning. Situated in the hippocampal hilus, MCs receive two principal excitatory projections: a major input via mossy fibers (MFs) from dentate gyrus (DG) granule cells, and a lesser input via collateral (CL) axons from CA3 pyramidal cells. MF boutons are complex and synapse onto similarly complex spines called thorny excrescences located (100 μm of the MC soma. CL axons attach to distal, more simple spines. Induction of TLE is associated with loss of many MCs and an increased relative abundance and amplitude of CL EPSPs. To understand the implications of these changes, it is necessary to determine how the properties of MCs and their excitatory inputs affect synaptic integration. Of particular interest

TABLE 1. *Kinetic properties of $GABA_A$ receptors*

	Imax	10–90% Rise Time	τDeact(5 ms)	τDeact (4000 ms)	% fast D	% slow D	% C
$\alpha1\beta3\gamma2$L	3260 ± 613 pA (17)	1.1 ± 0.1 ms (17)	187 ± 71 ms (4)	327 ± 41 ms (12)	23%	48%	28% (14)
$\alpha3\beta3\gamma2$L	1781 ± 243 pA (27)	10.3 ± 1.8 ms (27)	26 ± 4ms (4)	416 ± 89 (18)	1%	60%	40% (17)
$\alpha4\beta3\gamma2$L	3118 ± 500 pA (14)	1.4 ± 0.1 ms (9)	358 ± 82 ms (4)	464 ± 90 ms (8)	27%	55%	18% (10)
$\alpha5\beta3\gamma2$L	1325 ± 328 pA (11)	1.9 ± 0.2 ms (11)	235 ± 46 ms (5)	260 ± 42 ms (9)	5%	60%	37% (9)

Data expressed as mean± SE (n); I max = Maximal Current; τDeact(5ms or 4000 ms) = weighted tau of deactivation after a 5 ms or 4000 ms pulse of 1 mM GABA; % fast D = % fast desensitization (all τ <100 ms) with a 4000 ms pulse of 1 mM GABA; % slow D = Contribution all slow desensitization (τ > 100 ms); % C = Residual current at the end of a 4000 ms pulse of 1 mM GABA.

are the functional consequences of the spatial distribution (proximal vs. distal) and anatomical specializations (thorns vs. spines) of MF and CL inputs.

Methods: We simulated anatomically complex multicompartmental models using NEURON (Hines & Carnevale, 2001). Pending availability of detailed MC morphometric data, our model was based on measurements of a CA3 neuron by David Amaral (see http://www.krasnow.gmu.edu/L-Neuron (Ascoli et al., 2001). Specific Cm and Rm were adjusted to match the model to our measurements of MC input resistance and membrane time constant. We performed three families of simulations in which the soma was voltage clamped while a synapse (based on our mEPSC measurements from MCs) was marched over all dendritic compartments within 100 μm of the soma: control (synapse attached directly to dendritic shaft, clamp series resistance (Rclamp) 0); test 1 (synapse attached to the distal head of a complex thorn (Chicurel & Harris 1992); test 2 (Rclamp 10 MΩ).

Results: In all cases, the largest EPSCs corresponded to the most proximal locations, and the fastest EPSCs suffered the least attenuation. Uncompensated Rclamp produced strong attenuation of peak EPSC amplitude, but less increase in the rise time and decay time. Distance from the soma had little effect on rise time and amplitude for the first 30 μm. The thorn reduced EPSC amplitude by a few percent, most noticable in the largest EPSCs.

The largest events in our experimental data appeared to come from proximal locations, as they can be evoked by focal application of high sucrose near the soma (Livsey & Vicini, 1992). However, they were not the fastest events but had relatively slow rise and decay times. We applied deconvolution analysis (Diamond & Jahr, 1995) and found that asynchronous release might account for this unexpected result.

Conclusions: These results suggest that the largest EPSCs in MCs may actually be generated by asynchronous transmitter release, possibly occurring at multiple active zones on large thorns. (Supported by NIH.)

1.024
THE BRAIN BINDING SITE FOR THE ANTIEPILEPTIC DRUG LEVETIRACETAM IS THE SYNAPTIC VESICLE PROTEIN SV2A

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Rationale: Levetiracetam (KEPPRA®; LEV), possesses a unique activity profile in animal models of seizure and epilepsy, that correlates a novel mechanism of action different from other antiepileptic drugs (AEDs). LEV binds to a site in the CNS that appears to be distinct from the binding sites of other AEDs and CNS active drugs. Previous reports suggested a correlation between the affinity of a series of LEV analogs for the brain binding site and their potencies in a mouse audiogenic seizure model of epilepsy. This led to an extensive search to identify the protein(s) that comprise this novel binding site. Recent studies revealed that LEV binding was enriched in synaptic vesicles and photoaffinity labelling of purified synaptic vesicles shows that it had a molecular weight of approximately 90 kDa. Using these characteristics, an integral membrane synaptic vesicle protein, SV2, that includes three homologous isoforms, SV2A, B and C, was targeted as a potential binding site candidate.

Methods: A labelled LEV derivative, [^{3}H]ucb-30889, was utilized to study binding to brain membranes and purified synaptic vesicle fractions from WT and SV2 KO mice, and to heterologously expressed SV2 isoforms. Binding of [^{3}H]ucb-30889 to individual SV2 isoforms was studied using heterologously expressed proteins in COS-7 cells. Anti-seizure activities of LEV and analogues were assessed in sound-susceptible mice (20) by exposing the mice to acoustic stimuli of 90-db, 10 to 20-kHz for 30sec, 60 min following intraperitoneal pre-treatment.

Results: LEV and related compounds bind to cloned SV2A (but not significantly to SV2B or SV2C), expressed heterologously in a fibroblast cell line, suggesting that SV2A is the source of the brain binding site. Brain membranes and purified synaptic vesicles from SV2A knockout mice do not bind a tritiated LEV derivative, further supporting that SV2A is responsible for LEV binding. The binding affinities of a series of LEV derivatives to SV2A expressed in fibroblasts correlates strongly to their binding affinities in brain tissue. Finally, there is also a strong correlation between the affinity of LEV derivatives for SV2A expressed in fibroblasts and their potency against seizures in the audiogenic mouse model of epilepsy.

Conclusions: These results identify SV2A as the binding site of LEV in the brain and support the hypothesis that the antiepileptic activity of LEV may, in part, be acting through an interaction with the synaptic vesicle protein SV2A. The identification of SV2A as the LEV brain binding site supports previous claims that LEV possesses a mechanism of action that is truly distinct from that of other antiepileptic drugs. (Supported by UCB Pharma.)

1.025
THE *BIS2* GENE INVOLVED IN BETA-CARBOLINE-INDUCED SEIZURE SUSCEPTIBILITY IN MICE IS ALSO CONTROLLING SPIKES AND WAVES DISCHARGES

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Rationale: Four genes, *Bis1*, *Bis2*, *Bis3* and *Bis4* have been identified for their involvement in beta-carboline-induced seizures in mice. These genes have been respectively mapped on chromosome 4, 13, 9 and 7 (1). *Bis2* have been localized in a linkage-strain of mice C3XtEso bred in our colony and derived from C3HeB/FeJ *Xt*/+ *Eso*/+. This strain is maintained with forced heterozygocity ($Gli3^{Xt-J}/Gli3^{+}$ vs $Gli3^{+}/Gli3^{+}$) for a small chromosomal fragment surrounding the *Gli3* gene on chromosome 13. $Gli3^{Xt-J}$ is a mutated form for the *Gli3* gene, coding for an extra digit on the pre-axial site of the limb. And it has been observed that the mutated mice $Gli3^{Xt-J}/Gli3^{+}$ were significantly more resistant to the convulsive effect of a single injection of methyl-β-carboline-3-carboxylate (beta-CCM - a beta-carboline) than the wild mice $Gli3^{+}/Gli3^{+}$. This result has been interpreted as the influence of a polymorphic gene - named *Bis2* - included in the heterozygous fragment surrounding and co-segregating with *Gli3*.

The genetic mechanism which underlies the reactivity to the beta-carbolines and those which controls spikes and waves discharges (SWD) characterizing absence epilepsy appear genetically dependent. Since *Bis2* regulated the beta-CCM-induced seizure susceptibility, the

question whether *Bis2* would also be involved in SWD control and/or genesis was addressed in the present study.

Methods: Two groups of C3XtEso male mice - $Gli3^{Xt-J}/Gli3^{+}$ and $Gli3^{+}/Gli3^{+}$- were formed. All animals were implanted under general anaesthesia (chloral hydrate, 400 mg/kg, i.p.) with five monopolar tungsten rod electrodes; four placed bilaterally over the frontal and parietal cortex and one placed over the cerebellum as reference electrode. Animals were allowed at least two weeks for recovery.

EEG activities were recorded in freely moving animals placed in a plexiglas cage placed in a Faraday cage. The mice were connected to the EEG apparatus with flexible wires and recorded for 40 minutes. Animals were continuously observed and the duration and number of seizures were evaluated.

Results: A significant difference was observed between $Gli3^{Xt-J}/Gli3^{+}$ and $Gli3^{+}/Gli3^{+}$as well as for SWD frequency ($p < 0.0001$) than for SWD cumulated duration ($p < 0.0001$).

Conclusions: This result confirms the dependence between beta-CCM-induced seizure regulation and SWD activity previously observed. The next stage of this work will consist in a fine-mapping of the *Bis2* gene.

REFERENCE

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1.026
DELAYED DEVELOPMENT OF AREA CA3 EPILEPTIFORM BURSTS IN VITRO AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: In hippocampal slices, acute ionic or pharmacological manipulations produce spontaneous rhythmic burst discharges. We asked whether such discharges would occur spontaneously in slices made during the weeks after pilocarpine-induced status epilepticus, when animals often exhibit spontaneous seizures.

Methods: Eighteeen male Sprague Dawley rats (150–250g) were treated with atropine methylbromide (1 mg/kg) followed after 30 minutes by pilocarpine hydrochloride (380 mg/kg). One hour after the onset of status epilepticus, animals received an injection of diazepam (5 mg) to truncate status.

At time points ranging from 2–18 weeks following status epilepticus, 400 μm thick horizontal hippocampal-entorhinal slices were made using a Vibroslice, placed in an interface recording chamber, maintained at 31.5°C, superfused with 95% O_2/5% CO_2 and bathed in a solution containing (in mM) 126.0 NaCl, 5.0 KCl, 2.0 CaCl, 2.0 $MgSO_4$, 26.0 $NaHCO_3$, 1.25 NaH_2PO_4, and 10 D-glucose (pH 7.4). Extracellular potassium concentration $[K^+]_o$ was altered in some slices by altering the KCl concentration in the bathing medium.

All areas were recorded for a minimum of 5 minutes, prior to adding the stimulating electrode to the slice, to determine the presence of spontaneous bursts. In some slices, simultaneous recordings were made in the pyramidal cell layer of area CA3 and area CA1 or the subiculum. Only slices that were determined to have an adequate response to stimulation of the hilus, Schaffer collateral pathway, or fimbria, were used in the analysis.

Results: Animals that exhibited spontaneous seizures had at least one slice that produced spontaneous CA3 bursts. During the first month after status, bursts occurred in only 4% of slices (1/23 slices, n = 4 rats), however this number increased to 45% in the second month (9/23, n = 4), and 100% in the third and fourth months (23/23, n = 4; 31/31, n = 6 respectively).

When area CA1 or the subiculum were simultaneously recorded, bursts were smaller in amplitude and followed CA3 bursts, suggesting CA3 was a burst generator. However, the subiculum exhibited secondary bursts that were not recorded in CA3, suggesting the existence of a second burst generator**.**

In bursting slices (6/6), reducing $[K^+]_o$ to 3.5 mM decreased the amplitude and frequency of bursts, but did not block them. Conversely, raising $[K^+]_o$ to 7.0 mM increased burst amplitude and frequency. In non-bursting slices (7/7*)*, raising $[K^+]_o$ to 7.0 mM could induce bursts.

Conclusions: Area CA3 develops spontaneous rhythmic burst discharges during the weeks after pilocarpine-induced status. The onset of these events appears to coincide with the onset of spontaneous seizures in the intact animal. These bursts appear to progress from only a small section of CA3 initially to all dorso-ventral levels tested later on. The fact that these bursts invade areas such as the subiculum suggests that they could leave the hippocampus and influence the rest of the brain. (Supported by NS 41490.)

1.027
DIACYLGLYCEROL KINASE EPSILON MODULATES RAPID KINDLING EPILEPTOGENESIS

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Rationale: Diacylglycerol kinase ε (DGK ε) regulates seizure susceptibility and long-term potentiation through arachidonoyl-inositol lipid signaling (*Proc Natl Acad Sci U S A* 2001;98:4740). To study the significance of arachidonoyl-diacylglycerol (20:4 DAG) in epileptogenesis, we used mice deficient in DGK ε (DGKε -/-) in the rapid kindling epileptogenesis model.

Methods: Male mice (C57BL/6; 20–25 g) were used. Tripolar electrode units (Plastic One Inc., Roanoke, VA) were implanted in the right dorsal hippocampus. Ten days post surgery, kindling was achieved by stimulating 6 times daily for 4 days with a subconvulsive electrical stimulation (a 10-s train containing 50-Hz biphasic pulses of 300-μA amplitude) at 30-min intervals. After 1 week another session of stimulation (rekindling) was given. Seizures were graded according to Racine's Scale. Mice are considered kindled when they display three consecutive stage-5 seizures. The EEG was recorded through electrodes using Enhanced Graphics Acquisition for Analysis (Version 3.63 RS Electronics Inc. Santa Barbara, CA.) and the EEG was analyzed using Neuroexplorer Software (Next Technology) in order to characterize the epileptogenic events as spike, sharp waves, or abnormal amplitude and rhythms.

Results: DGK ε −/− mice displayed significantly fewer motor seizure and epileptic events as compared to wild-type mice from the second day of stimulation, and these differences were maintained during the rekindling session. DGK ε −/− mice also exhibited a low-amplitude spike-wave complex, short spreading depression, and a predominant lower (1 Hz – 4 Hz)-frequency band throughout stimulation, while wild-type mice exhibited increased high-frequency band (4 Hz-8 Hz; 8 Hz-15 Hz) from the second day of the stimulation, as determined by power spectral analysis.

Conclusions: DGK ε modulates kindling epileptogenesis through inositol lipid signaling. Because arachidonate-containing diacylglycerol phosphorylation to phosphatidic acid is selectively blocked in the −/− mice, we postulate that the shortage of arachidonoyl-moiety inositol lipids and/or the messengers derived thereof are engaged in the changes uncovered by our work. We are currently studying how lipid synaptic circuitry is inter-regulated during epileptogenesis. (Supported by NIH NS23002.)

1.028
A STUDY ON NEUROGENESIS AFTER KAINIC ACID-INDUCED SEIZURES IN MICE

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Rationale: Neurogenesis of dentate granule cells of the hippocampal formation continues well into the postnatal period in primates and in the rat at least, occurs throughout adult life. Furthermore, epileptic seizures have been shown to stimulate the proliferation rate of granule

cell progenitors in the adult rat brain. In the present study, we investigated whether the proliferation of granule cell progenitors is increased in mice in a model of kainic acid (KA)-induced seizure, by using systemic bromodeoxyuridine (BrdU) injections to label dividing cells.

Methods: Ten male ICR mice were dived into two equal groups. Seizures were chemically induced by intraperitoneal injection of KA (30 mg/kg). Seizure severity was evaluated using a seizure behavior grading system: 0, no response; 1, front or hid limb pawing, staring; 2, rearing, staring, nodding, bilateral pawing; 3, rearing, staring, nodding, bilateral pawing, jumping, wobbling, falling; 4, status epilepticus or death. The mice injected with equal volume of normal saline were used as controls. BrdU (50 mg/kg) was then subsequently administered intraperitoneally for 6 consecutive days, starting at 24 hours after KA or saline injection. All mice were sacrificed 24 hours after the last BrdU injection, and the brains were removed for tissue fixation and immunohistochemistry. BrdU-labeled cells in the combined hippocampal dentate gyrus and hilar regions were counted in every seventh sections in a series of 30 μm sagittal sections (210 μm apart) covering the complete left and right hippocampi.

Results: After KA administration, every seizure behavior was grade 2 or more. BrdU-labeled cells increased significantly ($p < 0.00001$) after KA-induced seizures (83.38 ± 44.33) compared to controls (35.61 ± 17.87). Most of newborn cells migrated into the granule cell layer from the subgranular zone after KA-induced seizures.

Conclusions: In this study, quantitative analysis of BrdU labeling revealed a significant increase in the proliferation rate of neuronal progenitor cells after KA-induced seizures in mice. Our results suggest that increased neurogenesis may be a general response to seizure activity. The functional significance of dentate granule cell neurogenesis in epileptogenesis still remains unknown and should be investigated. [Supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea. (02-PJ1-PG10-21301-0001).]

1.029
MICRODISSECTION OF RAT HIPPOCAMPAL HETEROTOPIC NEURONS: WHAT CAN FUNCTIONAL GENOMICS TELL US ABOUT EPILEPTOGENESIS

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Rationale: Malformations of cortical development are a leading cause of medication resistant epilepsy. Methylazoxymethanol (MAM) treated rats develop neuroanatomical abnormalities including neuronal nodular heterotopias that exhibit similar characteristics to those found in human epilepsy surgery pathology specimens. These animals are more susceptible to induced seizures and hippocampal heterotopias are capable of generating seizure-like activity in vitro. Hippocampal heterotopic neurons exhibit altered levels of a potassium channel subunit, Kv4.2 (Castro et al., 2001) and decreased expression of GABA reuptake proteins (Calcagnotto et al., 2002). Here, we hypothesize that these changes are part of a larger pattern of alteration in excitatory/inhibitory systems as evidenced by alterations in gene transcription.

Methods: Pregnant S-D rats were injected with MAM on embryonic day 15. Slides of prenatally-MAM treated rat pup hippocampus were immunolabeled with murine neuronal nuclear antigen (NeuN) antibody and then in situ transcription was performed. Single cell dissection was used to isolate contents of heterotopic neurons and normotopic CA2 neurons and then mRNA amplification was used to amplify mRNA signal from each cell. Resulting p32-CTP labeled mRNA was used to probe macroarrays consisting of full length cDNA transcripts of neurotransmitter related candidate genes. Hybridization intensity was determined using a phosphoimager and results were analyzed using a one-way ANOVA.

Results: Expression of mRNA for candidate genes including transcription factors, neurotransmitter receptor subunits, ion channels, and select cell signaling molecules were examined from single MAM-induced NeuN labeled hippocampal heterotopic neurons. These were compared to normotopic NeuN labeled CA2 hippocampal cells also from MAM treated animals. The most significant differences in mRNA expression were found in Calcium and Calmodulin regulated Kinase II alpha, where the MAM nodule neurons exhibited more than twice the expression found in control neurons ($P < 0.05$).

Conclusions: While differences were found between heterotopic and normotopic neuron mRNA expression of several genes, the most profound difference was the finding that heterotopic hippocampal neurons have double the amount of CaMKII alpha. This finding is consistent with published neurophysiologic and immunohistochemical data suggesting that both excitatory and inhibitory systems are altered in MAM induced hippocampal heterotopias. Further analysis of gene transcription changes in this animal model of cortical malformations could provide valuable insights to the clinical condition. [Supported by NINDS R010405, R21-NS39938, R21NS40231, Parents Against Childhood Epilepsy (PACE) to P.B.C and NIH R01-NS40272 to S.C.B.]

1.030
SOMATOSTATIN RECEPTOR SUBTYPE 4 MEDIATES THE ANTIEPILEPTIC ACTIONS OF SOMATOSTATIN IN HIPPOCAMPUS

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Rationale: A hallmark of post-seizure hippocampus is the loss of somatostatin-containing GABAergic interneurons in the hilus of the dentate gyrus. This neuronal loss can extend into CA1 in some epilepsy models. Previous studies from our laboratory have shown that the neuropeptide somatostatin (SST) has antiepileptic properties in hippocampus, suggesting loss of the SST system may contribute to post-seizure hyperexcitability. We utilized SST receptor knockout mice and subtype-selective agonists to investigate the receptor subtype that mediates SST actions in hippocampus.

Methods: We made hippocampal slices from C57Bl/6J and SST_2 and SST_4 knockout mice, and used intracellular and extracellular recording techniques to examine the action of SST and subtype selective SST agonists on synaptic physiology and plasticity and in vitro seizure models. We used pentylenetetrazole (i.p.) as a chemoconvulsant to examine changes in seizure thresholds and latencies in SST_2 and SST_4 knockout mice compared to wildtype. We performed receptor autoradiography with [^{125}I]-Tyr^0-SST to determine the contribution of SST_2 and SST_4 to high affinity SST binding in hippocampus.

Results: In SST_4 knockout mice, all high affinity SST binding detectable using autoradiography is lost in CA1. High affinity binding in cortex, amygdala, and the rest of the brain is maintained in SST_4 knockouts. Likewise, electrophysiological effects of SST in CA1 are much diminished in SST_4 knockout mice, thus this receptor mediates the majority of SST effects in this region. In contrast, effects of SST in dentate gyrus are maintained in SST_4 knockout mice, suggesting another receptor, likely SST_2, mediates SST actions in this hippocampal region. Latencies to different seizure stages evoked by pentylenetetrazole are decreased in SST_4 but not SST_2 knockout mice.

Conclusions: Our results show SST_4 is the predominant somatostatin receptor subtype in hippocampus and mediates the majority of SST actions in CA1. Further, mice lacking the SST_4 receptor subtype have shorter latencies to different seizures stages when challenged with pentylenetetrazole. These results suggest that SST is released during seizures and interacts with SST_4 to act as an endogenous antiepileptic. Thus the seizure-induced reduction of SST in hippocampus likely contributes to post-seizure hyperexcitability and the development of secondary seizures. SST_4 receptors could therefore be important novel targets for new antiepileptic and antiepileptogenic drugs. [Supported by NIH grants NS 38633 (M.K.T.) and MH 58543 (L.d.L.), and an EFA predoctoral fellowship (C.Q.).]

1.031
PROGESTERONE'S ANTI-SEIZURE EFFECTS INVOLVE ACTIONS AT PROGESTIN, $GABA_A$, AND NMDA RECEPTORS IN THE HIPPOCAMPUS

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Rationale: Although progestins have long been known to mediate seizure processes, the brain areas and mechanisms for progestins' anti-seizure effects are not entirely understood. The present studies investigated whether progesterone (P)'s anti-seizure effects involve actions at intracellular progestin receptors (PRs), $GABA_A$ receptors, and/or NMDA receptors in the hippocampus of female rats.

Methods: Rats were administered progesterone or vehicle followed 1 hour later by receptor antagonists or vehicle, as described below. Two hours following antagonist or vehicle administration, seizures were induced by pentylenetetrazole (70 mg/kg). Rats were monitored for tonic-clonic seizures for 10 minutes.

Experiment 1: Ovariectomized (ovx) rats were administered P (500 μg, SC) or vehicle (sesame oil) and/or the PR antagonist, RU38486 (10 μg), or vehicle (ß-cyclodextran) infusions to the hippocampus. Experiment 2: Ovx rats were administered P (500 μg, SC) or vehicle (sesame oil) and/or the $GABA_A$ receptor antagonist, bicuculline (100 ng), or vehicle (saline) infusions to the hippocampus. Experiment 3: Ovx rats were administered P (500 μg, SC) or vehicle (sesame oil) and/or the NMDA receptor antagonist, MK801 (200 ng), or vehicle (saline) to the hippocampus.

Results: Experiment 1: Rats administered P had significantly longer latencies to, and fewer incidences of, tonic-clonic seizures compared to vehicle-administered rats. Administration of RU38486 to the hippocampus of P-primed rats attenuated P's anti-seizure effects. There were no intrinsic effects of RU38486 on ictal activity.

Experiment 2: P administration decreased ictal activity of ovx rats. P-primed rats infused with bicuculline had increased ictal activity compared to P-administered rats infused with vehicle. Bicuculline infusions alone did not alter seizures. Experiment 3: Administration of P decreased seizures of ovx rats. Infusions of MK801 to the hippocampus of P-primed rats attenuated P's anti-seizure effects. Infusions of MK801 alone did not alter ictal activity of rats.

Conclusions: Together these data suggest that P's anti-seizure effects involve actions at PRs, $GABA_A$ and NMDA receptors in the hippocampus. [Supported by The Epilepsy Foundation of America and The National Science Foundation (98–96263, 03–16083).]

1.032
ELECTROGRAPHIC EFFECTS OF 5-HT_{1A} AGONIST IN THE STATUS EPILEPTICUS INDUCED BY KAINIC ACID IN RATS

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Rationale: To evaluate the changes induced by 5-HT_{1A} agonists, 8-hydroxi-2-(di-n-propylamino) tetralin (8–0H-DPAT) and indorenate, in the electrographic activity during the kainic acid (KA)- induced status epilepticus (SE) in rats.

Methods: Male Wistar rats (250–300 g) were estereotactically implanted with a bipolar electrode in CA1 field from ventral hippocampus (HIP) and two stainless steel screws on the frontal cortex (FCX). Electrodes were attached to a connector and fixed to the skull with dental acrylic. One week after surgery, rats received KA administration (10 mg/kg, i.p.) after one of the following treatments: 90 min after indorenate (10 mg/Kg, i.p.; KA+INDO group); 20 min after 8-OH-DPAT (1 mg/kg, s.c.; KA+8-OH-DPAT group); 30 min after diazepam (10 mg/kg, i.p.; KA+DZP group). The following electrographic parameters were evaluated after KA administration for 3 h: latencies to the first epileptiform spike, the first ictus and synchronization of HIP and FCX; the spike frequency at different intervals. Values were compared with those obtained from a control group pretreated with saline sol. (KA+SS).

Results: DZP increased the latency to the first epileptiform spike (128%) and to the first ictus (160%) and diminished the frequency of the spikes at 30 (79%), 45 (55%) and 90 (41%) min after KA administration in FCX. DZP also augmented the latency to the synchronization of both HIP and FCX (158%) and to the electrographic status epilepticus ($p < 0.05$) when compared with the KA+SS group. 8-OH-DPAT enhanced the latency to the synchronization (125%) and diminished the frequency of the spikes in FCX at 120 and 180 min (38% in both) after the application of KA. INDO decreased the frequency of the spikes in HIP during the first wet dog shake (37%) and at 90 min (40%) after KA, and diminished the frequency of the spikes in FCX at 180 min (44%) of recordings. Additionally, DZP, 8-OH-DPAT and INDO diminished the frequency of the spikes during all the recording in FCX, whereas INDO decreased also this parameter in HIP.

Conclusions: The present results indicate that 8-OH-DPAT and indorenate diminish the severity of SE induced by KA, an effect that is different with that produced by DZP. It is suggested that the serotonergic $5HT_{1A}$ agonists reduce the intensity of the KA-induced status epilepticus.

1.033
FACTORS CONTRIBUTING TO POST-TRAUMATIC DENTATE HYPEREXCITABILITY: A NETWORK MODEL INCORPORATING TOPOGRAPHIC CONNECTIVITY PATTERNS

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Rationale: Head injury is a major risk factor in the etiology of temporal lobe epilepsy (TLE). Studies using a rodent model of concussive head trauma have identified specific patterns of cell loss and synaptic reorganization in the dentate gyrus after brain injury, which are similar to the changes in human TLE. However, the contribution of each of these cellular and synaptic alterations to increased excitability in the dentate neuronal circuits is not known. This study used a reduced network model of the dentate gyrus to independently examine the factors critical to post-traumatic dentate hyperexcitability.

Methods: The model dentate gyrus with 500 granule cells, 15 mossy cells 6 basket cells and 6 hilar interneurons was simulated using NEURON (Hines, 1993). Topographic networks were constructed with connectivity patterns constrained by the spatial distribution of the axonal arbors of the cell types. In the non-topographic networks, the postsynaptic cells were selected at random leading to a network with connection probabilities similar to the topographic network but without the spatial structure. Sprouting was simulated by addition of mossy fiber to granule cell connections. The maximum sprouting (100%) was estimated from the distribution of sprouted axons in a rodent model of spontaneous recurrent seizures (Buckmaster and Dudek, 1999). The unitary conductance of the recurrent excitatory synapse was set to obtain maximum sprouting with 100 sprouted synaptic contacts.

Results: The simulations show that perforant path stimulation evoked greater granule cell firing in the dentate excitatory network with as low as 10% sprouting compared to the control topographic network. Additionally, the topographic network was more hyperexcitable than the non-topographic network with the same degree of sprouting. Mossy cell loss decreased the spread of hyperexcitability in the network with 10% sprouting. With increasing sprouting, even the complete loss of mossy cells was unable to prevent the spread of hyperexcitability. Simulations of both purely excitatory network and the full network showed that mossy fiber sprouting was sufficient to elicit hyperexcitable perforant path evoked responses in all cell types examined.

Conclusions: Mossy fiber sprouting can contribute to increased excitability in the dentate gyrus even in the absence of cell loss or changes in the intrinsic properties of the cells. The data from the topographically constrained simulations indicate that the lamellar topology of the sprouted mossy fibers is important for the spread of granule cell excitability. Mossy cells enhance granule cell excitability both in the control network and in the presence of sprouting. The results suggest that the moderate sprouting observed after concussive head trauma is a major factor in post-traumatic dentate hyperexcitability. [Supported by NIH (NS35915) to I.S.]

1.034
QUANTITATIVE RT-PCR OF $GABA_A$ α_1 SUBUNIT IN ADULT RATS FOLLOWING PHOTOTHROMBOTIC INFARCTION OF NEOCORTEX

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Rationale: Photothrombotic brain infarction resusts in altered expression of cortical $GABA_A$ receptors in rats. To better understand potential time-dependent changes in $GABA_A$ receptor α_1 subunit mRNA expression associated with epileptogenesis, we quantified the mRNA levels at 1, 3, 7, and 30 days after photothrombosis.

Methods: Photothrombosis was performed on 3 mo old Sprague-Dawley rats. Lesioned ($n = 32$) and sham-operated ($n = 32$) rats were sacrificed at 1, 3, 7, and 30 days post-lesioning (lesioned, $n = 4$, and sham-operated, $n = 4$, at each time point). Naïve controls ($n = 6$) were used for comparison. Quantitative competitive RT-PCR was performed on cortical tissue samples taken from two concentric arcs of tissue surrounding the lesion (L1 and L2), and also from homotopic cortex (R1 and R2). Subunit mRNA levels were expressed as mean ± SEM. Unpaired *t*-tests ($p < 0.01$) compared mean mRNA expressed in areas in lesioned rats with the corresponding mean mRNA values of sham-operated rats. One-way ANOVA testing ($p < 0.01$), with Bonferroni multiple comparisons post-testing ($p < 0.01$) was used to compare mean mRNA expression at different timepoints for each area of ipsilateral or contralateral hemispheres in lesioned and sham-operated cohorts.

Results: There was no significant difference in α_1 subunit mRNA expression for lesioned vs. sham-operated animals at 1 and 3 days ($p < 0.01$; unpaired *t*-test). A significant decrease in mRNA at 7 days in lesioned animals was determined for L1 (41.2 ± 7.4 pg, $p = 0.0093$), R1 (39.0 ± 4.9 pg, $p = 0.0062$), and R2 (31.2 ± 3.4 pg, $p < 0.0001$) cortical areas compared with the corresponding areas of sham-operated animals. In contrast, mRNA at 30 days increased in lesioned animals for L1 (197.8 ± 25.6 pg, $p = 0.0019$) and L2 (258.4 ± 26.5 pg, $p = 0.0001$) compared with sham-operated animals. One-way ANOVA ($p < 0.01$) of mean mRNA at 30 days in lesioned animals indicated that L1 (197.8 ± 25.6 pg), L2 (258.4 ± 26.5 pg), R1 (153.6 ± 13.2 pg), and R2 (141.4 ± 16.0 pg) increased significantly compared to all other time points ($p < 0.01$); mean mRNA expression at day 7 for R1 (39.0 ± 4.9 pg) was decreased compared with R1 (47.0 ± 5.7 pg) at 1 day ($p < 0.01$). Expression in sham-operated animals at 30 days for R1 (115.7 ± 7.5 pg) was increased compared with 3 and 7 days (64.7 ± 6.6 pg and 80.5 ± 8.5 pg), respectively. Naïve animals were not included in statistical comparisons.

Conclusions: $GABA_A$ receptor α_1 subunit mRNA expression was unchanged at 1 and 3 days, reduced bilaterally at 7 days, and increased bilaterally at 30 days. Changes in $GABA_A$ receptor α_1 subunit mRNA expression may coincide with the development of poststroke epileptogenesis demonstrated previously in this model. (Supported by American Heart Association Award 0151398U to K.M.K.)

1.035
POSTSYNAPTIC CALCIUM INFLUX ALTERS THE TIMING OF IN VITRO INTERICTAL ACTIVITY VIA ADENOSINE A1R ACTIVATION

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Rationale: Adenosine is an inhibitory synaptic modulator in the central nervous system (CNS). The main adenosine receptor in the CNS is A1R and its activation inhibits neurotransmitter release and hyperpolarizes neurons. Since adenosine release appears to be activity dependent, it may play an important role in regulating synaptic activity during periods of heightened neuronal firing such as occurs during epileptiform activity. We investigated the effects of modulating calcium influx on adenosine release during spontaneuous CA3 hippocampal network interictal discharges.

Methods: We used extracellular and intracellular recordings to investigate the effects of decreasing postsynaptic calcium entry through NMDA receptors and L-type calcium channels on the probability of spontaneuous CA3 hippocampal network interictal discharges before and after pharmacological block of the adenosine A1Rs [theophylline (250 microM) of DPCPX (100nM)]. Hippocampal coronal slices were prepared from 4–6 week old Sprague-Dauley rats. Spontaneous bursting of the CA3 network was induced by blockade of $GABA_A$ and $_B$ conductances with 100mM picrotoxin and 1mM CGP55845A, respectively. Intracellular recordings were performed in the presence of picrotoxin (100microM), CGP55845A (1 microM).

Results: Lowering of postsynaptic calcium influx (through block of NMDA and/or L-type calcium channels) resulted in a significant increase in the frequency of CA3 interictal discharges ($n = 5$, $p < 0.01$, one tailed t-test). This frequency increase was reversed by prior blockade of adenosine A1Rs ($n = 5$, $p < 0.001$, one tailed t-test), suggesting that postsynaptic calcium entry in the CA3 pyramidal cells plays a modulatory role in adenosine A1R activity. Intracellular voltage clamp recordings revealed that the time constant of recovery of spontaneuous EPSCs following an interictal discharge is dependent on adenosine A1R activity. The frequency, but not the amplitude recovery of spontaneous EPSCs was markedly affected by adenosine A1R activation, consistent with a presynaptic locus of adenosine action.

Conclusions: These data suggest that postsynaptic calcium entry during hippocampal CA3 synchronous network activity results in significant modulation of adenosine release and, consequently, glutamate release. The dependence of adenosine release on postsynaptic calcium suggests that adenosine may act as a trans-synaptic neuromodulator at CA3 pyramidal synapses. Further, the adenosine modulation of post-burst synaptic recovery may control hippocampal CA3 network timing of synchronization. (Supported by NIH.)

1.036
NEOCORTICAL SPREAD OF LIMBIC KINDLED SEIZURES

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Rationale: Amygdala kindled seizures are a standard rodent model of epileptogenesis, however, the spread of limbic seizures to the neocortex has not been extensively studied. Involvement of the neocortex and subcortical structures such as the thalamus may play an important role in behavioral manifestations, including convulsive motor activity. Therefore, we investigated relationships between electrical activity in limbic, medial thalamic, and neocortical structures during the progression from limbic to neocortical seizures induced by kindling.

Methods: Male Sprague-Dawley rats were implanted with electrodes in the basolateral amygdala, ipsilateral mediodorsal nucleus of the thalamus, and the frontal cingulate cortex. Afterdischarge threshold was determined for each animal, and kindling performed twice daily with stimulus current set at the afterdischarge threshold. Kindling was continued until animals had 3 consecutive class 5 seizures by the Racine scale. EEG power analysis and cross correlation analyses were performed using Spike2 software.

Results: Seizure duration increased progressively during kindling, and was linearly related to the behavioral Racine rating ($r = 0.994$, $p = 0.001$). EEG power during the first 30s of seizures compared to preictal baseline did not change significantly in the amygdala between class 1 and class 5 seizures. However, the frontal cortex showed a significant increase in EEG power between class 1 and class 5 seizures ($n = 24$; $p = 0.0003$, two tailed t-test). EEG power in the medial thalamus showed a similar dramatic increase between class 1 and class 5 seizures ($p < 0.00001$). Cross correlation analysis revealed a striking change in cortical-subcortical relationships during kindling. Thus, during class 1 seizures there was a low correlation between amygdala and frontal EEG (mean peak correlation $= 0.16 \pm 0.05$) which increased significantly during class 5 seizures (0.40 ± 0.06; $p = 0.015$). In contrast, correlation between frontal and medial thalamic EEG was relatively high during class 1 seizures (0.47 ± 0.17) and tended to decrease during class 5 seizures (0.22 ± 0.11). Correlation between amygdala and medial thalamic EEG did not change significantly between class 1 and class 5 seizures.

Conclusions: Kindling produces a change in limbic and neocortical networks resulting in increased seizure duration and more dramatic motor convulsive activity. Even when analyses are confined to the initial 30s of seizures, kindling produces increased EEG power in the frontal neocortex and medial thalamus. Meanwhile, there is a switch in frontal networks from high fronto-thalamic correlation to high fronto-amygdalar correlation. These results suggest that during kindling, connections between the amygdala and neocortex are strengthened, facilitating spread of seizures from limbic to neocortical networks, and producing more dramatic motor convulsions. [Supported by NIH NS02060 and the Patterson Trust (to H.B.).]

1.037

ENHANCED VULNERABILITY TO SEIZURES AND SEIZURE-INDUCED HIPPOCAMPAL CELL DEATH IN GALANIN RECEPTOR SUBTYPE 1 KNOCKOUT MICE

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Rationale: Galanin is a neuropeptide with both anticonvulsant and neuroprotective effects. In the hippocampus galanin acts through two receptor subtypes, GalR1 and GalR2. GalR1 knockout (KO) mice have been reported to exhibit spontaneous seizures, leading to the suggestion on the critical role of GalR1 in seizure regulation. We compared seizure susceptibility and neuronal injury in GalR1 KO mice in two models of status epilepticus (SE): induced by systemic kainic acid (KASE), and by LiCl-pilocarpine (LiPC-SE).

Methods: Adult male C57Bl GalR1 KO mice, or their wild type (WT) littermates, were implanted with the recording electrode into the hippocampus. SE was induced by either i.p. injection of kainic acid (20 mg/kg), or of LiCl (3 meq/L, 1 ml/kg i.p.) followed by s.c. pilocarpine, 200, or 100 mg/kg. Seizure activity was acquired and analyzed using Harmonie software (Stellate systems). Neuronal injury was assessed using FluoroJade B and TUNEL staining in coronal brain sections from mice euthanized 3 days after SE induction.

Results: None of KO, or WT animals displayed spontaneous seizures during 1 week of observation and EEG recording prior to SE induction. No differences in seizure severity and duration were observed between KO and WT animals subjected to KASE. LiPC- SE was more severe in GalR1 KO animals, as compared to WT. Augmented severity of LiPC-SE was evident as higher mortality (40% vs. <10% in WT); increased cumulative seizure time (3.5–5 hrs vs. 1–2.5 hrs) and a number of seizure episodes (215–310 vs. 50–95 in WT). KASE led to neuronal injury in neither GalR1 KO, nor WT animals, which was in line with previously reported enhanced resistance of hippocampal cells to kainic-acid- induced neuronal injury in C57Bl mice. Neuronal injury in GalR1 KO mice subjected to LiPC-SE was more severe in CA1 (75–90% vs. 35–55% in WT), but not CA3. In addition, KO animals showed cell injury to hilar interneurons (15–25%), which was never observed in WT. Administration of lower dose of pilocarpine to GalR1 KO (100 mg/kg) led to the development of SE comparable to the one observed after 200 mg/kg in WT. However, despite milder seizures, the severity and the pattern of neuronal injury was not different from those observed after 100 mg/kg.

Conclusions: KO mice showed higher seizure severity and more profound and widespread injury after LIPC-SE, but not after KASE, suggesting specific interference of GalR1 with cholinergic, rather than with AMPA-kainate mechanisms. The fact that LiPC-SE of different severity (induced by two different doses of pilocarpine) led to similarly severe hippocampal injury suggests that galanin acting through GalR1 is neuroprotective aside from its anticonvulsant effects. The data are useful for understanding the endogenous brain mechanisms involved in seizure control and neuroprotection. (Supported by NIH grant NS 43409.)

1.038

SHORT-TERM SYNAPTIC PLASTICITY OF $GABA_A$ RECEPTOR MEDIATED IPSCs IN LAYER II STELLATE CELLS OF THE MEDIAL ENTORHINAL CORTEX

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Rationale: Animal models of temporal lobe epilepsy (TLE) demonstrate loss of layer III neurons in the mEC and marked hyperexcitability in layer II neurons, despite sparing of GABAergic interneurons. Altered $GABA_A$ receptor mediated synaptic transmission may contribute to the hyperexcitability observed in mEC Layer II stellate cells. To address this question, we used whole cell recording techniques in combined mEC-HC brain slices obtained from saline-treated and kainic acid (KA)-treated rats to examine the short-term synaptic plasticity of inhibitory postsynaptic currents (eIPSCs) evoked via minimal stimulation in layer II neurons.

Methods: Male Sprague-Dawley rats (150g) were injected hourly with KA (5 mg/kg, *ip*) or saline (0.9%) to stage 4/5 seizure activity (Racine, 1972). Whole cell voltage clamp recordings of eIPSCs were recorded from visualized layer II neurons of the mEC in combined mEC-HC ventral brain slices (400 μm) at 31 $\pm$ 1°C. GABA mediated eIPSCs were isolated in oxygenated ACSF containing APV (50 μM) and CNQX (10 μM). The internal pipette solution contained (in mM): CsGluconate (125), CsCl (10), HEPES (10), EGTA (1), $CaCl_2$ (0.5), glucose (10), and QX-314 (5) (pH = 7.28; mOsm = 290). The short-term synaptic plasticity of eIPSCs were evaluated following paired- and triple-pulse stimulation paradigms (100–200 ms interstimulus intervals). In addition, eIPSC peak amplitude ratios were compared following tetanic stimulation (10Hz-20Hz).

Results: Paired pulse depression (PPD) of GABAergic eIPSCs in Layer II mEC was detected in slices from both control rats and rats which had undergone KA-induced seizures 1–2 weeks prior: IPSC2/IPSC1 ratio = 0.821 $\pm$ 0.02 (KA) vs 0.839 $\pm$ 0.1 (control). In addition, eIPSC peak ampitudes were further depressed in triple-pulse comparisons in mEC Layer II neurons from both control and KA-treated groups: IPSC3/IPSC2 ratio = 0.823 $\pm$ 0.09 (KA) vs 0.823 $\pm$ 0.08 (control). These results suggest that alterations in the probability of release of GABA from presynaptic cells does not contribute to the hyperexcitability observed in Layer II of the mEC after KA-induced seizure activity.

Conclusions: Short-term synaptic plasticity in inhibitory circuits is a critical component in the maintenance of balance between excitatory/inhibitory transmission in the mEC-HC circuit. Altered inhibitory synaptic transmission can lead to hyperexcitability by disrupting this balance, potentially facilitating the development and/or spread of seizure activity throughout the temporal lobe. Although Layer II neurons from both control and KA-treated rats showed similar depression of GABAergic postsynaptic currents, characterization of postsynaptic and presynaptic changes taking place during epileptogenesis may provide insight into the hyperexcitability observed in Layer II stellate neurons following KA-induced seizures. [Supported by EFA Postdoctoral Fellowship (M.D.S.Y.), NS-040049 (H.S.W.), and NS-044210 (K.S.W.).]

1.039

INHIBITION OF GLIAL FUNCTION INCREASES SENSITIVITY TO CHEMICAL CONVULSANTS

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Rationale: Although there is evidence that astrocytes support neuronal function, the contribution of astrocytes to seizure onset and termination is unknown. The goal of this study was to determine whether there are changes in seizure susceptibility or neuronal damage when the ability of astrocytes to generate ATP is reduced by inhibition of the Krebs' cycle enzyme, aconitase.

Methods: Adult male Sprague-Dawley rats were anesthetized with ketamine cocktail and 0.5 nmol of fluorocitrate (FC) was injected into the right ventricle. Rats were assigned to one of following groups (6–8 animals each): 1) FC alone at 0.05 or 0.075 mM; 2) kainic acid (7 mg/kg) or pilocarpine (240 mg/kg) alone; 3) FC at 0.05 or 0.075 mM followed by kainic acid (7 mg/kg) or pilocarpine (240 mg/kg); 4) isocitrate (15mM or 30 mM) and FC followed by kainic acid (7 mg/kg) or pilocarpine (240 mg/kg); 5) kainic acid (10 mg/kg) or pilocarpine (320 mg/kg); 6) isocitrate alone (15 or 30 mM) followed by kainic acid (10 mg/kg) or pilocarpine (320 mg/kg). The behavior of all animals was observed for at least 4 hours. In some animals, intrahippocampal recording of electrical activity was carried out. Histological analysis for neuronal damage was carried out 24 hours after injection of the convulsant. Measurements of ATP levels were carried out in a second set of animals sacrificed at 4 hours.

Results: Animals that received injections of FC, either 0.5 or 0.75 nmol, into the right ventricle had no observable seizure activity or neuronal damage, as measured with silver stain and immunohistochemistry for HSP32 or HSP72, or on basal ATP levels. In addition, no electrographic seizures were recorded in the hippocampus after the ventricular injection of 0.75 nmol FC (n = 5). In animals pretreated with FC, administration of kainic acid, at a dose that does not initiate seizures in control animals (7 mg/kg), caused wet dog shakes and neuronal damage in the hilus. Wet dog shakes did not cause any neuronal damage in control animals. If the dose of FC was increased to 0.75 nmol, then subsequent administration of the same dose of kainic acid (7 mg/kg) caused stage 3–5 seizures and damage throughout the hippocampus and cortex.

Injection of FC also reduced the dose of pilocarpine needed to produce seizures. Given simultaneously with FC, isocitrate, which bypasses the inhibition of aconitase, blocked the effects of FC in both kainic acid and pilocarpine treated animals. To test whether isocitrate has a direct neuroprotective role, the effect of isocitrate on the neuronal damage induced by kainic acid and pilocarpine was determined. There was no difference in the pattern of HSP72 expression in animals treated with convulsant alone (who had stage 3–5 seizures) and those pretreated with isocitrate.

Conclusions: The results demonstrate that a decrease in astrocytic function in the adult brain increases the susceptibility to kainic acid and pilocarpine. The results suggest that some function of normal astrocytes can delay the onset of seizures or raise the seizure threshold. (Supported by NS39941.)

1.040

VISUALIZING ENDOGENOUS EXCITATION IN A RODENT SEIZURE MODEL WITH A CHANNEL-PERMEANT ORGANIC CATION

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Rationale: We sought to visualize the activity of entire populations of neurons in a rat seizure model. Endogenous excitation in hippocampal brain slices can be mapped with the channel-permeant organic cation 1-amino-4-guanidobutane (AGB), which is highly selective for ionotropic glutamate receptor (iGluR) activation (Marc, 1999). Quantitative immunogold labeling of small amino acids (such as GABA, glycine, taurine, etc) can be performed on the same sections in which AGB mapping is evaluated (Marc and Jones, 2002). We used these approaches to test the hypothesis that functional excitatory neural circuits would be altered in medial entorhinal (mEC)-hippocampal (HC) brain slices obtained from kainic acid (KA)-treated rats.

Methods: Sprague-Dawley rats were repeatedly injected with KA (5 mg/kg, i.p.) until stage 4/5 seizures were observed. mEC-HC brain slices (400 μm) were prepared 1 wk later from KA-treated or age-matched control rats. Slices were incubated in oxygenated ACSF at room temperature for 35 min, after which 5 mM AGB was added to the solution for 10 min. Slices were fixed, dehydrated, embedded in epoxy resin and serially sectioned at 250 nm onto 12-spot Teflon-coated slides and probed for AGB and other targets. Signals were detected with goat anti-rabbit IgGs adsorbed to 1nm gold particles (Amersham), silver intensified, and captured as 8 bit images. Images were computationally registered with 200 nm precision and visualized as multichannel datasets.

Results: AGB signals indicative of iGluR activation could be detected in slices obtained from control and KA-treated animals, although the distribution and intensity of staining was quite different between groups. Sections from control animal brain slices showed minimal AGB signals in the CA3 and CA1 pyramidal cell body layer and the hilar region of the dentate gyrus. In contrast, sections from slices of KA-treated animals displayed high AGB signals in select cells of the hilus, along with heterogeneous expression in the CA3 and CA1 pyramidal cell body layer. In slices obtained from KA-treated animals, AGB signals were observed in layers 2 and 4/5 of the mEC as well, with diminished activity in layer 3. In addition, glutamine, glutamate, GABA, taurine, and aspartate profiling revealed heterogeneous metabolite signatures in CA1 pyramidal cells as well as alterations in those signatures in KA-treated rats.

Conclusions: AGB mapping of brain slices from normal and epileptic tissue is a viable and valuable technique with which to assess changes in functional neural circuits. Our data also suggests that combined approaches of AGB mapping and quantitative immunogold labeling of small amino acids will provide insight into classes of neurons participating in seizure generation and propagation. [Supported by R01 EY02576 (R.E.M.), RPB Senior Research Scholar Award (R.E.M.), RO1-NS44210 (K.S.W.).]

1.041

ALTERATION OF HIPPOCAMPAL EXCITABILITY AFTER HYPERTHERMIA-INDUCED SEIZURES IN INFANT RATS

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Rationale: Febrile seizures are the most common seizure type in children between 3 months and 6 years old. It is unclear whether febrile seizures are detrimental to the developing or adult brain. The main goal of this research is to investigate changes in synaptic transmission and excitability in the hippocamus following febrile seizures. We hypothesized that neuronal inhibition in hippocampus is altered following a hyperthermia-induced seizure in immature rats.

Methods: Febrile seizures were induced by hyperthermia given by a heat lamp in rats of postnatal day 15, and control rats were separated from the dam but not heated. Eleven or 30 days following the hyperthermia-induced seizure, extracellular synaptic responses in the hippocampus were assessed in urethane-anesthetized rats. Laminar field potentials were recorded by 16-channel silicon probes in CA1 and dentate gyrus (DG), in response to the paired-pulse stimulation of CA3 and medial perforant path. Current source density analysis revealed population excitatory postsynaptic potentials (pEPSPs) at the dendrites and population spikes (PS) at the cell layer. The ratio of the 2^{nd}PS (P2) to the 1^{st}PS (P1), and of the 2^{nd} pEPSP slope (E2) to 1^{st} pEPSP slope (E1), were analyzed.

Results: The ratios of P2/P1 and E2/E1 were decreased with age in CA1 and DG, for both control and seizure rats. When recorded at 11 days but not 30 days after seizures, P2/P1 ratio was increased in CA1, at 150 to 200 ms IPIs, as compared to control rats ($P < 0.01$, ANOVA following posthoc Newman-Keuls test). P1 was not significantly different between seizure and control rats. E2/E1 ratio in CA1, and P2/P1 (or E2/E1) in DG were not different between seizure and control rats at any time after seizures.

Conclusions: Paired-pulse inhibition in CA1 was decreased for about 10 days after a single hyperthermia seizure in immature rats, suggesting a short-term alteration of GABAergic inhibition that normalized with time after the seizure or with age. Alteration of paired-pulse inhibition at 150 to 200 ms suggests a difference in $GABA_B$ receptor mediated inhibition. (Supported by CIHR MOP-64433.)

1.042

LOW EXTRACELLULAR GLUCOSE CONCENTRATIONS SUPPRESS IN VITRO LOW-Mg^{2+}-INDUCED EPILEPTIFORM ACTIVITY IN MEDIAL ENTORHINAL CORTEX AND HIPPOCAMPAL CA1

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Rationale: Patients in severe hypoglycemia irrespective of its origin may experience neurological side effects including frequent seizures. In rats and mice, insulin-induced hypoglycemia is also associated with seizures. However, hypoglycemia also attenuates synaptic transmission; this effect has been studied repeatedly in vitro in slices from hippocampus and dorsolateral septal nucleus. We were interested whether hypoglycemia promotes or inhibits epileptiform activity in vitro.

Methods: We used preexisting epileptiform activity induced by low Mg2+ in combined hippocampus-entorhinal cortex slices to study the effects of decreased extracellular glucose concentration. Two baseline glucose concentrations were used (10 mM common in the in vitro electrophysiology and more physiological 5 mM). We determined the effects of glucose concentration decreases (baseline to 2 or 1 mM for 30 min) on the frequency and amplitude of late recurrent discharges in the medial entorhinal cortex (MEC) and interictal discharges in hippocampal CA1. For osmolarity control experiments, glucose was replaced either by 2-deoxyglucose or mannitol.

Results: In the MEC, decreases from 10 mM glucose baseline to 5 or 2 mM reversibly suppressed amplitude and frequency of late recurrent discharges. The effect was more prominent with 2 mM glucose. Using 2 mM glucose + 8mM 2-deoxyglucose had similar suppressive effects as 2 mM glucose itself, however the recovery was not complete. Decreases from 5 mM glucose baseline to either 2 or 1 mM consistently and reversibly suppressed frequency and inconsistently the amplitude of discharges. Using 1 mM glucose + 4 mM mannitol as control arrangement diminished frequency of discharges, however the recovery was very poor. In the CA1, decreasing 5 mM baseline glucose concentration

to either 2 or 1 mM consistently decreased the frequency of interictal discharges and 1 mM glucose suppressed also the amplitude. During our glucose transients, we have never seen a transition from interictal to ictal activity in the CA1. Using 4 mM mannitol with 1 mM glucose had similar suppressive effects on CA1 discharges as 1 mM glucose itself, however there was no recovery.

Conclusions: We did not discover any proconvulsant effects of hypoglycemia in our study. In contrast, hypoglycemia suppressed preexisting epileptiform activity in both MEC and CA1. There were no temporary increases in expression of discharges during hypoglycemic transients. This suggests that that at least in some forebrain structures, significant hypoglycemia may suppress epileptiform activity. Additions of glucose analogues for osmolarity control had invariably worsening effect on recovery suggesting hypothetical compensatory mechanisms of hypoosmolarity during hypoglycemia. (Supported by NIH NS-20253 and NS-41366 and Heffer Family Medical Foundation.)

1.043

TEMPORAL EVOLUTION OF THE CEREBRAL INFLAMMATORY RESPONSE AND NEURONAL DAMAGE IN THE LITHIUM-PILOCARPINE MODEL OF EPILEPSY IN ADULT RATS

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Rationale: Lithium-pilocarpine (li-pilo) status epilepticus (SE) leads to extended brain lesions, mainly in hippocampus, parahippocampal cortices, amygdala and thalamus. Neuronal damage underlies the genesis of a hyperexcitable circuit leading to spontaneous recurrent seizures (SRS). To better understand the role of the inflammatory response in the genesis of lesions, we characterized Interleukin1-β (IL1-β), Nuclear Factor-κB (NF-kB) and Cyclooxygenase-2 (COX-2) expression together with neurodegeneration in the li-pilo model in the adult rat.

Methods: SE was induced by the injection of LiCl (3 meq/kg) followed 18h later by 25 mg/kg pilocarpine. Rats (4 per group) were sacrificed at 4, 12 and 24 h after SE onset (acute phase) and at 3 and 6 days after SE (latent phase). Brains were perfused and 40-μm coronal sections were cut. The immunoreactivity for the inflammation factors IL1-β, NF-kB, COX-2 and for the astrocytic marker GFAP was studied and correlated with neuronal degeneration assessed with Fluoro-Jade B staining. Double immunostaining with markers for astrocytes (GFAP and GLUT1), neurons (MAP2), and activated microglia (B4-isolectin) was performed at all times.

Results: The immunohistochemical expression of IL1-β, NF-kB and COX-2 started by 12 h after SE, persisted for 24 h and returned to basal levels by 3 and 6 days. The expression of IL1-β, NF-kB and COX-2 occurred mainly in structures prone to develop neuronal damage, such as piriform and entorhinal cortex, amygdala, hippocampus, thalamus and septum, but also in hypothalamus. IL1-β expression was detected in glial cells, COX-2 in neurons and NF-kB in both cell types. The distribution of Fluoro-Jade B-positive neurons was associated with IL1-β, NF-kB and COX-2 proteins expression during SE but not during the latent period while neurons were still degenerating. By 12 h, Fluoro-Jade B staining was strong in cerebral cortex, moderate in amygdala and dentate gyrus, weak in caudate-putamen, thalamus and hypothalamus and lacking in CA1-CA3 pyramidal cell layers. Between 12 and 24 h after SE, Fluoro-Jade B staining intensified in amygdala, and thalamus and appeared in CA1-CA3 areas.

Conclusions: These data indicate that during the acute phase of li-pilo SE, glial cells and neurons participate in the selective vulnerability of some brain regions by inducing an inflammatory reaction mediated by molecules such as IL1-β, NF-kB and COX-2. The timing of expression of these factors and temporal sequence of neuronal damage are in good accordance with our previous reports showing the primary involvement of cerebral cortex, thalamus, amygdala and hilus, and delayed response in hippocampal pyramidal cell layers. Thus, inflammation factors appear to contribute to the pathophysiology of epilepsy by inducing neuronal death and astrocytic activation. (Supported by INSERM U 405 and Fondation de l'Avenir.)

1.044

NEUROPROTECTIVE EFFICACY OF THE MITOCHONDRIAL ATP-SENSITIVE POTASSIUM CHANNEL OPENER, DIAZOXIDE, AGAINST DEPOLARIZATION INJURY TO CA1 PYRAMIDAL NEURONS IN RAT HIPPOCAMPAL SLICES

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Rationale: Mitochondria play a central role in energy production and processes of cell death. These organelles also regulate Ca^{2+} homeostasis, and thereby modulate neuronal excitability and synaptic transmission. More recently, mitochondrial dysfunction has been shown to occur in seizure foci from humans and experimental models of epilepsy. In addition, a number mitochondrial DNA mutations have been identified which lead to the inhibition of the mitochondrial respiratory chain. Because neuronal injury during prolonged seizure activity may occur via modulation of mitochondrial channels and mitochondrial membrane depolarization, we hypothesized that the opening of mitochondrial ATP-sensitive potassium (mitoK_{ATP}) channels would provide protection against CA1 depolarization-induced injury.

Methods: Using paired rat hippocampal slices, we monitored the CA1 orthodromic and antidromic population spike (PS) amplitude during depolarization injury with and without calcineurin inhibitor treatment. To induce depolarization injury, slices were exposed to 25 mM KCl for 8 min. Treatment with diazoxide was begun 30 minutes prior to KCl exposure and continued for the first 15 min. of recovery.

Results: Diazoxide, a mitoK_{ATP} channel opener, provided robust neuroprotection of CA1 PS amplitude in hippocampal slices subjected to depolarization-induced injury. Slices exposed to 25 mM KCl demonstrated rapid loss of evoked response with a mean CA1 orthodromic and antidromic recovery of only 11% $\pm$ 3 and 13% $\pm$ 2, respectively. Treatment with diazoxide (100 uM) provided significant protection against this depolarization injury with CA1 orthodromic and antidromic PS amplitude recovering to 94% $\pm$ 3 and 95% $\pm$ 3. Treatment with 100 uM diazoxide during depolarization injury also produced significant recovery of mean excitatory post-synaptic potential slope (94% $\pm$ 6) after depolarization when compared to paired, unmedicated slices which did not recover (0% $\pm$ 0). Mean fiber volley responses were slightly resistant to depolarization injury with a mean recovery of 32% $\pm$ 2 in paired, unmedicated slices. In contrast, treatment with diazoxide showed full recovery with a mean 100% $\pm$ 0.

Conclusions: These studies demonstrate that diazoxide, a mitoK_{ATP} channel opener provides neuroprotection against CA1 depolarization injury. In addition, these data suggest that the use of agents that modulate the mitoK_{ATP} channel may provide a useful strategy in the prevention of brain injury during status epilepticus. (Supported by VA Research Service and the UCLA Brain Injury Research Center.)

1.045

HIGH RESOLUTION TIME-LAPSE TWO-PHOTON IMAGING OF NEOCORTICAL DENDRITIC SPINES *IN VIVO* DURING ELECTROGRAPHIC SEIZURES IN MICE

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Rationale: Seizure-induced neuronal death is well-described, but less is known about non-lethal cellular sequelae of seizures on neurons. Previous clinical and animal studies suggest that seizures have pathological effects on dendritic spines, thus potentially altering normal synaptic function. However, most previous studies have only demonstrated long-term, chronic effects of seizures on spines using conventional fixed tissue analysis. Recent advances in cellular imaging technology allow high-resolution time-lapse imaging of dendritic spines in living tissue and have demonstrated rapid effects of physiological activity on spines on a time scale of minutes. Thus, we hypothesized that pathological seizure activity may also induce acute, rapid changes in dendritic spines. We have developed a method for directly imaging the effects of electrographic seizures on dendritic spines of neocortical neurons in intact mice *in vivo*.

Methods: Two-to-three month old green-fluorescent protein (GFP)-expressing trangenic mice (M-line, Washington University) were anesthetized with isoflurane and placed in a stereotaxic frame. A craniotomy was performed over frontal neocortex and a coverslip cemented over the craniotomy to form an imaging window. Wire EEG electrodes and a cannula for drug application were placed under the coverslip along the lateral aspect of the craniotomy and over an incision in the dura. A Zeiss LSM 510 Multiphoton microscope was used to image GFP-positive dendrites approximately 25–75 microns below the neocortical surface. We acquired Z-stacks of the same dendrites and associated spines every 15–30 minutes over three hours in control mice and mice infused with 4-aminopyridine locally below the cranial window to elicit electrographic seizures. We analyzed images off-line to assess changes in spine number (gain or loss) under control conditions and during/after seizures.

Results: Individual dendritic spines from neocortical dendrites in anesthetized mice *in vivo* could be imaged repetitively over three hours with good resolution. Repetitive electrographic seizures could be induced following local application of 4-aminopyridine. In both control and seizure conditions, almost all existing spines remained stable over a three hour period, with loss of existing spines or formation of new spines occuring only rarely. Compared to controls, there was no significant effect of seizures on spine number.

Conclusions: Surprisingly, seizures had no obvious, acute effects on dendritic spine number in the neocortex of anesthetized mice. Additional studies, involving more detailed analysis of spine morphology and motility, effects of anesthesia, longer-term chronic imaging, or other seizure models may reveal pathological effects of seizures on dendritic spines. (Supported by NIH 1 K02 NS045583-01.)

1.046

NOVEL INTERPLAY BETWEEN INHIBITORY AND EXCITATORY NETWORKS DURING SEIZURES

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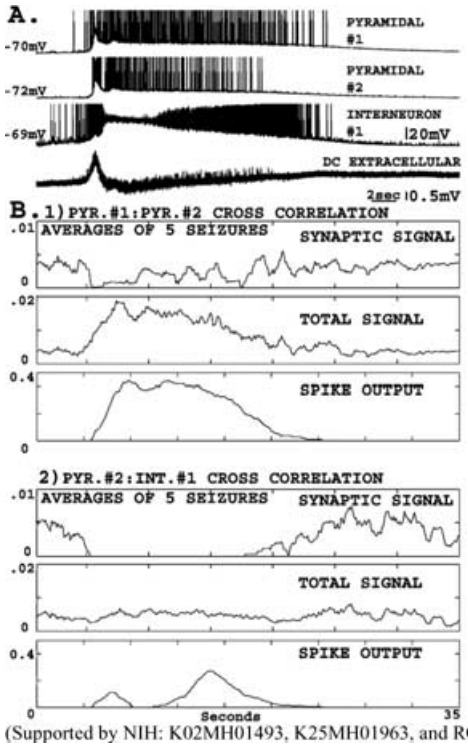
Rationale: Seizures have been called "hypersynchronous" events, but recent work indicates that neurons may receive more synchronous inputs at seizure termination. We describe the dynamics of synaptic activity and spike output in CA1 pyramidal-pyramidal and pyramidal-interneuron cell pairs before, during, and after *in vitro* seizures.

Methods: Simultaneous dual (n = 40) and triple (n = 5) whole-cell and extracellular recordings of network activity were performed in CA1 using transverse hippocampal slice preparations of juvenile rats (P18-P30). Inhibitory interneurons (fast spiking, burst firing, stuttering, and regular spiking) from the CA1 strata were distinguished from pyramidal cells by differential infrared contrast microscopy, membrane firing properties, and *post-hoc* morphological analysis of neurobiotin histochemistry. To induce seizures, neurons were held at resting membrane potentials in current-clamp and bathed in 50–250 μM 4-Amino Pyridine. Seizures here are defined as sustained long-lasting (>10s) paroxysmal network events accompanied by a substantial extracellular negative DC shift and clear initiation, body, and termination phases (Fig.1, A). Synchrony was assessed using a unique approach involving separate correlation analyses of output spikes, synaptic inputs, and the complete signals between each pair of neuronal subtypes.

Results: 43% of all cell pairs showed multiple repetitive seizures. Synaptic input correlation was complex and varied greatly. Pyramidal cell pairs showed a small decrease in synaptic correlation in the seizure body and an increase during the termination. During seizures, depolarization block of interneurons was common and interleaved with pyramidal spiking sequences (Fig. 1A). Pyramidal cell pair spike output exhibited strong correlation (may be required for seizure propagation *en route* to cortex). Spike output between pyramidal cells and interneurons revealed a complex interplay between these networks.

Conclusions: The interactions between different neurons (pyramidal-pyramidal and interneuron-pyramidal) in seizures are complex and cannot be described simply by "synchrony." The interactions between neurons can be qualitatively different when characterized by either synaptic input current or output spike correlation. The dynamical interplay between inhibitory and excitatory networks appears to orchestrate the initiation, persistence, and termination of these seizure events.



(Supported by NIH: K02MH01493, K25MH01963, and RO1MH50006.)

Translational Research: Human Tissue and Pathology

1.047

RESPONSE PATTERNS *IN VITRO* OF THE HUMAN HIPPOCAMPUS FROM PATIENTS WITH EPILEPSY BY MESIAL TEMPORAL LOBE SCLEROSIS

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Rationale: To study *in vitro* electrophysiological responses of human hippocampus obtained from patients with temporal lobe epilepsy and their responsiveness upon antiepileptic drugs.

Methods: The hippocampus resection has been made in block intending to preserve its structure and vitality. Thus, twenty five specimens were obtained and submitted to *in vitro* hyperexcitation protocols through the application of artificial cerebral spinal fluid with high potassium concentrations either GABAergic antagonist or magnesium free. Fifteen specimens perfused with Phenytoin and ten with Carbamazepine and Topiramate had their responses recorded for further assessment.

Results: Spontaneous epileptic discharges were obtained only in four specimens. Threshold decreasing and the increase of the evoked spikes amplitude were observed after high potassium and bicuculline hyper excitation protocols, promoting the appearance of two groups: one demonstrating few multiple spikes (1 to 2) and another with many multiple spikes (9 to20). After Mg++ free hyperexcitation protocol we also observed a threshold decrease and the increase of the population spike, although the most peculiar fact was an ictal spontaneous discharge during 81,7 seconds. We believe that the different responses are related to epileptogenic variability since we have used three different hyperexcitation protocols. A slight decrease in the number of population

spikes after Phenytoin, topiramate and carbamazepine perfusion had no significance.

Conclusions: This study presents the characterization of two kinds of responses upon different hyperexcitation protocols. This may be due to the major variability of the tissue obtained from surgical resection therapy since the mechanisms of epileptogenesis are not totally cleared and the absence of the control tissues make this work more difficult. (Supported by CAPES, CNPq, FAPESP, PRONEX.)

1.048

DETECTION OF HUMAN HERPESVIRUS-6 IN PRIMARY ADULT ASTROCYTE CULTURES FROM EPILEPSY PATIENTS WITH MESIAL TEMPORAL SCLEROSIS

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Rationale: Mesial temporal sclerosis (MTS) is one of the most common pathological conditions associated with medically refractory epilepsy, often, requiring brain surgery to control seizures. Children with a history of complex febrile seizures have an increased risk of developing MTS. Complex febrile seizures have a strong association with primary human herpesvirus-6 (HHV-6) infection. HHV-6 is a ubiquitous virus associated with several neurological disorders. It has been suggested that HHV-6 has a higher prevalence in temporal lobe of patients with MTS and epilepsy than in controls. HHV-6 can infect a variety of cells including astrocytes.

Methods: We studied 12 patients with MTS that underwent temporal lobectomy for control of their epilepsy and tissue from 7 controls that had other brain resections. The brain tissue was immediately brought to the laboratory and used for DNA and RNA analysis and primary cell cultures. Briefly, the tissue was minced, digested with papain, separated using a Percoll gradient and the astrocyte fraction was then cultured. PCR, nested PCR and quantitative real-time PCR were performed on DNA extracted from brain tissue, from PBMCs and from serum from each patient. The astrocytes were characterized using immunofluorescence assay for glial fibrillary acidic protein (GFAP). HHV-6 infection was determined by immunofluorescence assay using an antibody to gp116. DNA was extracted from cultured astrocytes and nested PCR was performed to demonstrate the presence of HHV-6 DNA.

Results: Elevated viral loads of HHV-6 were demonstrated in brain tissue from epilepsy patients with MTS in comparison to control tissue. Astrocytes stained positive for gp116 using immunohistochemistry. Adult astrocytes were successfully grown in culture and expression of HHV-6 was confirmed by immunofluorescence staining for gp116. HHV-6 was co-localized to GFAP-positive cells. DNA was extracted from cultured human adult astrocytes and nested-PCR for HHV-6 DNA in these astrocytes was positive.

Conclusions: HHV-6 was present in brain specimens from patients with epilepsy and MTS and was localized to astrocytes. HHV-6 infection of human adult astrocytes in culture can be demonstrated by nested-PCR and immunofluoresence. The strength of the relationship between HHV-6 and mesial temporal sclerosis still needs to be determined. Introducing a potential relationship between a specific virus and epilepsy with MTS opens up the avenue for the development of new therapeutic strategies for treatment and possible prevention of a type of epilepsy that frequently can only be controlled by brain surgery. (Supported by NINDS/DIR.)

1.049

COMPARISON OF AUTONOMIC FUNCTIONS BETWEEN PATIENTS OF WELL-CONTROLLED AND INTRACTABLE EPILEPSY

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Rationale: Changes in cardiovascular tone is noted in Temporal Lobe Epilepsy [TLE] patients. Surgical removal of the foci might alter the equation of epileptogenicity and autonomic controls.

Methods: In this study, two groups of epilepsy patients were studied: 1) Those that were under medication and seizure free for at least a period of last three months, i.e. well-controlled (WC) and 2) Those that were intractable. Both the groups underwent a battery of autonomic function tests which were aimed at testing their autonomic reactivity.

Results: Baseline autonomic activity (tone) was also measured by Heart rate variability (HRV) analysis. Autonomic functions were compared between 18 WC patients (mean age 23.67 $\pm$ 12.62, 11 males and 7 females) and 10 IE patients (mean age 22.9 $\pm$ 10.8, 9 males and 1 female). WC group showed higher values as compared to the IE group i.e. E: I ratio (1.41 $\pm$ 0.19 vs. 1.3 $\pm$ 0.12), delta HR changes during DBT (26.56 $\pm$ 11.5 vs. 21.8 $\pm$ 8.27), tachycardia ratio (1.38 $\pm$ 0.2 vs. 1.34 $\pm$ 0.14), bradycardia ratio (0.79 $\pm$ 0.12 vs. 0.7 $\pm$ 0.17), 30: 15 ratio of the HUT (1.21 $\pm$ 0.38 vs. 1.1 $\pm$ 0.05), except the Valsalva ratio (VR) (1.8 $\pm$ 90.44 vs. 2.06 $\pm$ 0.48), this denotes a trend towards a lower parasympathetic reactivity in the intractable epileptic group. Among the indices for sympathetic reactivity which were studied, i.e. rise in diastolic B.P during HGT (20.59 $\pm$ 8.85 vs. 23.6 $\pm$ 7.65), rise in diastolic BP during CPT (13.29 $\pm$ 8.03 vs. 13.56 $\pm$ 7.54) exhibited higher values in the IE group. i.e. suffered from recurrent seizures despite optimal treatment under an experienced neurologist over a period of more than one year (IE) Previous studies have shown that epileptic patients exhibit varied autonomic responses, either as part of seizure symptoms or as interictal manifestations which possibly result from propagation of electrical impulses from the seizure focus to the central autonomic nuclei. The time domain measures which give an idea of parasympathetic tone, i.e. SDNN (44.5 $\pm$ 927.4 vs. 28.96 $\pm$ 6.86), SDSD (46.68 $\pm$ 34.4 vs. 22.58 $\pm$ 7.62), RMSSD (46.61 $\pm$ 34.35 vs. 22.55 $\pm$ 7.61) NN50 (38.534 $\pm$ 1.97 vs. 9.710 $\pm$ .26) and pNN50 (11.04 $\pm$ 12.74 vs. 2.53 $\pm$ 2.8) consistently showed lower values in IE group as compared to WC group, which suggests a lower parasympathetic tone when compared to the WC group. In the frequency domain measures, LF(nu) (40.13 $\pm$ 13.72 vs. 45.95 $\pm$ 20.47),%LF (30.64 $\pm$ 7.57 vs. 27.821 $\pm$ 3.13)and LF/HF ratio (1.030 $\pm$ .58 vs. 1.43 +/- 1.08) showed that the IE group had a higher sympathetic tone while the HF(nu) (46.55 $\pm$ 16.86 vs. 44.39 $\pm$ 19.55), showed that this group also had a lower parasympathetic tone when compared to the WC group.

Conclusions: The intractable group had both a higher basal sympathetic tone and sympathetic reactivity when compared to the well-controlled group.

1.050

SURFACE VERSUS DEPTH ANALYSIS OF INITIAL SLOW WAVE EEG SEIZURE ONSETS IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: Hypersynchronous and low voltage fast seizure onsets are the most common types of seizure onsets in depth EEG recordings of temporal lobe epilepsy (TLE) patients. Previously, we showed that low voltage fast seizure onsets are accompanied by an initial slow wave (ISW). In order to assess the spatial-temporal distribution of the ISW, we performed a comparison of surface versus depth profiles of these seizure onsets.

Methods: For seizure onset localization purposes, 10 patients (9M, 1F) with refractory TLE were bilaterally implanted with depth electrodes in the amygdala and hippocampus. Additionally, each patient was implanted with subdural grid electrodes on different cortical areas, depending on previous noninvasive findings. EEG seizure onsets ($n = 40$) were analyzed visually using wide band filter settings (0.1 to 70 Hz). Averaging of ISW and EEG interictal spikes was performed to verify the reliability of the ISW and associated seizure onset patterns.

Results: An ISW preceding seizure onset activity was found in seven out of ten patients corresponding to 72.5% of all seizures. Its duration

varied between 0.5 and 3 seconds (1.5 ± 0.6). In five patients an ISW was present in all recorded seizures (23/23 seizures), in two patients an ISW was detected in some seizures (6/10 seizures) and in three patients no seizure contained an ISW (0/7 seizures). Averaging procedures revealed clear phase reversal of ISW between depth electrode recordings and subdural neocortical electrodes. ISW for each patient had a consistent spatial-temporal pattern, which could be distinguished from interictal EEG discharges. ISW had a widespread spatial distribution and were visible on both amygdalohippocampal structures and on temporal and frontal neocortical areas. Focal or regional rhythmic seizure activity followed the ISW, starting with low amplitude on the ISW descending part and increasing in amplitude as the seizure progressed.

Conclusions: Analysis of low frequency EEG components provides additional information regarding seizure onset localization which is not discernable when recording with conventional bandwidth (1–70 Hz). ISW occupy a relatively large area of the brain and are more widespread than the following onset of focal rhythmic seizure activity. The distinct spatial-temporal pattern of the ISW suggests that seizures with an ISW onset are generated by different mechanisms than other types of seizures, such as seizures with a hypersynchronous onset. [Supported by Fund for Scientific Research (FWO)-Flanders grant B/02514 and National Institutes of Health grants NS-02808 and NS-33310.]

1.051

ACTIVATION OF THE mTOR CASCADE DISTINGUISHES CORTICAL TUBERS FROM FOCAL CORTICAL DYSPLASIA

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Rationale: Balloon cells (BCs) in focal cortical dysplasia (FCD) and giant cells (GCs) in tubers of the tuberous sclerosis complex (TSC) share phenotypic similarities. TSC1 or TSC2 gene mutations in TSC lead to mTOR pathway activation and result in phosphorylation of p70S6kinase (phospho-S6K) and ribosomal S6 (phospho-S6) proteins. We hypothesized that downstream components of the mTOR pathway are activated in FCD and that BCs and GCs exhibit distinct gene expression profiles.

Methods: FCD tissue specimens (n = 10; mean age = 12.3 years, 5 females, 5 males) and tubers (n = 10, mean age = 8.25 years, 4 males and 6 females) resected for the treatment of medically intractable epilepsy were analyzed by immunohistochemistry and single cell gene expression analysis. Sections were probed with either NeuN (1:100, Chemicon), phospho-S6 (Ser235/236; 1:200 dilution), phospho-S6K (Thr389; 1:200 dilution), 4EBP1 (Tyr 305, 1:100; all from Cell Signaling, New England Biolabs, Beverly, MA) or STAT3 (1:250, LabVison, Fremont, CA) antibodies. Amplified, radiolabeled mRNA from single phospho-S6 labeled BCs, GCs, or NeuN labeled control neurons was used to probe cDNA arrays containing candidate genes including cell signaling molecules, cell adhesion molecules, growth factors/receptors, and transcription factors. TSC genotyping on genomic DNA extracted from the tubers revealed 7 TSC2 and 3 TSC1 mutations.

Results: Selective expression of phospho-S6K and phospho-S6 was detected immunohistochemically in GCs whereas only phospho-S6 was observed in BCs. Two proteins activated by phospho-S6K, phospho-STAT3, and phospho-4EBP1, were detected in GCs but not BCs. Among 60 candidate genes assayed in phospho-S6 immunolabeled BCs and GCs, differential expression of 24 mRNAs distinguished BCs, GCs, and control neurons. Only 4 genes showed similar expression profiles between BCs and GCs. The observed changes in expression of BF-1, BMP-6, EGFR, CaMKII, CREB, IGF-1, IGF-2, OTX-1, TGFRbeta1, and TGFRbeta3 mRNAs represent the first report of altered transcription of these genes in FCD. Tuberin mRNA levels were reduced in GCs from TSC patients with identified TSC2 gene mutations but were unchanged in BCs.

Conclusions: Phospho-S6K, -S6, -STAT3, and -4EBP1 expression in GCs results from loss of hamartin-tuberin mediated mTOR pathway inhibition whereas phospho-S6 expression in BCs does not support mTOR cascade activation in FCD. Differential gene expression profiles found in BCs and GCs supports the hypothesis that these cell types derive by distinct pathogenic mechanisms. [Supported by NINDS R010405, R21-NS39938, R21NS40231, Parents Against Childhood Epilepsy (PACE).]

1.052

ANTIEPILEPTIC EFFECT OF THE ACYLPOLYAMINETOXIN JSTX-3 IN HUMAN HIPPOCAMPAL CA1 NEURONS *IN VITRO*

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Rationale: The Spider toxin JSTX is an acylpolyaminetoxin that blocks the postsynaptic glutamate synapse in hippocampal pyramidal neurons (*Brain Res* 1985; 346:397–9). Since glutamatergic receptors are involved in the epilepsy physiopathology, the aim of this study was to verify a possible effect of the synthetic acylpolyaminetoxin JSTX-3 on epileptogenic discharges induced by perfusion of human hippocampal slices with a free-magnesium medium.

Methods: Hippocampal samples from seven patients with medically refractory mesial temporal lobe epilepsy underwent surgical treatment were collected. The hippocampal tissue was sliced in 500 mm coronal sections. The slices (n:7) were kept in a prechamber at room temperature in Ringer, which was continuously bubbled with 95% O2, 5% CO2. The slices were then transferred into an interface recording chamber continuously perfused with an oxygenated Ringer solution. Intra- and extracellular recordings were simultaneously obtained from CA1 pyramidal neurons. Ictal-like activity and interictal discharges were induced by perfusing the slice with oxygenated Magnesium-free Ringer solution.

Results: In all neurons (n:10) the epileptogenic activity was blocked with the application of JSTX-3 toxin. This effect was similar to the one obtained for 2-amino-5-phosphonovaleric acid (APV) perfusion. Recurrent epileptiform discharges were induced by iontophoretic application of N-methyl-D-aspartate (NMDA) and they were also blocked by the JSTX-3 pressure ejection.

Conclusions: Our findings suggest that the synthetic acylpolyaminetoxin JSTX-3 has an antiepileptic effect on CA1 human hippocampal neurons. (Supported by CAPES, CNPq, FAPERGS, PUCRS, Secretaria de C&T do RS, CAT/CEPID- FAPESP.)

1.053

AQUAPORIN-4 AND HIPPOCAMPAL SCLEROSIS IN HUMAN TEMPORAL LOBE EPILEPSY: A MICROARRAY ANALYSIS

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Rationale: Hippocampal sclerosis is often seen in patients with medial temporal lobe epilepsy and the sclerotic hippocampus appears to be the origin of seizures in these patients. However little is known about the molecular nature of sclerosis. An increased T2 weighted signal in MRI and a higher apparent diffusion coefficient in diffusion weighted imaging are features of the sclerotic hippocampus, which indicate increased water content. Perturbed water homeostasis in the sclerotic hippocampus may be important in epileptogenesis as water transport appears to be coupled to K+ clearance and neuronal excitability. Aquaporin-4 (AQP4) is the predominant water channel in the brain.

Methods: Expression of AQP4 was studied with quantitative real time PCR, light microscpic immunohistochemistry and high resolution immunogold labeling. Microarray analysis with Affymetrix GeneChip U133A was used to study gene expression patterns associated with AQP4.

Results: A significant increase in AQP4 was observed in the sclerotic but not in the non sclerotic hippocampus. This increase was positively correlated with the astrocytic marker glial fibrillary acidic protein (GFAP). Quantitative immunogold experiments showed that non-sclerotic hippocampi had a polarized distribution of AQP4 with the highest concentrations on the astrocytic end feet membranes facing blood vessels. In astrocytes of the sclerotic hippocampi this polarity was lost. High throughput gene expression analysis revealed that the increase in AQP4 was associated with a decreased expression of the dystrophin gene, whose protein is implicated in the anchoring of AQP4 to the perivascular end feet.

Conclusions: We conclude that the perturbed expression of AQP4 and the loss of dystrophin may be critical factors underlying the loss of ion and water homeostasis in the hippocampus, and hypothesize that these changes may contribute to the epileptogenic properties of the sclerotic tissue. (Supported by NS048434 to N.C.de L.)

1.054

THE JUVENILE MYOCLONIC EPIELPSY $GABA_A$ RECEPTOR α1 SUBUNIT MUTATION A322D CAUSES α1 SUBUNIT RETENTION AND DEGRADATION IN THE ENDOPLASMIC RETICULUM

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Rationale: We recently reported that the $GABA_A$ receptor (GABAR) α1 subunit mutation (α1A322D) that is associated with human autosomal dominant juvenile myoclonic epilepsy (ADJME) substantially reduced total and surface α1 subunit expression in transiently transfected HEK293T cells. The mechanism by which this point mutation reduces α1 subunit is unknown, but it has been postulated that A322D causes α1 retention and degradation in the endoplasmic reticulum (ER). Here we utilize confocal microscopy to visualize and quantify the amount of green fluorescent protein- (GFP) tagged wild type and A322D α1 that colocalizes to the ER.

Methods: We constructed GFP tagged wild type (GFPα1) and mutant (GFPα1A322D) α1 subunits in which GFP is connected to the N-termini of α1. We transiently transfected HEK293T cells with wild type human GABAR β2S and γ2S subunits and either GFPα1 or GFPα1A322D. Whole cell voltage-clamp GABA-evoked currents were obtained with rapid GABA perfusion to measure the current kinetics of each GABAR type. Western blots cell lysates were probed with a monoclonal antibody directed against GFP, and quantified. GFP fluorescence from the cellular lysates was measured in a fuorometer. We then transfected HEK293T cells with 25 ng pDsRed2-ER (to selectively label the ER), GABAR β2S and γ2S, subunits, and either GFPα1 or GFPα1A322D. The cells were imaged via confocal microscopy 48 hours after transfection. Both total GFP fluorescence as well as GFP fluorescence that was colocalized with pDsRed2-ER was quantified for each cell using Metamorph software.

Results: Peak whole cell currents from GABARs containing the GFPα1A322D subunit had 1% of peak currents from GABARs containing the GFPα1 subunit and lacked fast and intermediate phases of desensitization. Western blots of whole cell lysates demonstrated that GFPα1A322D expression was 95 $\pm$ 2% smaller than GFPα1 expression. Lysates from GABARs containing the GFPα1A322D subunit had 18% of the GFP fluorescence compared with GFPα1 subunit-containing GABARs. Confocal microscopy revealed that cells transfected with β2S and γ2S subunit and the GFPα1 subunit cDNAs had 83 $\pm$ 3% of the GFP fluorescence colocalized with the ER and cells transfected with β2S and γ2S and GFPα1A322D subunit cDNAs had 100 $\pm$ 4% ($P < 0.05$) of the GFP fluorescence colocalized with the ER.

Conclusions: GABARs containing the GFPα1A322D subunit lacked fast and intermediate components of desensitization and had smaller peak currents and α1 subunit expression levels than GABARs containing the GFPα1 subunit, differences that were similar to non-GFP tagged wild type and mutant GABARs. GFPα1A322D subunit-containing GABARs had reduced total GFP fluorescence and a significantly higher percentage of the GFP fluorescence colocalized to the ER compared with GFPα1 subunit-containing GABARs. These data suggest that the α1A322D mutation in ADJME causes α1 subunit retention and degradation in the ER. (Supported by NIH 1 K08 NS44257–01 NS 39479.)

1.055

STUDY OF HIPOCAMPAL NEURONAL DENSITY AND MOSSY FIBERS IN PATIENTS WITH ALZHEIMER DISEASE AND TEMPORAL LOBE EPILEPSY

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Rationale: Alzheimer disease (AD), an important cause of dementia, generally not associated to epilepsy, is characterized by entorhinal cortex neuronal degeneration and consequent loss of innervation of the *fascia dentata (FD)*. Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis generally presents abnormal mossy fiber sprouting in the inner molecular layer of the FD. The main goal of this work was to study neuron density and mossy fiber distribution in the hippocampus of patients with AD and to compare them to those observed in MTLE patients in order to check if the innervation loss of the FD is always associated to abnormal mossy fiber sprouting.

Methods: Hippocampal histological sections from AD patients without epilepsy ($n = 7$), surgically treated MTLE patients ($n = 8$) and autopsy controls ($n = 7$ and 8, respectively) were studied for granule cell, hilar, CA4, CA3, CA2, CA1 and subiculum neuron densities and semiquantitative immunoreactivity to dynorphin as a marker of mossy fibers.

Results: Results showed the following: 1) compared to autopsies, AD patients showed a similar neuron densities in all evaluated areas; 2) in contrast, compared to autopsies, MTLE patients showed less granular cells (176427 $\pm$ 20465 and 313854 $\pm$ 26705) and CA1 (9953 $\pm$ 1925 and 24390 $\pm$ 956), CA2 (8567 $\pm$ 1545 and 22421 $\pm$ 1605), CA3 (7328 $\pm$ 1236 and 21875 $\pm$ 1826) and CA4 (7000 $\pm$ 1237 and 17937 $\pm$ 1005) pyramidal cells/cubic millimeter; 3) compared to autopsies, AD patients presented a similar distribution of dynorphin immunoreactivity in the outer and inner molecular, granular layer and hilus of the *FD* as well in CA4; 4) MLTE patients presented higher dynorphin immunoreactivity in the inner molecular layer of the *FD* than their autopsy controls (gray level 136 $\pm$ 4 and 116,6 $\pm$ 1, respectively).

Conclusions: Data indicate that the loss of human *FD* innervation is not necessarily associated with mossy fiber sprouting in contrast with results observed in rats with induced unilateral entorhinal lesions and experimental models of MTLE. (Supported by CNPq and FAPESP.)

1.056

NEUROGENESIS IN HUMAN NEOCORTICAL EPILEPSY

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Rationale: Neurogenesis has been described in specific areas in the normal human brain. This study was undertaken to investigate whether neurogenesis occurs in epileptogenic areas in patients with intractable epilepsy.

Methods: We studied 14 patients (mean age: 19.1 years old) with medically intractable epilepsy who underwent epilepsy surgery. During surgical resections, en bloc cortical and subcortical samples were collected and cultured with BrdU (a marker for proliferating cells) for 24, 48 and 72 hours. Cultured slices were later fixed for immunocytochemistry (ICC) and immunofluorescence (for double labeling). The following primary antibodies were used: anti-BrdU, anti-TUJ1, anti- MAP2 and anti-NeuN (for neurons), anti-GFAP (for glial cells), anti-Nestin and anti-CD133 (for stem-cells).

Results: Histology revealed MCD in 9 patients: 3 patients with hemimegalencephaly and 6 focal cortical dysplasia. Perinatal infarction (PI) was confirmed in 3 patients and 2 had the diagnosis of gliosis secondary to trauma. Eight patients were analyzed as controls (normal

temporal cortex). There was significant BrdU uptake in 5 out of 8 patients with MCD and in all 3 patients with PI, that was mainly located but not restricted to the subventricular zone (SVZ). Positive BrdU cells were found in all abnormal samples resected from frontal, parietal, temporal or occipital lobes. There were no BrdU positive cells seen in any of the 8 "control" temporal lobe samples. Intense BrDU uptake was found in SVZ with progressive decrement in its expression toward cortical surface in samples that were cultured for 24 hours. In samples that were cultured for 48 and 72 hours, a more diffuse BrdU immunoreactivity was observed with presence of an increased number of BrdU stained cells in white matter (intermediate zone). Nestin and BrdU co-localization was found in the SVZ cells only. BrdU and Tuj1 co-localization was observed in the entire length of the cortical mantle. No co-localization was observed between BrdU and GFAP.

Conclusions: Our results suggest the presence of replication, migration and preferential differentiation of stem cells into neurons in neocortical epilepsy. Our study shows a clear trend toward early neuronal differentiation in the epileptic and histologically abnormal samples. The role and function of these cells in neocortical epilepsies remain unknown. [Supported by NINDS grant for Imad M Najm (K08NS02046 and 1R21 NS42354).]

1.057

NEUROPATHOLOGICAL BASIS OF POLYMICROGYRIA

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Rationale: Polymicrogyria (PMG) is a relatively common malformation of cortical development. However, the pathogenesis, epileptogenesis and anatomo-clinical correlation of PMG require further clarification. We aim to 1. study the extent and type of pathological changes in polymicrogyric lesions as well as in adjacent non-polymicrogyric tissue 2. study the presence of other malformations of cortical development, as well as other pathological conditions previously reported in association with PMG 3. study the anatomo-clinical correlation in order to better understand language impairment and motor involvement frequently seen in PMG patients 4. study the correlation between pathology and imaging findings 5. obtain further insight into the pathogenesis and epileptogenesis of PMG.

Methods: Medical records, EEG, imaging and autopsy data on seven patients from four tertiary centers were reviewed.

Results: Two patients had symmetrical and 2 had asymmetrical bilateral perisylvian PMG, 1 had unilateral hemispheric PMG and a small contralateral PMG lesion, 1 had parieto-occipital PMG. Multiple associated CNS lesions were identified, including periventricular nodular heterotopia, non-laminated heterotopic neurons in the cerebral white matter, microscopic neuroglial heterotopias in the cerebellar white matter, and DNT. Associated congenital malformations included cardiac malformations, congenital hemiparesis, club foot, arthrogryposis, and cranio-facial dysmorphism. When detailed seizure history was available, pathology findings correlated with seizure patterns present during life. The cause of death was seizure related in 2 patients.

Conclusions: This is the first series of brain autopsy findings in PMG patients. Our study illustrates that PMG is often associated with diffuse microscopic migration disorders that may contribute to the epileptogenesis in PMG patients. The absence of underlying infectious or vascular pathology reflects the developmental origin of PMG and supports the involvement of genetic factors in its pathogenesis. The extent of the polymicrogyric lesion can be more widespread than detected by current MRI techniques. Associated congenital malformations seem more frequent than recognized to date. (Supported by Savoy Foundation for Epilepsy Research.)

1.058

FUROSEMIDE AND MANNITOL SUPPRESS EPILEPTIC ACTIVITY IN THE HUMAN BRAIN

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Rationale: Neuronal hyperexcitability has been a major focus in research on basic mechanisms of epilepsy and in the design of antiepileptic medications. Previous *in vitro* studies suggested that furosemide (Lasix), a commonly used diuretic, could block 'hypersynchronized' epileptiform activity *without* suppressing neuronal excitability. It has been suggested that furosemide mediates its antiepileptic effects through nonsynaptic mechanisms, possibly involving changes in the size of the extracellular space (ECS). Here we study the effects of furosemide and mannitol (an osmolyte that is also known to modulate the ECS) in human patients with medically intractable epilepsy.

Methods: Intraoperative studies were performed on 13 patients with medically intractable epilepsy, who had given informed consent and adhered to a protocol that was approved by the Duke Human Subject Committee (IRB Protocol #2082). The age of the patients varied from 12 to 56 years old, with 3 male/11 female. All experiments were performed intraoperatively on patients during their surgical procedure for the treatment of intractable epilepsy. After the cortex was exposed, optical imaging was performed while electrophysiological recordings were acquired from an array of EEG electrodes placed directly on the cortical surface. Patients were given intravenous injections of either furosemide (20 mg) or mannitol (50 g). The effects of these treatments were studied on spontaneous interictal spiking and electrical stimulation-evoked afterdischarge activity.

Results: Intravenously injected furosemide significantly suppressed spontaneous interictal epileptic spikes and electrical stimulation-evoked epileptiform activity in all patients tested. Neither the response of the cortex to electrical stimulation as measured with optical imaging, nor EEG activity recorded from non-epileptic cortex, was suppressed by furosemide, suggesting the furosemide did not suppress cortical excitability. Mannitol, an osmolyte, similarly suppressed epileptic activity.

Conclusions: These studies indicate that i) furosemide suppresses epileptic activity, and ii) nonsynaptic mechanisms may play a significant role in the maintenance of epileptic activity in the human brain. These results suggest novel nonsynaptic pharmacological targets for the development of new antiepileptic medications. Molecules that modulate the extracellular space, either directly or through antagonism of the cation-chloride cotransport system, might provide a potent means to control seizure activity while avoiding the side effects associated with current therapies that suppress neuronal excitability. [Supported by Junior Investigator Research Grant Award from the Epilepsy Foundation of America, and NIH/NINDS R21NS042341 (D.W.H.); NIH/NINDS K08NS01828 (M.M.H.).]

1.059

HIPPOCAMPAL GLIAL DENSITY IN TEMPORAL LOBE EPILEPSY

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Rationale: Hippocampal changes in temporal lobe epilepsy include neuronal loss and glial proliferation. The majority of quantitative studies on hippocampal cells involve the neuronal population. Recent studies suggest possible participation of glial cells in epileptogenesis, but the hippocampal glial density has been rarely investigated.

Methods: We studied the hippocampal glial density in surgically resected hippocampi from 192 patients, who underwent partial anterior temporal lobectomy for intractable temporal lobe epilepsy. Six-micrometer thin paraffin sections of the hippocampus were made, and Nissl and/or hematoxylin and eosin stains were done. The hippocampus was divided into four CA sectors, and glial cells (astrocytes and oligodendroglial cells) were counted in multiple consecutive 200 × 400 micrometer unit areas. Twenty-three age-and gender-matched postmortem cases were included for control.

Results: In the epilepsy group, every CA sector showed a moderate to marked increase in glial density (165% in CA2 to 349% in CA1, compared with the control group). There was statistically significant inverse correlation between the glial and neuronal density in each sector (p, <0.001, all sectors). History of febrile seizures, absence of extra-hippocampal pathology and long duration of seizure history were positively correlated with the glial density. However, family history of seizures, gender and age at the time of surgery failed to reveal any correlation with the glial density. More interestingly, the CA1 glial density in the group with an improved clinical outcome was significantly higher than that of the non-improved group. Further, the glial density in the improved group was numerically higher in the rest of CA sectors compared with the non-improved group.

Conclusions: The hippocampal glial density is significantly higher in temporal lobe epilepsy, and is inversely correlated with the neuronal density. Enhanced hippocampal glial density may predict a better surgical outcome, which, in turn, speaks for a role of glial cells in epileptogenesis. (Supported by 2PO1 NS039092.)

1.060

MATURATIONAL EFFECTS OF SEZIURES ON AMPA RECEPTORS IN RATS AND HUMANS

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Rationale: In adult rats, a loss of GluR2 subunit expression and subsequent increases in AMPA receptor mediated Ca^{2+} currents were thought to enhance glutamate excitotoxicity after status epilepticus because, GluR2 protein is selectively decreased in vulnerable CA3 neurons before cell death. However, we now know that expression of AMPA receptors after status epilepticus depends upon the age of the animal and history of perinatal seizures as does the seizure-induced pattern of damage.

Methods: We characterized maturational changes in AMPA receptor levels of the hippocampus with immunohistochemistry and westerns in rats and humans of adolescent and adult ages with and without a history of seizures. Kainic acid (KA) was used to induce a single episode of status epilepticus in rats on P13, P20 and P30 and two earlier episodes of KA seizures were induced on P6 and P9 in half of the animals. Parallel experiments were conducted in human resected hippocampus from several ages.

Results: In young P20 and P30 rats sensitive to CA1 damage GluR1 immunoreactivity was depleted in CA1 stratum pyramidale and stratum lucidum and only the morphologically healthy cells were labeled. At P30, GluR2 subunit expression was nearly absent in the healthy cells and highly upregulated within the injured CA1 neuronal population. A history of perinatal seizures prevented alterations in CA1 but not CA3. In humans, decreases, increases or sustained levels of the GluR2 subunit have been reported within sclerotic hippocampal regions but we found the discrepancies may be due to maturational differences. In a 28 yr old patient, GluR2 protein was increased in H1 neurons and decreased in H3, whereas GluR1 was sustained, increased or decreased depending on the area. The opposite was found in an older patient where GluR1 was nearly absent in surviving regions of the H1, however, GluR2 was sustained in adjacent sections. In H3, both GluR1 and GluR2 proteins were decreased in cell somata, GluR1 was increased in the neuropil and marked cell loss was noted. In a 6 yr old patient GluR2 was increased in H1 and decreased in H3 where cell loss was noted.

Conclusions: There are age-dependent effects of seizures on AMPA receptor expression in rats and humans such that the non-selective and varied expression patterns of AMPA receptors do not support the original assumption that Ca^{2+} permeable AMPA receptors induce neuronal cell death. The particular history of seizures and antiepileptic protocols appear critical to the clinical outcome. Loss of both GluR1 and GluR2 in principal cells and an increase of GluR1 within interneurons may be a mechanism underlying seizure-induced tolerance. (Supported by New Jersey Neuroscience Institute.)

1.061

DECREASED GLUTAMINE SYNTHESIS IN HUMAN TEMPORAL LOBE EPILEPSY: CHICKEN OR EGG?

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Rationale: Deficiency in glutamine synthetase (GS), the astrocytic enzyme that converts glutamate to glutamine, was reported as an explanation for elevated extracellular glutamate levels and seizure initiation in mesial temporal lobe epilepsy (MTLE). We studied astrocytes from resected human TLE to determine whether alterations in GS are a primary etiological factor or are secondary to existing alterations in the epileptic hippocampus.

Methods: Resected human hippocampi from MTLE (n = 11) and non-MTLE (n = 6) patients were studied by a combination of quantitative immunohistochemistry and acute hippocampal slice electrophysiology. We investigated glutamate uptake and glutamine synthesis by astrocytes in the CA1 subfield in these two pathologies.

Results: Astrocytes from non-MTLE epileptic hippocampi express a high level of glutamate transporters and GS (Fig. 1D,H), and demonstrate inward transporter currents in response to glutamate application (Fig. 1G). In contrast, in areas with prominent neuronal loss and astrogliosis in the MTLE epileptic hippocampus, there is markedly decreased expression of both of the astrocytic glutamate transporters, EAAT1 (not shown) and EAAT2 (Fig. 1E,H). This decrease parallels the observed downregulation of GS in these areas (Fig. 1B,E,H). There is little to no inward glutamate induced current in individual astrocytes recorded in areas of sclerosis in acute hippocampal slices from MTLE patients (Fig. 1G).

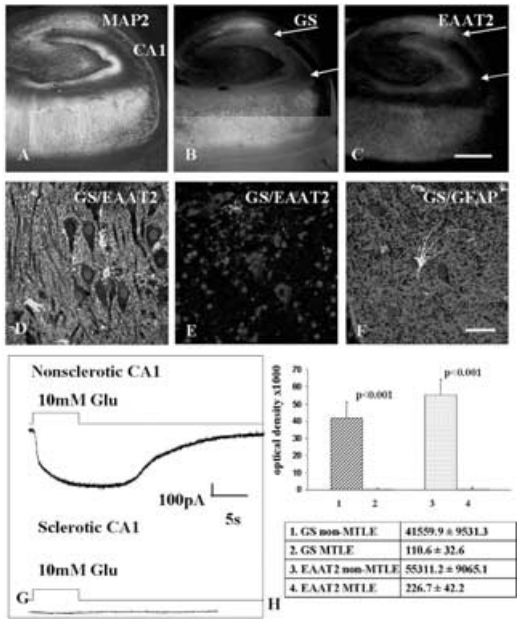

FIG. 1. A-C: Confocal images are shown of: A) Immunohistochemical staining with the neuronal marker MAP2 from a patient with MTLE. There is little expression of GS (B) or EAAT2 (C) in astrocytes in areas of neuronal loss (arrows in B,C delineate the CA1 region). D-E. Immunolabelling for GS (red) and EAAT2 (green) from non-MTLE (D) and MTLE (E) epileptic hippocampi (CA1). Scale bars: A,B,C – 1.5 mm; D,E,F – 80 mm. G. Astrocytes recorded from non-MTLE and MTLE CA1 subfields. H. Quantitative immunohistochemistry. [Supported by Klingenstein Foundation (G.M.). NIH R21 NS 42334 (G.M., P.C.). New York Academy of Medicine Elsberg Fellowship (G.M.)]

Conclusions: Our results demonstrate that there is decreased glutamate transporter expression together with impaired glutamate

uptake by astrocytes in areas of sclerosis in MTLE. These findings suggest that downregulation of GS in MTLE is a secondary phenomenon in response to glutamate not entering these cells, rather than a primary enzymatic defect. Defective glial glutamate uptake has also been implicated in astrocytic tumor growth, neurotoxicity, and seizures.

1.062

NEURONAL NITRIC OXIDE SYNTHASE (nNOS) INHIBITION EXERTS DIFFERENTIAL ANTICONVULSANT EFFECTS IN EPILEPTIC HUMAN NEOCORTEX

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Rationale: Animal studies suggest a role of nitric oxide (NO) in the pathogenesis of epilepsy, but little is known about the role of NO in human epilepsy. In this study, (1) we compare the effect of NOS inhibition on 0 Mg^{2+}-induced epileptiform field potentials (EFP) recorded from the hippocampus (CA1) and the neocortex of rat brain slices, (2) we investigate the effect of NOS inhibition on EFP in epileptic-focal, compared to non-epileptic human neocortex, and (3) correlate the effect of NOS inhibition in human neocortex with the response to NR2B-specific NMDA receptor inhibition.

Methods: Rat brain slices (n = 4) were prepared from male Sprague Dawley rats. Human neocortical tissue was acquired from 14 patients undergoing epilepsy surgery. Epileptic samples (n = 7) were taken from the seizure onset zone of patients with cortical dysplasia. Non-epileptic tissue (n = 7) was acquired from lateral temporal neocortex of patients with hippocampal sclerosis and normal neocortical MRI and histopathology. Zero Mg^{2+}-induced EFP were recorded. The NOS inhibitors 7-nitroindazole (NI; 250 μM) or nitro-L-arginine-methylester (L-NAME; 200 μM), and the NO donor S-nitroso-N-acetylpenicillamine (SNAP; 200 μM) were applied. In four experiments, the NR2B-subunit specific NMDA receptor inhibitor ifenprodil (10 μM) was applied. The following burst parameters were measured: repetition rate, burst duration, and burst integral.

Results: In rat slices, NOS inhibition with 7-NI (n = 2) or L-NAME (n = 2) suppressed EFP in the hippocampus (CA1) and reduced repetition rate, duration and integral of EFP in the neocortex. In epileptic human slices, 7-NI (n = 9) and L-NAME (n = 4) reduced the duration and integral of EFP, without affecting repetition rate. The effects of 7-NI and L-NAME were reversible after washout with 0 Mg^{2+} ACSF or after addition of SNAP (n = 3). In non-epileptic human slices, none of the burst parameters was significantly changed with application of either 7-NI (n = 8 slices) or L-NAME (n = 4). Addition of SNAP had no measurable effect. Ifenprodil suppressed EFP in dysplastic epileptic (n = 2), but not in non-epileptic (n = 2) slices.

Conclusions: Our results suggest: (1) NO is essential for neuronal synchronization in normal rat hippocampus, but not in the normal neocortex. (2) In human epileptic dysplastic neocortex, NO delays the repolarization of EFP. In non-epileptic human cortex, NO has no considerable effect on various burst parameters. (3) The NOS-NO pathway is linked to NMDA receptor activation; sensitivity of EFP to NOS inhibition correlates with their sensitivity to NR2B-specific NMDA receptor inhibition. [Supported by NIH 1R21 NS42354, NIH K08 NS02046 to I.N.; NIH 2RO1 HL51614, NIH RO1 NS43284 to D.J.; IMF, University of Munster, Germany (MO 620202) to G.M.]

1.063

MALFORMATIONS OF CORTICAL DEVELOPMENT: PATHOLOGIC FINDINGS IN PATIENTS WITH INTRACTABLE EPILEPSY

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Rationale: Malformations of cortical development (MCD) are a significant cause of chronic epilepsy. Inconsistent histopathologic classification of MCD has created diagnostic confusion and, at times, obscured clinical relevance. This study attempts to mitigate ongoing confusion and offer clinical correlation by utilizing a practical immunohistochemical protocol that allows reproducible histopathologic description within a contemporary MCD classification system.

Methods: Searching the Mayo Clinic pathology database from 1/1987 to 1/2003, a cohort of 54 patients (34 male) with a previous histologic diagnosis of MCD was identified. The cohort's medical records were reviewed and relevant clinical data was abstracted. Available tissue from each patient was resectioned, stained with H&E and Luxol Fast Blue, and immunostained for neurofilament and glial fibrillary acidic proteins. A blinded neuropathologist reviewed each specimen and classified the findings as either: architectural dysplasia, cytoarchitectural dysplasia without balloon cells, cytoarchitectural dysplasia with balloon cells, or polymicrogyria.

Results: A MCD was identified in 49/54 patient specimens. Ten patients exhibited architectural dysplasia only; eleven patients exhibited cytoarchitectural dysplasia characterized by large dysmorphic neurons in addition to altered cortical lamination; and nineteen patients possessed cytoarchitectural dysplasia characterized by large dysmorphic neurons and balloon cells. Balloon cells demonstrated varied neuronal and/or glial immunoreactivity. Nine patients had findings consistent with polymicrogyria. Gliosis, "no pathology," or mesial temporal sclerosis was found in five patients with a previous histologic diagnosis of MCD. The overall concordance between original diagnosis and diagnosis utilizing a contemporary MCD classification scheme was 90%. Patients possessing polymicrogyria demonstrated earlier seizure onset and increased seizure frequency, while, those with architectural dysplasia developed later onset epilepsy. Malformations of cortical development characterized by cytoarchitectural dysplasia (with or without balloon cells) had similar pre-surgical clinical presentations in terms of seizure onset and frequency.

Conclusions: This study examines a relatively large epilepsy surgical cohort and presents a practical yet systematic pathologic approach to malformations of cortical development. Using standard immunohistochemistry and a recently published classification scheme, consistent description of MCD is achieved and, notably, offers improved diagnostic precision. As seen in previous studies, patients with polymicrogyria present with more severe epilepsy than patients with architectural or cytoarchitectural dysplasia. Historical features alone cannot accurately differentiate patients who possess balloon cells from those patients with cytoarchitectural dysplasia alone.

1.064

EARLY SEIZURE DETECTION BY NONLINEAR ANALYSIS OF EEG RECORDED SIMULTANEOUSLY FROM SCALP AND DEPTH ELECTRODES

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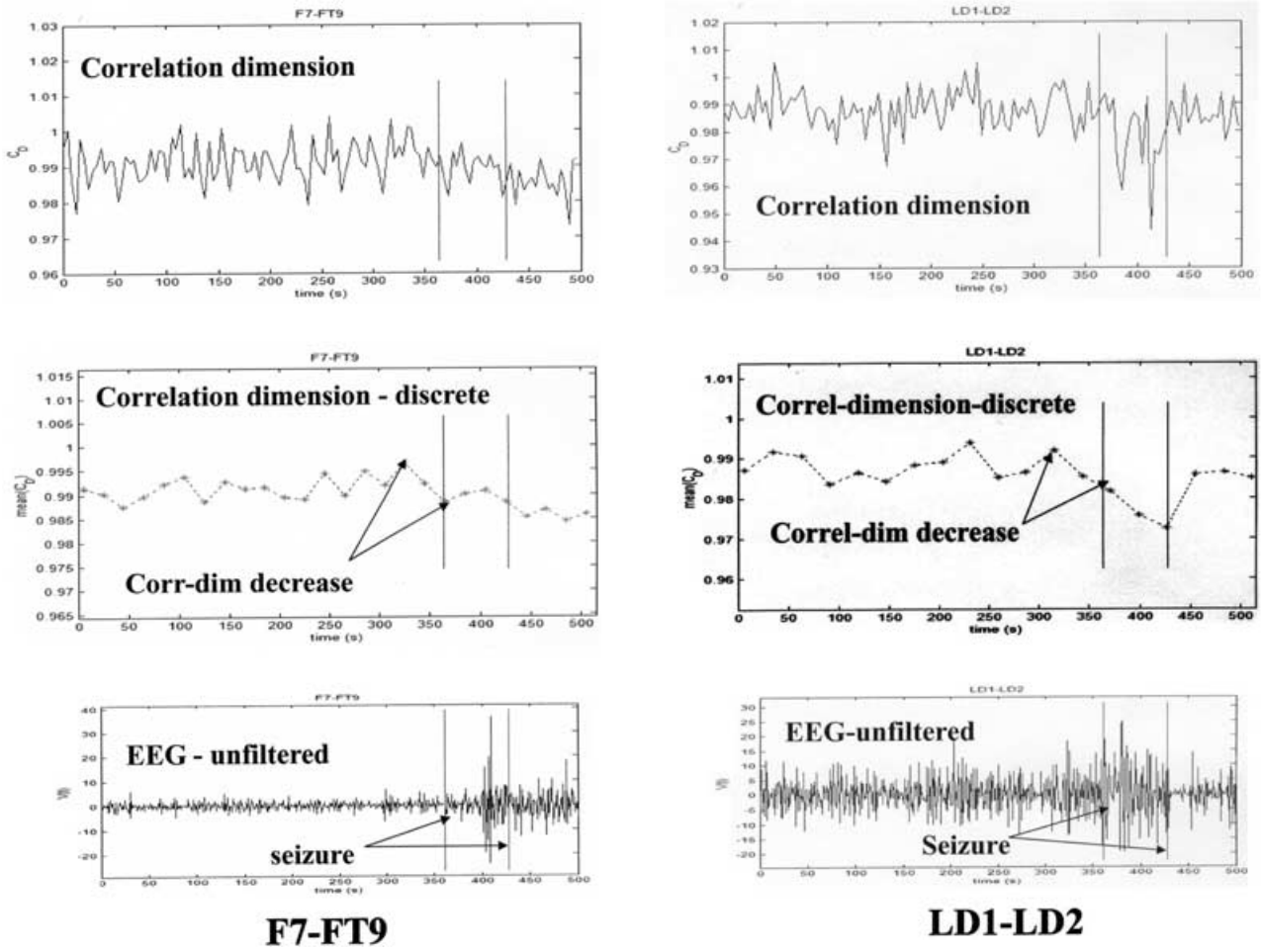
Rationale: Early seizure detection is one of the fundamental problems in modern epileptology. It allows for timely intervention including pharmacotherapy, electrical stimulation and avoiding injury. It may also permit better localization in the workup for epilepsy surgery.

Methods: Two complex partial seizures recorded simultaneously from intracranial and scalp electrodes in an awake patient undergoing evaluation for left temporal lobectomy were analyzed. The temporal evolution of the correlation dimension was computed using methods of nonlinear analysis.

Results: Decrease in the correlation dimension was observed for 20 seconds prior to the recognizable seizure onset in the F7-FT9 scalp lead (Fig. 1) as well as in the left hippocampal LD1-LD2 lead (Fig. 2). The same pattern was observed in two separate seizures.

Conclusions: If confirmed by similar findings in other patients, the method of correlation dimension analysis may provide means of early seizure detection using either intracranial or scalp electrodes.



1.065

ANALYSIS OF INTERLEUKIN 1-β GENE POLYMORPHISM IN PATIENTS WITH TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

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Rationale: Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLS-HS) is the most common form of intractable partial epilepsy. Febrile seizures (FS) and association of FS with pro and anti inflammatory cytokines are stated in the pathogenesis of HS. Interleukin (IL)1-β is a proinflammatory cytokine abundant in hippocampus which is synthesized in macrophage, glia, and neuronal cells in case of an infection or an inflammation. The protein production of the IL-1 β gene which is placed in the long arm of chromosome 2, is affected by two polymorphisms, in 511 promotor region and in 3953 position of exon 5. Hippocampal injury is thought to be related to increased expression of the coded protein. An association of allele 2 homozygosity in IL-1 β (511) position was demonstrated in Japanese patients but this finding wasn't confirmed in European and Chinese patients. Therefore we sought to investigate IL- β (511 C/T) and (3953 T/C) polymorphism frequency and their relationship with FS in Turkish MTL-HS patients

Methods: Forty-seven patients with MTLE-HS were recruited from our epilepsy outpatient clinic. DNA was isolated from the genomic blood, IL- β (511) and (3953) genotypes were determined by PCR-RFLP technique then compared with control group of 71 people. Chi-square test was used for statistical analysis.

Results: IL- β (511) and (3953) genotypes didn't show any significant difference in patients and controls ($p = 0{,}58$, $p = 0{,}45$ respectively). No association was also found with FS in the history and genotype. The most common IL- β genotypes in both groups were (3953$*$1/1) and (511$*$1/2).

Conclusions: Our results, similar to European and Chinese studies indicated that IL-1 β polymorphism is not a significant risk factor in Turkish MTLE-HS patients as well. (Supported by Research fund of the University of Istanbul.)

1.066

DETRENDED FLUCTUATION ANALYSIS (DFA) OF INTRACRANIAL ELECTROENCEPHALOGRAPHY (iEEG) IN SLEEP, WAKE AND PRE-ICTAL STATES

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Rationale: Detrended Fluctuation Analysis (Peng CK et al. *Physiol Rev E* 1994; 49:1685–9) has proven to be a robust method for characterizing long-range temporal correlations in signals from complex non-stationary systems. This algorithm has revealed power-law scaling behavior when applied to scalp electroencephalography and magnetoencephalography. We applied DFA to intracranial EEG signals with respect to sleep, wakefulness, preictal state and location in epileptogenic cortex.

Methods: 146 iEEG 20 minute recordings were analyzed from 684 intracranial cortical electrodes in 6 patients with medical refractory epilepsy. Sleep and wake recordings were selected based on video inspection and presence or absence of sleep related EEG changes. Pre-ictal recordings were selected prior to EEG changes suggestive of ictal onset. DFA scaling α exponents were computed in 5–10 sleep vs wake states, and 3–10 pre-ictal states within each patient. State dependent relationships in DFA exponents of each recording site were then determined and correlated with location in epileptogenic or nonepileptogenic cortex, using unpaired t-test and anova statistical methods with statistical signficance reported only for $p < 0.01$.

Results: DFA scaling exponents from analysis of all recordings showed power-law behavior ($0.5 < \alpha < 1$). Significant differences in mean α exponents were found between pre-ictal, wake, and sleep states. These respective differences varied between patients and as a function of location in epileptogenic or nonepileptogenic cortex. Significant differences between sleep and wake α were seen in all 6 patients at epileptogenic sites, and 5 of 6 patients at nonepileptogenic sites. Pre-ictal α in nonepileptogenic sites were significantly different from wake in all patients and in epileptogenic sites in 5 of 6 patients. Pre-ictal α differed from sleep in all patients at epileptogenic sites but in only 3 of 6 patients at nonepileptogenic sites.

Conclusions: This study of DFA on cortical iEEG demonstrates the presence of long-range power law scaling behavior with distinct state dependent differences in epileptogenic and nonepileptogenic cortex. DFA differences between pre-ictal vs sleep and wake recordings were found in all 6 patients but were most significant in nonepileptogenic cortex for preictal vs wake states and in epileptogenic cortex for preictal vs sleep states. These findings may have important implications in seizure prediction and clinical epilepsy. (Supported by NIH R01-MH55687, NIH R01-MH061975,

Brigham and Women's Hospital training grant for translational neuroscience.)

1.067

ANALYSIS OF NEURONAL GENE EXPRESSION IN GANGLIOGLIOMAS: LESSONS LEARNED AT THE TUMOR'S EDGE

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Rationale: Gangliogliomas are mixed glial-neuronal tumors with a predilection for epileptogenesis. Unlike higher grade infiltrating gliomas, these low-grade tumors generally have discrete margins. Resection of gangliogliomas may result in decreased seizure incidence, suggesting that the focus of epileptogenicity lies within the tumor itself. In cases where resection fails to achieve seizure reduction, adjacent cortex may also provide a seizure focus.

Comparison of gene expression between ganglioglioma neurons, and neurons from the adjacent cortex provides insight into the mechanisms of epileptogenesis.

Methods: We performed in situ RNA transcription on sectioned pathology specimens from patients who had undergone partial lobectomy for seizure-inducing gangliogliomas in the temporal lobe. Patient outcomes at a mean of four years after resection ranged from Engels 1A (completely seizure-free), to 3A (worthwhile reduction in seizures). Individual neurons were microdissected from the tumors and their adjacent cortex. Amplified single cell RNA was radiolabelled, and hybridized to lab-generated cDNA arrays for analysis of gene expression which was performed using JMP statistical software.

Results: Comparisons of gene expression between ganglioglioma neurons and neurons from adjacent temporal cortex revealed differential expression of inhibitory ($GABA_A$)and excitatory (NMDA/GluR) neurotransmitter and receptor subunits. Expression of proinflammatory cytokines, growth factors, growth factor receptors, signal transducers and transcription factor mRNAs were distinct between these cell populations.

Conclusions: Analysis of gene expression in neurons microdissected from ganglioglioma and its adjacent cortex provides insight into the mechanisms by which these tumors cause seizures. (Supported by NINDS RO1NS04542 and R21NS39928.)

1.068

DYNAMICAL EVOLUTION OF SEIZURES

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Rationale: We here apply, to our knowledge, the first formal analysis of the sequential stages of seizure dynamics. Our goal was to seek unique properties of the initial and termination phases of seizures, to better understand how seizures start and stop.

Methods: We studied 24 seizures from 9 children: 12 scalp seizures from 5 children with partial complex epilepsy (selected as relatively artifact free from 79 consecutive records), and 12 intracranial records (from 16 consecutive records) from 4 children with a variety of seizure types and etiologies (gliosis, dysgenesis, mesial temporal sclerosis, and peritumoral). Work was performed with approval from CNMC and GMU Institutional Review Boards.

We developed a novel approach to multivariate linear discrimination of Fisher (1937). We measured 6 independent aspects of synchronization, using a variety of techniques to quantify amplitude and phase correlations between channels, within 1 second non-overlapping windows of EEG (23–64 channels). Careful statistical controls were used to guard against spurious correlations due to frequency content. We examined all possible partitions of these seizures into beginnings, middles, and ends, seeking the best separation and examining significance with both normal theory and bootstrap. We then examined the grand averaged results for common dynamical characteristics during seizure beginning, middle, and termination.

Results: Discrimination into 3 groups was clear for 11 of 12 intracranial seizures (chi-square $p < 0.05$ for 12/12 and bootstrap $p < 0.02$ for 11/12). Analysis of variance demonstrated that phase amplitude variances were significantly elevated during the middle of scalp seizures ($df = 59, F = 7.39, p < 0.0001$), and during the initial period of intracranial seizures ($df = 59, F = 3.4, p < 0.02$), reflecting decreased phase synchrony (Fig. 1). For both scalp and intracranial records, no consistent evidence of increased synchronization was evident in any seizure phase.

Conclusions: We here report the first study of dynamical discrimination of seizure evolution. We found significant extraction of distinct initial and terminal phases from 23 of 24 scalp and intracranial recordings. No consistent evidence of increased synchronization was evident within any of these stages by any measure, consistent with recent intracellular findings (*J Neurosci* 2002;22:7297–7). Significantly decreased synchronization was evident within both scalp and intracranial seizures.

1.069

MICROSCOPIC HIPPOCAMPAL MALFORMATION IN PATIENTS WITH MESIAL TEMPORAL SCLEROSIS

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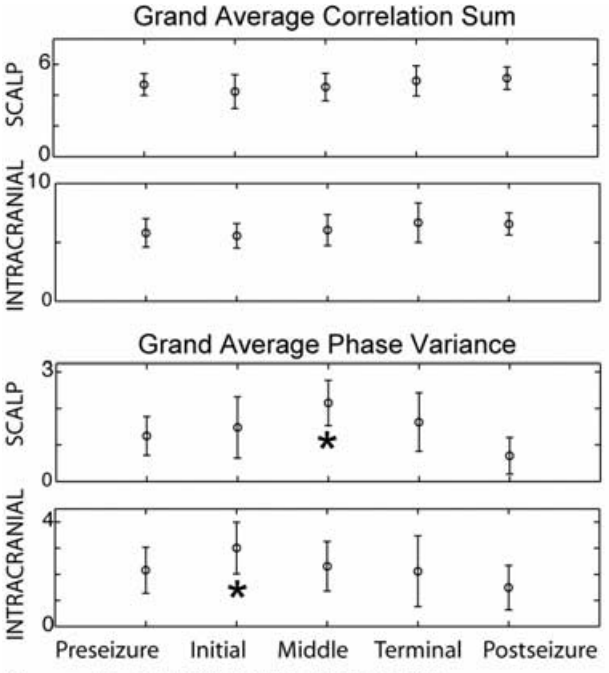
Rationale: Mesial temporal sclerosis (MTS) is the most frequent substrate of refractory epilepsy in adult patients. Despite the recent progress in epileptology, the question whether MTS represents the cause or the consequence of repeated seizures in temporal lobe epilepsy (TLE) remains open to more accurate studies. To address this issue, we studied surgical specimens from seventeen TLE patients and five necropsy controls.

Methods: Hippocampal and neocortical sections were processed for immunocytochemistry using monoclonal antibodies against neuronal and glial components. All patients had detailed anamnesis, interictal and ictal video-EEG recordings for seizure detection and electroclinical correlation and MRI studies, including volumetric evaluation of the hippocampi.



(Supported by NIH R02MH5006, K02MH01493.)

Results: Typical MTS findings on MRI and routine histopathological examination were observed in all patients. The immunocytochemical study of the hippocampi demonstrated the presence of dysmorphic neurons, persistent Cajal-Retzius cells and bilamination of the dentate gyrus in 7/17 (41%) of cases. Neocortical temporal lobe abnormalities included cortical dyslamination (3/17), excess of white matter heterotopic neurons (6/17), numerous Cajal-Retzius cells in layer 1 (7/17), and focal or diffuse cortical astrogliosis (11/17). Temporal pole MRI abnormalities were present in 10 out of 14 patients in whom this could be evaluated and included atrophy, white matter hypersignal and inaccurate limits between gray and white matter.

Conclusions: Altogether, our results indicate that subtle malformation of cortical development (not detectable in routine histopathological examination) involving mesial/hippocampal and lateral/neocortical structures may constitute an important physiopathological substrate underlying TLE. [Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).]

1.070
NG2-EXPRESSING CELLS IN HUMAN EPILEPTIC HIPPOCAMPUS

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Rationale: Chondroitin sulphate proteoglycan expressing cells (NG2 cells) comprise a population of unique glial cells in the adult CNS. They are differentiated from other types of glia by their immunophenotype. NG2 cells have traditionally been considered as oligodendrocyte precursors, although their abundance and direct synaptic connections (in rodents) suggests that they not only function as progenitors but also may actively participate in neuron-glia interactions in healthy and pathologic brain. We sought to characterize NG2 cells in the human TLE brain.

Methods: Hippocampi and neocortex resected from patients with intractable TLE (n = 42; 29 with HS and 13 without HS) were studied with immunohistochemistry combined with confocal and electron microscopy, electrophysiology (patch-clamp technique on brain slices), and Western blotting for detection of NG2 cells andother glial cell subtypes. Pilocarpine and kainic acid mouse models of epilepsy were used for comparative purposes.

Results: NG2 cells were detected in all areas of hippocampus, as well as in neocortex. Immunolabelling was higher in white matter than gray matter. Using electron microscopy and patch-clamp techniques, we detected that human NG2 cells have synaptic contacts, as well as postsynaptic excitatory currents (4/6 cells studied). All recorded NG2 cells revealed complex electrophysiological current features that differentiated them from "passive" astrocytes. Two types of NG2 cells were determined: multipolar stellate, predominating type revealed S100β expression, while spindle-like bipolar cells expressed a basal level of nestin and vimentin but lack S100β.

In ~30% of specimens in both pathologies, multipolar NG2-cells revealed unusually high levels of nestin and vimentin IR. Such nestin/vimentin+ NG2 reactive cells were observed mainly in dentate gyrus and rarely in CA3. In ~15% of cases examined, proliferationof these reactive NG2 cells was found in dentate gyrus, as detected by Ki-67 labelling. Reactive NG2 cells occupied focal areas in the hippocampus or neocortex; they were usually found in parallel with reactive astrocytes, but not with reactive microglial cells. In kainic acid and pilocarpine mouse models of epilepsy, reactive NG-2 cells were visulaized, based on morphological alterations and increased NG2 IR. However, colocalization of nestin and/or vimentin was never observed in these cells, either acutely (up to 7 days) or chronically (up to 4 months).

Conclusions: NG2 cells in the human epileptic brain comprise at least two populations of cells. The bipolar cells are likely oligodendrocyte progenitors that are preserved in adult human brain. Multipolar cells make synaptic connections with neurons and become "reactive" in both HS and non-HS TLE. How these cells participate in hippocampal pathology in epilepsy remains to be determined. [Supported by Klingenstein Foundation, NIH R21 NS 42334, Parents Against Childhood Epilepsy (G.M.)]

1.071
INVESTIGATIONS INTO THE ORIGIN OF LONG-RANGE TEMPORAL CORRELATIONS IN HUMAN INTRACRANIAL EEG

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Rationale: We and others have shown that long range temporal correlations (LRTCs) exist in the energy time series of human intracranial EEG. The energy time series can be generated in multiple ways such as squaring, absolute value, or an envelope function with only minor differences in outcome. However on 20 minute segments of EEG the raw signal does not show this characteristic persistence. As LRTCs can arise in multiple ways in a time series, we pursued a series of investigations to reveal the nature of the LRTC in human EEG.

Methods: Intracranial EEG data were collected from a series of patients at our centers who were implanted with chronic depth electrodes as part of a presurgical evaluation of their seizure disorders. LRTCs were calculated with detrended fluctuation analysis (DFA). Analyses of the energy time series included comparisons of high and low frequency bands; between seizure-onset, and contralateral seizure-remote electrodes; and between sleep, wake, and awake preseizure states. Analyses of raw EEG included 8 to 24 hour segments. Simulation data was generated and analyzed by superimposing regular sinusoidal signals on a background of simulated data with LRTC of known scaling constant.

Results: The raw EEG showed a plateau, absence of scaling behavior, beginning at time windows of about one second, but restored scaling at windows greater than one hour. The asymptopic scaling seen in the EEG voltage time series can be recovered from short time windows (~15 minutes) using the energy time series. The simulated data provided a model of the raw EEG with replication of the plateau and restored scaling in the energy time series. We consistently found greater scaling constants in the low frequency bands compared to the high frequency bands, but no significant differences between behavioral states or brain regions studied.

Conclusions: Hippocampal EEG recordings demonstrate robust LRTC that extend over hours of recording time. We show that to accurately recover the scaling behavior prolonged continuous raw EEG

recordings (hours in duration) are required, and previous studies reporting scaling constants from short time series must be interpeted with caution. However, investigation of the energy time series appears to extract the scaling behavior from more limited time series (~10 minutes). The pronounced LRTCs in the energy transform of human EEG are present in the raw signal, but are obliterated in windows less than about one hour, possibly due to the regular oscillations generally considered to be the relevant signal. The origin and biophysical role of LRTC in hippocampal neuronal dynamics remains unclear.

1.072
LAMOTRIGINE IN A VARIETY OF EPILEPSY: CLINICAL EXPERIENCE

Ronald A. Turck, Jr. and Mary Andriola (Neurology, Epilepsy, Stony Brook University Hospital, Stony Brook, NY)

Rationale: Lamotrigine (LTG) is fairly new Anti-epileptic drug (AED) that is FDA approved for adjunctive use in partial epilepsy, as well as first line use in primary generalized epilepsy. The objective of this study was to evaluate our clinical experience with this medication in an academic referral center.

Methods: A retrospective review of twenty-two charts was performed. Patients were treated from the date of May 2003 to March 2004 The patients had been started on low doses, 25 mg/day, and titrated up to maintenance doses of 100mg bid, in some cases as high as 200mg bid. The patients were evaluated regarding efficacy and side effects (SE).

Results: LTG was used in twenty-two patients, their ages ranging from 4 years to 72 years. Five patients were lost to follow up, and attempted contact was not successful. Out of the remaining 17, eight (47%) had partial-onset epilepsy, the other nine (53%) had primary generalized epilepsy. For nine patients (53%) this was their first and only AED. For the others, they were on one other AED (in one case two other AED's). The most common other AED was Oxcarbamazepine (3 patients, 38%). Fewer than 30% (5 patients) suffered SE. The most common SE was rash in 3 patients. The rash was not serious, and medication was stopped immediately. One patient's rash occurred due to rapid increase in medication that was not followed per protocol. Of the 12 patients who did not have SE, 100% of them had an improvement in their seizure activity. 8 patients (67%) had a reduction of seizure activity >50%. 4 patients (33%) remained seizure free for the time period.

Conclusions: LTG is well tolerated in patients with both partial and primary epilepsy. It can be given as mono-therapy or as adjunctive therapy. The most common side effect is a rash. LTG has a favorable out come for both pediatric and adult populations.

Translational Research: Animal Models 1

1.073
EARLY DEVELOPMENTAL PROFILE OF NMDA SUBUNITS NR1 AND NR2B IN IN-UTERO IRRADIATED RAT PUPS

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Rationale: Cortical dysplasia (CD) is a frequent pathology in infants and children with intractable epilepsy. Molecular characterizations of pediatric dysplastic cortex have previously revealed alterations in the subunit proteins of the N-methyl-D-aspartate (NMDA) receptor. The purpose of the study was to determine if and when the dysplastic cortex of postnatal rat pups showed altered NMDA subunit expressions compared to age matched controls.

Methods: Dams were irradiated with 145 Rads (cGy) at embryonic day 17, and their offspring were studied at 24-hour intervals, postnatal ages zero through six. Cresyl violet staining allowed for dysplasia confirmation, and provided the imaging necessary for obtaining neuronal lengths and diameters from pyramidal neurons in Layer III of the cortex. The expression levels of NMDA receptor subunits NR1 and NR2B were determined using Western blotting. Statistical comparisons were made between control and irradiated age matched pups and within treatment groups between adjacent ages.

Results: Cresyl violet staining showed that all histologically examined tissue from irradiated pups was dysplastic. For NR1 and NR2B expression, there was a significant difference across ages within control and irradiated groups, but not between age-matched control and irradiated groups. In Layer III of the cortex, averaged lengths and diameters from pyramidal neurons correlated significantly across ages within control ($p = 0.002$) and irradiated ($p = 0.001$). Additionally, the correlation between control and irradiated age-matched samples was more significant for neuronal length ($p = 0.002$) than for neuronal diameter ($p = 0.065$).

Conclusions: In this study, we used a well-known model of cortical dysplasia to determine the earliest postnatal NR1 and NR2B protein subunit expression changes. NR1 and NR2B subunits appear to be developmentally regulated at these young ages. Though expression differences between age-matched control and irradiated samples are not significant, it is possible that these expression differences will be significant at later ages when these animals are known be susceptible to seizure activity (Kondo et al., 2001). Despite the fact that all histologically examined tissue showed characteristics of cortical dysplasia, neuronal growth and NMDA subunit expression was not significantly different between control and irradiated groups during postnatal days zero through six. These young pups may not have yet developed axonal and dendritic growth sufficient for synaptic formations to allow feedforward excitation and feedback inhibition.

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(Supported by National Institutes of Health, 5 R01 NS41375–03, and the Children's Research Center of Michigan at Children's Hospital of Michigan.)

1.074
ABNORMAL BRAIN DEVELOPMENT IN MAM-EXPOSED RATS

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Rationale: Cortical malformations are a frequent cause of pediatric epilepsy and are best understood in terms of brain development. In rats, prenatal exposure to methyazoxymethanol (MAM) consistently yields offspring with cortical malformations mimicking those seen clinically. Here we designed studies to establish a timeline of the two hallmark abnormalities in the MAM brain: (i) widespread neocortical dysplasia and (ii) nodular heterotopia in hippocampus. Results of antibody staining in tissue sections obtained from MAM-exposed offspring and analysis of organotypic slice cultures are presented.

Methods: *MAM exposure:* Pregnant S-D rats were injected with 25 mg/kg (i.p.)methylazoxymethanol (MAM) on day 15 of gestation (E15). *Immunohistochemistry:* Tissue sections (30 μm-thick coronal slices) were cut on a cryostat, and sections were treated with an various antibodies. Staining was visualized using the Vectastain ABC kit. *Slice Culture:* E16 embryos and P0 rat brains were embedded in 5% low melting point agarose and cut into 250 μm-thick sections. Slices were cultured on serum free Neurobasal media. Slices were fixed in 4% PFA, cryoprotected, and stained with the DNA dye, TO-PRO 3.

Results: In the MAM model, abnormal cortical development is evident as early as E17 and increases with time. Invasion of the hippocampal heterotopia begins with the postnatal erosion of ventricular zone and subsequent interruption of CA1 region. Cortical markers, such as Lis1, show that there is severe disorganization soon after MAM exposure and complete disruption of the cortical plate. Nestin staining, a radial glial marker, shows the breakdown of the radial glia scaffold in neocortex; the hippocampal scaffold remains intact. We also observed an expansion of neocortex marginal zone with an increase in reelin-positive cells; this change is first evident at E18. There is no abnormality seen with the reelin-positive cells in the hippocampus. Immunostaining for calretinin

and reelin identifies the departing cells of Layer I as Cajal-Retzius cells. P75 expression shows that the subplate is disorganized and has lost its integrity. Interneuronal migration is also disturbed in the MAM brain; the expression pattern for GABA, an interneuronal marker, shows their migratory path is distorted.

Conclusions: This study uses a well-established rat model of cortical malformation (prenatal MAM exposure) and shows that the emergence of a hippocampal heterotopia is a postnatal event, with the cluster first appearing at P2. Dramatic changes in the expression of molecular markers such as p75, nestin, and reelin demonstrate that the abnormal developmental changes in the MAM-treated rat begin prenatally. Knowledge of how the abnormal brain is formed will provide insight into the cause(s) of epileptogenesis and can contribute to advances in therapies for patients with cortical malformations. [Supported by EFA Predoctoral Fellowship (M.F.P.) and NIH NS40272 (S.C.B.)]

1.075

A COMPARATIVE STUDY OF ELECTRICALLY AND CHEMICALLY INDUCED SEIZURE THRESHOLDS IN MGLUR4 WILD TYPE AND KNOCKOUT MICE

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Rationale: Group III metabotropic glutamate receptors are selectively activated by L-AP4, which in the CNS has been shown to inhibit neurotransmitter release. Studies suggest that L-AP4 produces this effect through activation of presynaptic autoreceptors. The high potency of both glutamate and L-AP4 at mGluR4 receptors suggests that these receptors may regulate neuronal excitability. Receptor pharmacology combined with a protein expression pattern which includes entorhinal cortex, the hilar region of the dentate gyrus and the primary terminal fields of the associational fiber-commissural pathway suggest that presynaptic mGluR4 receptors might influence seizure thresholds through modulation of glutamate release. The present study was designed to compare electrically- and chemically induced seizure thresholds in mGluR4 knockout (-/-; KO) and wild type (+/+; WT) mice.

Methods: Seizure thresholds were determined for mGluR4 WT and KO mice.

Electrically induced seizures: The median convulsant currents (CC50's) were determined for minimal (clonic), maximal (tonic-clonic), and limbic seizures, which were induced via transcorneal stimulation (60 Hz, 0.2 s and 6 Hz, 3 s, respectively).

Kindling: A bipolar electrode was stereotaxically placed into the right amygdala. Following a one-week recovery period, WT and KO animals were stimulated once daily at their individual afterdischarge thresholds (20 stimulations). Behavioral scores and afterdischarge durations were recorded throughout.

Chemically induced seizures: Pentylenetetrazol (0.5%) was infused into the lateral tail vein at a constant rate. Time in seconds was recorded from the infusion start to the appearance of the first twitch and clonic activity. Time was subsequently converted to mg/kg PTZ. Kainic acid (20 mg/kg) or pilocarpine (100 mg/kg) was injected intraperitoneally (i.p.) every 20 min until limbic seizures were observed.

Results: Minimal and maximal seizure thresholds did not differ significantly between WT and KO mice (minimal CC50: 7.4 vs 6.6 mA; maximal CC50: 15.1 vs 13.4 mA, WT and KO, respectively). Limbic seizure thresholds were lower in KO mice when compared to WT animals (CC50: 22.5 vs 19.2 mA, WT and KO, respectively). No significant difference was observed in kindling rate or in afterdischarge thresholds. Similarly, no significant difference was observed in PTZ thresholds or in the number of doses of kainic acid or pilocarpine required to produce limbic seizures.

Conclusions: Although limbic seizure thresholds were lower in mGluR4 KO mice, the magnitude of the difference was small. No difference between WT and KO animals was observed however in minimal, maximal, kindling, or chemical seizure thresholds, suggesting that mGluR4 receptors are, at best, minimally involved in seizure thresholds. (Supported by Eli Lilly and Company.)

1.076

PERMANENT HISTOLOGICAL AND BEHAVIOURAL CHANGES PRODUCED BY NEONATAL KAINATE RECEPTOR STIMULATION: A NEW DEVELOPMENTAL RAT MODEL FOR TLE?

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Rationale: We have previously reported on a seizure-like syndrome (NIS-L) in adult rats treated with low doses of kainate agonists during postnatal development (postnatal days 8–14). NIS-L is characterized by reproducible behavioural sequelae reminiscent of a stage 2 seizure, that manifests on exposure to a novel environment.

Acute injections of high doses of kainic acid to adult animals, with subsequent status epilepticus, is a widely used model for temporal lobe epilepsy (TLE). Animals that survive injection subsequently develop spontaneous recurrent seizures weeks to months later. These animal models, as well as clinical TLE, are typically associated with specific anatomical changes in the hippocampus (eg. mossy fiber sprouting and cell loss).

The purpose of this study was to determine whether the treatment paradigm that induces NIS-L results in anatomical changes in the hippocampus that are similar to those seen in both conventional animal models and clinical temporal lobe epilepsy. Identifying and quantifying hippocampal anatomical changes in NIS-L animals is an important step in defining the utility and characteristics of what appears to be a unique developmental rat model of temporal lobe epilepsy.

Methods: SD rats were injected daily with either saline or subconvulsive doses of the kainate agonists domoic acid ($n = 9$) or kainic acid ($n = 9$) from post-natal day 8–14. When the animals reached adulthood they where exposed to the Morris Water Maze and the incidence of the NIS-L syndrome was recorded. Hippocampal anatomy was then analyzed using Timm's Stain for mossy fiber sprouting, as well as cresyl violet staining for cell counts. Cell counts were performed in CA3 (a,b, and c), CA1 and the dentate gyrus. Mossy fiber sprouting was assessed in area CA3 and in the dentate gyrus, using a standard qualitative scale.

Results: Results indicated that drug treated animals reliably displayed the NIS-L syndrome ($p < 0.01$) whereas saline treated animals did not. Drug treated animals also had significantly increased dentate granule cell axon sprouting (mossy fiber sprouting) in the inner molecular layer of the dentate hilus ($F = 3.96$, $p = 0.04$), as well as in the stratum oriens of area CA3 ($F = 5.68$, $p = 0.015$). Treated animals also displayed significantly diminished cell counts in hippocampal areas CA1 ($F = 4.7$, $p = 0.024$), CA3b ($F = 10.54$, $p = 0.001$) and CA3c ($F = 5.18$, $p = 0.017$).

Conclusions: These results confirm that perinatal injections of low doses of kainate agonists reliably produce a seizure-like syndrome (NIS-L) in adult rats, and demonstrate that this treatment paradigm also produces changes in hippocampal cytoarchitecture that are consistent with existing animal models of TLE. (Supported by Canadian Institutes of Health Research, Natural Sciences and Egineering Research Council of Canada PEI Health Research Program.)

1.077

CHARACTERIZATION OF A FOCAL MODEL OF MOTOR EPILEPSY IN RAT USING INTRACORTICAL PENICILLIN

Stephan Chabardes, Imad Najm, Kenneth Rosplock, Richard Burgess, and Hans O. Luders (Neurology, Cleveland Clinic Foundation, Cleveland, OH)

Rationale: The testing of the effectiveness of novel drugs and other therapeutic modalities using reproducible focal animals epilepsy models is of major importance. Few models of reproducible acute focal neocortical seizures have been described. Penicillin (topical application) was previously used in cats, rabbits, and sheep to induce acute seizures. We developed a model of acute induction of long lasting focal motor seizures using small focal intracortical injections of penicillin in the motor cortex of the rats.

Methods: Five adult male Sprague Dawley rats (Charles River, MA, USA) weighing 260–300 g were used according to a protocol approved by the CCF ARC. Under ketamine anesthesia (0.1ml/100 g i.p.), a stainless-steel canula (Plastic One,VA, USA) with an inner needle (0.3mm in diameter) was stereotaxically inserted into the right motor cortex (A = 3mm, L = 2mm, D = -1mm). For EEG recordings, the canula was also used as a recording electrode and a screw electrode was implanted 1mm lateral. Four additional epidural screw electrodes were implanted (bi-parietal and bi-frontal areas, the right frontal electrode used as reference). Seven days after surgery, under light ketamine general anesthesia (0.05ml/100 g), penicillin (2,250 units in 7.5 μl) was injected over 15 minutes using a Hamilton syringe. Fifteen video EEG recording sessions (total of 3 injections/rat every 3 days) were performed using the Vangard digital EEG system (Lamont Inc, USA).

Results: All the rats exhibited focal seizures that typically started 5 to 10 min after the start of penicillin injection and lasted for 2 to 5 hours. We identified 4 consecutive electro-clinical patterns: I consisted of irregular focal spiking ($<$800 μV in amplitude, 5 to 20 min in duration) with no behavior manifestation; II consisted of burst of rhythmic focal spiking (800 to 1200 μV in amplitude, 3 to 20 mn in duration) associated with controlateral forelimb clonic movements; III consisted of continuous rhythmic focal or lateralized (ipsilateral parietal area) spikes or polyspikes (1200 to 3000 μV in amplitude, 1 to 4 hours in duration); IV consisted of secondary generalization of EEG electrical patterns (occurred once in one rat).

Conclusions: The intracortical injection of penicillin leads to reproducible and stereotypical electro-clinical patterns in the rat. This model may be ideal for the testing of novel therapeutics or surgical intervention designed for the control of focal neocortical seizures. [Supported by a grant from the French League Against Epilepsy, the French society for Neurosurgery and the city of Vias, France. I.N. was supported by R21 NS42354 and K08 NS02046 grants from the National Iinstitutes of Health (NINDs).]

1.078

SUCCINIC SEMIALDEHYDE DEHYDROGENASE (SSADH) DEFICIENT MICE: EEG, PHARMACOLOGY, AND DEVELOPMENTAL CHARACTERIZATION

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Rationale: The succinic semialdehyde dehydrogenase (SSADH) null mouse represents a viable animal model for human SSADH deficiency and is characterized by markedly elevated levels of both g-hydroxybutyric acid (GHB) and γ-aminobutyric acid (GABA) in brain, blood, and urine. GHB is known to induce absence-like seizures that have been shown to decrease expression of the glutamate receptor subunit B (GluR2). We tested the hypothesis that the high levels of GHB in the $SSDH^{-/-}$ mouse cause absence-like seizures.

Methods: Sequential ECoG and prolonged video ECoG recordings from chronically implanted electrodes, were done on $SSADH^{-/-}$, $SSADH^{+/-}$, and $SSADH^{+/+}$ mice from postnatal day (P) 10 to (P) 21.

Results: Spontaneous absence-like seizures appeared in the $SSADH^{-/-}$during the second week of life and evolved into generalized convulsive seizures late in the third week of life that were associated with an explosive onset of status epilepticus which was lethal. The SWD were significantly prolonged by g-hydroxybutyrate. Seizures in SSADH-/- were abolished by, ethosuximide, and the GABABR antagonist CGP 35348 but returned as the drugs were eliminated. Atypical features of Absence seizures in this model are spike–wave (SWD) from thalamocortical origin, and are associated with vibrissal twitching and frozen immobility.

Conclusions: Seizures in SSADH null mice may be a useful tool to further investigate the molecular mechanisms involved in the pathogenesis of absence and generalized tonic clonic seizures associated with SSADH deficiency. (Supported by NINDS NS-40270, Bloorview Childrens Hospital Foundation.)

1.079

LONG-TERM BEHAVIORAL CONSEQUENCES OF LITHIUM-PILOCARPINE STATUS EPILEPTICUS INDUCED IN ADULT RATS

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Rationale: The lithium-pilocarpine (li-pilo) model of epilepsy is characterized by occurrence of spontaneous recurrent seizures (SRS) originating in a hyperexcitable circuit generated by the extensive lesions induced by status epilepticus (SE). These are mainly located in hippocampus, parahippocampal cortices, amygdala and thalamus. Many of these structures, also lesioned in humans, are involved in cognitive functions and anxiety and impact on patients quality of life. Here, we explored the performance of adult rats rendered epileptic by li-pilo SE in behavioral tasks reflecting spatial working memory, anxiety and object recognition.

Methods: 11 adult male rats survived li-pilo SE and 11 control rats received lithium and saline (li-saline rats). Li-pilo rats were observed until the occurrence of the first SRS and studied at 4–5 months later. Spatial working memory was tested in an eight-arm maze, anxiety in an elevated plus-maze and object recognition in a standard size cage. Neurons were counted on thionine brain sections obtained from the 22 animals sacrificed after the behavioral testing.

Results: In the elevated plus-maze, li-pilo rats entered more often and spent more time than li-saline rats in open arms, and made far more head-dips. In the eight-arm maze, the total time to enter all eight arms decreased over five days from 192 to 73 s in li-saline rats while it remained constant in li-pilo rats (171–230 s). In li-saline rats, the number of arms visited and the number of errors per session decreased over five days but remained unchanged in li-pilo rats. The total time, total number of arms visited per session and total number of errors per day were significantly higher in li-pilo than in li-saline rats. In the object recognition task, the two groups spent a higher median time sniffing the new object, reflecting a comparable novelty preference. Neuronal loss reached 47–90% in hilus, hippocampal CA1 area, basolateral and medial amygdala, piriform and entorhinal cortex.

Conclusions: These data confirm that in epileptic li-pilo rats, neuronal loss is extended in regions involved in memory such as hippocampus and entorhinal cortex which reflects the major impairments in spatial memory and the lack of strategy acquisition in the eight arm-maze also reported in rats with a shorter history of epilepsy. Likewise, the extended lesions in amygdala which mediates anxiety reflect the increase in the entries in open arms in the elevated plus-maze that are usually avoided by control rodents. In both tests, the animals were quite hyperactive reflecting a lack of goal-oriented activity. However, the performance in the object recognition task was similar in both groups which confirms previous data reporting that memory for objects is left relatively intact after hippocampal damage and appears to be spared even after a 5 months period of SRS. (Supported by INSERM grant U 398.)

1.080

A PARAMETRIC STUDY OF THE ANTIEPILEPTIC EFFECTS OF HIGH-FREQUENCY STIMULATION OF THE SUBSTANTIA NIGRA PARS RETICULATA IN A GENETIC MODEL OF ABSENCE EPILEPSY IN THE RAT

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Rationale: Pharmacological inhibition and high-frequency stimulation (HFS) of the substantia nigra pars reticulata (SNr) have been shown to suppress seizures in different animal models. The aim of the present study was to determine the most effective stimulation parameters to interrupt spike-and-wave discharges (SWD) by HFS of the SNr, in a genetic model of absence epilepsy in the rat (GAERS).

Methods: Nineteen male GAERS were stereotaxically implanted bilaterally with bipolar electrodes in the SNr and with monopolar epidural electrodes. After one week of recovery, the effects of either (i) isolated 5-s or (ii) continous bipolar HFS were investigated. For each conditions,

the effects of changes in the following parameters were determined: universus bilateral, mono- versus biphasic mode, frequencies and pulse widths.

Results: Bilateral isolated HFS with a frequency of 130Hz and a pulse width of 60us were the most effective to interrupt SWD at a threshold significantly different from intensity inducing motor side effects. However, repetition of such stimulations on 3 (+0,25) (monophasic) or 6 (+1,33) (biphasic) consecutive seizures, was found to become ineffective. At antiepileptic thresholds, continuous bilateral HFS (130Hz, 60us) did not suppress seizures. However when intensity was progressively increased by 5uA steps after each seizure, suppression of SWD could be obtained.

Conclusions: These results show that bilateral and biphasic isolated stimulation of SNr with a frequency of 130Hz and a pulse width of 60us interrupt absence seizures without motor side effects. Repetition of such stimulation leads to a loss of the antiepileptic effects. Continuous chronic stimulation has no significant effect. These results suggest that continuous stimulation protocols need to be further evaluated. (Supported by a ENS Fellowship, French Ministry of Research and Fondation pour la Recherche sur le Cerveau.)

1.081

ATTENUATION OF AMYGDALA-KINDLED SEZIURES IN RATS BY CONVECTION-ENHANCED DELIVERY OF ω-CONOTOXINS GVIA AND MVIIA

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Rationale: Convection-enhanced delivery (CED) permits safe and precise delivery of high-weight therapeutic agents (e.g., peptides, proteins, gene vectors) in therapeutically relevant concentrations into the brain (Bobo et al., 1994). Site-specific delivery of such agents may be an approach to the treatment of some forms of epilepsy. The present study tested if CED could be used to deliver highly selective N-type calcium channel antagonists of natural origin, ω-conotoxins GVIA (*Conus geographus*) and MVIIA (*Conus magus*), to attenuate seizures in rats that had been previously subjected to amygdala kindling.

Methods: Each rat was implanted with a combination of guide cannula and stimulation electrode into the right basolateral amygdala. Daily kindling stimulations continued until the kindling criterion was met (stage 5 seizures for at least five consecutive days). Then, the rats received four infusions of GVIA (vehicle, 0.005, 0.05, 0.5 nmol) or MVIIA (vehicle, 0.05, 0.15, 0.5 nmol) into the stimulation site. Each infusion (5 microL volume, 0.25 microL/min rate) was separated by at least two weeks. Electrophysiological (afterdischarge threshold and duration) and behavioral (seizure stage and duration) measures of amygdala-kindled seizures were recorded at 20 min, 24 hrs, 48 hrs, 72 hrs, 96 hrs and 1 week after the infusion.

Results: CED of vehicle failed to alter stimulation-induced afterdischarge threshold and duration. The vehicle also had no effect on the stage and duration of behavioral seizures. In contrast, infusions of GVIA resulted in a dose- and time-dependent attenuation of kindled seizures as reflected by significant increases in the afterdischarge threshold with accompanying decreases in the other measures of amygdala-kindled seizures. The protective effects of GVIA reached a maximum at 48 h post infusion and then gradually dissipated within the next five days. MVIIA also had protective properties. Compared to GVIA, the protective effects of MVIIA appeared to have more rapid onset.

Conclusions: These studies support the use of CED delivery of anticonvulsant peptides in the treatment of focal epilepsy. (Supported by ERS\NINDS\NIH.)

1.082

ATYPICAL HYPERTHERMIC SEIZURES IN RATS WITH FOCAL CORTICAL DYSPLASIA LEAD TO A PROGRESSIVE LOSS IN CEREBRAL VOLUME

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Rationale: The consequences of atypical febrile seizures on brain development remain poorly understood. It has been shown that patients with mesial temporal lobe epilepsy and a history of atypical febrile seizures in early life have a reduction of cerebral volume. Recently, we have demonstrated that a localized cortical microgyrus predisposes immature rats to atypical hyperthermic seizures (HS). The purpose of this study is to investigate the effect of HS in lesioned rats on the total cerebral volume (TCV) of the developing brain.

Methods: Freeze lesions (focal microgyri) were induced in the right fronto-parietal cortex of rats on postnatal day (P)1. HS were then induced at P10 by exposure to moderately-heated dry air. The TCVs were then estimated at P12, P22 and at P>60 using the method of water immersion volumetry. To evaluate the impact of the HS on the asymmetry between the hemispheres; hemispheric volumes at P22 were estimated using the Cavalieri method after having sectioned the brains and determined the area of each section using the public domain NIH Image program. The degree of hemispheric asymmetry was estimated by calculating a ratio between the volumes of the right and left hemispheres. Controls were sham-operated and naïve rats with and without HS (non-lesioned controls) and rats that only received the lesion (lesioned controls).

Results: At all ages, there was no difference in the TCV between non-lesion control groups. The TCV of lesioned controls (mean ± SD cm3; 0.65 ± 0.06, n = 8) differed from non-lesioned controls only at P12 where it was significantly smaller (0.76 ± 0.06, n = 26, $P < 0.001$). Although at P12 the TCV of lesioned rats with HS and lesioned controls were similar, the TCV of the former was significantly reduced at P22 (0.96 ± 0.05, n = 28) vs. (1.01 ± 0.05, n = 22, $P < 0.005$) and at P>60 (1.28 ± 0.08, n = 7) vs (1.46 ± 0.11, n = 7, $P < 0.01$), respectively. Regarding the ratio of the volumes between the hemispheres, there was no difference between the non-lesion controls therefore these results were pooled. This ratio, in lesioned rats with HS (0.96 ± 0.04, n = 9) was significantly smaller than that observed in these controls (1.00 ± 0.04, n = 17, $P < 0.05$). Lesioned controls had a smaller ratio than non-lesioned controls but this was not statistically different.

Conclusions: Our results show a progressive loss of cerebral volume and greater hemispheric asymmetry compared to controls in lesioned rats following HS. This indicates that atypical HS lead to an abnormality in brain growth. These results are in line with studies supporting that atypical febrile seizures may have adverse affects on the developing brain. (Supported by The Hospital for Sick Children Foundation, Epilepsy Canada/CIHR, The Ste-Justine Research Foundation.)

1.083

BRAIN DYNAMICAL DISENTRAINMENT FOLLOWING SUCCESSFUL ANTIEPILEPTIC DRUG TREATMENTS IN RAT AND HUMAN STATUS EPILEPTICUS

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Rationale: Nonlinear dynamical analysis of EEG has provided useful insights into the progressive preictal entrainment, and the subsequent postictal disentrainment of the epileptic brain's spatio-temporal EEG activity (*IEEE TBME* 2003;50:616–27). This transition at seizures is described as dynamical resetting of the epileptic brain (*IEEE TBME* 2004;51:493–506). We used nonlinear dynamical analysis of EEG data in a human status epilepticus (SE) patient and cobalt/homocysteine (Co/HCT) induced experimental SE in rats treated with antiepileptic drugs (AEDs) to test the hypothesis of dynamical resetting by AEDs.

Methods: Following the Co/HCT procedure described in (*Epilepsy Res* 1988;2:79–86), four male Sprague-Dawley rats (240–280 g) were induced into SE. EEG was continuously recorded and rats were AED treated with intraperitoneal diazepam (10 mg/kg) and phenobarbital (25 mg/kg) at SE stage I, III, or V (*Epilepsy Res* 1990; 5:49–60). EEG data from an episode of SE (stage III and IV) was recorded from a 6 year old patient treated unsuccessfully with rectal diazepam (10 mg) 18 minutes into the episode. He was subsequently treated successfully with intravenous lorazepam (0.1 mg/kg) 54 minutes into the episode. The rat and patient EEG data were analyzed using nonlinear dynamical techniques that use the convergence of the largest short-term Lyapunov

exponent over time at each electrode site to statistically quantify the brain's dynamical entrainment ($\alpha = 0.01$).

Results: The brain of all four rats was dynamically entrained before AED treatment. Two of the four rats were successfully treated (one at stage I and one at stage V). The successful AED treatment resulted in immediate brain dynamical disentrainment, whereas dynamical entrainment at focal electrode pairs (pairs including a focal electrode) remained in unsuccessful treatments. Similar results were found in the patient data. Focal electrode pairs remained entrained following the unsuccessful treatment of diazepam, whereas the successful treatment of lorazepam resulted in disentrainment at both focal and non-focal electrode pair sites within 10 minutes of the treatment and sustained for the remainder of the recording.

Conclusions: These results support the hypothesis of dynamical resetting of the epileptic brain following successful treatments with AEDs in both SE-induced rats and a human case. We have shown for the first time, a very good correspondence between measures defined from nonlinear analysis and clinical morphology of EEG with the treatment efficacy of AEDs in stopping status epilepticus. These results indicate that our measures may provide useful information about the state of the patient, as well as the evaluation and development of AEDs with maximum efficacy in dynamical resetting of the brain. (Supported by Barrow Neurological Foundation and NIH EB002089 BRP grant on Brain Dynamics.)

1.084
THE ROLE OF THE INHERITED BACKGROUND IN GAERS AND WISTAR AS ON THE CONSEQUENCES OF LITHIUM-PILOCARPINE INDUCED STATUS EPILECTICUS

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Rationale: The lithium-pilocarpine (Li-pilo) model in rats reproduces the main clinical, neuropathological, and developmental of human mesial temporal lobe epilepsy (MTLE). This model is characterized by an acute status epilepticus (SE) followed by a latent seizure free period and spontaneous recurrent seizures (SRS). Damage is present in hippocampus, thalamus, amygdala and ventral cortices. However, there is no indication on how an epileptic genetically inherited background could interfere with this model of MTLE. Therefore we induced Li-pilo SE in two strains of genetic epileptic rats, GAERS (Genetically Absence Epilepsy Rats from Strasbourg) which show non-convulsive absence epilepsy with spike-and-wave discharges (SWD) on the cortical EEG, and Wistar AS (AS) which display audiogenic convulsive seizures without paroxysmal activity on the EEG.

Methods: Adult male, 4–5 month-old, GAERS, AS, and genetically non-epileptic rats (NE) as controls were subjected to Li-pilo SE induced by LiCl (3 meq/kg) 18 h before pilocarpine (20, 18, and 12.5 mg/kg in NE, GAERS, and AS, respectively). SE-induced mortality was recorded and the number of neurons in regions of interest was counted six weeks after the first spontaneous seizure.

Results: 13/24 NE rats (54%), 32/40 GAERS (80%) and 34/41 AS (83%) died during SE. AS experienced severe generalized seizures with a tonic component. The latency to the first SRS was 39 ± 13 days in NE, 36 ± 11 days in GAERS and 9 ± 4 days in AS. In control conditions, the number of neurons was reduced in CA1 in GAERS and substantia nigra in AS, and increased in the hilus of GAERS and ventroposteromedian thalamus of GAERS and AS, compared to NE rats. Li-pilo SE led to damage which was most often similar in the three strains. Neuronal loss was severe in piriform cortex (90–99%) in the three strains, severe in thalamus (70–96%) of NE and GAERS and less marked in AS (53–81%), severe in the hilus of the dentate gyrus (41–55%) in the three strains, moderate in CA1 (47%) of NE and AS and less marked in GAERS (32%) and in entorhinal cortex and amygdala (17–36%) of the three strains.

Conclusions: These results show the high vulnerability of AS to the consequences of limbic SE with a very fast transfer of activation to the sensitive brainstem of this strain leading to lethal tonic seizures during SE and a rapid appearance of SRS. The extent and location of neuronal damage does not seem to depend much on the strain. In GAERS, the expression of SWD does not seem to be impaired by recurrent seizures but the final analysis of their duration and characteristics is still ongoing. (Supported by INSERM U405.)

1.085
LEVETIRACETAM INCREASES GLYCINE LEVELS IN PONS/MEDULLA OBLONGATA AFTER CHRONIC TREATMENT OF WISTAR RATS

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Rationale: The new antiepileptic drug levetiracetam is effective against various types of epileptic attacks including myoclonic seizures (1,2). Its mechanism of action is still not known. However, levetiracetam may influence glycinergic transmission (3). The aim of the present study was to investigate the effect of levetiracetam and two other commonly used antiepileptic drugs on amino acid levels in different brain regions.

Methods: Female Wistar rats were fed twice daily for 90 days through a gastric tube with either levetiracetam 50 mg/kg (n = 6), 150 mg/kg (n = 7), valproate 300 mg/kg (n = 7), phenytoin 75 mg/kg (n = 7) or control solution (n = 7). We looked for changes in the levels of amino acids in frontal cortex, parietal cortex, hippocampus, cerebellum and pons/medulla oblongata.

Results: Levetiracetam (50 and 150 mg/kg) produced a significant increase in the tissue level of glycine in pons/medulla oblongata, but not in the other structures. In contrast, valproate and phenytoin decreased glycine levels compared to the control group in pons/medulla oblongata.

Conclusions: Levetiracetam increased glycine levels in pons/medulla oblongata after chronic treatment. The increase in glycine levels by levetiracetam may contribute to augmentation of glycinergic neurotransmission in the brain stem, a structure believed to be important for the generation and control of myoclonus. This finding may help to explain the effect of levetiracetam on myoclonic seizures.

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1.086
EFFECT OF RECURRENT SEIZURES ON COGNITIVE OUTCOME FOLLOWING STATUS EPILEPTICUS IN IMMATURE RATS

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Rationale: While status epilepticus (SE) results in less brain damage in immature animals than mature animals, SE does predispose the immature brain to greater injury following a second seizure, the so-called "second-hit" phenomenon. Whether this increased vulnerability occurs immediately following the SE is not yet known. In this study we addressed the question of whether repeated seizures following status epilepticus in young rats has any effect on subsequent learning or memory.

Methods: Male Long Evans rats were divided into 4 groups at postnatal (P) day 10: SE induced by lithium-pilocarpine followed by 5 flurothyl-induced seizure for 5 days (P11-P15)(n = 11); SE followed by saline injections (n = 11); Sham SE followed by flurothyl-induced seizures (n = 6); and Sham SE followed by saline injections (controls)(n = 10). Flurothyl was administered by inhalation and animals were exposed until they had tonic seizures. At P30 animals were evaluated for visual-spatial learning and memory in the Morris water maze. Histological evaluations were performed following completion of the water maze testing.

Results: Lithium-pilocarpine resulted in SE in all animals with bilateral forelimb clonus, head nodding, and chewing. All animals learned

the position of the hidden platform over four days of testing. Animals subjected to SE followed by 25 flurothyl-induced seizures performed significantly worse than animals with SE only or flurothyl-induced seizures only ($p < 0.05$). No significant differences in motivation or swimming speed were found.

Conclusions: SE followed by recurrent flurothyl seizures results in greater impairment in visual-spatial memory than SE alone or flurothyl seizures alone. These findings demonstrate that despite the lack of SE-induced pathological lesions in immature animals, SE immediately predisposes the brain to subsequent seizure-induced cognitive impairment. These finding suggest that the time window for intervention following SE in the immature brain is limited. [Supported by The Western Massachusetts Epilepsy Awareness Committee and National Institutes of Health, NINDS (NS41495 and NS044296).]

1.087
ANALYSIS OF METABOTROPIC GLUTAMATE RECEPTORS 4 ABLATED MICE IN PILOCARPINE-INDUCED TEMPORAL LOBE EPILEPSY

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Rationale: Impaired hippocampal excitability constitutes a pathogenetic key aspect in temporal lobe epilepsy (TLE). Altered expressio) 5{of a variety of neurotransmitter receptors have been reported in human and experimental TLE. Metabotropic glutamate receptors (mGluRs) constitute a family of transmembrane domain receptors. Group III mGluRs (mGluR 4, 7 and 8) couple to cAMP-dependent signal transduction cascades, are localized presynaptically, and act to inhibit glutamate release at numerous central terminals. mGluR4 exhibits significantly increased expression in human epileptic dentate gyrus granule cells. Here, we have used mice with ablation of mGluR4 (mGluR4 KO) in order to study alterations with respect to hippocampal damage and the TLE phenotype.

Methods: Status epilepticus (SE) was induced by systemic application of pilocarpine to mGluR4 ablated as well as control mGluR4 +/+ mice. Seizure susceptibility was determined after induction of SE. The frequency and severity of chronic recurrent seizures is currently analyzed with a telemetric EEG system (DSI) and parallel video analysis. In order to study hippocampal damage, the amount of segmental hippocampal loss of neurons and gliosis were analyzed in mGluR4 KO mice after SE. Using real time quantitative RT-PCR, compensatory expression alterations of other mGluRs are excluded.

Results: mGluR4 KO mice exhibit a significantly reduced survival in response to pilocarpine treatment (mGluR4 KO 31%, $n = 16$, vs. controls 56%, $n = 9$; $p < 0.001$). Preliminary data indicate a higher incidence of stage IV seizures in mGluR4 KO mice after SE compared to controls. Histopathological comparisons revealed increased neuronal cell loss and gliosis in all observed hippocampal subfields in mGluR4 KO (CA1: mGluR4 KO 54%, controls 79%, $p < 0.05$; DG: mGluR4 KO 40%, controls 74%, $p < 0{,}05$; CA3 + CA4: mGluR4 KO 34%, controls 65%, $p < 0{,}001$; mGluR4 $n = 3$; control $n = 5$).

Conclusions: Our results indicate mGluR4 to be correlated with an attenuated epileptic phenotype and hippocampal damage. These data underline mGluRs to constitute interesting targets in order to interfere with hippocampal damage and epileptic attacks in TLE. [Supported by DFG (SFB TR3) and BONFOR.]

1.088
A FERRET MODEL OF MICROGYRIA: THE EFFECT OF VARYING LESION DAYS

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Rationale: In the rat freeze-lesion model of microgyria, there is a delay to onset of epileptogenesis and an apparent recovery that occurs selectively in animals lesioned on the day of birth as opposed to the first postnatal day after birth (P1, Jacobs *JNP* 1999; 81:159). In order to investigate mechanisms of hyperexcitability onset and recovery over an expanded period of development, we have created a model of microgyria in the more altricial ferret. An important difference between P1 and P0 in the rat is the presence of a greater number of layer IV neurons within the cortical plate. Anatomical experiments have shown that thalamic axons innervate the paramicrogyral cortex heavily, where layer IV cells are present while avoiding the microgyrus (Jacobs. *Epilepsy Res* 199; 36:165; Rosen *J Comp Neurol* 2000; 418:423). Hyperinnervation of paramicrogyral neurons by excitatory afferents has also been demonstrated, suggesting this may contribute to hyperexcitability that is selectively found adjacent to the microgyrus. We hypothesize that the greater proportion of layer IV neurons lesioned, the more epileptogenic the adjacent cortex will be and the less likely are the chances of recovery. We have tested this by altering the lesion day for the ferret and testing for the presence of epileptiform activity.

Methods: Transcranial freeze lesions were made in ferrets aged 0, 3, or 6 days after birth, by applying a rectangular probe 2×5 mm, at –70°C to the skull overlying occipital cortex for 6–10 seconds. Coronal slices were prepared from occipital cortex in ferrets aged 30 to 70 days. Field potential recordings were made in superficial layers in response to deep layer stimulation from 4–12 locations in each slice. Slices were subsequently fixed in 4% paraformaldehyde, resectioned at 60 μm, and stained with cresyl violet.

Results: Nissl-stained sections showed that at least one additional sulcus was created in freeze-lesioned ferrets. Microgyri surrounding the sulcus appeared similar to those in rats, having 4 layers and being bordered by a cell-sparse column of tissue. Heterotopia bordering the microgyrus were common in P3 lesioned cortex, while large ectopia above the pia were found in P6 lesions. In slices from control (unlesioned) ferrets, field potentials contained an early sharp negativity graded with intensity followed by a smaller amplitude, long lasting (typically 400 msec) negativity (N_2). Qualitative inspection showed that the amplitude of the N_2 component of the field was enhanced in slices from lesioned animals. Long latency events having characteristics of interictal-like epileptiform activity were seen in 100% of slices from P6 lesions, 10% of P3 lesions, 0% of P0 lesions, and 0% of controls ($n = 8$, 20, 4, and 24 respectively).

Conclusions: These results show that a lesion early in development produces a similar pattern of histopathology in gyral and lissencephalic cortex. The ferret model of microgyria will be particularly useful in studying mechanisms of epleptogenesis onset and recovery. (Supported by NIH grant NS045901 from the NINDS.)

1.089
MULTIPLE NEONATAL SEIZURES ATTENUATE SEIZURE-INDUCED $[Ca^{2+}]_i$ ELEVATIONS OF HIPPOCAMPAL NEURONS

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Rationale: An increase in intracellular Ca^{2+} concentration has been considered as a precursor of cell death mechanisms following seizures or other neurological insults. In order to determine whether protracted elevations of Ca^{2+} can occur during the neonatal period when the brain is relatively resistant to seizure-induced damage, we examined hippocampal $[Ca^{2+}]_i$ with Fura-2 AM imaging at times after single and multiple episodes of status epilepticus.

Methods: Kainic acid (KA) was administered s.c. once (1xKA) on P6 or P9 or P13 or three times (3xKA) on P6, P9, and P13 (2.2–2.5 mg/kg). Intracellular Ca^{2+} imaging of individual neurons in slices was performed with Fura 2 AM and $[Ca^{2+}]_i$ measured by the ratiometric method.

Results: In control slices, $[Ca^{2+}]_i$ was low at the three ages (51 ± 8 nM). After 1xKA, Ca^{2+} influx increased rapidly, peaked at 5 hrs (Table 1) and remained elevated above control levels for many hours at the three ages examined. Age-dependent patterns of seizure-induced Ca^{2+} uptake were observed such that the increase of $[Ca^{2+}]_i$ after seizures was more pronounced at P9 and P13 relative to P6 (Table 1). The time course for $[Ca^{2+}]_i$ decay also varied with age. At 20 hrs post-KA, $[Ca^{2+}]_i$ returned to baseline in slices prepared from P6 and P9 rats whereas P13 slices maintained peak $[Ca^{2+}]_i$ in all sub-regions that only diminished to control values at 30 hrs. Application of excitatory agonists showed marked increases in $[Ca^{2+}]_i$ relative to control responses in the same

sites that already showed elevated $[Ca^{2+}]_i$ at 5hrs post-KA. High NMDA responses in the presence of DNQX and TTX were particularly notable in CA1/subiculum and DG (140–270% of control) at the three ages. After 3 × KA, P13 slices had a comparatively lower seizure-induced $[Ca^{2+}]_i$ elevation (CA1: 157 ± 11 vs 274 ± 19; CA3: 95 ± 2 vs 241 ± 34; DG: 110 ± 5 vs 258 ± 23). Moreover, baseline $[Ca^{2+}]_i$ recovered more rapidly in all hippocampal sub-regions and in less than 20 hours post-KA.

Conclusions: A single episode of status epilepticus leads to protracted elevations of $[Ca^{2+}]_i$ that do not lead to neurotoxicity in neonates. In contrast, a seizure history consisting of multiple neonatal seizures induces tolerance by attenuating basal $[Ca^{2+}]_i$ elevations and reducing subsequent glutamatergic responses.

TABLE. *$[Ca^{2+}]_i$ at 5 hrs post-KA*

Age	CA1(nM)	CA3(nM)	DG(nM)
P6	225 ± 10	162 ± 19	216 ± 17
P9	333 ± 57	281 ± 63	325 ± 59
P13	273 ± 25	241 ± 29	258 ± 29

(Supported by New Jersey Neuroscience Institute.)

1.090

ASSOCIATION OF HIPPOCAMPAL DAMAGE WITH THE SEVERITY OF EPILEPTOGENESIS INDUCED BY FLUID PERCUSSION INJURY IN RAT

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Rationale: The contribution of hippocampal damage to the generation of chronic spontaneous seizures is under dispute. The aim of the study was to address this controversial question by examining whether the severity of neuronal loss and density of mossy fiber sprouting correlate with the seizure frequency in epilepsy induced by traumatic brain injury (TBI).

Methods: The recently developed rat model for post-traumatic epilepsy was used in the study. Epileptogenesis was induced in 18 rats by lateral fluid percussion injury (FPI). After FPI long term video-electroencephalographic monitoring was performed for 10 months to prove development of post-traumatic epilepsy and follow seizure frequency. The density of mossy fiber sprouting was analysed from Timm-stained sections. The loss of hippocampal neurons was assessed from thionin-stained sections.

Results: In the overall group of 18 traumatized animals the correlation was found between density of mossy fiber sprouting and hilar cell loss in hippocampus ipsilateral to trauma ($p < 0.01$). In the group of epileptic animals (9 out of 18) there was no correlation between density of mossy fiber sprouting and hilar cell loss. Further, no correlation between seizure frequency and density of mossy fiber sprouting or seizure frequency and hilar cell loss was found in the epileptic group. In contrast to that, there was a clear correlation between seizure frequency and overall hippocampal damage (dentate gyrus+CA3+CA1) both ipsilaterally ($p < 0.05$) and contralaterally ($p < 0.05$).

Conclusions: Our data indicate that the overall neuronal damage in the hippocampus after fluid percussion injury in rat can contribute to the occurance of chronic spontaneous seizures and the severity of post-traumatic epilepsy. (Supported by Academy of Finland, CIMO, EU-CARE, Sigrid Juselius Foundation.)

1.091

VITAMIN D INDUCES THE EXPRESSION OF CALBINDIN D28k AND DELAYS SEIZURE-INDUCED LOSS OF CALBINDIN D28k IN THE HIPPOCAMPUS OF RATS: A POSSIBLE MECHANISM OF NEUROPROTECTION

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Rationale: Calbindin is a 28 kDa calcium-binding protein expressed in restricted neuronal populations in the mammalian brain where it may play a role in protecting neurons against excitotoxic insults. Recent findings indicate that vitamin D can induce the expression of calbindin D28k in kidney, but chronic treatment results in a clinically mild hypervitaminosis can not affect the content of calbindin-D28k in the cerebral cortex and hippocampus. Calbindin D28k immunoreactivity decreased in the CA1/CA2 fields 1 and 3 days after kainic acid-induced seizure, and was lost extensively in the pyramidal layer 10 days after seizure, but the exact role of calbindin D28k in the hippocampus has been unknown. To evaluate the function of calbindin D28k in the hippocampus, we investigated whether Mega-dose vitamin D can induce the expression of calbindin D28k in the neurons of the hippocampus and examined the changes of calbindin D28k during lithium-pilocarpine-induced status epilepticus (LPSE) and the neuronal damage in the hippocampus 72 hours after seizure.

Methods: Vitamin D (1 μg/kg/ml) was administered daily intraperitoneally in Sprague-Dawley rats for 7 days and ethanol (1 μl/kg/ml) was injected as control. Lithium chloride (3 mEq/kg) followed 24 h later by pilocarpine (35 mg/kg) was administered intraperitoneally 7days after vitamin D treatment. The expression of calbindin D28k was assessed by immunohistochemistry ($N = 3$, each group) and Western blot ($N = 3$, each group) in the hippocampus isolated at various times (0, 4, 8, 24 hours) after LPSE. Neuronal injuries were assessed by cresyl violet stain ($N = 6$, each group).

Results: Calbindin D28k immunoreactivity was increased in dentate granule cells, the pyramidal cells of the CA1/CA2 area of the hippocampus in the vitamin D group than that of the control group. The control group showed decreased calbindin D28k immunoreactivity in the CA1/CA2 areas 4 and 8 hours after LPSE, and extensively in the pyramidal layer 24 hours after seizure, whereas the vitamin D group revealed that Calbindin D28k immunoreactivity maintained in CA1/CA2 areas until 24 hours after seizure. The neuronal injury by cresyl violet stain at 72 h after the LPSE was more severe in CA1 area of the control group than that of the vitamin D group.

Conclusions: Vitamin D induced calbindin D28k in the pyramidal cells of CA1/CA2 areas of the hippocampus and delayed the seizure-induced loss of calbindin D 28k. Also vitamin D had neuroprotective effect in the pyramidal cells of CA1/CA2 areas of the hippocampus. These findings suggest that neuroprotective effect of vitamin D may be mediated partially by induction of calbindin D28k.

1.092

THE VOLTAGE-DEPENDENT CALCIUM CHANNEL SUBUNIT, CACNG4, IS ASSOCIATED WITH ABSENCE SEIZURES AND EXPRESSED IN THE THALAMUS

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Rationale: Stargazer mice are mutated in the *Cacng2* gene and have frequent spontaneous absence seizures. In addition to *Cacng2*, there are seven closely-related genes encoding CACNG (gamma) proteins. We have focused our studies on the CACNG4 protein as it is closely related to CACNG2 and is expressed in the brain. By introducing a lacZ targeted mutation into the *Cacng4* gene, we were able to both disrupt the gene and follow chimeric protein expression in the mouse brain.

Methods: We introduced the LacZ gene into the carboxy terminus of *Cacng4* and generated homozygous mice with the targeted deletion of the *Cacng4* gene. This mutation was combined with the *Cacng2* mutations in the stargazer, waggler and stargazer3J allelic series. EEGs were recorded from implanted electrodes to measure spontaneous absence seizure activity. Brain sections were stained with X-Gal to reveal the regions with LacZ (beta-galactosidase) activity.

Results: The homozygous *Cacng4* targeted mutant appeared normal and had no absence seizure activity. However, by constructing double mutants carrying both this mutation and a mutation in the *Cacng2* gene, we were able to detect increased seizure activity compared to the single mutants. The LacZ staining revealed that the chimeric gamma4 –LacZ protein is expressed, especially in the caudate putamen, the

habenulae, the inferior colliculus, the CA3 region of the hippocampus and the Purkinje cell layer of the cerebellum. Staining was also observed within the thalamus, but there was no staining within any of the cortical regions.

Conclusions: The *Cacng4* targeted mutant revealed no obvious phenotype, including no incidence of seizures. However when this mutation was introduced onto the *Cacng2* mutant background, the double homozygotes had increased absence seizure activity indicating that the CACNG4 protein does have a role in seizure suppression but this could only be revealed in a compromised *Cacng2* background. *Cacng4* is expressed in the thalamus, and this region, along with the cortex, has been implicated in the etiology of absence seizures. [Supported by NS32801 (V.A.L.).]

1.093

GABA RECEPTOR SUBUNIT AND NEUROPEPTIDE-Y EXPRESSION DO NOT DIFFER IN BRAINS OF RATS WITH GENETIC ABSENCE-LIKE EPILEPSY COMPARED WITH NON-EPILEPTIC CONTROL RATS

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Rationale: Genetic Absence Epilepsy Rats of Strasbourg (GAERS) are a well-validated model of absence epilepsy. Like the human condition, the nature of the underlying defect resulting in the epileptic phenotype in GAERS is still unknown, but the inhibitory neurotransmitter GABA has been implicated and neuropeptide Y (NPY) may be important. We investigated whether there was a regional localization of specific GABA receptor subtypes or NPY in brain structures involved in generating epileptiform activity in GAERS vs. non-epileptic control (NEC) rats.

Methods: Male GAERS and NECs were given a 30-minute EEG recording to verify animal phenotype. Regional localization of NPY and GABA receptor subtypes; $GABA_A$ gamma$_2$, $GABA_A$ alpha2 and $GABA_B$ was compared in brain sections of GAERS ($n = 7$) vs. NECs ($n = 6$) using immunohistochemistry. Staining was graded by a blinded observer on a scale of 0–4 for the following brain regions important in thalmocortical circuitry: reticular thalamus, ventrobasal thalamus, centromedial thalamus, inferomedial thalamus, superomedial thalamus, dorsal thalamus, and somatosensory cortex.

Results: Moderate to high levels (Grade 2–4) of neuronal staining was seen in all thalamocortical areas examined for all GABA receptor subtypes and for NPY. However, no significant differences were found between GAERS and NECs in staining for the GABA receptor subtypes or for NPY for any of the brain regions examined (all $p > 0.05$).

Conclusions: The demonstrated lack of difference in the topographic pattern of staining for GABA receptor subtypes or NPY between GAERS and NEC rats, suggests that alterations in their expression is unlikely to be a major contributor to the epileptic phenotype of GAERS. (GABA receptor antibodies were a gift of Professor W Sieghart, University of Vienna, Austria.)

1.094

ABSENCE OF MOSSY FIBERS IN NEUROD/BETA2 NULL MICE PREVENTS PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: Neurod/beta2 is a basic helix loop helix transcription factor required for granule cell determination and differentiation. Anatomically, homozygous neurod/beta2 (ND) null mice show a complete lack of granule cells in the dentate gyrus and a neurological phenotype of spontaneous limbic epilepsy. While studying the mechanisms of neuronal plasticity caused by this striking defect, we observed that these mice are resistant to all but lethal doses of pilocarpine, while displaying normal sensitivity to kainate-induced seizures. This phenotype has also been described in mice deficient in the gene for the m1 muscarinic receptor, the molecular target of pilocarpine (Hamilton et al., 1997). We therefore investigated the cholinergic innervation of the ND hippocampus to determine whether the loss of granule cells, an important target of hippocampal cholinergic synapses, resulted in a decrease in m1 receptor expression.

Methods: Homozygous adult ND and +/+ mice were injected with either kainate (40–45 mg/kg) or pilocarpine (250–370 mg/kg) and monitored behaviorally and with EEG recordings. M1 receptor (Alomone, Israel), VAChT (R Edwards, UCSF), CAT (Chemicon, CA), BrdU (Boehringer Mannheim, IN) immunohistochemistry were performed using specific antibodies. Septal cholinergic neurons were injected with DiI (Molecular Probes, OR) and terminal innervation patterns were examined by microscopy.

Results: ND mice showed typical status epilepticus when injected with kainate at doses effective in +/+ mice. Pilocarpine in doses up to 370 mg/kg i.p. failed to initiate *status epilepticus*. M1 receptor immunohistochemistry revealed apparently normal levels of receptor expression in hippocampal pyramidal cell layers, neocortex, and other brain regions. DiI tracing studies show that cholinergic axons make some direct contacts onto cells in the CAP region. Although the number of cholinergic neurons in medial septum was normal, there was a large overall decrease in hippocampal terminal innervation.

Conclusions: Despite the presence of M1 receptors, ND mice are resistant to pilocarpine-induced *status epilepticus*. This strongly implies that pilocarpine-induced activation of the CA3 pyramidal cells alone is insufficient to produce prolonged seizures, and that intact hippocampal circuitry, including cholinergic innervation of a normal dentate granule cell-CA3 pathway is necessary for sustaining the prolonged seizures triggered by this muscarinic agonist. [Supported by National Institutes of Health (NIH) grants 29709 (J.L.N.) and FAPESP (M.M.).]

1.095

AUTOMATED SLEEP-WAKE STATE DISCRIMINATION IN CHRONICALLY IMPLANTED ANIMALS USING ELECTROPHYSIOLOGICAL AND KINEMATIC VARIABLES

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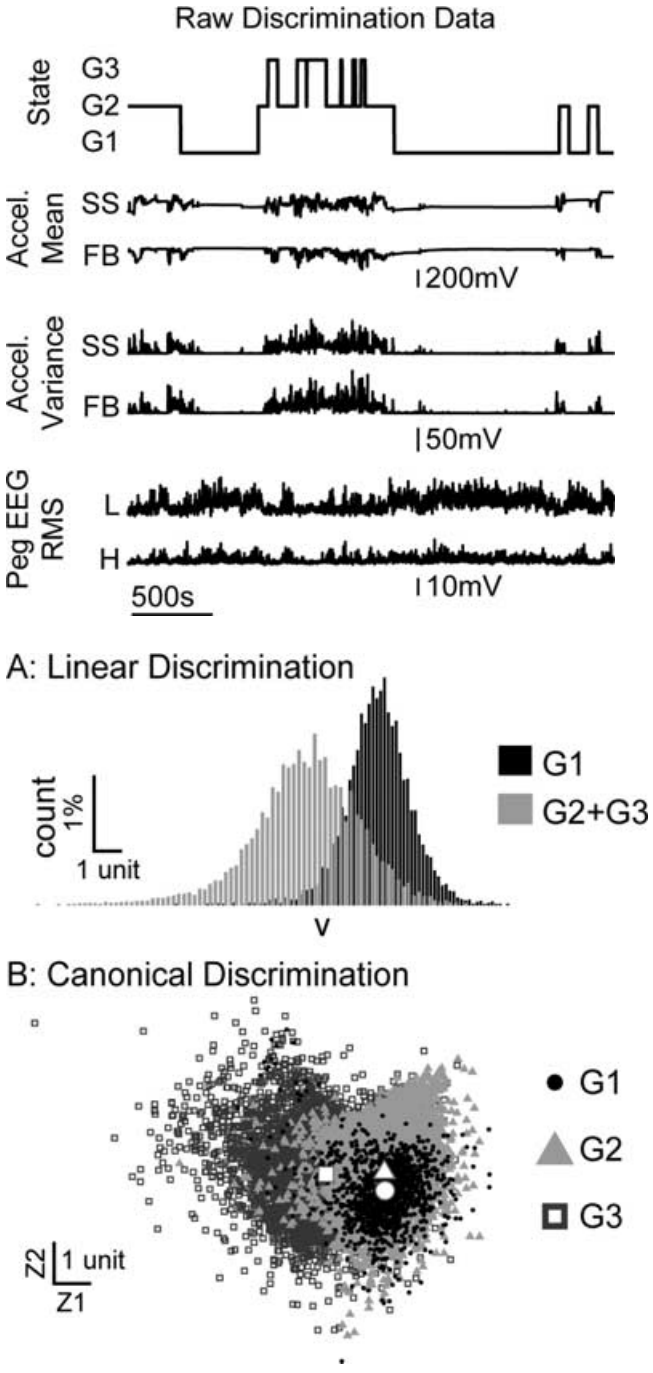
Rationale: Automated sleep-wake state discrimination is required for real-time seizure prediction, detection, and control. We present a novel method for state discrimination in chronically implanted rats by introducing kinematic data utilized with EEG. The methodology uses automated analysis of head acceleration, along with epidural and hippocampal depth EEG using integrated power of low (< 10Hz) and high (> 10Hz) frequencies.

Methods: Procedures were carried out under GMU ACUC approval. Male Sprague-Dawley rats (300g) were anesthetized and implanted with electrodes into both hippocampi, and with 5 epidural screws, with differential EEG recorded. Head acceleration and tilt were measured with a double axis DC-accelerometer, and behavior documented with a low-light camera. Starting 1 week post-operatively, recordings were made for 24h, and stored in digital format for later processing. 1s epochs were chosen for data reduction.

Results: Multivariate linear discriminant analysis was used for classification of groups: stationary-not-moving (G1), stationary-moving (G2), exploratory (G3). State identification over time was independently obtained from video inspection (Fig 1 top). Discrimination variables included mean and variance for each accelerometer axis (front to back, FB; side to side, SS), and EEG power quantified in low (L) and high (H) frequencies. Combining groups 2 and 3, linear discrimination demonstrated that the 2 states were significantly different ($p < 0.001$ histogram Fig 2A), although the overlap and error rate was considerable. The scatter plot of the canonical discriminant functions for 3 states is shown in Fig 2B, demonstrating significantly reduced overlap and error rates.

Conclusions: We show that the addition of accelerometer data and multivariate discrimination analysis can improve automated sleep-wake



state classification. This methodology will be applied to real-time state discrimination in epileptic rats submitted to adaptive electric field stimulation, allowing the refinement of algorithms to detect, predict, and control seizures. (Supported by NIH grants R01EB001507, K02MH01493, and R01MH50006.)

1.096

MOSSY CELL AXON SYNAPTIC CONTACTS ON ECTOPIC GRANULE CELLS THAT ARE BORN AFTER PILOCARPINE-INDUCED SEIZURES

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Rationale: Granule cell (GC) neurogenesis increases following seizures, and some newly born GCs migrate to abnormal locations within the hilus. These ectopic GCs (EGCs) display robust evoked potentials in response to perforant path stimulation, comparable in intensity to what is observed with GC layer GCs. However, EGCs which migrate into central portions of the hilus and have dendrites almost exclusively restricted to the hilus display significantly longer latencies, suggesting the involvement of polysynaptic pathways. Mossy cells would seem to be a prime candidate for involvement in these pathways. They normally provide feedforward excitation to GCs through connections in the inner molecular layer (IML), and many survive pilocarpine-induced seizures. Electron microscopic (EM) immunolabeling was therefore used to determine if mossy cell axon terminals synaptically contact hilar EGC dendrites.

Methods: Pilocarpine (380 mg/kg i.p.) was given to adult male Sprague-Dawley rats 30 min after atropine methylbromide (1 mg/kg s.c.). Diazepam (5 mg/kg i.p.) was given 1 hr after the onset of status epilepticus. Over 1 month later, after spontaneous seizures developed, animals were transcardially-perfused, and hippocampal sections were processed for dual EM immunolabeling. Mossy cell axon terminals were immunoperoxidase-labeled with an antibody to calcitonin gene-related peptide (CGRP) (Peninsula, 1:5000) and EGC postsynaptic processes were immunogold-labeled with an antibody to calbindin (CaBP) (Sigma, 1:200). Controls were treated the same, except that pilocarpine was replaced by saline.

Results: Light microscopically, large CGRP-immunoreactive (-IR) cells were seen in the hilus, in both control and experimental tissue. These cells had the appearance and distribution of mossy cells. Diffuse labeling was concentrated in the hilus, and the inner IML, although this labeling appeared to be lighter in experimental tissue. EM analysis revealed numerous CaBP-IR dendrites in the hilus of experimental animals. In addition, CGRP-IR axonal terminals were observed forming synapses with CaBP-IR dendrites.

Conclusions: Within the hilus of pilocarpine-treated animals, excitatory axonal processes must reorganize to form functional synaptic connections with EGC dendrites as they develop, since EGCs display robust responses to perforant path stimulation. The fact that CGRP-IR terminals can be seen synaptically-contacting CaBP-IR dendrites strongly suggests that mossy cells participate in the polysynaptic curcuits which support the longer latency potentials that are observed. These types of polysynaptic connections could support recurrent excitation, and thus potentially affect seizure threshold. (Supported by NS 41490.)

1.097

ANTIEPILEPTIC EFFECTS OF BRIEF ELECTRICAL STIMULATION OF LIMBIC STRUCTURES IN KINDLED RATS

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Rationale: Different procedures of deep brain and cortical stimulation have been proposed in the treatment of drug resistant epilepsy, including electrical stimulation of the epileptogenic zone proper, such as the hippocampus, without consensus regarding their respective efficacy. One of the major limitations in designing such study and defining the optimal stimulation parameters is the paucity of experimental data. The aim of this study was to evaluate various parameters which could influence the anti-epileptic efficacy of brief electrical stimulation applied to the limbic structures of kindled rats.

Methods: Forty Sprague-Dawley rats were used in this study.

Experiment 1: Ten rats received a fully complete stage 5 hippocampal kindling. They then underwent 60 additional stimulation-induced seizures at 3 days interval, during which a second brief electrical pulse (50 ms duration, intensity twice that of after-discharge threshold) was applied 5 seconds after the end of the first stimulation. In each animal, this pulse was either applied to the hippocampus, to the entorhinal cortex, or was replaced by sham stimulation.

Experiment 2: Thirty rats were fully kindled in the amygdala, and then also underwent additional stimulation-induced seizures during which a brief electrical stimulation was applied in the same amygdala 5 seconds later. Animals were distributed in 5 groups: G1: stimulation with a single pulse of 50 ms, G2: stimulation with a single pulse of 130 ms, G3: 50 Hz stimulation during 1 second, G4: 130 Hz stimulation during 1 second, G5: sham stimulation.

The duration of after-discharges was used as the endpoint measure in both experiments.

Results: Experiment 1: A significant reduction of hippocampal after-discharges duration was associated with the delivery of brief electrical pulse in the hippocampus (96 ± 22 sec, $p < 0.01$), but not in the entorhinal cortex (103 ± 27 sec), as compared to controls (113 ± 28 sec).

Experiment 2: Two types of brief electrical stimulation were associated with a significant reduction of the duration of amygdala after-discharge, i.e. single pulse of 130 ms duration (101 ± 8 sec, $p < 0.0001$), and 50 Hz stimulation of 1 second duration (89 ± 14 sec,$p < 0.00001$) as compared to sham stimulation (114 ± 11sec).

Conclusions: In the kindling model of epilepsy, brief electrical stimulations delivered after the onset of stimulation-induced after-discharge can reduce the duration of the latter. This proved to be more effective when applied to the site of seizure onset than to a connected distant site, with 50 Hz rather 130 Hz 1 second duration train, and with 130 ms rather than 50 ms duration single pulse. (Supported by Universite Claude Bernard Lyon 1.)

1.098

NEUROBEHAVIORAL MATURATION OF RAT OFFSPRING BORN FROM EPILEPTIC DAMS

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Rationale: It has been reported that female rats exposed to lithium-pilocarpine (li-pilo) status epilepticus (SE) and exhibiting spontaneous recurrent seizures (SRS) display a complete absence of maternal behavior. This lack of maternal behavior was partly attributed to the neuronal damage induced by SE. Therefore, in the present study we explored the neurobehavioral maturation of rat offspring born from control dams and dams rendered epileptic by li-pilo SE using different behavioral tasks.

Methods: Nine adult female rats were subjected to li-pilo SE and 28 control rats received lithium and saline instead of pilocarpine. Li-pilo-exposed rats were observed until the occurrence of the first spontaneous seizure. All rats were mated and 8 and 27 viable litters corresponding to 61 and 257 pups were obtained from li-pilo and li-saline females, respectively. Then, the litters were cross-fostered to obtain control pups raised by li-pilo (control/li-pilo) or control dams (control/control), li-pilo pups raised by li-pilo (li-pilo/li-pilo) or control dams (li-pilo/control). Pups were tested for the following performance: static righting reflex at P4 and P5, antigravity reaction at P9, suspension duration at P10, locomotor coordination at P18 and open field at P19.

Results: The frequency of seizures of li-pilo dams was quite similar before and during pregnancy, i.e. 2–10 per week. In the group of pups raised by li-pilo dams, almost none survived because of the lack of maternal behavior and feeding, leading to undernutrition and dehydration. In the three other groups of rats, the weight of pups was similar in control/control and li-pilo/control pups while the lack of maternal behavior of li-pilo dams induced a delay in weight gain of control/li-pilo pups until weaning. In all tests, the performance of li-pilo/control pups was highest followed by control/control pups and by control/li-pilo pups. In the static righting reflex, the antigravity reaction, suspension test and locomotor coordination, li-pilo/control pups performed significantly better than the two other groups. In the open field, the spontaneous locomotion of the two groups of pups raised by control dams was faster while activity of control/li-pilo pups was reduced in this test.

Conclusions: The data of this study emphasize the cardinal role of the mother-pup interaction in the development of neurobehavioral abilities of the rats. Indeed, control pups raised by li-pilo dams do not develop as well as control congeners raised by control dams while li-pilo pups are able not only to perform and develop as well as control pups raised by control dams but even better than the latter group. This difference may originate in the stress that these animals are exposed to in utero as a result of the spontaneous seizures of the pregnant dam. Indeed, prenatal stress was shown to alter neurotransmitter systems and brain development and to be counteracted by cross-fostering. (Supported by INSERM U 398.)

1.099

GABA-A α3-SELECTIVE BENZODIAZEPINE AGONISTS ARE ANTI-CONVULSANT BUT TOLERATED LIKE DIAZEPAM

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Rationale: Classical benzodiazepines (BZs) are extremely efficacious anti-convulsants but suffer from a number of serious side effects. Sedation, amnesia and abuse potential all limit their use in a clinical setting. However, the main reason benzodiazepines are not more widely used to treat epilepsy is because their effects tolerate with chronic dosing. BZs bind to 4 subtypes of GABA-A receptor (those containing an α1, α2, α3 or α5 subunit in combination with a γ2) and recent work has shown that the different functional properties of BZs can be assigned to certain subtypes. The subtype(s) that mediate the anti-convulsant and tolerance effects of BZs have not been studied in detail. Here we have investigated the properties of an α3-selective BZ agonist, TP003.

Methods: Three seizure models were used: mouse pentylenetetrazol (PTZ), mouse maximal electroshock (MES) and rat amygdala kindling (AK). Mice were pre-treated with TP003 (0.3–5 mg/kg p.o.) and then 30 minutes later either dosed with 120 mg/kg s.c. PTZ or given a trans-auricular shock (20 mA, 100 Hz, 1.5 sec). Seizures were scored on a modified Racine scale for the PTZ and as protection from tonic seizures for the MES. For the amygdala kindling unilateral electrodes were implanted and daily stimulations were given to elicit AK. Once kindled to stage 5 seizures, TP003 (0.3–5 mg/kg p.o.) was administered 30 minutes before stimulation and behavioural and electrical seizure activity measured. The tolerance experiment involved daily dosing of TP003 or diazepam and stimulations were carried out 30 minutes after drug dosing.

Results: TP003 dose-dependently decreased PTZ, MES and AK seizures after acute dosing to a similar extent to that seen with the standard BZ diazepam. In the chronic dosing experiment TP003 was anti-convulsant on day 1 of testing, but by day 3 the anti-convulsant effects had largely tolerated. In contrast diazepam still produced a robust anti-convulsant effect.

Conclusions: α3-selective BZ agonists display equivalent anti-convulsant efficacy to those of the non-selective BZ diazepam following acute dosing. However, like non-selective BZs, they show tolerance on chronic dosing. (Supported by Merck Sharp & Dohme.)

1.100

NEURONAL INJURY IN THE DEVELOPING RAT BRAIN FOLLOWING VARYING DURATIONS OF STATUS EPILEPTICUS

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Rationale: Studies in adult rats have shown neuronal injury following status epilepticus (SE) for periods as brief as 20 min. High dose pilocarpine or Li-Pilocarpine (LiPC) results in SE that lasts several hours. We have previously demonstrated that LiPC-SE that is allowed to endure uninterrupted causes widespread neuronal injury in the developing rat brain and subsequent epilepsy that is a function of the age. Here, we examine the role that the duration of SE has in the immature rat brain.

Methods: P14 Wistar rats were pretreated with 3mEq/kg LiCl (i.p.) 16–24 hr prior to induction of SE with pilocarpine (s.c.).The following day, rats were implanted with cortical electrodes and monitored for the onset and termination of SE. After 30 or 90 min, electrographic SE was terminated with i.p injections of diazepam (10 mg/kg) and phenobarbital (25 mg/kg). Rats were monitored overnight and perfused with 4% paraformaldehyde 24 hr after cessation of SE. Control, non-seizure

animals were given AEDs following the same durations after saline injections. Brains were processed for routine histological examination for acute neuronal injury using hematoxylin/eosin or Fluoro-Jade B.

Results: Pilocarpine resulted in a rapid onset of behavioral alterations followed by cortical electrographic SE in the 2 week old rats (13.5 +/- 1.2 min). High dose diazepam/phenobarbital was effective in terminating SE (13.0 +/- 5.3 min after administration). Only scattered damage was seen after 30 min of SE. While 90 min of SE resulted in more injury to the principal cells of the hippocampus, the most extensive labeling was seen in extra-hippocampal structures, primarily the amygdala and dorsal thalamus.

Conclusions: Previous studies in 2 week old rats revealed widespread neuronal injury when LiPC-SE was allowed to proceed without disruption. In particular, the presence of CA1 injury and the absence of hilar damage was especially prominent in these animals with 25% of the population going on to demonstrate spontaneous seizures. Here, we show that terminating SE after even 30 min greatly attenuates the subsequent injury at this developmental stage. Additionally, as SE continues for longer periods, exta-hippocampal structures suffer more extensive damage prior to that seen in the hippocampus. Whether this duration of SE and the resulting pattern of injury are sufficient to induce epilepsy is under investigation. [Supported by NS046516 (R.S.) and the DAPA Foundation.]

1.101

HIPPOCAMPAL PRESERVATION WITH EXTRAHIPPOCAMPAL DEGENERATION AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS FOLLOWED BY PENTOBARBITAL ANESTHESIA

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Rationale: The goal of this study was to modify the pilocarpine model to allow an examination of the effects of extrahippocampal but not hippocampal degeneration. To this end, pilocarpine-induced status epilepticus was induced, and then status was abbreviated by anesthesia. We hypothesized that anesthesia would reduce the typical pattern of hippocampal degeneration that follows pilocarpine-induced status epilepticus, but not necessarily block damage in other vulnerable areas of the brain.

Methods: Adult male Sprague-Dawley rats (~200 g) were pretreated with atropine methylbromide (1 mg/kg i.p.) and 30′ later with pilocarpine hydrochloride (380 mg/kg i.p.). Status epilepticus was truncated at different times and with different anesthetics (pentobarbital, phenobarbital, ketamine) systematically. Animals were sacrificed 1 day, 3 days, 1 wk, or 1 month after status. Fluorojade, silver degeneration, or immunocytochemistry (NeuN, neuropeptide Y) was conducted on 50 μm sections after 4% paraformaldehyde transcardial perfusion.

Results: Only pentobarbital protected the hippocampus consistently (n = 11/13 rats; 20 mg/kg i.p. within 10′ of the onset of status and 10 mg/kg i.p. 50′ later), and only if anesthesia began <70′ after status onset (or, if anesthesia began between 70′ and 120′, head bobbing stopped by 20′). Animals not reaching these critieria had hippocampal damage (n = 11/11). Protected hippocampi showed no fluorojade or silver degeneration of principal cells. But extrahippocampal damage occurred, and had a specific pattern, including entorhinal cortex (mostly medial layers III & V/VI), lateral amygdala, perirhinal cortex (mostly deep horizontal cells), anterior dorsal midline thalamus, piriform and endopiriform nuclei (mostly deep layers), and basal hypothalamus. A few subicular pyramidal cells were degenerated in dorsal sections of 5/11 rats with protected hippocampi. In the 2 exceptional rats (anesthetized as above, but hippocampal damage occurred), hippocampal damage was restricted to dorsal CA1and subicular neurons. At 1 month, animals that reached criteria for anesthesia demonstrated degeneration in the same areas as animals killed at 1 or 3 days, but there was more terminal degeneration within these regions; hippocampal pyramidal cells remained protected.

Conclusions: The hippocampus can be preserved after systemic pilocarpine if status is limited, yet specific extrahippocampal sites sustain damage even after these minimal periods of status. Results at 1 month indicate a possible progression of damage within extrahippocampal areas, but the results may also be explained by protracted neuronal death. Regardless, the hippocampus remained protected at 1 month, suggesting that this method can be used to produce an animal model of extrahippocampal damage. (Supported by NS 16109.)

1.102

GENETIC REGULATION OF ADULT NEUROGENESIS IN THE DENTATE GYRUS OF INBRED STRAINS OF MICE

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Rationale: Previous studies have suggested that genetic factors can modulate adult hippocampal neurogenesis (Zhao et al., 2003; Kempermann and Gage, 2002). However, the links between perturbations in neurogenesis and genomic control are unclear. To investigate the degree to which genetic strain differences influence adult dentate granule cell neurogenesis and the stage(s) of the neurogenic program that is affected, we examined proliferating progenitor cells and their progeny in young male FVB/N and C57BL/6 mice using the thymidine analog, bromodeoxyuridine (BrdU).

Methods: Six-week old male C57BL/6 and FVB/N mice were obtained and given two daily BrdU injections, 6 hours apart, and were killed 1 hour, 3 days, 7 days, 14 days or 28 days following the last BrdU injection to allow for discrimination between proliferation and cell survival. Stereologic analysis of the numbers of BrdU-immunoreactive cells in the dentate gyrus by immunohistochemistry and immunofluorescence was performed to assess the number of proliferating dentate granule cells. Colocalization of BrdU immunoreactivity with an immunoreaction for either the neuronal cell marker, NeuN, or astrocytic marker, GFAP, was investigated to determine the phenotype of newborn cells.

Results: In both strains, we found adult hippocampal neurogenesis and identified strain differences in proliferation. While numerous BrdU immunoreactive cells were detected in the dentate gyrus in both strains of animals, stereologic analysis of the numbers of BrdU-immunoreactive cells revealed a strain difference with significantly higher cell proliferation and net neurogenesis in C57BL/6 mice. Qualitatively, the appearance and general distribution of BrdU-labeled cells did not differ between the strains. In addition, no strain differences were observed in the relative ratio of neurogenesis versus gliogenesis. The number of BrdU-labeled cells 28 days after the last injection of BrdU was used to estimate the survival of newborn cells in the dentate gyrus. Regardless of strain, the number of BrdU-positive cells at 28 days after injection was similar.

Conclusions: These results suggest that genetic background can influence proliferative activity in the adult hippocampus. While results from this study imply that genetic factors that are presumably divergent between the two strains can modify the neurogenic response, it is, as yet, unclear which genes are responsible for regulating this response. Future studies will address cellular and genetic mechanisms that may contribute to strain-dependent differences in the neurogenic program. An understanding of the role of cellular proliferation as it relates to the development and maintenance of epilepsy may provide novel avenues for therapeutic interventions. (Supported by NIH grant NS04763 to P.E.S.)

1.103

EFFECT OF DEEP BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS IN LITHIUM-PILOCARPINE STATUS EPILEPTICUS OF RATS: THE FUNCTIONAL ANATOMY USING FOS IMMUNOHISTOCHEMISTRY

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Rationale: Currently, STN is presented as a new target of DBS for the anticonvulsant treatment, but its exact mechanism and route of action has not been elucidated yet. Seizure-induced Fos protein expression has been used extensively to identify spatially and temporally distributed neural systems activated by seizures. We investigated the effect of STN stimulation on the development and propagation of seizures in the rats with lithium-pilocarpine induced status epilepticus in course of disclosing its functional anatomy.

Methods: Bipolar electrodes were inserted on the bilateral STN 7 days before pilocarpine injection (30 mg/kg) with lithium pretreatment. After conditioning electrical stimulation (about 3min), both pilocarpine injection and STN DBS was provided to rats under the EEG recording (group A, n = 15) with only injection on sham group (group B, n = 10). Time to first discrete spikes, clinical seizure onset and seizure patterns (limbic seizure and/or generalized convulsion) were analyzed and the electrical stimulation was continued for 30, 60, 90, 120, 150 minutes after its first discrete spikes. After stimulation, the rats were immediately killed for immunohistochemistry and histologic examination.

Results: Marked prolonged latency for discrete spikes was seen in the group A (41.3 ± 20.7 min vs. 30.0 ± 7.8 min in group B) ($p < 0.01$). All rats showed discrete spikes and clinical seizures by 90minutes after pilocarpine injection, but only 6 rats showed generalized convulsion in group A (40%) in contrast to 9 rats in group B (90%) ($p < 0.01$). Early Fos immunoreactivity was seen in the regions including the piriform and entorhinal cortex, hippocampus, the amygdala, and the anterior and medial thalamic nucleus (limbic system) in both groups. In group A, the rats without generalized convulsion showed a decreased staining on the thalamic regions (ventrolateral nucleus, ventroposterolateral and ventroposteromedial nuclei) and their associated cortical regions. No definite changes were seen in the paraventricular, centromedial, and ventrolateral geniculate nuclei.

Conclusions: We found that STN DBS in lithium-pilocarpine induced status model may suppress ictal propagation to generalized convulsion and delay its beginning but can not prevent seizure onset. Decreased immunoreactivity in the thalamic areas during DBS suggested the activation of STN efferent to substantia nigra pars reticulata (SNpr) which inhibit lateral parts of thalamic nuclei. Although unreliable Fos induction in the SNpr during limbic seizures, SNpr may be a key structure modulating seizure propagation during STN DBS via thalamo-cortical inhibition.

1.104
USE OF COMPETITIVE NMDA ANTAGONISTS TO ELICIT LONG-TERM DECREASES IN SEIZURE FREQUENCY IN THE KAINATE-TREATED RAT MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: In hippocampal slice preparations, long-term decreases in CA3 burst frequency can be induced by competitive NMDA antagonists due to long-term depression (LTD) at CA3-CA3 synapses. In vitro, this effect is enhanced by application of sequentially lower concentrations of NMDA antagonists. Based on these in vitro results, we hypothesized that administration of successively lower doses of NMDA antagonists would decrease the incidence of electrographic and spontaneous motor seizures in kainate-treated rats.

Methods: Four 1-year-old rats with kainate-induced epilepsy were implanted with single-channel subdural EEG radiotelemetry units. Baseline EEG and behavioral data was recorded prior to treatment. Each rat was given a series of 3 decreasing doses of SDZ-220–581 (20 mg/kg, 10 mg/kg, and 5 mg/kg, PO) over 3 consecutive days each week for 4 weeks. Continuous EEG recordings and video records were obtained. The computer data were analyzed both by hand and also through routines written in Visual Basic 6.0 to determine seizure frequency before, during and after treatment.

Results: The most robust results based on behavioral and EEG analysis were 1) a decrease in seizure duration during SDZ treatment, and 2) a transient increase in total seizure minutes per day, beginning 24 hours after the last dose and peaking 48 hours after the last dose of SDZ. A trend that did not reach significance in these first four animals was a cumulative decline over the 4-week treatment period in seizure duration averaged over the 4 post-SDZ days in each treatment week.

Conclusions: The transient increase in seizure activity 48 hours after SDZ likely represents a rebound effect. Given the study design, this rebound obscured most of the anticipated long-term effects of NMDA antagonism. The timing of the rebound suggests that the effective half-life of SDZ was significantly longer than anticipated, so that the concentration-time profile that was effective in vitro was not likely to have been achieved in this in vivo study. To optimize NMDA antagonist dosing in the next series of experiments, in vivo measures of NMDA receptor-dependent LTP and LTD induction will be used to assay the degree of NMDA receptor block. (Supported by NIH, EFA, AES.)

1.105
A PREDICTABLE SEQUENCE OF EEG CHANGES DURING PILOCARPINE-INDUCED STATUS EPILEPTICUS IN JUVENILE RATS

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Rationale: Treiman et al. (*Epilepsy Res* 1990; 5:49–60) reported a predictable sequence of EEG changes during status epilepticus (SE) in human generalized convulsive SE and three experimental models of SE. Since then this same sequence has been reported in six other experimental models and in human complex partial SE. All but one report has been in adult humans, rats, or monkeys. Mikati et al. (*Epilepsy Res* 2003;55:9–19) found the same sequence in kainate-induced SE in juvenile (P15 and P35) rats. We studied EEG changes during high dose pilocarpine-induced SE in juvenile rats (P25) to see if the same pattern would be observed in this model.

Methods: Female Sprague-Dawley rats with 14 day old litters were obtained from Charles River Labs. 16 pups were implanted with epidural screw electrodes at age P21. Electrode placements were: Bregma + 1.5 mm ± 2.3 mm; −3.0 mm ± 2.3 mm. At age P25 SE was induced with 400 mg/kg pilocarpine IP. Video/EEG was recorded continuously from 60 minutes prior to the injection until animals exhibited periodic epileptiform discharges (PEDs) on the EEG or died. The sequence and timing of observed EEG patterns was recorded.

Results: All of the animals exhibited, sequentially, in the following order, some or all of the five EEG patterns previously described by Treiman et al.: I. Discrete electrographic seizures, II. Waxiing and waning of EEG rhythms, III. Continuous ictal discharges, IV. Continuous discharges punctuated by periods of relative flattening, V. PEDs on a relatively flat background. Quantitative data for each stage are shown in the table.

Conclusions: These results support the hypothesis that the sequence of five EEG patterns described by Treiman et al. represent a fundamental sequence of EEG changes during status epilepticus. Variations in duration of a given pattern, morphological appearance, and time required for progression through the five patterns have been reported, but the fundamental sequence appears to hold true, regardless of the specific type of human SE (GCSE or CPSE), of the species (humans, monkeys, rats), the specific model (kainate, cobalt/homocysteine, LiCl/pilocarpine, high dose pilocarpine, electrical stimulation at various sites, hippocampal slice), or the age of the animal (juvenile rat, adult rats, monkeys, humans). Thus the EEG stage can be used as a marker to study dynamic changes during SE. These results also confirm that pilocarpine induces a severe, frequently lethal, form of SE. (Supported by Barrow Neurological Foundation and St. Joseph's Hospital & Medical Center, Phoenix, AZ.)

1.106
ALTERATIONS OF GLUTAMATE AND GABA TRANSPORTERS IN THE HIPPOCAMPUS OF PENTYLENETETRAZOL-KINDLED RATS

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Rationale: Kindling is thought to model complex partial seizures. Although the specific mechanism remains unknown, the long-lasting excitatory synaptic transmission efficacy found in pentylenetetrazol (PTZ)-kindled animals that is related to extracellular glutamate concentration is of interest. Glutamate-mediated responses of NMDA receptors combined with collapse of GABA-mediated inhibition suggest both molecular and cellular mechanisms. In these experiments we wondered if altered glutamatergic and GABAergic synaptic transmission in PTZ kindling

EEG Stage	Number at start of stage	Mean time from pilocarpine injection to start of stage (min)	Mean duration of EEG stage (survivors) (min)	Number survived to next stage	Number died during stage
I.	16	11.79 ± 11.85	10.27 ± 10.59	14	2
II.	14	22.78 ± 22.11	8.44 ± 5.13	6	8
III.	6	34.90 ± 13.15	13.52 ± 1.95	4	1
IV.	5	61.64 ± 21.76	108.35	1	4
V.	1	160.67		0	1

were associated with changes in glutamate transporter proteins. We used semiquantitative western blotting with antibodies specific to individual excitatory amino acid transporters (EAATs) and GABA transporters (GATs) to test our hypothesis.

Methods: Using male Wistar rats, we induced kindling with PTZ (16 mg per ml in saline) given i.p. three times a week as a 40 mg per kg injection. Animals were considered kindled after two consecutive stage 5 seizures (generalized tonic-clonic seizure). Twenty-four hours after the last stage 5 seizure animals were killed and both hippocampi were removed and a crude membrane fraction was prepared for western immunoblotting.

Results: We found that levels of GLAST, GLT-1 and EAAC-1 glutamate transporters were elevated significantly. However, no change was found in any of the GABA transporters.

Conclusions: Chronic seizures induced by amygdalar Fe+++ or kainic acid injection are associated with down-regulation of glial glutamate transporters. While our PTZ-kindled animals have enduring behaviors consistent with chronic kindling, the changes we found in EAATs are more consistent with reports of expression of transporters found in acute models of seizures such as status epilepticus. In fact, administration of glutamatergic receptor agonists or GABAergic receptor antagonists result in increased levels of glutamate transporters. Elevation of expression of EAATs would be important as a molecular regulatory response associated with increased glutamate metabolism in the acute phase of kindling with reverse glutamate transport and re-uptake into the hippocampal neurons. While our preliminary observations are of interest, we believe that observation of EAATs and GATs expression over prolonged periods may provide clues to enduring changes fundamental to kindling. [Supported by a Grant-in-Aid for Encouragement of Young Scientists (10770490) from the Ministry of Education, Science, Sport and Culture, Japan (to Y.U.).]

1.107
FEBRILE SEIZURES: SCREENING OF ENU MUTAGENIZED MICE AND OBSERVATION OF STRAIN DIFFERENCES IN INBRED MICE

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Rationale: Febrile seizures (FS) are the most common form of convulsion, occurring in 2–5% of infants in Europe and North America and 6–9% of infants in Japan. Mouse models for febrile seizures will provide a system in which to study the molecular events involved.

Methods: In humans, febrile seizures occur in infants (6 months to 5 years) and are associated with a rise in body temperature. We simulate febrile seizures in infant mice by subjecting them to whole body hyperthermia. A method originally used to induce febrile seizures in rats (Baram et al. Dev. Brain Res. 1997;98:265–270) is currently being used to determine the threshold of febrile seizures in mice. Mice that are 14 days old are subjected to hyperthermia by gradually raising the air temperature. After approximately 5 minutes the mice exhibit motor seizures. The time to seizure onset and core body temperature at the time of onset are recorded. Detailed protocols are available at: http://www.tnmouse.org/neuromutagenesis/epilepsy.html

Results: To date we have tested over 30 ENU mutagenized pedigrees. Several pedigrees showed significant deviation from the controls for either the temperature at which the seizure occurred or the time taken to onset of the seizure. These pedigrees are currently being retested prior to mapping and identification of the underlying mutation. Mortality is normally low for the hyperthermia procedure (<5%), however certain pedigrees (eg DBA2J) show high mortality rates. Pedigrees with high mortality also had delayed seizure onset with a higher core body temperature at onset. The increased mortality may be due to the higher core temperature reached during the extended time in the hyperthermia chamber. An extended strain survey is currently underway.

Conclusions: We have developed a reliable and rapid screen for febrile seizures which is ideal for testing ENU mutagenized mice. We have also demonstrated strain differences in inbred mice, suggesting that genetic background plays a role in susceptibility to febrile seizures. [Supported by the Epilepsy Foundation (Wallace) and National Institutes of Health U01MH06197 (Goldowitz).]

1.108
RELATIONSHIP BETWEEN FREQUENCY OF INTERICTAL SPIKES AND SPONTANEOUS RECURRENT SEIZURES IN AN ANIMAL MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: After CNS injuries in humans, an interval of several months or years usually occurs before the subsequent onset of spontaneous recurrent seizures (i.e., epilepsy). Thus, a "latent period" is generally observed between a brain injury and the onset of the spontaneous recurrent seizures that represents chronic epilepsy. Relatively little is known about the temporal progression of epileptogenesis. We hypothesized that, in an animal model of temporal lobe epilepsy, interictal spike frequency increases in proportion to seizure frequency during epileptogenesis.

Methods: Eight 2-month-old Sprague Dawley rats were each implanted with a three-channel radiotelemetry system (DSI) to record electrical activity from each dentate gyrus and the neocortex. Five of these rats were treated with kainic acid until status epilepticus occurred for >3 h. These rats were then monitored nearly continuously using video EEG for the next 5 months. The recordings were processed using analysis routines written in Visual Basic 6.0 to isolate and quantify interictal spikes and seizures.

Results: Interictal spikes were consistently present immediately after the kainate-induced status epilepticus, and occasional electrographic seizures could occur at any time after kainate treatment. This period of low and stable electrographic seizure frequency lasted between 2 and 23 weeks. Subsequently there was a dramatic increase in both the number of seizures and the number of interictal spikes per day in all 5 animals. This increase resulted in unambiguous inflection points in plots of seizure and interictal spike frequency versus time after kainate-induced status epilepticus. In all five cases, the inflection point for the interictal spikes either preceded or was coincident with that of the seizures. The times from kainate-induced status to the spike vs. seizure inflection points were not significantly different in the first 5 animals (paired t-test, $p = 0.10$).

Conclusions: After the onset of occasional spontaneous seizures following kainate-induced status epilepticus, there is a point in time when

seizure frequency undergoes a substantial increase (i.e., an inflection in the plot of seizures per day versus time after kainate treatment). A relationship was detected between the appearance of an increased frequency of interictal spikes and an increase in the number of seizures per day. One of the implications of these data is that the interictal spike frequency in EEG recordings may be predictive of an increase in seizure probability, which may useful in the clinical management of human brain injury. (Supported by National Institute of Health, Epilepsy Foundation of America, and American Epilepsy Society.)

1.109
ANALYSIS OF THE RELATIONSHIP BETWEEN THE SEVERITY OF CHEMOCONVULSIVE STATUS EPILEPTICUS AND ELECTROGRAPHIC AND ANATOMIC MARKERS OF SEIZURE PROGRESSION IN THE KAINATE MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: It has been hypothesized that the severity of brain injury at the time of the initiating incident determines - or at least affects - the progression of epileptogenesis. We hypothesized that the severity of convulsive status epilepticus during kainate treatment is positively related to the time to the first electrographic seizure and to the amount of Timm stain in the inner molecular layer of the dentate gyrus.

Methods: Eight rats were implanted with electroencephalographic radiotelemetry monitors, and both electrographic and behavioral data were recorded continuously for the next 120–150 days. One week after the surgery, five rats were treated with kainic acid (5 mg/kg, IP) until each rat experienced convulsive status epilepticus. Motor seizures were observed during the 24-h period after the initial kainate injection. Seizures were quantified based on the number of motor seizures, the duration of individual motor seizures, and seizure type (Racine, *Electroencephalogr Clin Neurophysiol* 1997;32:281). The animals were then ranked by the total duration of seizures (i.e., total number of seizures x the mean seizure duration) and by a scaling of the seizure type (i.e., type 3 = 1, type 4 = 2, type 5 = 3; followed by summation of the total of the seizure types); these two indices were then summed, resulting in an overall seizure score. At the end of the 120–150 day recording period, the animals were euthanized and processed for Timm staining, which was graded using the Tauck and Nadler scale (*J Neurosci* 1985; 5:106) by an observer blind to the animals' treatment.

Results: The total number of seizures observed during the 24 h following kainate treatment ranged from 59–123 seizures per rat, and the mean seizure duration was 48 $\pm$ 6 sec. The mean number of days to the first observed electrographic seizure was 12 $\pm$ 10 days. Mean Timm stain scores ranged from 1.00 to 2.42. There was a positive correlation between the seizure score derived during treatment and the time to the first electrographic seizure ($r^2 = 0.79$, $p = 0.04$), and a positive correlation between the seizure score and Timm stain in the inner molecular layer of the dentate gyrus ($r^2 = 0.84$, $p = 0.02$). Timm stain in the inner molecular layer was also positively correlated with the time to the first electrographic seizure ($r^2 = 0.93$, $p = 0.008$).

Conclusions: These results suggest a strong association between the severity of the convulsive seizures during kainate treatment and the progression of epileptogenesis. The data suggest that it may be possible to predict the rate of seizure progression in groups of animals, based on the motor seizure response during chemoconvulsant-induced status epilepticus. (Supported by NS 45144 and NS 034360.)

Nursing/Psychosocial/Health Services 1

1.110
A SURVEY OF EPILEPSY PATIENTS LISTING GOALS FOR TREATMENT

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Rationale: Patients with epilepsy have many reasons to seek care for their chronic illness. Patients may have goals for their healthcare that may contribute to institutional and therapeutic choices. We surveyed patients in our university epilepsy clinic to determine what they would list as their top three goals in seeking treatment.

Methods: We asked 20 epilepsy patients at the University of North Carolina Epilepsy Clinic to spontaneously list their top three goals in seeking treatment and the most important reason for attending a university epilepsy clinic.

Results: Twenty epilepsy patients completed the survey and the mean age was 44.1 years, with 12 subjects being female. The subjects averaged taking 2 anti-epileptic medications (AEDs) and the majority of patients (55%) averaged a seizure frequency of having at least one seizure per month. We found the most common primary goal for seizure treatment was to be free of seizures (50%). Additionally, 15% of subjects had a primary goal of being off all anti-seizure medication and 35% had goals other than seizure freedom or discontinuing medication. We found that 70% of patients reported that they sought care in our clinic based on institutional or physician reputation, whereas only 10% received care based on physician referral.

Conclusions: In our cohort study we found that most of our epilepsy patients are seeking to be free of seizures, and a significant group wish to be off all anti-seizure medications. However, approximately one-third of the patients did not list seizure freedom or discontinuing medications as their primary goal for treatment. These findings highlight the need for continued dialogue between physicians and patients regarding goals.

1.111
A NURSE-LED EPILEPSY CLINIC SUPPORTED BY TELEMEDICINE IS FEASIBLE, ACCEPTABLE, EFFICIENT, AND SUSTAINABLE

Ena Bingham and Victor Patterson (Neurology, Royal Victoria Hospital, Belfast, N. Ireland, United Kingdom)

Rationale: People with epilepsy express a desire to see nurse specialists as well as neurologists. Epilepsy Centres are one way of achieving this but are impractical for patients in rural areas.We had used real-time telemedicine previously for acute neurological emergencies and neurological outpatients and wished to see if we could use this technique to improve the care of people with epilepsy in rural areas.

Methods: Patients with epilepsy attending the neurology clinic at 2 rural hospitals were studied. They were seen by an epilepsy specialist nurse (E.B.); if necessary telephone consultation was made to a neurologist (V.P.) who was at the Regional Neurology Centre 80 miles away; if the neurologist was still uncertain a videolink consultation was started directly using commercially-available videoconferencing equipment over ISDN lines at a bandwith of 384 kilobits per second. Specifically we measured the proportion of patients seen by each of the 3 possible consultation methods, the savings in the time of a neurologist, and satisfaction by means of a 3-question questionnaire at the beginning and end of a 3-year period.

Results: The total number of patients seen increased from 214 in 2001 to 365 in 2003. The percentage of patients requiring videolinks to the neurologist decreased from 23% to 13%. Satisfaction levels were similarly high at the beginning and end of the study. The saving in the direct time of the neurologist over the period studied was 79%.

Conclusions: This method of practice is highly acceptable, saves neurologists' time, and is sustainable in practice. It should become the norm for patients with epilepsy in rural areas where the problems of transport to epilepsy centres-of-excellence are often prohibitive.

1.112
PSYCHOSOCIAL CARE NEEDS OF CHILDREN WITH BOTH EPILEPSY AND MILD MENTAL RETARDATION AND OF THEIR FAMILIES

Janice M. Buelow (School of Nursing, Indiana University, Indianapolis, IN)

Rationale: Children with epilepsy and mild mental retardation (MMR) and their families are at risk for significant quality of life problems but the nature of these problems has not been examined. Greater

understanding is necessary before effective interventions can be designed to help these children and their families. The purpose of this study is to identify and examine the specific problems experienced by children with epilepsy and MMR and their families.

Methods: We invited parents to participate in the study if they had a child with a diagnosis of epilepsy and MMR (IQ between 55 and 75) and who was between the ages of 8 and 16. Twenty parents of children with epilepsy and MMR were interviewed using a semi-structured open-ended interview guide to explore specific problems regarding school, community, medical community, and child/family. The interviews were tape-recorded and transcribed verbatim. Qualitative data analysis was completed using a code start list of school, child/family, community and medical community. Categories were established and data were compared within categories to identify themes.

Results: Qualitative data analysis identified problems in general areas, which were 1) communication at school, 2) need for information, and 3) child and family. The central theme regarding schools was a disconnect between the schools' goals and the parents' goals for their children. The central theme regarding the medical community included need for information about the seizure condition and behavior management. The central theme regarding children and family included behavior problems, concern about their children's self-esteem and socialization. An overriding concern of parents was uncertainty about what the future held for their children.

Conclusions: Analysis of the interviews pointed out problems affecting both children and families. This study provides a foundation for better understanding these problems and for developing interventions to address them. (Supported by NR 04536 and NR 005035.)

1.113
RECREATIONAL DRUG USE IN PEOPLE WITH EPILEPSY IN ARIZONA

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Rationale: Quality of life (QOL) issues have gained attention in the epilepsy community. Little is known about the use of alcohol and recreational drugs (RD) in persons with epilepsy (PWE). The consequences of using RD in a PWE may potentially cause serious injury, seizure exacerbation, or worse. Understanding RD use among PWE has important implications for the health of PWE.

Methods: An educational needs analysis survey was conducted in conjunction with Mayo School of Continuing Medical Education and the Epilepsy Foundation of Arizona (EF Az). The EFAz is the singular organization of PWE and their caregivers for Arizona and their demographics mirror those of the Southwest USA. Thus surveying the EFAz provides representative opinions regarding RD. PWE and their caregivers were asked about the usage of RD, alcohol, and tobacco. Demographic variables included sex, age, educational level,and diagnosis of drug abuse. People in the data base were asked about casual use and possible abuse of non-prescribed substances both illigal and legal. Surveys were mailed to all persons in the data base and people were asked to return completed surveys. Results were analyzed using computer scoring.

Results: A return rate of approximately 10% was achieved. Two hundred and sixty responses were analyzed representing approximately 10% of the EFAz. 59% of the respondents were female. 65% had a high school education or less and 35% had a college degree or more. 88% of the PWE were 30 years or older. 87% of the PWE had epilepsy greater than 3 years. 9% of PWE are currently using alcohol on a regular basis. 81% of PWE felt there was a history of alcohol use causing some "problem" in their life. Overall, at least 13% PWE reported having used illicit RD, habitual illicit drug use was 4.3%. Alcohol (legal), followed by marijuana (illegal) were the two top drugs identified as being used habitually by PWE. After being diagnosed with epilepsy, 13.5% have used marijuana, 11% have used cocaine or amphetamine, 6.5% hallucinogens (mushrooms, peyote, LSD, PCP), and 2% have used inhalants (toluene, paint, nitrous oxide). 29% have used over the counter cough preparations without consulting their health care provider. 15.4% of PWE have used a benzodiazepine and 29.2% have used a narcotic analgesic which had not been prescribed. 79% used one or more caffeinated drinks per day and 83.5% use no tobacco products. 5.7% of PWE have been arrested for drug or alcohol related offences and 5.8% have been treated for drug or alcohol dependence.

Conclusions: Illicit drug use in PWE in Arizona mirrors national use estimates for the general population. The fact that PWE are using any dangerous RD at all suggests a significant educational need exists for PWE and their caregivers. The motivation for use of these substances and their effect on the PWE remains unclear and would benefit from further study. (Supported by Mayo School of Continuing Medical Education.)

1.114
THE EPILEPSY TELEPHONE ADVICE LINE: A REVIEW

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Rationale: The role of the Clinical Nurse Specialist in Epilepsy (CNSE) has been well defined (Brown et al. 1998, Kwan et al. 2000, Castledine 2002). Nurse telephone support to epilepsy patients is a relatively new concept with few documented studies. This study examines tele-nurse advice to epilepsy patients, its indirect effects on other medical services and seeks to find out what patients would do if this service was unavailable.

Methods: A retrospective audit of phone interactions was carried out, reviewing 6 weeks of calls. During this time patients were asked to choose from the following options of what they would do if the service was not available:

(a) attend their GP, (b) contact consultant neurologist, (c) contact hospital doctor, (d) attend A& E department, (e) contact secretary to have their OPD appointment brought forward, (e) do nothing or (f) other.

Results: The results showed that 57% of patients would contact a hospital doctor if the service was not available. 27% said they would attend theri GP. 6% said they would attend A&E department while 7% would contact the secretary to have their appointment brought forward. 70% of patients contacted the CNSE for urgent advice on ongoing seisures, medication and side effects. Medications were adjusted over the phone with occassional assistance of a GP in 45% cases.

Conclusions: This study suggests that this service is valuable in the care of epilepsy patients and shows positive effects on other medical services. It also highlights the CNSE as a key member of the multidisciplinary epilepsy team.

1.115
DEVELOPMENT OF AN INSTRUMENT TO IDENTIFY POSITIVE PSYCHOTROPIC PROPERTIES OF ANTIEPILEPTIC DRUGS AND THE VAGUS NERVE STIMULATOR

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Rationale: Psychiatric diagnostic instruments are usually used to determine whether antiepileptic drugs (AED) or the vagus nerve stimulator (VNS) can exhibi positive psychotropic properties in epilepsy patients. Yet, in the absence of co-morbid psychiatric disorders, these instruments are unlikely to show any changes. We set-out to develop an instrument capable of identifying positive psychotropic properties of AED and the VNS in the *presence or absence* of co-morbid psychiatric comorbidity.The process of developing this instrument is presented here.

Methods: ***Phase-1Version***: We elaborated an initial self-rating questionnaire with 61 items intended to identify changes in the following domains: motivation, concentration, memory, socialization, mood and anxiety. The items were scored on a 1 to 5 Likert scale (1 = never, 2 = occasionally [1 – 2 days/week], 3 = half of the time [3–4 days a week], 4 = majority of the time [5 – 6 days/week], 5 = all the time). Patients rated each item according to the way they felt in the previous two weeks. 53 outpatients with epilepsy from the Rush Epilepsy Center completed the questionnaire and commented on the clarity and relevance of each item. From these 61 items we eliminated any item that two or more patients rated as confusing, poorly written, irrelevant as well as items considered to screen the same properties. We selected 22 items that identified the same domains for a ***phase-2 version.***

Results: 98 consecutive patients with epilepsy completed the 22-item phase-2 version scale. The phase 2 scale had a good internal consistency as its Cronbach's alpha was 0.63. A factor analysis identified

four separate factors. All, but three items were rated favorably by most patients.

We finally developed a ***Phase-3Version*** was developed with the 19 items unanimously accepted by all patients; we added 5 new items and we started giving the 25 item scale to 100 consecutive epilepsy patient. Patients were asked to complete a self-rating scale of depression (The Beck Depression Inventory –II [BDI-II]), the Hamilton Anxiety Rating Scale (HARS), and the Adverse Event Profile (AEP), an instrument validated to identify common adverse events of AEDs, as well as the Quality of Life in Epilepsy Inventory (QOLIE-89). To date, data of 53 has been obtained. Once data are obtained from 100 consecutive patients, we will calculate a Cronbach's alpha, the 25 items will be submitted for a new factor analysis and the total score of our scale will be correlated with the scores of the above cited instruments for validation of our scale. At the present time, 53 patients have completed the phase 3 scale together with the BDI-II, HARS, AEP and QOLIE-89.

Conclusions: The data gathered so far with the second-phase version indicates that an instrument to identify positive psychotropic properties of AEDs and the VNS in the absence of co-morbid psychiatric disorders have good psychometric properties. (Supported by Elan Pharmaceutical.)

1.116
IS THERE AN INDICATION FOR A STANDARD RESPONSE TIME TO SEIZURES IN AN EPILEPSY MONITORING UNIT?

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Rationale: To date, there has been no established nursing research conducted evaluating the effect nursing response time to epileptic seizures has on patient safety.

In response to the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) focus on patient safety, a study was initiated. The purpose of this project was to identify (1) if a benchmark response time to seizures is needed, and (2) to examine the relationship between response time and patient safety.

Methods: This project involved retrospectively looking at archived EEG and video files to determine how quickly nurses responded to epileptic seizures in a dedicated epilepsy monitoring unit. The data was collected over 23 months and involved 130 patients. Initially, a target response time was set at 15 seconds. Following preliminary analysis, it was determined that at least 10 seconds of abnormal EEG was needed to establish whether the pattern was indicative of a seizure or epileptiform discharges not requiring nursing intervention. Therefore, a decision was made to increase the threshold to 25 seconds from onset of EEG change to nurse at the bedside.

Results: This study sample yielded no injuries involving unassisted falls, fractures, wounds requiring sutures, or ER visits. On occasion, patients sustained buccal trauma, minor bruising or abrasions which were directly attributable to the ictal or postictal periods. None of these required additional labs, diagnostic radiology, or increased length of stay.

It was found that nurses responded to seizures an average of 23 seconds from EEG onset over the study period of 23 months. Throughout these months, there were variances in the response times ranging from zero seconds (nurse present at seizure onset) to over 60 seconds or more. These variances did not appear to significantly impact patient safety.

Conclusions: The results of this study underscore the importance of establishing a benchmark response time but falls short of identifying what specific amount of time is indicated. Perhaps a response time of 20 to 35 seconds should be considered. There are benefits to prompt response which can be identified. These include providing supportive care to patients during the ictal and post-ictal states (i.e. administration of oxygen, airway management, comfort measures, and safety), an enhanced feeling of comfort for patients and their families, and improving quality of ictal SPECT scans performed on pre-surgical candidates.

This study does demonstrate that further research on this subject is warranted and a future multi-center study of response time to epileptic seizures would be beneficial in determining a standard of care to be utilized by dedicated epilepsy monitoring units.

Also, it would be of interest to examine nursing response time as it relates to safety on a dedicated epilepsy monitoring unit versus an epilepsy monitoring unit that is incorporated in a non-dedicated hospital area.

1.117
A STRUCTURED NURSE INTERVENTION PROGRAMME IMPROVES QUALITY OF LIFE IN PATIENTS WITH EPILEPSY. A RANDOMISED CONTROLLED TRIAL

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Rationale: A recent Cochrane review concludes that there is insufficient evidence that people with epilepsy benefit from specialist nurse intervention, and that further research is needed to investigate the role and effectiveness of specialist epilepsy nurses. We tested the hypothesis that structured epilepsy nursing in an outpatient neurology clinic improves quality of life (QOL) measured by the questionnaire QOLIE-89.

Methods: 114 adult patients with uncontrolled epilepsy were randomly assigned either to an intervention ($n = 58$) or a control ($n = 56$) group. The intervention group was offered extended follow-up and teaching with one nurse permanently attached to the project in close collaboration with a neurologist. An interactive, 1-day group education programme was arranged. The nurse was present at as many outpatient consultations as possible to enable reliable, mutual assessment of the patient. The nurse performed follow up by telephone at least every three months. The overall goal was availability and continuity. All patients completed the QOLIE-89 before randomization and after 2 years. Student's t-test was used to compare QOLIE-89 data between groups; paired t-test was used to compare patients before and after intervention.

Results: QOL was significantly improved in the intervention group ($p = 0.019$), but not in the control group ($p = 0.13$). An improvement was mainly seen in the sub-items for "health discouragement" ($p = 0.007$), and "medication effects" ($p = 0.035$). The difference between the groups was not significant.

Conclusions: To our knowledge, this is the first study to demonstrate a significant effect of a structured nurse intervention programme in QOL of patients with epilepsy. (Supported by GlaxoSmithKline.)

1.118
DO PATIENTS WITH EPILEPSY AND THEIR COMPANIONS DIFFER IN THE RECOGNITION OF THE PATIENTS' PSYCHIATRIC SYMPTOMS

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Rationale: Psychiatric symptoms are often unreported by patients. In fact, spouses and companions of patients with epilepsy (PWE) are often the ones recognizing and reporting the presence of symptoms of depression to the treating clinician. The agreement between PWE and their spouses (or comapnions) on the existance of psychiatric symptoms has yet to be investiogated in a systematic manner. The purpose of this study was to establish the level of disagreement between PWE and their spouse/companion with respect to the presence of common psychiatric symptoms in epilepsy and to identify the type of symptoms with best and worst agreement.

Methods: 42 pairs (PWE + spouse/companion) were asked to complete a 46 item self-rating questionnaire (Common Psychiatric Symptoms in Epilepsy Item Pool developed to identify symptoms of depreesion in the previous 2 weeks ($n = 14$ items), anxiety ($n = 7$), irritability ($n = 9$), socialization difficulties ($n = 5$), paranoia ($n = 3$) hypomanic-like symptoms ($n = 3$) and physical symptoms ($n = 2$). The instrument had a high internal consistency (Alpha Chronbach $= 0.96$). Each item was rated on a 1 to 4 Likert scale (1 = never, 2 = rarely, 3 = sometimes, 4 = always). A rating of 3 or 4 was considered to reflect the existence of a symptom. We compared the frequency of disagreement between PWE and spouse/companion among each of these symptom categories.

Results: OVERALL AGREEMENT BY SYMPTOM CATEGORY: Depression: 70% (range: 56–83%), Anxiety: 74% (62–83%), Irritability: 65% (55–83%), Socialization difficulties: 73% (55–83%), Paranoia: 75% (69–90%), Hypomanic-like symptoms: 65% (60–78%).

TYPE OF PSYCHIATRIC SYMPTOM RECOGNIZED BY SPOUSE BUT NOT REPORTED BY PATIENT: Irritability = median disagreement in 37% of pairs, (range: 14 to 55%), depression, 28% (9–42%), anxiety, 26% (3–31%) hypomanic-like symptoms, 20% (9–26%), paranoia, 19% (0 0- 20%), socialization difficulties, 16% (6–23%).

TYPE OF PSYCHIATRIC SYMPTOM REPORTED BY PATIENT BUT NOT RECOGNIZED BY SPOUSE: Hypomanic-like symptom, median disagremment in 80% of pairs, (range: 75 to 86%), socialization difficulties, 63% (36–70%), paranoia, 59% (52–80%), anxiety, 39% (23–67%), irritability, 38% (22–45%), depression, 38% (14–63%).

Conclusions: These findings suggest an adeqaute agreement between PWE and spouse/companion in the recognition of psychiatric symptoms. However, patients are more likely to deny symptoms of irritability identified by spouse/companion, while spouses are less likely to recognize hypomanic-like symptoms. (Supported by Glaxo-Smith-Kline.)

1.119

THE IMPACT OF SARS ON EPILEPSY: THE EXPERIENCE OF DRUG WITHDRAWAL IN EPILEPTIC PATIENTS

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Rationale: During the 2003 SARS outbreak, many patients avoided hospital visit because of fear of infection. Antiepileptic drug (AED) withdrawal is a risk factor for seizure recurrence. Therefore, seizure control during the SARS outbreak is a good model for examining the impact of drug withdrawal in seizure control.

Methods: All seizures experienced by each patient before, during, and after the SARS outbreak periods were registered in each patient's seizure diary. The patients were divided into four groups according to the presence of drug withdrawal as well as seizure attack. In each group, seizures occurring during three different periods were compared. Risk factors for seizure recurrence were also examined.

Results: Of 227 cases, 49 stopped taking medication during the outbreak. Among them, 28 suffered seizure attacks during AED withdrawal. Four cases developed cluster attacks and two cases had status epilepticus after AED withdrawal. AED withdrawal produced a significant increase in seizure frequency. The major risk factors for withdrawal seizures were symptomatic etiologies, polytherapy and non-seizure free before AED withdrawal.

Conclusions: The SARS outbreak adversely affected seizure control because of AED withdrawal. Patients with polytherapy, non-seizure free and symptomatic etiologies were more susceptible to recurrence of seizures after AED withdrawal.

1.120

ATTITUDES OF BRAZILIAN PSYCHIATRISTS TO PEOPLE WITH EPILEPSY

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Rationale: To evaluate the experience of treating people with epilepsy, and the formal training, attitudes and knowledge in relation to epilepsy (and associated mental disorders) of Brazilian psychiatrists.

Methods: 157 Brazilian psychiatrists responded to a specially developed questionnaire consisting of 14 questions related to epilepsy and associated mental disturbances: two questions about their experience treating people with epilepsy, three questions about formal training, one question about the satisfaction about their knowledge, two questions on prejudice and three questions testing knowledge.

Results: The majority of Brazilian psychiatrists completing the questionnaire (95%) have treated patients with epilepsy and mental disorders, (48% frequently). About one third (35%) considered they did not receive any formal training on epilepsy and only 46% confirmed that they have received formal training on mental disorders related to epilepsy. Eighty percent were dissatisfied with their own knowledge and 98% of those who had not already received any formal training wished to do so. Only 10% of the participants answered correctly the three knowledge-based questions and 60% answered wrongly at least two out of the three questions, showing a significant lack of knowledge. Nearly half (48%) considered that prejudice exists among psychiatrists toward patients with epilepsy. These professionals indicated difficulty with treatment (50%) and lack of knowledge on epilepsy (50%) as being the main causes for this.

Conclusions: Such data indicates an urgent need of improvement in the area of education about epilepsy and associated mental disorders and formal training on epilepsy during psychiatric residency.

1.121

BELLS ARE RINGING: REVIEW OF NON-REVENUE CALLS

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Rationale: During the Nurses' Special Interest Group at the American Epilepsy Society 57th Annual Meeting, the complex problem of non-revenue generating activities was discussed. General consensus revealed a universal consternation and frustration with this issue. Optimal patient care requires conscientious allocation of time and effort that cannot be billed as separate items in a medical practice. Theoretically, these costs should be recouped as overhead expenses through office visit fees. Realistically, the costs to maintain a practice are increasing disproportionately to the amount of revenue coming in. Patient related phone calls, a major non-revenue generating activity, need to be defined and evaluated.

Methods: The International Center for Epilepsy is a university-based, adult practice with three Epileptologists and three full-time Patient Coordinators. In order to identify non-revenue generating activities and substantiate a time commitment, our center decided to track phone calls for six weeks. A form was devised to capture the type and time elements of daily phone calls. Each coordinator was instructed to record aspects of phone calls to monitor subsequent investments of time and actions. Items tracked were calls from patients, to patients, calls requiring physician input, requests for prescriptions, letters or forms, faxing information, providing samples, calling other facilities or physicians.

Results: The number of calls was tabulated for six weeks. There were 843 contacts recorded. (The average call time was 10 to 30 minutes.) Patient initiated calls represented 35%. The coordinators' time was 55% which included returned calls (17%); completion of form/letters (4%); prescriptions called and/or faxed (20%) and miscellaneous requests (14%). Ten percent of calls required physicians' time.

Conclusions: This six week effort of monitoring calls was underrecorded due to: (1) time required in keeping track; (2) developing new habit; (3) not tracking calls handled by the receptionist/office manager. Our need is to establish a record-keeping system and incorporate a practical methodology to clearly demonstrate patient care versus cost-effectiveness. We must improve documentation since non-revenue generating, patient care activities provided by the coordinators appear to reduce demands on the physicians' time. Time is money.

1.122

QUALITY OF LIFE (QOL) MEASURED WITH SF-36 IN POLISH PATIENTS WITH EPILEPSY

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Rationale: Prior work has shown that the effects of epilepsy on QOL are dependent on many factors including seizure control, physical and social well being, and the ability to drive. In this study we use Short-Form Health Survey-36 (SF36), a generic QOL measure, to compare the QOL in Polish patients with medication-controlled and medication-resistant epilepsy.

Methods: We collected data on 85 epilepsy patients who presented for followup to the Antiepileptic Outpatient Clinic and to the Neurological Department of City Hospital, both in Bydgoszcz,Poland. Patients were eligible to participate if they were 18 years of age or older, had no significant mental handicap,and were able to and completed the questionnaire on their own. Demographic characteristics and medical history were collected through review of medical chart and self-reports. Comorbidities are defined as chronic health problems other than epilepsy.The study was approved by the Local Ethics Committee.

Results: Data on 60 patients with medication-resistant and 25 with medication-controlled epilepsy were collected. There were no differences between groups in age of onset (22.7 vs.22.7; $P = 0.99$), number of types of seizures(1.7vs.1.6; $P = 0.48$) or number of comorbidities(0.62 vs.0.32; $P = 0.08$),respectively. Differences were noted in age (40.3 vs. 32.2; $P = 0.014$)and number of AEDs(2.8 vs. 1.8; $P = 0.004$). On all subscales of SF-36, the scores were lower in patients with medication refractory epilepsy (all $P < 0.001$).

Conclusions: This initial study verifies the utility of SF-36 instrument in evaluation of HRQOL in Polish patients with epilepsy. Our findings confirm the differences in HRQOL between patients with medication-controlled and medication-resistant epilepsy that are observed in other countries.

1.123
IMPLEMENTATION AND EVALUATION OF SEIZURE POLICY AND PROCEDURES IN A TERTIARY CARE FACILITY

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Rationale: Few hospitals have formal policy and procedures (P&P) addressing seizure precautions and management. Hospital policy and procedures improve patient safety by standardizing patient care and providing a framework for evidence-based practice. Challenges for developing seizure P&P include: nursing staff turnover and variation in nursing knowledge and experience on non-neuroscience hospital units. The objective of this project was to assess the implementation of standardized hospital-wide guidelines for management of seizures.

Methods: P&P were developed and implemented at an adult tertiary care hospital. The P&P addressed: acute seizure management, seizure precautions, seizure assessment and documentation. Prior to implementation educational sessions were held to familiarize the nursing staff with the P&P. A standardized multiple-choice questionnaire was developed to assess nursing knowledge on the management of seizures. The nurses were also asked to rate their personal experience and comfort level in caring for patients with seizures on 100mm visual analog scales. Registered and licensed practical nurses from general medicine and surgical units were surveyed: prior to P&P education, following the education session and three months after implementation of P&P.

Results: Implementation of seizure P&P improved nursing knowledge and comfort level regarding management of seizure disorders.

Conclusions: P&P are important in achieving optimal hospital-wide management of patients with seizure disorders. The use of a standardized questionnaire provided a mechanism for evaluating the implementation process and monitoring the need for ongoing staff education.

1.124
THE INTRACTABLE EPILEPSY PROBLEM IN DEVELOPING COUNTRIES- IS THERE A WAY OUT?

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Rationale: Epidemiological studies estimate 1 million people in India with intractable epilepsy. However only 650 cases have been operated at 2 major centres. The non-availability of intra-operative ECoG and SPECT/VEEG has restricted epilepsy surgery programmes to big centres.

We wished to see how many cases could have been operated at smaller centers equipped with only EEG, MRI and facilities for a standard anteromedial-temporal-lobectomy (AMTL).

The other reason for the underutilisation of the surgical option in developing countries is unawareness leading to delayed referrals. We sought to compare and contrast surgical outcome for certain selected entities against delay in referrals.

Methods: 155 cases of intractable epilepsy operated at our centre were included for analysis.

Results: Figure 1 below reveals the following:

99 of our 155 patients underwent AMTL without ECoG guidance. *Among these 99, SPECT/VEEG was useful in only 9 with equivocal MRI findings (5 with bilateral MTS and 4 with normal MRI's). All 90 patients with clear-cut MRI localization had nothing added by VEEG/SPECT.*

Therefore 90 patients (58%) could have undergone surgery at a centre equipped with only EEG, MRI and AMTL facilities.

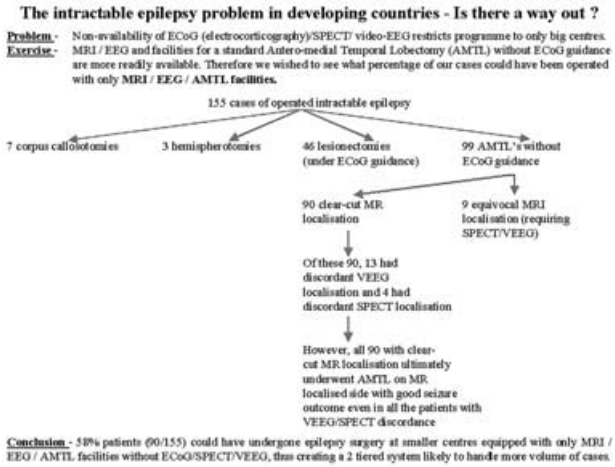

Table 1 below indicates that even though entities such as MTS/DNET's/gangliogliomas/occult vascular malformations (constituting 62% of our cases) have good seizure outcome rates of an average of 84.7%, the median delay in referral has often been an appalling 7 to 8 years.

Conclusions: The need of the hour for developing countries is to promote awareness and creation of a 2-tiered epilepsy surgery programme. The first tier equipped with EEG, MRI and trained superspecialists can undertake AMTL which is a large proportion of the epilepsy surgery burden. This strategy is likely to help handle a larger volume of cases but would definitely require strict surveillance.

Awareness regarding epilepsy surgery can be boosted by promoting a concept of surgically remediable epilepsy syndromes such as MTS/DNET's/gangliogliomas/occult vascular malformations.

1.125
EPILEPSY MONITORING UNITS: HOW MUCH STAFF TRAINING IS NECESSARY?

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Rationale: The number of staff working in epilepsy monitoring units (EMU's) is increasing due to a proliferation of units and the complexity of delivering care for these patients has also increased. The staff may include: monitoring/health care/EEG technicians, and nurses. Limited information is available regarding how much training is necessary for staff working in an EMU as few surveys or educational assessments

Referral delay versus surgical outcome-need for increased awareness

Entity	Number (96/155) {52%}	Engel's class I seizure outcome	Complications Field defects*	Transient complications**	Delay in referral (median years of suffering from intractable epilepsy before exercise of surgical option) Persisting deficits***	
MTS	46	35 (76%)	10	6	1	8 yrs
DNET's	21	19 (90.5%)	1	1	1	8 yrs
Ganglio-gliomas	14	13 (93%)	1	1	0	7.5 yrs
Vascular malformations	6	5 (84%)	1	1	0	5.5 yrs
Low grade glial tumors	9	9 (100%)	1	0	0	3.5 yrs

*Visual field defects is the only major price one may have to pay for seizure control especially following AMTL. **These patients had transient nominal dysphasia after dominant AMTL/meningitis. ***Both of them had persistent hemiparesis.

have been conducted. A new EMU was opened in Hawaii allowing the study of what may be required when training new staff. An educational questionnaire was developed to assess new staff competency before and after orientation. The information obtained from our survey may help guide the formation of standardized guidelines to establish EMU staff competencies.

Methods: Initial training involved a three hour class which included information about: classification of seizures, medications, an overview of EMU, unique EMU patient care and safety issues. All new hires undergo uniform training and there is ongoing education conducted by an epilepsy nurse coordinator. All staff assigned to the EMU were given a 20 question instrument to assess attitudes and knowledge about patients with seizures prior to training. The survey included questions regarding adequacy of classroom and bedside training before and after working within the EMU. They were also given a 10 question test regarding their knowledge about epilepsy.

Results: 25 surveys were completed, 11 nurses, 8 HCT's, and 6 monitor technicians. 40% rated (high or very high) their anxiety level upon learning that an EMU would be opening but this dropped to 13% after working in the EMU. 52% rated their knowledge level of seizures as high or very high before training and after working in the EMU 38% believed they could teach others to work in this unit. 64% thought they received enough classroom training and 58% believed they received enough bedside training, however, the education tool revealed major mismatches in staff perception of knowledge versus actual competency. 86% responded that automatisms such as lip smacking were part of a simple partial seizure versus the correct answer of complex partial seizures. 100% of the respondents correctly answered safety questions and 98% correctly identified appropriate nursing interventions for patients having seizures.

Conclusions: Working within an EMU can account for a high level of anxiety and requires a special level of competency for working with these patients. Expectations of the work involved may differ greatly from what actually occurs, however, proper training may help to bridge this gap and improve patient care. Further studies are needed looking at training done at other centers, and possible development of standards for training new staff for the EMU.

1.126

COMPREHENSIVE SHORT TERM REHABILITATION PROGRAM FOR PEOPLE WITH EPILEPSY: POSITIVE EFFECTS ON QUALITY OF LIFE AND PERFORMANCE

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Rationale: In 1997, a specialized rehabilitation unit for people with epilepsy was launched, offering a comprehensive 3 to 6 weeks program in order to ameliorate negative psychological, social and vocational consequences associated with the epilepsy. The effects of the rehabilitation treatment were evaluated.

Methods: Ninety-six consecutive non-surgical patients (mean age, 35 years, 66% male) completed a validated questionnaire (PESOS) before admission (T1) and after a mean of 19 months after discharge (T2). T1 and T2 data on quality of life (QL), seizure frequency, performance in daily life (including epilepsy self-management) were compared.

Results: Seventy-nine patients (82%) had focal epilepsy. Physical co-morbidity was found in 21%, and psychiatric co-morbidity in 53% of the cohort. Compared with T1, seizure frequency and number of hospital admissions due to epilepsy were reduced at T2 ($p < 0.01$). Significant improvements were found in 6 out of 7 QL domains (epilepsy related fear, emotional adaptation, perceived restrictions, perceived stigma, mobility/independent living, and physical/emotional health), and in performance in daily life (e.g. going out alone, driving a car). Regarding patients whose seizures were not markedly improved at T2, and patients with psychiatric co-morbidity, both subgroups had also significant positive effects on QL and performance.

Conclusions: A comprehensive rehabilitation program seems to have favorable long-term effects on seizures, performance (including epilepsy self-management), emotional adaptation and quality of life. Most of these effects were also observed in patients without improvement of seizure control, and in patients with psychiatric co-morbidity.

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1.127

GROUP PSYCHOTHERAPY FOR PATIENTS WITH NON-EPILEPTIC SEIZURES: A PILOT STUDY

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Rationale: Patients with non-epileptic seizures (NES) are often seen in in-patient video-EEG monitoring units with a frequency of up to 40%–50% of admissions. There have been a plethora of studies investigating the diagnosis of this disorder which note the common occurrence of histories of abuse, depressive complaints, dissociative symptoms, etc. Outcome studies have noted a good prognosis in children with the disorder, but rates for adults are not as promising with only 29% to 45% who achieve seizure freedom 5 years after evaluation. Treatment strategies for patients with this disorder have been sparse, at best. The authors attempted to develop a group therapy intervention with a cohort of patients with refractory, chronic NES. In most cases, when possible, this was coupled with individual and pharmacotherapy.

Methods: Eight women (n = 8) participated in the group treatment for two 16 week intervals. Outcomes included the SCL-90 and frequency of seizures measured on a weekly basis. The researchers hypothesized that the scores on the SCL-90 subscales and seizure frequency would decrease as a result of the intervention. The group intervention was psychodynamic and process oriented focusing on educational, interpersonal and communication issues both in and out of the group.

Results: Regression lines were fit to each individual's data yielding a slope and intercept. Descriptive statistics indicated a mean reduction on ten of the twelve SCL-90 subscales. Effect sizes ranged from 0.03 to 0.92 with the most substantial reductions found on the SCL-90 obsessive compulsive (effect size = 0.92), phobic anxiety (effect size = 0.71), depression (effect size = 0.67), and the somatization (effect size = 0.31) scales. Six of the women experienced a decrease in seizure frequency over the treatment period. Overall subjective quality of life improved, in some cases dramatically.

Conclusions: Although seizure frequencies did not decline substantially in all patients, it appeared that ongoing and unresolved emotional and psychological conflicts were present in those patients with unchanged seizure activity. The group intervention allowed patients to see the seizure activity in other patients and develop a strong emotional bond with others suffering the same illness. The group also fostered the delineation of psychological issues and provided an easy conduit into individual therapy. These preliminary data suggest that people with non-epileptic seizures could experience both a psychological benefit and a concomitant reduction in seizures from participating in group psychotherapy treatment.

Clinical Neurophysiology–Adult 1

1.128
DOES ANTIEPILEPTIC DRUG WITHDRAWAL AFFECT PARTIAL SEIZURE DURATION?

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Rationale: Patients admitted to epilepsy monitoring units (EMU) often have their antiepileptic drugs (AED) reduced or withdrawn to increase seizure frequency and facilitate analysis within the limits of the typical admission. Seizure classification and localization are typical goals of EMU admissions. There has been relatively little study of seizure dynamics, evolution, and duration.

Methods: Sequential seizures from 8 patients with mesial temporal onset seizures requiring intracranial electrode arrays; and whose AEDs were discontinued during the EMU stay were analyzed. A total of 62 seizures were analyzed. The duration of partial seizures was determined by visual analysis of intracranial EEG (ICEEG) recordings of ictal activity from the electrode closest to the seizure focus. In addition, seizure duration was measured by the duration of the increase in Gabor atom density (GAD), a complexity measure derived from time-frequency decomposition of the ICEEG, previously developed and shown (Jouny et al., 2003) to correlate with seizure duration.

Results: Seizure durations measured independently by visual analysis of ICEEG and GAD were not statistically different (paired t-test, p = 0.507). Seizures occurring in clusters (operationally defined as 3 or more seizures in a 4-hr period) did not significantly differ in duration and dynamical composition from non-clustered seizures. We could analyze the effects of AED withdrawal in 5 patients whose seizures were spread over more than 24 hours. For these 5 patients, the duration of partial seizures that did not secondarily generalize did not show a significant increase with AED withdrawal during the EMU stay.

Conclusions: While the numbers of patients analyzed do not allow conclusions regarding specific AED effects, the results of this study do not indicate that AED withdrawal affects the duration of partial seizures. The results here provide further confirmation of the utility of the GAD method as a quantitative measure of seizure duration. In addition these preliminary results suggest that AED therapy, while reducing seizure number and secondary generalization, may not significantly alter the intrinsic dynamics of individual partial seizures. (Supported by NIH grant NS 33732.)

1.129
SPEECH-INDUCED APHASIC SEIZURES IN EPILEPSY CAUSED BY LGI1 MUTATION

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Rationale: Patients with autosomal dominant lateral temporal lobe epilepsy (ADLTE) may have seizures precipitated by sound or speech. We have performed a clinical and EEG study of a speech-induced seizure in a patient with ADLTE caused by an LGI1 mutation.

Methods: A 23 year old male belonging to a large pedigree with ADTLE caused by an LGI1 missense mutation (c136C>T) was examined prior to antiepileptic drug therapy seven days after a first generalized tonic-clonic seizure (GTC). A detailed clinical history was obtained. A video-EEG recording with interrogative speech as activation procedure was performed.

Results: For several months the patient had experienced occasional episodes of loss of understanding when spoken to. The attacks particularly occurred when he was unprepared for being addressed and was required to give a reply. They lasted only a few seconds and often occurred when he was called to from a neighbouring room. The voices became distorted and he could not comprehend the meaning despite hearing the words. He denied that sudden onset of music or other sounds could precipitate such symptoms. The day after a late party, while parking his car, his girlfriend spoke to him. Her speech became unintelligible to him. He did not reply and had a GTC.

When resting after hyperventilation during EEG, he was suddenly asked for the names of his siblings. He answered immediately, and was then asked how he felt. By then, he had lost any understanding and described how syllables floated together with an echoing character. He uttered "Now!," but could not remember this afterwards. He had a blank stare for some seconds, turned his head to the right and developed a GTC.

In the EEG, rhythmic 6 Hz activity built up in the frontotemporal areas starting on the left side at the time of his first reply with a later bilateral and posterior spreading. After about 20 seconds cerebral activity was concealed by muscle artefacts. Postictal slowing was symmetrical and no aphasia was noted on awakening.

Conclusions: To our knowledge, this is the first video-EEG recorded seizure in LGI1-caused ADTLE. This peculiar seizure semiology and precipitating effect of speech may serve as a marker for identifying further individuals with this particular pheno- and genotype and may indicate that the LGI1 gene may have a physiological function connected to the human capacity for speech and language.

1.130
HIPPOCAMPAL CONNECTIVITY IN HUMAN: AN ELECTRICAL STIMULATION STUDY

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Rationale: In human, the functional connectivity of the hippocampus has been well established within the temporo-limbic structures, using intra-cerebral stimulation coupled with evoked potentials (EP). Conversely, this approach has not yet been used to study the hippocampal connectivity with the majority of other brain regions. Taking advantage of stereotactic EEG procedures (SEEG), we have investigated this issue in 9 epileptic patients.

Methods: These nine patients proved to suffer from refractory partial epilepsy of temporal lobe origin in seven (including one bi-temporal), and frontal in two. Intracranial electrodes were placed in a single hemisphere in five patients, and bilaterally in four, with at least one electrode targeted to the hippocampus ipsilateral to the seizure onset zone in all. A total of 107 intra-cerebral electrodes were implanted, including 55 in the temporal lobe, 41 in the frontal lobe, and 7 in the parietal lobe. Nine of these electrodes also sampled the insula. Electrical bipolar

stimulations, produced by a current-regulated neurostimulator designed for a safe diagnostic stimulation of the human brain, were delivered at 45 hippocampal sites. The stimulations parameters were chosen to avoid tissue damage and consisted in two series of 25 pulses of 1 msec duration, 0.2 Hz frequency, and 3 mA intensity. EP were averaged over the 25 stimuli of each series, over all recorded sites, and considered significant when reproducible on the two consecutive series, with an amplitude at least twice that of the background level.

Results: Highly reproducible EP were elicited in many brain regions in all patients. However, the same anatomofunctional structure did not always demonstrate an EP across all patients. The structures which most often displayed an EP were the following : cingulate gyrus (85%), amygdala (83%), entorhinal cortex (80%), temporal pole (80%), orbito-frontal cortex (75%), insula (67%), mesial prefrontal (50%), lateral frontal (33%), SMA (28%), pre-central operculum (28%). No response were recorded in the post-central operculum nor in the contralateral hippocampus.

Conclusions: Our results show that the coupling of intra-cerebral low frequency stimulation and EP recordings is an effective method to study cortico-cortical connectivity, and could help to more precisely define the potential propagation pathways of epileptic discharges in human. Data from hippocampal stimulations appear generally consistent with our knowledge on hippocampal functionnal anatomy. However, to which extend the recorded EP reflect physiological responses or abnormal cortical activation related to the epilepsy remains to be determined. (Supported by Claude Bernard University.)

1.131
ICTAL INTRACRANIAL EEG IN TEMPORAL LOBE EPILEPSY: FREQUENCY IS RELATED TO ONSET LOCATION

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Rationale: We have shown that both the scalp EEG initial ictal discharge (IID) frequency and the intracranial EEG onset site are related to degree of hippocampal pathology in temporal lobe epilepsy (TLE). The goal of this study was to determine whether the intracranial EEG IID frequency (IF) is related to site of onset or to degree of hippocampal or neocortical pathology.

Methods: Patients with TLE on scalp EEG monitoring and varying degrees of hippocampal atrophy (HA) on MRI were studied prospectively with longitudinal depth electrodes and multiple subdural strip electrodes. IF and quantitative HA were measured as described (Vossler et al. *Ann Neurol* 1998;43:756–62). HS was graded using the Watson scheme, and neocortex pathology was examined by counting the number of astrocytes per 400X field in a survey of 10 random fields of layers III-V of the mid portion of the middle temporal gyrus [Vossler et al. *Epilepsia* 2004;45(5)].

Results: 36 patients had depth + strip electrodes; 9 had only strips. Four of the depth + strip and 6 of the strip only patients had substantial HA. 13 depth patients had grade 0-II and 6 had grade III-V HS. 32 of the 45 subjects had intracortical gliosis measured. The hippocampus (HF) IF was slower when the IID was confined to the HF than when it was in the HF + paleocortex +/- neocortex (8.7 vs. 16.5 Hz, $p = 0.06$). The neocortical IF was faster when the IID was confined to the neo- or paleocortex than when when the IID was over the whole lobe (25 vs.12 Hz, $p < 0.03$). IIDs confined to neo- or paleocortex were faster than those confined to the HF ($p = 0.09$). The IF in the HF when the IID was in the HF +/- paleo- or neocortex was not significantly faster in patients with little HA vs. substantial HA (16 Hz vs. 9.2 Hz) or with lower grade than higher grade HS (17 Hz vs. 15 Hz). Neocortical astrocyte count did not correlate with: 1. the neocortical frequency first attained regardless of the site of IID or 2. the neocortical IF when the IID was only in the neocortex. However, astrocyte counts were significantly higher in patients whose IID was in only the lateral neocortex vs. either the HF alone or any sites other than the lateral neocortex ($p = 0.05$ and 0.01).

Conclusions: This study suggests that when seizure onset is in the HF, the HF IF is slower and is not affected by degree of HS or HA. We previously showed the the scalp EEG IF is related to degree of HS or HA. Because scalp EEG IIDs are typically delayed after the IID begins in the HF, perhaps HS affects the frequency eventually seen at the scalp as the ictal discharge evolves. Neocortical IFs are faster than HF-only IFs, but are not correlated with degree of intracortical gliosis. The greatest astrocytosis occurred in seizures beginning only in lateral neocortex.

1.132
REAL-TIME SEIZURE DETECTION WITH CELLULAR NEURAL NETWORKS

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Rationale: Immediate detection of epileptic seizures in the EEG represents a significant problem in epileptology. The underlying morphology of a seizure usually exhibits a high intra- and interindividual variability and thus, a precise detection usually requires detailed analysis for every particular case. Previous studies have shown that neural networks represent an appropriate paradigm for the recognition of hidden patterns in noisy and non-stationary environments. Here, we propose a novel approach to the problem of automated real-time seizure recognition in EEG using Cellular Neural Networks (CNN). Such networks have a massive computing power, allow parallel computation, and are already available as integrated circuits.

Methods: The proposed method exploits the phenomenon of induced pattern formation within a locally perturbed nonlinear medium, simulated by a CNN. This system along with an appropriately chosen set of internal parameters exhibits spatial-temporal disorder. The process of induced pattern formation can be regarded as detection of certain transient rhythms within applied local perturbation, i.e., the EEG. In this retrospective study, we applied our method to automatically detect seizures in intracranial multi-channel, multi-day EEG recordings from patients undergoing presurgical evaluation.

Results: First observations show that our proposed technique allows to detect seizures with a high sensitivity and specificity. By construction, our method is able to immediately detect these events. However, we observed a trade-off between the number of false detections and the latency of detection relative to the electrical seizure onset as defined by an expert reader.

Conclusions: Our preliminary findings indicate that, in principle, the proposed method can be used as a real-time seizure detector. However, further improvements are necessary in order to achieve a high degree of generalization. Nevertheless, we expect a future implementation as a miniaturized real-time detection device to allow a variety of clinical applications. (Supported by The Deutsche Forschungsgemeinschaft.)

1.133
MOTOR CORTEX MAPPING AT THE BEDSIDE IN PATIENTS WITH IMPLANTED ELECTRODES USING HIGH-FREQUENCY PULSE TRAIN STIMULATION AND EMG PICKUP

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Rationale: The development of magnetic and electrical high-frequency pulse train methods for motor testing make it possible to stimulate the motor cortex safely and use the evoked EMG to quantify responses. We describe a similar method for use at the bedside in intracranial implant patients requiring motor mapping as part of their presurgical workup.

Methods: Pairs of adjacent subdural electrodes were systematically stimulated with brief trains of constant current pulses triggering single-trial EMG responses in a 100 msec observation window. Trains of 7 pulses with duration 300 usec/phase at 500 Hz and maximum 20 mA current were used, and repeated every 2 sec until threshold motor responses were elicited or the maximum current reached. A selection of 8 muscles on the contralateral face, arm and leg were used for the EMG. The same electrode pairs were stimulated using conventional 50 Hz pulse

trains lasting 2–5 sec with duration 500 usec/phase and maximum 12.5 mA current, and repeated approximately every 30 sec until a positive motor response was elicited or the maximum current was reached without interference from induced afterdischarges or seizures. These stimulation parameters are very comparable in conforming to accepted safety standards for cortical stimulation in terms of charge density per phase.

Results: In the 2 patients analyzed for this preliminary study, triggered EMG responses in contralateral muscles were elicited from electrodes located over primary motor cortex using a little as 1 mA current, whereas no discernible EMG responses were elicted from electrodes located over other cortical areas. Although the patients often felt brief twitches in the triggered muscles, this was not uncomfortable, and no afterdischarges or seizures were observed. In one patient, the cortical motor map derived in this way showed very good concordance with the same map made via conventional 50 Hz stimulation and also was supported by anatomical renderings as well as SSEP mapping. In the second patient, the conventional mapping using 50 Hz stimulation could not be completed due to repeatedly induced seizures at very low stimulation current, while the pulse train method provided a well-delineated motor map that was well-supported by anatomical renderings and SSEP mapping. Stimulation of the supplementary motor area in this patient did not produce motor responses, which may indicate the method is specific to primary motor cortex.

Conclusions: The described method appears to be a safe, efficient and quantitative approach for motor mapping in patients who are difficult to test due to a low seizure threshold or an inability to cooperate. It also has the advantage that it can be done (or repeated) in the OR to guide electrode implantation or resection. (Supported by Dartmouth-Hitchcock Medical Center.)

1.134
FUNCTIONAL ORGANIZATION OF SENSORIMOTOR CORTEX IN EPILEPTIC PATIENTS WITH FOCAL MOTOR SEIZURES

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Rationale: Epilepsy surgery in central regions is difficult because the risk of motor deficit. Epileptogenic network involving central regions with or without brain lesions may be accompanied by reorganization of the sensorimotor areas. The aim of this study was to explore this plasticity by noninvasive methods

Methods: We explored 8 epileptic patients with focal motor seizures. We used 3 different electrophysiological methods to perform a cortical mapping of sensorimotor areas: the transcranial magnetic stimulation (TMS); the somatosensory evoked potentials (SEP); and the cortical event-related (de)synchronization (ERD/ERS) of central rhythms during a self-paced movement. Electroencephalogram (EEG) was recorded from 128 channels. SEP and ERD/ERS were computed from the deblurred EEG.

Results: Clinically, no patients displayed motor or sensory deficit out of epileptic seizures. Compared to the healthy cortical hemisphere, sensory and motor functions were shifted to cortical regions contiguous to epileptogenic region. In most of patients, results obtained with different electrophysiological methods showed a good concordance.

Conclusions: We conclude that abnormal excitability of epileptogenic region induces a reorganization of motor and sensory functions within adjacent cortical regions. This plasticity can be investigated by noninvasive electrophysiological methods. It could allow treating these patients by surgery even in rolandic regions. [Supported by Fondation Française de la Recherche sur l'Epilepsie (FFRE).]

1.135
DETERMINANTS OF HEALTH-RELATED QUALITY OF LIFE IN A COMMUNITY NEUROLOGY SETTING

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Rationale: To determine factors that contribute to health-related quality of life (HRQOL) in patients with epilepsy. The goals of successful antiepileptic drug (AED) therapy are seizure freedom, lack of side effects and normal quality of life. Recent studies indicate that a change to an AED with a lower adverse event burden may improve quality of life in patients with epilepsy without sacrificing seizure control (Gilliam. *Neurology* 2002;58:S9–S20).

Methods: Data for this analysis were collected at time of enrollment as part of a large outpatient epilepsy study. Patients with epilepsy age 16 years and older enrolled due to poor seizure control or unacceptable side effects on their current AED therapy. We measured the Quality of Life in Epilepsy-31 (QOLIE-31), Profile of Mood States (POMS), and Adverse Events Profile (AEP). The QOLIE-31 is a 31-item assessment of overall quality of life with higher scores indicating better quality of life scores; scores range from 0–100. The POMS is a 65-item assessment of overall mood with higher scores indicating greater mood disturbance; total mood disturbance scores range from 32 to 200. The AEP is a 19-item assessment of AED adverse event burden with higher scores indicating greater burden; scores range from 19–76.

The primary outcome measure for this analysis was QOLIE-31 overall score. Variables analyzed included: age, gender, ethnic origin, seizure duration, seizure etiology, seizure type, reason for entry into study, average monthly seizure frequency, POMS subscales (depression/dejection, tension/anxiety, fatigue/inertia, confusion/bewilderment, anger/hostility, and vigor/activity) and the AEP score. Stepwise linear regression was performed to determine which factors independently correlate with overall QOL.

Results: 196 patients enrolled (mean age 43 years, 58% female, median baseline seizure frequency 2/month). The majority of patients were taking older AEDs, including carbamazepine, phenytoin, and valproate. Multiple Linear Regression revealed that AEP score ($P = <0.0001$), total POMS score ($P = <0.0001$), anger/hostility subscale ($P = 0.0002$) and confusion/bewilderment subscale ($P = <0.0001$) were independent predictors of the overall QOL. Seizure frequency was not an independent predictor of overall QOL.

Conclusions: These preliminary results suggest that medication side effects and overall mood state are the most important determinants of the variability in HRQOL in patients with epilepsy in a community neurology setting. (Supported by GSK Research and Development.)

1.136
EFFECT OF DEXMEDETOMIDINE ON EPILEPTIFORM DISCHARGES IN ADULTS WITH MEDICALLY REFRACTORY EPILEPSY

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Rationale: Dexmedetomidine, a selective α_2-agonist, exerts anesthetic and analgesic effects without suppressing respiratory function. It has been reported to lower the seizure threshold in animals but this effect has not been noted in humans. To determine its potential utility for epilepsy surgery, we studied this agent's effect on epileptiform activity in patients with refractory epilepsy.

Methods: An anesthesiologist administered dexmedetomidine intravenously over the course of one hour to five patients undergoing inpatient video/EEG monitoring. EEG was recorded for at least 15 minutes prior to the infusion and for at least one hour after the infusion was stopped. EEG was reviewed by a board certified clinical neurophysiologist. Epileptiform discharges and bursts of epileptiform discharges were counted for 15 one-minute epochs prior to the infusion and after the infusion. Comparison of spiking rates before and after the infusion was performed for each patient using two-tailed student t tests.

Results: The spiking rate was not significantly changed in two patients. The spiking rate was at least modestly increased in three patients. Two patients with increased spiking also had an increase in the frequency of bursts of spikes and subclinical, electrographic seizures. One of the patients that did not have an increase in spiking had a typical, clinical seizure 30 minutes after the infusion ceased. Localization of all epileptiform discharges during the infusion was identical to the pre-infusion localization.

Conclusions: Dexmedetomidine does not suppress epileptiform activity. It seems to modestly enhance epileptiform activity in some patients. These findings suggest that it may be a useful anesthetic agent during seizure surgery.

1.137

PROPAGATION OF PARTIAL SEIZURES IS ASSOCIATED WITH INCREASED SIGNAL COMPLEXITY NEAR SEIZURE FOCUS

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Rationale: Epileptic seizures are network phenomena involving synchronous activity of multiple neurons. Partial seizures originate from focal regions of epileptogenesis and have variable patterns of regional propagation. The influences of these regional networks on the seizure focus and subsequent seizure evolution is not fully understood. To investigate these influences, measures of seizure complexity and propagation are studied using methods derived from time-frequency decomposition.

Methods: We analyzed data from 61 partial seizures from 8 different patients with mesial temporal onset epilepsy (MTLE) and 117 seizures from 10 patients with neocortical lesional epilepsy (NLE) monitored in the epilepsy monitoring unit for pre-surgery evaluation with intracranial subdural grid arrays in 2000–2003. We applied the matching pursuit (MP) method developed by Mallat and Zhang (1993). The Gabor atom density (GAD) method (Jouny et al. 2003), derived from MP, provides a measure of signal complexity. Propagation index (PI) was defined by the average number of channels involved (GAD larger than threshold). The same threshold was used for all patients within the same group (MTLE,NLE) but different values were used for each group.

Results: GAD reveals that mesial temporal onset seizures and neocortical onset seizures have similar complexity patterns when comparing similar types of seizures. But overall MTLE seizures exhibit higher GAD values than NLE seizures (0.63 ± 0.29 versus 0.58 ± 0.17; $p < 0.05$). In both groups, partial seizures which secondarily generalized have longer duration at the focus than those that did not generalized. For all partial seizures, the extent of seizure propagation max(PI) and the signal complexity of the seizure GAD_{max} at the contact closest to the seizure focus were correlated for both groups. This correlation was stronger for NLE ($R^2 = 0.579$; $F = 23.8$; $p < 0.05$) than MTLE ($R^2 = 0.287$; $F = 158.1$; $p < 0.05$).

Conclusions: Partial seizures that propagate regionally result in increased complexity of the ictal signal near the seizure focus. This suggests that regional networks are not merely passive pathways for seizure spread, but that these networks have the potential to influence the activity of the seizure focus itself. The possibility that such remote network influences may contribute to focal seizure dynamics and subsequent seizure evolution and spread should be considered. Similarly, interventions (e.g. stimulation) that affect these regional networks somewhat remote from the focus may have the potential to influence seizure evolution and duration. (Supported by NIH grant NS 33732.)

1.138

VAGUS NERVE STIMULATION EFFECTS ON POWER AND COHERENCE SPECTRA OF INTRACRANIAL ELECTROENCEPHALOGRAPHY

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Rationale: To date, Vagus Nerve Stimulation (VNS) is the only FDA approved effective electrical stimulation treatment of epilepsy. Although recent studies hypothesize how VNS effectively reduces seizure frequency in many medication refractory patients, its mechanism of action remains unclear.

Human studies of scalp recorded EEG have shown variable results with respect to VNS related changes. Although some EEG studies demonstrate changes in occurrence of interictal epileptiform discharges with VNS, corresponding electrocorticography (ECoG) studies are virtually nonexistent. To our knowledge, there have been no frequency analyses of ECoG with VNS. Power spectra demonstrate the relative power of regional cortical activity at a broad range of frequencies. Coherence is the cross-correlation of frequency content between regions.

In this study, we analyze the effects of VNS on power spectra and coherence of interictal ECoG.

Methods: Two patients with medication refractory seizures and functioning VNS were admitted to our epilepsy monitoring unit for intracranial EEG monitoring for epilepsy surgery evaluation. ECoG was recorded with subdural electrodes placed over the most active cortical regions, as determined by video-EEG scalp recordings. 12 hours of continuous video-ECoG were recorded, 6 hours prior to turning VNS ON, and 6 hours after. Two hours of ECoG were analyzed, one hour with VNS ON and one hour with VNS OFF. Power and coherence spectra during these two epochs were compared for regions with greatest interictal epileptiform activity.

Results: In patient 1 a broad reduction in ECoG power occurred with VNS ON. For patient 2 the opposite effect was observed. For patient 1, the coherence between adjacent electrode pairs was decreased at lower frequencies (3–7 Hz) with VNS ON, but was unchanged at the remaining frequencies. A broad peak in coherence at 7–9 Hz (the interictal spike rate) occurred with VNS ON for patient 2. Above 11 Hz there was a broad decrease in coherence with VNS ON for patient 2.

Conclusions: VNS had opposite effects on ECoG power spectra from the two patients.

VNS resulted in opposite changes in ECoG coherence at lower frequencies, and a broad decrease in ECoG coherence in one patient at higher frequencies.

Different patterns of ECoG frequency response to VNS can occur both within and between regions. This may reflect different mechanisms of action for VNS.

Further frequency analyses of ECoG in these and other patients will be performed to determine the different patterns of change with VNS in regions adjacent to and remote from the epileptic focus. This could elucidate what response patterns can be predictive indices of VNS efficacy.

1.139

TEMPORAL "THIRD RHYTHM" RESULTING IN ERRONEOUS DIAGNOSIS OF EPILEPSY

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Rationale: The third rhythm is a temporal alpha range rhythm, which may have a relationship to wicket spikes. This may occasionally contribute to misdiagnosis of epilepsy. We have encountered seven patients who received the erroneous diagnosis of epilepsy based on misinterpretation of the third rhythm.

Methods: We reviewed medical records and EEG data in seven patient misdiagnosed with epilepsy because of a third rhythm. Four patients received EEG-video monitoring, three with sphenoidal electrodes. Three others had only standard EEG.

Results: Four patients with no skull defect had video EEG monitoring, three with sphenoidal electrodes. Three with skull defects had only standard EEG. The third rhythm consisted of rhythmic alpha range activity recorded from the sphenoidal electrode or the anterior-mid temporal region (Fig. 1). It was at times particularly sharp in the sphenoidal electrode. The third rhythm disappeared with deepening sleep. Nonepileptic psychogenic seizures were recorded in three patients. These patients were discharged on no antiepileptic drugs (AEDs), and stopped having attacks. One other without video-EEG was taken off AEDs, with no seizures.

Conclusions: The third rhythm can have a sharp appearance in some patients, particularly on sphenoidal recordings, and can be easily misdiagnosed. A sharp third rhythm should be added to the list of "benign variants" misdiagnosed as epileptiform.

1.140

CAN WE PREDICT WHICH PATIENTS WITH REFRACTORY EPILEPSY WILL HAVE OBSTRUCTIVE SLEEP APNEA?

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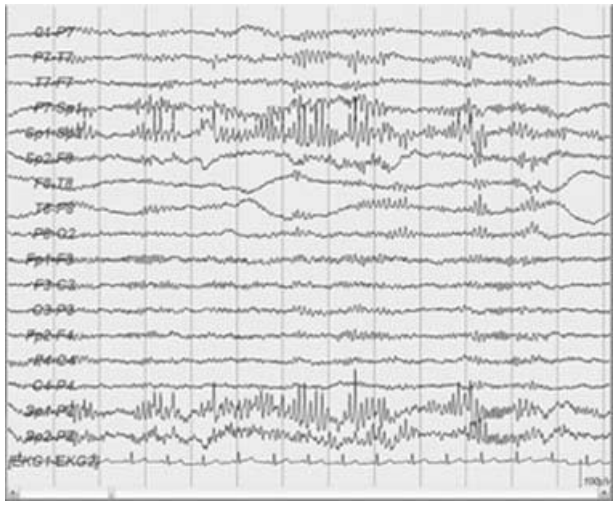

Rationale: To identify characteristics predictive of obstructive sleep apnea (OSA) on polysomnography (PSG) in medically refractory epilepsy patients who have already completed a screening questionnaire and clinical interview suggesting OSA. These patients were participating in a pilot clinical trial of the effects of treating sleep-disordered breathing on seizure frequency. Minimizing false positives who appear to have symptoms of OSA by survey with confirmatory clinical history, but not by PSG, will contribute to the success of a phase 3 trial.

Methods: Thirty adults with four or more seizures a month and a score of 26 for women or 29 for men on the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ) were invited to a screening interview with one of the authors. The SA-SDQ is a validated instrument for predicting OSA which has been used in the general population and in those with epilepsy. If the suspicion of OSA was confirmed by clinical interview and other criteria were met, patients were enrolled in a prospective study in which they underwent two nights of PSG to confirm OSA. OSA was defined by an apnea-hypopnea index (AHI) of 10 events/hour on either PSG night.

Results: Eighteen of 30 patients (60%) had OSA on PSG. The only two variables that predicted OSA on PSG were age at PSG and gender. Subjects with OSA were older (45.5 $\pm$ 11.8 vs. 35.8 $\pm$ 11.8, mean $\pm$ standard deviation; $t = 2.3$; $p = 0.03$; two-tailed student t-test) and more likely to be male (pearson chi-square 3.8, $p = 0.05$). Epworth sleepiness scale, body mass index (BMI), number of seizures/month, habitual loud snoring or witnessed apneas, number or type of antiepileptic drugs, hypertension, SA-SDQ score, or nocturnal seizures were not helpful in predicting which patients suspected of having OSA actually had PSG-documented OSA.

Conclusions: Age and gender were useful variables in predicting which patients with suspected OSA had PSG-documented OSA. Variables useful for predicting OSA in the general population (daytime sleepiness, hypertension, BMI) and those unique to the epilepsy patient (seizure frequency, antiepileptic drugs, and nocturnal seizures), were not informative, although the small sample size may bias our results. Identification of OSA in epilepsy patients is challenging. Questionnaires, while useful, are not foolproof in detection of OSA. Clinical trials may need to plan for a proportion of patients testing as false positives for OSA. Using PSG in epilepsy monitoring units to screen patients for OSA may also be an effective strategy to explore. [Supported by NINDS R01 NS 042698 (B.A.M.), NINDS K02 NS2099 (B.A.M.), and GCRC grants RR000095 (Vanderbilt), RR00042 (Michigan), and RR00046 (University of North Carolina).]

1.141
INCREASED CORTICAL EXCITABILITY AND REDUCED INTRACORTICAL INHIBITION IN SEIZURE GENERATION IN FOCAL CORTICAL DYSPLASIA: A PAIRED PULSE DIRECT CORTICAL STIMULATION STUDY

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Rationale: Alternation of intracortical excitatory and inhibitory system in focal cortical dysplasia has not been well elucidated in vivo in humans. We here report the ictal alternation of the cortical excitability and intracortical inhibition.

Methods: A 31-year-old man with intractable partial epilepsy who underwent invasive monitoring with subdural electrodes was investigated. The seizures started with somatosensory auras of the left foot, which evolved into either left foot clonic seizures or bilateral asymmetric tonic seizures. Invasive evaluation revealed a seizure onset zone in the primary sensorimotor area of the left foot. The pathology was cortical dysplasia. The subject gave a written consent to this protocol (IRB No. 443).

Repetitive single pulse electrical stimuli (1Hz, alternating polarity, duration of 0.3 msec) were first delivered to the left foot primary sensory area (SI) (focus) as well as the left hand SI (control). Corticocortical evoked potentials (CCEPs) were recorded by averaging electrocorticograms recorded from the adjacent areas time-locked to the stimulus (bandpass 0.5–1500 Hz, a total of 40–60 trials). The threshold intensity (TH) to elicit CCEPs was determined in this single pulse stimulation study. Then, the paired pulse stimulation was performed by conditioning (TH x 50%) and testing (TH+1 mA) stimuli with interstimulus interval (ISI) of 1–100 ms. Intracortical inhibition (ICI) at the stimulated site was investigated by analyzing amplitude change of CCEPs.

Results: 1) Single pulse stimulation at the foot and hand SI elicited CCEPs from the surrounding areas with the maximum CCEP at the primary motor area (MI) of the foot and hand, respectively. Compared with the control stimulation (hand SI), ICI by paired pulse stimulation of the focus (foot SI) was more intense (7–31% of decrease vs. 17–18%) in a wider range of ISI (1–10 ms vs. 1–2 ms). 2) Incidental recording of CCEPs during a somatosensory aura revealed the increased amplitude of CCEP (141% of interictally recorded CCEP) at the foot MI in response to single pulse stimulation of the foot SI. Different from the aforementioned interictal finding, ICI by paired pulse stimulation of the focus (foot SI) disappeared during the aura. No seizure pattern was seen at the foot SI or MI during the somatosensory aura before its evolution into the left foot clonic seizure.

Conclusions: Increased cortical excitability and decreased intracortical inhibition during the aura is likely the underlying pathophysiology of seizure generation in this particular patient with focal cortical dysplasia. (Supported by a research grant from the Japan Epilepsy Research Foundation.)

1.142
SEIZURE PREDICTION: INFLUENCE OF EEG BAND-PASS FILTERING ON THE PREDICTIVE PERFORMANCE OF SYNCHRONIZATION MEASURES

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Rationale: An important issue in epileptology is whether epileptic seizures can be anticipated prior to their occurrence. Of particular interest is the question whether information extracted from the EEG of epilepsy patients can be used for the prediction of seizures. Recent studies have shown a superiority of bivariate measures (which characterize the synchronization between two EEG signals recorded simultaneously from different locations in the brain) over univariate measures (derived from a single EEG signal) in distinguishing the seizure-free interval from the pre-seizure period. For a particular class of bivariate measures, namely, measures for phase synchronization, it is an unresolved issue whether the predictive performance of these measures can be improved by band-pass filtering the EEG prior to analysis. In this study we examine the influence of band-pass filtering on the predictive performance of these measures.

Methods: We analyzed continuous multi-day multi-channel intracranial EEG recordings from up to now 5 patients undergoing invasive presurgical diagnostics. Recordings covered more than 600 hours and contained 25 seizures. Using two different classes of measures for phase synchronization, one based on the wavelet transform (providing intrinsic band-pass filtering) and one based on the Hilbert transform (no filtering),

we calculated time profiles of these measures for the different channel combinations using a moving window technique. Wavelet filtering was performed according to the classical EEG bands and sub-bands. Using ROC statistics to discriminate between the preictal and interictal amplitude distributions of the obtained profiles, we quantified and compared the predictive performance of the synchronization measures with and without band-pass filtering.

Results: For the patients under investigation, the predictive performance of the synchronization measures using band-pass filtering did not vary significantly among the different EEG frequency bands, but reached the same values as the synchronization measures without filtering.

Conclusions: Findings indicate that the overall predictive performance of synchronization measures of the EEG is not significantly improved by band-pass filtering of the signals. The changes in phase synchronization preceding epileptic seizures appear not to be generally confined to certain frequency bands. (Supported by the intramural research fund BONFOR of the University of Bonn and by the Deutsche Forschungsgemeinschaft.)

1.143
CORTICO-CORTICAL CONNECTION BETWEEN LATERAL AND MESIAL MOTOR CORTICES: A CORTICO-CORTICAL EVOKED POTENTIAL STUDY

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Rationale: In order to better comprehend the cortico-cortical networks involved in ictal motor manifestation (or phenomenology), it is essential to know cortico-cortical connections in the human motor system in vivo. The knowledge of neuronal in vivo connectivity in humans has been limited. Our understanding of thi subject comes from tracer injection techniques or in vivo studies in the nonhuman primate. Our aim is to investigate, in vivo, the cortico-cortical connection between lateral (lateral premotor, sensorimotor) and mesial (pre-SMA, SMA) motor cortices by means of a cortico-cortical evoked potential (CCEP) study.

Methods: Seven patients with intractable partial epilepsy (age 1.6–46) underwent chronic subdural implantation in the lateral and mesial fronto-parietal regions for the presurgical evaluation. Single pulse electric stimuli (1Hz, alternating polarity, duration of 0.3 msec, at the intensity of subthreshold to clinical signs or afterdischarges) were delivered to the mesial (7 patients) and lateral motor (4) areas, and CCEPs were recorded by averaging electrocorticograms from the lateral and mesial motor areas, respectively, time-locked to the stimulus (bandpass 1–1000 Hz). The distribution of CCEPs were analyzed in relation to anatomical landmarks as well as functional regions.

Results: Short latency CCEPs were recognized both from the lateral (peak latency; mean 21.2 ms, range 9–47 ms) and mesial (mean 28.2 ms, range 11–59 ms) motor areas. Regression analysis revealed a consistent rostro-caudal correlation between the site of stimulation and the site of maximum CCEP on stimulation at both the lateral and mesial motor areas. Functionally, stimulation of the positive motor areas at the mesial and lateral motor cortices elicited CCEPs at the somatotopically homologous regions in the lateral (83%) and mesial (81%) motor cortices, respectively. In four subjects in whom stimuli were delivered to both the lateral and mesial cortices, reciprocality was observed between the two corresponding areas in the majority of connections (76–89%).

Conclusions: The present study demonstrated, for the first time in vivo in humans, a cortical network connecting the rostral and caudal subdivisions each in the lateral and mesial motor cortices. Functionally, the somatotopically homologous regions were connected between lateral and mesial motor cortices.

1.144
THE EEG IN OLD AGE EPILEPSY

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Rationale: Above the age of 60 years, there is an increase of prevalence and incidence of epileptic seizure disorders. Their EEG findings may be particularly informative with regard to etiology and epileptological analysis.

Methods: At this age, primary generalized epilepsy with its peak from 8 to 25 years and typical 3/sec spike-wave (absences) or polyspike (myoclonus) patterns is extremely rare. Absence status of "de novo" old age onset may appear to be generalized but the paroxysmal pattern suggests focal onset (frontal-central). In acute and mostly fatal anoxic encephalopathies, the epileptic phenomena are of secondary nature.

Epilepsies arising from the Rolandic area show some increase in old age. This suggests hyperexcitability of this region in elderlies.

Results: Most frequently affected by old age is the temporal lobe; due to ischemic pathology and possibly also to pathogenic effects of progenitor cells. From the EEG viewpoint, anterior-midtemporal minor slow and sharp activity (including "wicket spikes") are a very frequent old age pattern, mostly on the left and usually without seizures. Clinical problems (memory loss, dizziness, etc.), however, may benefit from antiepileptic medication.

Conclusions: All of these observations are based on personal data. The "take-home-message": old age acts differently on the major form of epilepsy.

1.145
MEG EVIDENCE FOR A NEUROBIOLOGICAL LINKAGE BETWEEN EPILEPSY AND PSYCHIATRY

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Rationale: The strong association between epilepsy and psychiatric disorders is probably related to a common neurobiological mechanism, which so far remains elusive. During the evaluation of patients with OCD and bipolar disease we found focal or regional MEG epileptiform activity (MEA) in the limbic system. We compared the source localization of this activity with the source localization of generalized spike-wave activity (G SWA) recorded in patients with generalized epilepsy.

Methods: Simultaneous MEG (Magnes 148 channels) and EEG (20 channels) were performed in 5 patients with medically refractory generalized epilepsy (mean age: 39 year), in 12 OCD patients (mean age: 33 years) and in 19 patients with bipolar disease (mean age: 39 years). Dipole source localization was performed for all epileptiform potentials (OCD and bipolar disorder) and for 84 generalized and bilaterally synchronous spike-waves (generalized epilepsy group), which generated 2.853 dipoles. Minimum requirements for dipole selection criteria included : correlation > 0.90, GOF > 0.90, volume < 15 cm3 and Q $<$ 400 nAm. MEG was also performed in 12 normal subjects for control purpose.

Results: 1) Generalized epilepsy: Most GSWA bursts had a frequency of 2 to 2 1/2 Hz. The anatomical distribution of dipole source localization for SWA was as follows: cingular cortex = 1768/2853 (62%), frontal-mesial = 304/2853 (10%) and frontal-lateral = 781/2853 (28%).

2) OCD : MEA consisting of spikes or polyspikes not followed by slow wave activity was seen in 11/12 patients (92%) involving the cingular cortex (11/12 paients), insula (7/12 patients) and orbito-frontal area (4/12 patients).

3) Bipolar disease: MEA was documented in 12/18 patients (68%) and the corresponding dipole source involved the following regions : posterior cingular cortex (7/12 patients) and posterior insular area (10/12 patients).

4) MEG recordings in control subjects was normal.

Conclusions: Our findings show that MEA can be recorded in patients with OCD and bipolar disorder with a predominant distribution in anterior and posterior cingular cortex respectively. Similarly, 62% of the dipole sources for GSWA in patients with generalized epilepsy, were localized in the cingular cortex. This implies that generalized epilepsy, OCD and bipolar disease share a common neurobiological substrate. We postulate a pathophysiological linkage involving a deficit in serotoninergic neurotransmission.

1.146

EFFECTS OF CLOMETHIAZOLE ON HUMAN MOTOR CORTEX EXCITABILITY: A TRANSCRANIAL MAGNETIC STIMULATION STUDY

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Rationale: Clomethiazole has been used since 1938 for treatment of states of agitation and ethanol withdrawal syndrome. Because of its anticonvulsant effect it is additionally indicated for intractable status epilepticus.

As demonstrated in in vitro and in vivo studies in rat the mechanism of action is a potentiating effect of the inhibitory action of GABA and glycine. The effect on the excitability of human motor cortex has not been sufficiently investigated yet.

Transcranial magnetic stimulation is a well-established method to investigate the excitability of the human motor cortex. Different TMS-measures using single and paired pulse paradigms reflect different actions of synaptic receptors (GABA-A/B-agonism, glutamate antagonism) and ion channels.

The aim of our study was to verify the acute effects of clomethiazole on human motor cortex excitability by single and paired pulse TMS.

Methods: In a double-blind, placebo-controlled, crossover study, the effect of single oral doses of 192 and 384 mg clomethiazole on resting motor tresholds (RMT), MEP recruitment curves (REC), cortical induced silent period (CSP) and on intracortical inhibition (ICI) and facilitation (ICF) was investigated in 15 healthy subjects. Peripheral excitability was monitored by means of F-Wave and M-latency. For statistical analysis the nonparametric Wilcoxon signed rank test with Bonferroni correction for the comparison placebo versus 384 mg clomethiazole was used. For the confirmatory analysis level of significance was set to 0.01 after Bonferroni correction applying five tests (RMT, REC, CSP, ICI, ICF). Other data were evaluated by explanatory analysis.

Results: 90 minutes after a single oral 384 mg dose clomethiazole a significant increase of ICI at short interstimulus intervals (ISI 2ms, $p = 0{,}008$) was noticed. Furthermore a dose-independent trend of CSP prolongation was noticed (192 mg: $p = 0{,}005$; 384 mg: $p = 0{,}033$). RMT, REC and ICF were not influenced. A peripheral impact of clomethiazole could be excluded. Serum concentrations of clomethiazole were below the therapeutic range in all subjects after 192 mg and in 8 subjects after 384 mg dose. All subjects developed dose-dependent moderate adverse effects, which were mainly flu like symptoms or CNS-related (somnolence, vertigo, ataxia).

Conclusions: The results of this study confirm the potentiating effect of GABA, possibly by affecting GABAA receptors, in human motor cortex as expressed by an increase of ICI. The dose-independent prolongation of the CSP suggests an effect on GABAB-ergic transmission.

This may explain the anticonvulsive efficacy of clomethiazole in intractable status epilepticus. The lack of dose dependence could be due to a low and variable oral bioavailibility. (Supported by ULRAN Professorship for Neurology/Epileptology.)

1.147

RESTRICTED HIGH-FREQUENCY COHERENT NEURAL ACTIVITY REVEALED BY WIDE-BAND MAGNETOENCEPHALOGRAPHY (MEG) IN EPILEPSIA PARTIALIS CONTINUA (EPC)

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Rationale: Epileptic source localization is frequently not possible in those patients with EPC due to the absence of epileptiform discharges on scalp EEG. It has been suggested that MEG may yield the critical localizing data necessary for curative surgery in these challenging cases. Combining wide-band MEG with corticomuscular coherence (CMC) analysis, we studied a 40-year-old female with EPC involving the left arm and hand, whose previous work up was extensive, but non-diagnostic.

Methods: A CTF 275-channel whole-head MEG System with 0.6 KHz and 6 KHz acquisition rates was used to simultaneously acquire MEG, EEG and EMG from 4 representative muscles (left biceps, extensor digitorum communis, abductor pollicis longus and first dorsal interosseous). Muscular events were used as a marker for back-averaging MEG-EEG events. The sources of the MEG-EEG events were localized using dipole analysis and the data were co-registered into a 3D-reconstructed 3T MRI using the CTF software. Band pass filtered (0–1500Hz) data of forty-one 0.5 second epochs centered on muscle activity was used to determine CMC from the spectral cross-correlograms at each sensor.

Results: Somatosensory evoked potentials were normal in all extremities. Visual analysis of the MEG-EEG recordings revealed different types of events according to recording condition. MEG events without EEG events were identified while the patient was on full medication doses, and a combination of events after two doses were held (MEG events only, simultaneous MEG-EEG events, and EEG events only corresponding with EMG events). A pre-twitch MEG dipole was localized in the right precentral gyrus corresponding anatomically with the cortical lesion identified on gradient-echo MRI as "hemosiderin," while the post-twitch MEG dipole was localized more sagittally in the supplementary motor cortex. Different CMC values above those expected were found. Significant CMC in the alpha (8–13Hz) and beta (13–30Hz) bands was found in the right central and parietal regions as well as the left central regions, while in the gamma band (30–70Hz), significant CMC was found primarily in the right central and parietal regions. There was no CMC in any regions at frequencies above the gamma range.

Conclusions: This is the first known report of non-invasively demonstrated high frequency CMC during spontaneously occurring muscle activity in EPC, suggesting that the rhythmical organization of the cortical drive to muscle extends into the high frequency (gamma) bands. This activity may be more specifically related to the spontaneous abnormal movements since CMC in the gamma band was spatially more localized and temporally more directly related to the movements. Advanced MEG methods may provide critical insights into understanding the complexity of sources in EPC, and may further clarify the physiological bases of CMC. (Supported by The NINDS protocol 01-N-0139.)

1.148

INTRACAROTID SODIUM AMOBARBITAL TEST: AN INTRACRANIAL EEG STUDY

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Rationale: Controversy exists in what structures are inactivated in the intracarotid sodium amobarbital (ISA) test. Therefore, intracranial EEG patterns were correlated to electrode location in patients with bilateral depth electrodes. To determine the EEG change that occurs with successful ISA testing, clinical and EEG findings were analyzed. A previous study described primarily increases in Δ activity.

Methods: 7 ISA injections were performed in 4 presurgical temporal lobe epilepsy patients with bilateral frontal and temporal depth electrodes. Each patient had angiography to determine crossfilling. An ISA bolus injection of 75 to 200 mg was given in the dose needed to achieve hemiplegia. Testing for language dominance and hemisphere memory support was then attempted. Digital EEG recorded was analyzed to determine duration, location, progression and type of change. In each case, the seizure focus showed EEG change. EEG baseline returned prior to contralateral testing. Clinical responses to ISA testing were correlated with EEG findings. The physician performing the ISA test and a physician blinded to the case reviewed each EEG.

Results: The most common pattern found was an increase in Δ activity with a striking superimposed β and/or θ activity, 5/7 injections (71%). Increased β activity was first seen in the frontal lobe followed by the temporal lobe. β activity was more prominent in mesial temporal structures than Δ activity. Presence of bifrontal EEG changes in 4 of 7 injections correlated with crossfilling in 3 cases. With increased Δ and β activity in the frontal and temporal lobe, clinical hemiplegia was achieved and patient attention was adequate for testing. EEG changes

averaged 402.2 ± 53.87 seconds before return to baseline. In one injection, a unilateral burst suppression pattern of high amplitude β and θ activity occurred. This patient's strength returned prematurely and EEG baseline returned significantly quicker than other injections, 260.5 ± 13.44 seconds ($p = 0.03$). A generalized low amplitude fast β activity not associated with crossfilling occurred in one injection. This was associated with somnolence and inability to complete any testing and the EEG returned to baseline in 653.5 ± 9.19 seconds, significantly slower than other injections ($p = 0.03$). Duration of EEG changes correlated highly between readers ($r = 0.95$, $p = 0.001$).

Conclusions: Increased Δ activity with a superimposed β and/or θ activity in frontal and temporal depth electrodes is often found with ipsilateral functional inactivation and successful completion of the ISA test. Mesial temporal structures show more prominent β activity than Δ activity suggesting direct inactivation of that area. Intracranial EEG may show low amplitude fast β activity or a burst suppression pattern with suboptimal amobarbital doses.

1.149
LANGUAGE-INDUCED EPILEPSY, STUTTERING, IDIOPATHIC GENERALIZED EPILEPSY: PHENOTYPIC STUDY OF ONE LARGE FAMILY

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Rationale: Language-induced epilepsy includes seizures precipitation by speaking, reading, and writing. The seizures are similar to those of primary reading epilepsy, and patients may report one or several seizure triggers related to language. The nosologic position of language-induced epilepsy is not clear: reported cases resemble reading epilepsy but are more heterogeneous than those of primary reading epilepsy. We have had the opportunity to better characterized this syndrome, we performed a clinical and neuro-physiological study in a multigenerational family.

Methods: Fifteen members (8 affected) on 3 generations were studied. All patients underwent an EEG-Video (awake and during sleep). A standardized protocol was applied in order to test the effect of reading, speech, praxis during EEG-Video monitoring.

Results: We found three cases of idiopathic generalized epilepsy (IGE). Five patients presented jaw jerking induced by language mimicking stuttering and corresponding to focal myoclonias involving orofacial muscles. We found rolandic EEG spikes, inter-ictal when spike were followed by a slow wave, symptomatic of facial myoclonias if isolated. CT scan or MRI when performed were normal. Levetiracetam was effective in four patients.

Conclusions: This family study demonstrates phenotypic heterogeneity. Patients may present isolated facial myoclonias induced by speech without generalized tonico-clonic seizures. Epileptic origin of stuttering may be investigated when familial history is positive for IGE. A common genetic base is under investigation.

1.150
EMERGENCY EEG USE IN THE INTENSIVE CARE UNITS OF A UNIVERSITY HOSPITAL

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Rationale: To investigate the reasons an emergent electroencephalogram (EmEEG) is ordered in the Intensive Care Units (ICUs) compared to the hospital Ward, examine its usefulness and find predictive variables for its results.

Methods: We retrospectively identified all EEGs ordered between December 1997 and March 2002 and performed within one hour from their request in our University hospital. We compared the tests ordered by the four hospital ICUs with those ordered by the Ward and developed predictive models for the results based on clinical variables.

Results: The ICUs ordered 129 (49.4%) of all EmEEGs during the study period and the Ward 132 (50.6%) of the tests. On the requisition forms, the test was ordered to rule out status epilepticus more frequently by the ICUs (68.2% vs 52.7%, chi square test $p < 0.01$) and to rule out seizures by the Ward (28.2% vs 17.8%, $p < 0.05$). The Neuro-ICU ordered the test more frequently to exclude non-convulsive status than the other ICUs (OR, 95% CI 16, 3.2–79, $p < 0.001$). Compared to non-ICU, ICU patients with head trauma or post cardiopulmonary arrest had the tests more frequently ordered (3.2, 1.2–8.4 and 17, 4–74, $p < 0.01$) and patients with stroke less (0.3, 0.12–0.6, $p = 0.001$). The frequency of suspicious clinical activity (subtle muscle twitching or strange dystonic posturing) or recent tonic-clonic seizure when ordering the test did not differ between ICUs and Ward. EEG findings consistent with convulsive status epilepticus and generalized slowing were found more frequently in the ICU recordings (4.8, 1.3–17, $p = 0.009$ and 1.7, 1.1, 2.8, $p = 0.03$). Normal EEG, interictal epileptiform activity or focal non-epileptic slowing were more frequently present on the Ward recordings (3.3, 1.1–10, $p = 0.02$, 2, 1.1–3.3, $p = 0.03$ and 2.5, 1.1–5, $p = 0.02$, respectively). In at least 12.4% of ICU patients the test was expected to lead to an anti-epileptic medication change. In multivariate logistic regression models, cardiopulmonary arrest (3, 1.2–8, $p < 0.05$) and age (1.03, 1.003–1.05, $p < 0.05$) were predictive of any epileptic activity found on EmEEGs in ICU patients.

Conclusions: In our university hospital, the ICUs order EmEEG more often than the Ward to exclude status epilepticus, although based on clinical signs the suspicion level may not be higher. The Neuro-ICU, particularly, orders the test more frequently than to other ICUs to exclude non-convulsive status epilepticus. Indeed, status epilepticus is confirmed more frequently in the ICUs than the Ward by the test. Cardiopulmonary arrest and increasing age are predictors of any epileptic activity on EmEEG in ICU patients.

1.151
ELECTROENCEPHALOGRAPHIC EVALUATION OF LEAD-INTOXICATED CHILDREN

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Rationale: The aim of our study was to establish the eletrencephalographic changes/patterns found in children from Adrianopolis (Parana, Brazil) with abnormally high blood levels of lead, as a result of environment contamination from a local factory. We also tried to correlate eletrencephalographic (EEG) changes with factors related to variation of lead blood levels.

Methods: Twenty children, range 2 to 14 years of age (mean 9,6 y/a), who suffered from chronic lead intoxication were studied. Blood lead levels were measured by atomic absorption spectroscopy and ranged from 20,1 to 35,8 mg/dL (mean 25,42 mg/dL). All subjects had an EEG recording and underwent either intelligence measurement or a more complete neuropsychological evaluation, depending on their age. Brain CAT scans and whole blood count (WBC) were also performed. EEG recording was standardized, with recordings samples of wakefulness, sleep (spontaneous or induced by chloral hydrate), photic stimulation and voluntary hyperventilation, if the subject was cooperative.

Results: All of the children had normal physical and neurological examinations and none of them had a history of seizures. Of the thirteen children who underwent neuropsychological testing, 6 had low range normal IQ and 7 had borderline for mental retardation results. Brain CAT scans were abnormal in only two subjects, both of which had parenquimal calcifications suggestive of neurocysticercosis. WBC disclosed anemia in 9 children. EEG evaluation failed to disclosed a specific pattern. However, 5 EEG recordings showed an irregular slow activity and in one of those epileptiform changes were also found. Statistical analysis (student's t test) showed no correlation between blood lead levels and abnormal EEG findings in either the normal or abnormal EEG groups

Conclusions: There's no specific EEG pattern in those children who suffered chronic lead intoxication. Higher blood lead levels do not predispose to EEG abnormalities, even though such abnormalities were found in a proportion higher than that expected for age-matched controls.

1.152
DISTRIBUTION OF SEIZURE PRECIPITANTS IN PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY: EVALUATION BASED ON QUESTIONNAIRE
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Rationale: Endogenous and exogenous seizure precipitants are commonly found in patients with epilepsy. Among the generalized idiopathic epilepsies, Juvenile Myoclonic Epilepsy (JME) in one of the syndromes with better defined precipitant factors (PF): sleep deprivation, stress, alcohol intake, hormone alterations and photosensitivity. The aim of this study was to evaluate the prevalence and nature of PF of seizures in a group of patients with JME through a questionnaire elaborated and based on the literature regarding these factors.

Methods: Seventy-five patients, 36 men, aged between 13 and 53 years, attended at the outpatient clinic with electroclinical diagnosis of JME, answered a semi-structured interview. This included questions with reference to a list of precipitants that might trigger or exacerbate their seizures: sleep deprivation, stress, menstrual cycle, circadian cycle, alcohol, photic stimulation, watching TV, movements of the hands, thinking, listening to music, games, calculating, writing, reading, eating, drawing, speaking in public or playing a musical instrument. Inhibitory factors were also inquired about.

Results: Sixty-nine patients (91.7%) identified at least one precipitant or aggravating factor of their seizures. Men were more capable of identifying these factors (34 out of 36). Among the usual PF these patients cited sleep deprivation (77.3%), stress (82.7%), menstruation (33.3%), photic stimulation (14.7%) and alcohol intake (10.7%). Movements of the hands (28%), thinking (22.7%), speaking in public (10.7%), playing games, calculating and reading, 6.7% each, writing (5.4%), playing a musical instrument (4%) and drawing (2.7%) were also described. Despite the above mentioned numbers only 17 (22.7%) patients were able to recognize inhibitory seizure factors. Among them, being at ease, 14 (18.7%), going to sleep or exercising (1 each).

Conclusions: Surprisingly, items rarely mentioned as PF were found in a significant percentage of cases. Unfortunately, the frequency of inhibitory factors was far from those of the precipitants. Not only the recognition of the above factors but also being aware of the importance of avoiding them is fundamental in treating patients with JME. [Supported by FAPESP (Fundação de Amparo a Pesquisa do Estado de São Paulo), CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).]

Clinical Neurophysiology—All Ages

1.153
NONLINEARITY: THE KEY TO A SUCCESSFUL CHARACTERIZATION OF THE SPATIAL DISTRIBUTION OF THE EPILEPTIC PROCESS
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Rationale: Nonlinear time series analysis allows characterizing dynamical systems in which nonlinearity gives rise to complex and irregular behavior. While several studies indicate that nonlinear methods can extract valuable information from electroencephalographic recordings from epilepsy patients, others doubt their necessity and conjecture that the same information can be obtained using classical linear techniques. To address this issue, we compared these two concepts but included also a combination of nonlinear measures with surrogates, an approach that has been designed to specifically focus on nonlinearity. As a benchmark for the comparison of the different techniques we used the discriminative power to detect the focal hemisphere in unilateral mesial temporal lobe epilepsy.

Methods: As linear measures we used the relative power in the delta band, the decay time of the autocorrelation function, the skewness of the amplitude distribution, and the Hjorth mobility. As nonlinear measures we used the prediction error, the local flow, an estimate of an effective correlation dimension, and the algorithmic complexity. For each nonlinear measure we defined a corresponding surrogate corrected measure. To this end each nonlinear measure was calculated for the original EEG time series and set of surrogate time series. The surrogate corrected measure was calculated from the difference between the value calculated from the original EEG time series and the mean value obtained for the surrogates. We analyzed intracranial multi-channel EEG recordings (on average130 min per patient) from the seizure-free interval of 29 patients with pharmaco-resistant unilateral mesial temporal lobe epilepsy.

Results: For the linear and nonlinear measures we obtained the following numbers of correct lateralizations of the focal hemisphere. Delta power: 24, decay time of the autocorrelation function: 23, skewness: 21, Hjorth mobility: not significant, nonlinear prediction error: 18, the local flow: not significant, correlation dimension: 21, algorithmic complexity: not significant. Hence, the performance of both linear and nonlinear measures was weak if not insignificant. In contrast to this, a high performance was obtained for the surrogate corrected measures. Surrogate corrected local flow: 27 correct lateralizations, surrogate corrected prediction error: 25, surrogate corrected correlation dimension: 26, surrogate corrected algorithmic complexity: 26.

Conclusions: Nonlinear methods can be highly relevant for the lateralization of the focal hemisphere in patients with mesial temporal lobe epilepsy, provided that they are combined with surrogates. Hence, focusing on nonlinearity appears as the key to a successful characterization of the spatial distribution of the epileptic process. (Supported by Deutsche Forschungsgemeinschaft.)

1.154
SHORT-TERM OUTPATIENT EEG-VIDEO WITH ACTIVATION FOR THE DIAGNOSIS OF PSYCHOGENIC NONEPILEPTIC SEIZURES
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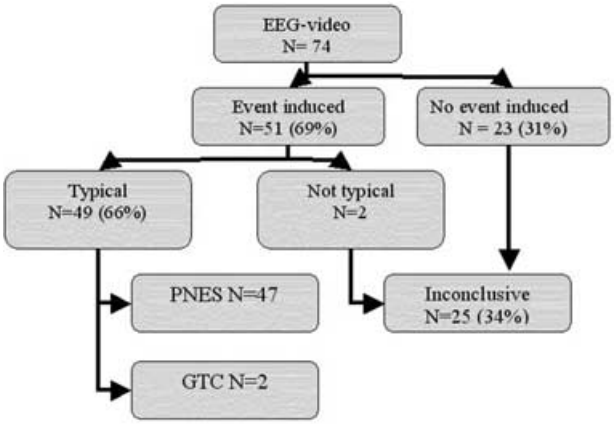
Rationale: When seizures do not respond to medications, EEG-video monitoring is the gold standard to clarify the diagnosis, and in particular to make the diagnosis of psychogenic nonepileptic seizures (PNES). However, inpatient long-term EEG-video monitoring is costly and time consuming. When the diagnosis of PNES is strongly suspected on clinical grounds, we often perform short-term (1 or 2-hour) outpatient EEG-video monitoring with activation to record an episode and obtain a diagnosis. The purpose of this study was to analyze the yield of this technique.

Methods: We reviewed data on all patients who underwent short-term outpatient (1 or 2-hour) EEG-video monitoring at our center (University of South Florida-Tampa General Hospital) over a 26-month period (October 2000 to January 2003). All patients were suspected of having PNES on clinical grounds. Activation was performed using verbal suggestion, hyperventilation, and photic stimulation, according to a published protocol [Benbadis et al, *Neurology* 2000;55: 1904–1905].

Results: See figure. The total number of short-term outpatient EEG-video monitoring was 74, and an event was induced in 51 (69%). In 49 (66%) of 74, the habitual event was induced patients, allowing a definitive diagnosis. Of these 49, 47 had definite PNES, and 2 had a typical generalized tonic clonic seizure (induced by photic stimulation), consistent with an idiopathic generalized epilepsy. In 25 (34%) of 74 patients, no conclusion could be reached, either because no event was triggered (23 patients), or because the induced event was not the habitual type (2 patients).

Conclusions: In 66% of cases, a suspected diagnosis of PNES can be confirmed by *short-term outpatient* (1or 2-hour) EEG-video monitoring with activation, thereby obviating the need for prolonged inpatient EEG-video monitoring.



1.155
STATUS EPILEPTICUS IN A PRIVATE GENERAL HOSPITAL IN SÃO PAULO, BRAZIL

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Rationale: The estimated incidence of status epilepticus (SE) is 60 cases per 100,000 population per year. Diagnosis of convulsive SE (CSE) is usually obvious, but nonconvulsive SE (NCSE) is frequently missed or mistaken for many other conditions. Therefore, any study concerning prevalence or incidence of SE may come to underestimated figures due to difficulties in diagnosis. The objective of this study is to report the incidence of SE in a private general hospital in São Paulo, Brazil, along a period of two consecutive years, and to describe the clinical and electrographic characteristics in each case.

Methods: Albert Einstein Hospital, a large private general hospital in São Paulo, Brazil, with over 500 beds including 40 beds in the intensive care unit, holds approximately 30,000 medical procedures each year. Charts of all patients who received EEG diagnosis of 'status epilepticus', 'repetitive seizures', 'clinical seizure', or 'electrographic seizure' along a period of 2 years (2002 and 2003) at the Division of Neurophysiology were reviewed. This period was chosen because most of the EEGs have been recorded on digital equipment since 2002, and were hence available for review. SE was defined as continuous or almost continuous EEG seizure activity for over 30 minutes with unequivocal impairment of consciousness and/or other clinical manifestations. Descriptions of the EEG exams were taken note, and all the available records were reviewed. Electrographic patterns were classified according to criteria proposed by Treiman *et al*.

Results: In two years 14 episodes of SE in 13 patients were identified. In 11 of the 14 episodes the ictal pattern was continuous epileptic discharges. There were 2 cases of recurrent seizures and 1 case of merging seizures. In three cases subtle motor manifestations were observed; the remaining constituted cases of NCSE. No cases of CSE were diagnosed with EEG. There was only one EEG recording showing unequivocal focal features; all others showed generalized epileptic discharges.

Conclusions: SE was less common than expected. Patients with CSE and patients with possible NCSE may have been treated before being submitted to EEG examination, thus reducing the number of documented cases. Only one EEG record showed focal discharges; in some cases of generalized discharges a focal onset may have been missed. No cases of CSE were diagnosed by EEG, most likely because these patients were treated promptly, and EEG performed after cessation of overt convulsive seizures. Finally, SE, at least in its nonconvulsive presentations, is frequently overlooked; this fact cannot be disregarded in this study. (Supported by Teaching and Research Institute, Hospital Israelita Albert Einstein.)

1.156
QUANTITATIVE EEG ANALYSIS CORRELATION WITH CLINICAL SEVERITY IN UNILATERAL STURGE-WEBER SYNDROME

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Rationale: Sturge-Weber syndrome is a neurocutaneous disorder presenting with vascular malformations of the skin, brain and eye that frequently results in seizures, hemiparesis, cognitive impairments and neurodegenerative changes, including brain calcification and atrophy. The objective of this study was to determine whether a typical pattern of quantitative EEG findings is present in Sturge-Weber syndrome and whether it correlates with the clinical severity of involvement.

Methods: Nine subjects (7 males, ages 9 months - 24 years) with unilateral Sturge-Weber syndrome had 16-channel EEG recordings. For each recording, two second, artifact-free epochs (N = 30) underwent a fast Fourier transform with frequency resolution of 0.5 Hz. In each epoch, absolute power values from pairs of symmetrical bipolar channels were used to calculate laterality scores (LS), where LS = (Left –Right)/(Left + Right). The LS was calculated for delta (2.0–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–12.5 Hz), and beta (13.0–32.0 Hz) bands, as well as for total power (2–32 Hz). A blinded investigator assigned clinical severity scores based on seizures, hemiparesis, visual field-cut, and cognitive impairments (scores ranged from 0 to 15; 0 = no abnormality and 15 = severe impairments in all domains). In addition, EEGs were assigned scores based on qualitative assessments of degree of asymmetry in frequency, amplitude, and background.

Results: Six subjects (67%) demonstrated significant decreases in absolute power on the affected side relative to the unaffected side and all six of these had clinical severity scores greater than four. All six had decreases in power in the delta and alpha frequency bands, four with additional decreases in theta and beta bands. Three subjects (33%) demonstrated either no significant changes or an increase in absolute power on the affected side. All three of these subjects received a clinical severity score less than or equal to four. Spearman's rho statistic for mean laterality score (total power) versus clinical score was significant with a value of -.941 ($p < 0.001$). There was no correlation between the qualitative EEG asymmetry score and clinical scores (Spearman's rho statistic = .377, $p = 0.317$). Band-specific asymmetries were also not consistently appreciated on clinical interpretation.

Conclusions: The majority of subjects demonstrated a decrease in absolute power on the affected side, most consistently involving the delta and alpha frequency bands. In this limited series, quantitative EEG correlated well with neurologic severity in Sturge-Weber syndrome, whereas standard EEG did not. Quantitative EEG also provided an objective measure of EEG abnormality. Further research is needed to determine whether quantitative EEG is a useful tool for early diagnosis or as a marker of disease progression. (Supported by RO1NS40596–01A1 supplementary funds NINDS/ORD and Hunter's Dream for a Cure Foundation Research grant.)

1.157
DIFFERENCES BETWEEN SPIKE IN EEG AND MEG: A QUANTIFICATION

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Rationale: MEG and EEG are two techniques used to characterize epileptiform activity in the brain. The typical events of the inter-ictal activity consist mainly of spikes and spike and waves. These events have been well defined in the EEG and these definitions have been used for

many years. With the emergence of MEG, the EEG based definitions of such events have been also applied in MEG recordings without objective definitions based on specific MEG studies. Nevertheless several studies have raised the question whether the same definitions of inter-ictal events derived from EEG may also be applied to MEG. The present work has the aim of determining quantitatively the characteristics of MEG spikes and of assessing the correctness of the current clinical practice of using EEG spike definitions in the context of MEG studies.

Methods: The method consisted of analysing quantitative characteristics of 120 coincident EEG and MEG epileptiform events from three patients suffering from drug resistant epilepsy. For each pair of events, the waveforms were analysed according to a morphological model (amplitudes, slopes, sharpness).

A paired t-test statistical analysis was performed on the extracted metrics.

Results: Statistical significant differences were found between corresponding EEG and MEG spike events. The MEG spikes were sharper ($p < 0.01$) and had shorter durations ($p < 0.01$).

Conclusions: MEG spikes are statistically different from those seen in the EEG. Thus the criteria for visual detection of these events in MEG should be adjusted accordingly. These results imply that automatic spike detector algorithms should use different criteria for MEG in comparison with EEG recordings.

The present abstract is part of the work that was recently accepted for publication in the Journal of Clinical Neurophysiology. (Supported by the grant PRAXIS XXI/BD/19676/99, project POSI/EEI/12150/98 and POSI/CPS/39758/2001 from "Fundação para a Ciência e Tecnologia," Portugal and co-sponsored by the FEDER program.)

1.158
ACCURACY OF SEIZURE DETECTION USING ABBREVIATED EEG DURING POLYSOMNOGRAPHY

Nancy Foldvary-Schaefer, Jose De Ocampo, Edward Mascha, Richard Burgess, Dudley Dinner, and Harold Morris (Department of Neurology, Cleveland Clinic Foundation, Cleveland, OH)

Rationale: Seizure recognition during polysomnography (PSG) is challenging due to the limited number of channels devoted to EEG. The addition of extended EEG montages during PSG is thought to improve the detection of seizures and epileptic discharges. The purpose of this study is to determine the validity of abbreviated EEG montage seizure detection during PSG.

Methods: Three blinded electroencephalographers reviewed 116 5-minute digital files containing focal seizures ($N = 56$) or nonepileptic events (sleep-wake transition/artifact; $N = 60$) using an 8-channel montage and an 18-channel montage. Files were rated in each of two ways. First, after deciding whether or not the file included a seizure, a "probability of seizure" score from 0–100% was assigned reflecting the confidence of the reader that it was a seizure. Second, for those events classi-fied as seizures, readers attempted to localize the epileptic activity as arising from the tempo-ral, frontal or parieto-occipital region. Readers were then asked to provide the probability of correct localization with 0–100% confidence. The data were analyzed using the Adjusted McNemar Test method of Obochuwski. The continuous probability of seizure score was measured using the Receiver Operating Characteristic Curve.

Results: Observed agreement among readers was 78% and 84% for the 8-channel and 18-channel montages, respectively, with a higher agreement beyond chance (kappa of 0.52 versus 0.69, respectively) for the 18-channel ($P = 0.013$). Readers were able to distinguish seizures from nonepileptic events better using the 18-channel montage (area under the curve $\{AUC\} = 0.91$ vs. 0.82 for the 8-channel montage; $P = 0.004$). Although both montages reliably detected nonepileptic events (92% vs. 96% for 18- vs. 8-channels), seizure detection was better using 18 channels (sensitivity = 85%) than 8 channels (sensitivity = 68%; $P < 0.001$). Seizures localized to the temporal and parieto-occipital regions were more likely to be identified as seizures and localized correctly while seizures localized to the frontal regions were commonly classified as nonepileptic events and/or had a higher tendency for mislocalization. The likelihood of correct seizure localization was significantly greater using the 18-channel montage, although neither montage did very well. Readers were able to correctly localize 27% of seizures using the 8-channel and 49% of seizures using the 18-channel montage ($P < 0.001$).

Conclusions: Despite the added time, labor and expertise involved in performing and interpreting 18-channel EEG recordings during PSG, we believe that abbreviated EEG montages fail to adequately differentiate epileptic seizures and nonepileptic events arising from sleep. This appears to be particularly true in frontal lobe epilepsy where seizures are most apt to be confused with disorders of arousal.

1.159
ARE "GENERALIZED" SEIZURES TRULY GENERALIZED? EVIDENCE OF LOCALIZED MESIAL FRONTAL AND FRONTOPOLAR DISCHARGES IN ABSENCE

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Rationale: To determine whether specific regions of cerebral cortex are activated at the onset and during the propagation of absence seizures.

Methods: 25 absence seizures were recorded in five subjects (all women; 19–58 years of age) with primary generalized epilepsy. To improve spatial resolution, all studies were performed with dense array, 256-channel scalp EEG. Source analysis was conducted with equivalent dipole (BESA) and smoothed linear inverse (LORETA) methods. Analyses were applied to the spike components of each spike-wave burst in each seizure, with sources visualized with standard brain models.

Results: For each patient the major findings were apparent on inspection of the scalp EEG maps and waveforms, and the two methods of source analysis gave generally convergent results. The onset of seizures was typically associated with activation of discrete, often unilateral areas of dorsolateral frontal or orbital frontal lobe. Consistently across all seizures, the negative slow wave was maximal over frontal cortex, and the spike that appeared to follow the slow wave was highly localized over frontopolar regions of orbital frontal lobe. In addition, sources in dorsomedial frontal cortex were engaged for each spike-wave cycle. Although each patient showed unique features, the absence seizures of all patients showed rapid, stereotyped evolution to engage both mesial frontal and orbital frontal cortex sources during the repeating cycles of wave-spike activity.

Conclusions: These data suggest that absence seizures are not truly "generalized," with immediate global cortical involvement, but rather involve selective cortical networks, including orbital frontal and mesial frontal regions, in the propagation of ictal discharges.

1.160
MAGNETOENCEPHALOGRAPHIC (MEG) INVESTIGATION OF PARADOXICAL LATERALIZATION IN PARIETO-OCCIPITAL INTERICTAL SPIKES

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Rationale: Pattern reversal hemi-field visual evoked potential (P-VEP) and posterior tibial nerve somatosensory evoked potential (PT-SEP) show higher amplitudes ipsilateral to the side of stimulation, which is known as paradoxical laterazation. Magnetoencephalogram (MEG) are reported to reveal the correct localization of dipoles showing the paradoxical laterazation, but there are a few reports concerning paradoxical lateralization of epileptic interictal spikes.

To reveal neurophysiological characteristics, we analysed parieto-occipital spikes by EEG and MEG because those are less concerned in transcallosal bilateralization than frontal spikes.

Methods: We analysed EEG and MEG of 13 epileptic patients (2–19y, 7 symptomatic, 6 cryptogenic) with parieto-occipital spikes. MEG was recorded with whole-head 64 channel gradiometer system (CTF, Canada). Localization of spikes was estimated by single dipole model and superimposed on MRI images. EEG was recorded with international 10–20 scalp electrodes simultaneously with MEG.

Spike lateralization was considered "concordant" (CL) or "paradoxical" (PL) whether MEG estimated dipoles and maximum negative EEG spikes were located on the same side or the opposite side.

Results: 1) Ten cases were considered to show CL, and 3 cases PL.

2) In the cases with CL, MEG dipoles were estimated on the base or lateral surface of occipital lobe. The direction of dipoles were not constant but vertical in many cases.

3) In the cases with PL, MEG dipoles were located on the mesial surface of parieto-occipital lobe. The direction of dipoles were horizontal antero-lateral oblique.

4) Positive EEG spikes were observed on the opposite side of the negative EEG spikes in all of PL cases and some of CL cases in whom MEG dipoles were located on the mesial surface.

Conclusions: 1) Interictal parieto-occipital spikes can show paradoxical lateralization only when the dipole is located on the mesial surface with horizontal antero-lateral oblique direction.

2) Above mentioned characteristics of paradoxical lateralization were common with P-VEP or PT-SEP which were also reported to show paradoxical lateralization.

3) Magnetoencephalographic (MEG) investigation was very useful in analyzing paradoxical lateralization of interictal spikes.

1.161

LONG-RANGE EEG SYNCHRONIZATION DURING LANGUAGE PROCESSING: A STUDY WITH SUBDURAL ELECTRODES

Masaki Iwasaki, Giridhar Kalamangalam, Nitin Tandon, Dileep Nair, Richard C. Burgess, and Hans O. Luders (Neurology, Cleveland Clinic Foundation, Cleveland, OH)

Rationale: The term "synchronization" means significant matching between two oscillatory activities. EEG (brain wave) synchronization has been used to investigate various types of brain function such as memory coding, learning, attention, cognition, and epileptic seizures. Several lines of evidence from animal studies suggest that increased neuronal synchronization occurs either locally or between two distant functional brain areas during object perception and/or motor action. One study with human intracranial EEG showed increased coherence between the primary motor and supplementary sensori-motor cortices during voluntary movements. The role of synchronization in memory or learning function is well studied in both animal and human subjects. A number of studies with human scalp EEG revealed global increase of synchronization during many types of cognitive tasks. However, no previous studies systematically investigated synchronization during language process using intracranial human EEG.

Methods: Two patients who underwent chronic implantation of subdural electrodes on the left hemisphere participated in the study. Subdural EEG was recorded during resting condition, during language task, and during pseudo-language task. The language task included passive listening of English speech and word generation task. The pseudo-language tasks included passive listening of the time reverse play of the English speech. The duration of each task was minimum 15 seconds.

The analysis was performed for three different frequency bands (10–30Hz, 30–50Hz, 50–70Hz). The "phase" of the EEG waveform on each channel was calculated using the Hilbert transform. Continuous trend of the phase was derived by unwrapping the phase cycle. Then, the difference of the phase trend between any pairs of electrode was calculated by subtraction. Highly persistent synchronization between the two channels was expressed as a stable or invariable time-course of the phase difference (low variance). A low degree of synchronization, on the other hand, was expressed as an unstable or highly variable course of the phase difference (high variance).

Results: Mean values of pair-wise synchrony were generally higher during the language task than during the resting or pseudo-language task. Significant synchronization occurred regionally between distant electrode pairs, but rarely between nearest neighbor pairs. It was possible to identify several electrodes as "key nodes" that have significant synchronization divergently to multiple electrodes located in a target area.

Conclusions: Phase synchronization analysis revealed the EEG changes specific to the language process. The long-range synchrony occurs in the area wider than the presumed "language" area which is typically mapped with direct cortical stimulation or functional MRI. The synchronization analysis is useful to elucidate dynamic aspects of the brain function.

1.162

DISCORDANT ICTAL EEG IS NOT A PREDICTOR OF POOR SURGICAL OUTCOME IN PATIENTS WITH EPILEPSY SECONDARY TO LOW-GRADE TEMPORAL LOBE TUMORS

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Rationale: Low grade tumors, especially of neuronal lineage are commonly associated with epilepsy. Refractory epilepsy in these cases is usually amenable to surgical treatment, often with good results. We studied a series of cases to analyze possible factors associated with good surgical outcome in patients with low grade temporal tumors.

Methods: Retrospective analysis of clinical, ictal and interictal EEG, neuroimaging and pathology data in a series of consecutive patients who underwent temporal resection for medically refractory epilepsy secondary to temporal lobe low grade tumors.

Results: Twenty eight patients (17 men, ages ranging from 2–51 years) with low grade temporal lobe tumors were operated between and 1993 and 2004. Sixteen patients had more than 20 seizures/month at the time of surgery. Gangliogliomas were the most common pathologic diagnosis, accounting for 50% of the cases. 22 patients underwent lesionectomy with amygdalo-hippocampectomy and 6 lesionectomy (partial in one). Mean follow-up period was 57,4 months (range 2–129 months). Surgical outcome was excellent (Engel 1) in 20/28 (71%) cases. There was no correlation between surgical outcome and age at epilepsy onset, frequency of seizures at the time of the surgery, lesion side, bilateral or unilateral ictal and interictal EEG activity, or ictal activity not congruent with the lesion. Patients with abnormal neurological exam (Engel 1: 2/7 or 28%), astrocytic tumors (Engel 1: 4/7 or 57%) or extratemporal interictal EEG activity (Engel 1 1/3 or 33%) had slightly poorer surgical outcome than those with normal neurological exam (18/21 or 85%, $p = 0,17$), or neuronal lineage tumors (15/21 or 71%) or interictal EEG activity restricted to the temporal lobe (19/25 or 76%).

Conclusions: In this series, bitemporal ictal or interictal EEG abnormalities or ictal EEG activity not concordant with the lesion did not determine a poor surgical outcome. Factors such as abnormal neurologic exam and presence of extratemporal epileptiform discharges on interictal EEG as predictors of poorer surgical outcome should be evaluated in larger series.

1.163

INDEPENDENT COMPONENT ANALYSIS OF GENERALIZED SPIKE-AND-WAVE DISCHARGES: DIFFERENTIATION BETWEEN PRIMARY AND SECONDARY BILATERAL SYNCHRONY

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Rationale: Identification of a focal nature from generalized spike-and-wave discharges (GSWD) may have important implications for the treatment of intractable epilepsy. Independent component analysis (ICA) can separate complex multichannel data into spatially fixed and temporally independent components. To differentiate between primary and secondary bilateral synchrony (PBS and SBS, respectively), we applied ICA to GSWD, and analyzed the characteristic patterns of independent components.

Methods: Electroencephalograms (EEGs) from 19 patients with GSWD (9 PBS patients, 10 SBS patients) were studied. Thirty GSWD epochs (from –0.2 to +0.3 s from the negative maximum of the spike) were selected and concatenated to construct an EEG data matrix that was subjected to ICA. Because spikes that have different spatial distributions produce different ICA components, selected independent components were localized by mapping them on a spherical model of the head by means of brain electrical source analysis (BESA) to define dipole sources.

Results: Epileptic components of GSWD were clearly separated by the ICA algorithm. Between one and three components per patient were responsible for GSWD. While the epileptic components

of GSWD in PBS patients were bilaterally symmetrical radial dipoles that were located primarily within the dorsolateral frontal region, epileptic components in SBS patients were asymmetrical mixed dipoles that were located primarily within the medial frontal region.

Conclusions: Spatiotemporal decomposition of independent components of GSWD by using ICA can be useful for differentiating SBS from PBS. The localization of the dipole sources of the independent components provides further insight into the pathophysiological origins of GSWD.

1.164

A NEW METHOD FOR QUANTIFYING AND ASSESSING EPILEPTIC ACTIVITY IN LONG-TERM EEG

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Rationale: Assessing epileptic activity in patients with continuous sharp wave during slow wave sleep (CSWS) has been difficult. Hence, the requirements for the diagnosis of CSWS have in this regard been poorly defined. This study presents a new method for an objective assessment of epileptic activity in CSWS and other diseases with large amounts of epileptic activity.

Methods: Sixteen channel 24 hour ambulatory EEG recordings from patients with continuous or almost continous epileptic activity were collected. Spikes were identified by template matching on a single channel or on principal components using the Besa software. The spike/time file thus collected was used for further calculations (Matlab). The percentage of time with spiking was calculated for every time epoch in the recording and the percentage was plotted versus time. A time sequence was tagged as epileptic if the next spike appeared within the given time period (1–7s). The epochs were either 2 or 10 minutes.

Results: Assessment of various combinations has shown that 10-minute epochs and 1s, 3s and 5s inter spike time, plotted together, are optimal parameters. Inter-patient and intra-patient reproducibility supports the notion of a robust method.

Conclusions: Most methods for assessing spikes have utilized histograms (number of spikes/epoch). This measure is very sensitive to spike frequency. Our method is almost independent of spike frequency and gives clinically more useful information as it quantifies spike activity and its temporal distribution through the recording. Furthermore, the method is practicable and not unacceptably time-consuming.

1.165

LEFT HEMISPHERE PREDOMINANCE OF INTERICTAL SPIKES: RESULTS FROM EEGS PERFORMED AT THE CCF IN THE LAST 10 YEARS

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Rationale: Several reports indicate that interictal epileptiform discharges (IED) may be more likely to occur over the left cerebral hemisphere than over the right. Some authors additionally assume that the left hemisphere is more likely to generate focal seizures from a localized left-sided epileptogenic zone. The objective of our study was to determine the frequency and type of IED on routine and multi-hour EEGs in a tertiary epilepsy center, to estimate the frequency of left versus right-sided IED and to determine interictal spike distribution pattern differences between adult and pediatric epilepsy patients. Discharges that were generalized with a lateralized component were excluded.

Methods: The current study retrospectively reviewed 31384 EEGs (25935 routine EEGs and 5449 multi-hour EEGs) recorded on 24003 patients during the period from 1993 to 2003. 7704 of these patients were under the age of 18 years All EEGs were read according to a systematic EEG classification system (Lüders et al., 1993) which included detailed localization and lateralization information about all epileptiform abnormalities. Every patient was only considered once by including the first abnormal EEG. Presurgical long-term video-EEG recordings were not included in the study.

Results: Regional IED were recorded in 1628 patients (6.78%). Left-sided regional IED were seen in 815 patients (664 sharp waves, 132 spikes, 13 spike and wave complexes and 6 polyspikes), and right-sided in 574 (450 sharp waves, 106 spikes, 9 spike and wave complexes and 9 polyspikes). Left-sided IED accounted for 58.6% of all regional unilateral regional IED. Right and left-sided regional IED were seen in 239 patients (163 sharp waves, 70 spikes, 4 spike and wave complexes and 2 polyspikes).

EEG recordings with regional IED were seen in 1032 (7.6%) pediatric epilepsy patients and 1032 (6.3%) adults. Among the adults left-sided IED were seen in 565 patients, right-sided in 361 and right and left sided in 106, with left-sided regional IED accounting for 61% of all regional unilateral IED. Among pediatric patients left-sided IED were seen in 260 patients, right-sided in 195 and right and left-sided in 136, with left-sided IED accounting for 57% of all regional IED.

Conclusions: Regional epileptiform discharges were seen in approximately 7% of patients.

Interictal epileptiform discharges were more frequently seen in the left hemisphere (59% of all unilateral regional epileptiform discharges). Age adjusted analysis of the data revealed that this left-sided predominance was only mildly increased in adults as compared to epilepsy patients under the age of 18 years.

1.166

SEIZURE SEMIOLOGY AND ICTAL SPECT, BUT NOT ICTAL OR INTERICTAL EEG, CORRELATE WITH LESION SIDE IN MEDICALLY REFRACTORY EPILEPSY ASSOCIATED WITH EARLY VASCULAR INSULTS

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Rationale: Patients with early vascular insults present with variable degree of motor weakness and cognitive impairment. Epilepsy may occur and may be refractory to medical treatment. We studied the correlation between presurgical evaluation and post-operative outcome in a series of patients with medically refractory epilepsy secondary to early vascular insults.

Methods: Retrospective analysis of the presurgical evaluation data (clinical semiology, video-EEG, sodium amytal test and SPECT) and post-operative outcome in a series of patients with early large vascular lesions.

Results: Nine patients with medically refractory epilepsy secondary to early vascular lesions were operated between January 2000 and April 2004. 5/9 patients were women, 7/9 were mentally retarded and 8/9 presented a hemiparesis. Epilepsy started in the first year of life in four patients. All cases had porencephalic lesions in the middle cerebral artery territory, 5 on the right hemisphere. Clinical seizure features were concordant with the lesion in 8/9 patients, while ictal EEG was concordant in only 5/9 patients and interictal EEG discharges in only 6/9 patients. All three data were concordant in only 5/9 patients. Ictal SPECT was concordant in all patients. Three patients with left sided lesions underwent the sodium amytal test, which showed right hemisphere language dominance in all. Seven patients underwent hemipherectomy (3 functional, 3 peri-insular and one anatomic). The remaining two patients underwent a bilobar lobectomy. Surgical outcome was excellent in 7/9 patients (Engel 1). No patients developed aphasia or worsening of the motor deficit. Two patients had poor surgical outcome: one had a limited resection (to preserve motor function) and the other presented atypical clinical features (autistic regression) and incongruent presurgical data.

Conclusions: In this series, ictal SPECT and ictal semiology were more useful in lateralizing seizure onset than ictal, interictal EEG or all data combined. Incongruent interictal or ictal EEG by itself did not influence surgical or cognitive outcome.

1.167

A NONINVASIVE METHOD FOR ANALYSIS OF EPILEPTOGENIC BRAIN CONNECTIVITY

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Rationale: Source analyses of interictal and ictal scalp EEG often implicate involvement of multiple cerebral regions. Fast neuroelectric

activity emitted from each region may be estimated on a macroscopic spatial scale using a local source estimator such as regional activity estimation (REGAE). From such derived time series, we aim to make causal inferences about (dys)functional connections between regions around the times of interictal or ictal onset discharges. We developed a new method to study cerebral connectivity and influences among regions involved with epileptogenicity.

Methods: The general method has three main steps: (i) transform scalp EEG time series to brain regional activity time series via REGAE; (ii) for each region A and time t, calculate a set of one-sided time derivatives that characterize the dynamic state of A at time t; and (iii) for each pair of brain regions A and B, time t, and lag u, compute *time-lagged causally predictive information*, $CPI_{AB}(t,u)$, an information theoretic measure of the degree to which the states of A in a time window positioned at time t-u predict the states of B in a time window positioned at time t, taking into account the possibility of mediating influences (e.g., the mediation of a third region C). $CPI_{AB}(t,u)$ has linear and nonlinear variants (previously studied using simulated data with known influences at given lags). To evaluate this technique, we applied CPI analysis to scalp ictal EEG recorded from 57-channels (10–10 system) obtained on two seizures recorded on two consecutive days from a temporal lobe epilepsy patient. Starting with 80 regions of interest (ROIs) that collectively covered brain gray matter (obtained from an MRI segmentation), a subset of 8 temporal lobe ROIs were selected as the potential underlying generators based on the magnitude of their estimated activity. Linear $CPI_{AB}(t,u)$ was computed using 1 s time windows for all pairs of ROI candidates for both seizure onsets, and peak lead-lag relationships were examined across time.

Results: Results comprise a matrix of 28 graphs of CPI as a function of time (s) and lead-lag (ms). $CPI_{AB}(t,u)$ disclosed consistent magnitude and lead-lag relationships among the 8 temporal regions both within and between the two seizure onsets. In particular, 2 of the 8 candidate ROIs demonstrated more causal influence than the others (with leads of 5 to 10 ms). These two regions were located in the antero-medial and infero-lateral posterior temporal areas.

Conclusions: CPI measures dynamic state predictability of one region with respect to another after accounting for causally confounding influences, and may provide clinically useful information about ictal rhythm onset and propagation sources. An inherent limitation is that regions unobservable by scalp EEG (such as deep brain structures) cannot be included as confounds. Larger series will be required for further evaluation of clinical utility. (Supported by NIBIB 1 R43 EB000614.)

1.168
OBJECT NAMING PRODUCES CHANGES IN SCALP EEG POWER SPECTRAL DENSITIES

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Rationale: This study was undertaken to determine if it is possible to detect changes in scalp EEG that correspond with the behavioral measures of overt and silent object naming.

Methods: Nine subjects with documented left temporal lobe epilepsy were selected for this study. All were surgical candidates. Language, in all cases, was shown by the intracarotid sodium amytal (Wada) test to be lateralized to the left hemisphere. EEG data (0.1–1000 bandwidth; 500 Hz sampling rate) was collected preoperatively during behavioral tasks. Dense array EEG recordings with 256 channels were utilized to improve spatial resolution. Subjects were presented with slides every 4 sec that contained images of 80 common objects. During one trial subjects named objects out loud and during a second trial objects were named silently. EEG data was analyzed in frequency bands that ranged from 25–50 Hz and were filtered with a Remez band-pass filter. Power spectral densities (PSDs) during baseline and object naming were calculated after obtaining Fourier transforms of the data. PSDs were averaged over the 80 data sets of each trial. Contour plot were constructed using the montage layout of the 256 channel array.

Results: In all cases, contour plots demonstrated that PSDs during both overt and silent naming were 2–3 times higher than the baseline values for all frequency bands. Maximal changes were localized to focal areas of the left cerebral hemisphere.

Conclusions: These findings suggest that it may be possible to noninvasively lateralize, and eventually localize, cerebral regions essential for language. This may be accomplished by analysis of scalp EEG recordings that have optimal spatial resolution.

1.169
COMPARISON OF LOCALIZATION OF ICTAL ONSET BETWEEN SPHENOIDAL ELECTRODES AND DIPOLE SOURCE LOCALIZATION IN TEMPORAL EPILEPSY

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Rationale: To compare the localizing yield of sphenoidal (SP) electrodes placed under fluoroscopic guidance and inferior electrodes (SO1/2, F9/10, T9/10, P9/10) in ictal recordings from patients with localization-related epilepsy of frontotemporal origin. Qualitative and quantitative dipole source localization measures were utilized.

Methods: Ten consecutive patients were prospectively identified, 6 females and 4 males, ages 18–54 with medically intractable localization-related epilepsy (frontotemporal). All patients were in the process of completing a presurgical evaluation.Sixteen electrographic seizures were de-identified and randomly coded. The 10/20 international system was used with 27 single density scalp electrodes. In addition, SP electrodes were placed under fluoroscopic guidance in all 10 patients. Both a referential montage to reference electrode Cz and a bipolar parasagittal montage were simultaneously used. A qualitative comparison of three montages for each EEG was blindly performed as follows: 1) SP with inferior electrodes (IE), 2) SP without IE and, 3) IE without SP electrodes. Measures included ictal onset latency from baseline background activity, and localization of onset. Following identification of the seizure onset epoch, sphenoidal electrodes were excluded from the montage and quantitative dipole source analysis of the ictal data was performed using a spherical head model in BESA Beta 5.0.6 and a realistic head model in Curry 4.6. MRI data for dipole source localization was acquired on a 1.5T GE scanner using 124 gapless coronal slices with a thickness of 1.6mm, 256x192 matrix, and 22 FOV.

Results: Qualitatively, a statistically significant difference was seen with respect to seizure onset latency between EEG records using montage 1 (SP + IE) and those using montage 3 (IE - SP), [$t = 2.159$, $df = 16$, $p = 0.0463$]. No significant difference in ictal onset latency was found between all other comparison groups ($p > 0.05$). Moreover, the addition of the SO1/2 electrodes as part of the IE set added concordant data for those seizures suspected by semiology of involving basal/mesial frontal regions as part of the ictal onset zone. Quantitatively, dipole source localization was influenced by the presence of sphenoidal electrodes when attempting to identify the ictal onset by visual inspection for software analysis.

Conclusions: A comparison of sphenoidal electrodes placed fluoroscopically and inferior electrodes yielded an earlier onset when using both IE and SP sets. In addition, localization of seizure onset was improved in those patients suspected of having an ictal onset zone that includes the basal frontal or mesial-basal frontal regions. These data influenced dipole source modeling of the ictal onset zone. These findings can potentially improve surgical outcome by better delineating the ictal onset zone with the concomitant use of sphenoidal and inferior electrodes.

1.170
IMPROVED SPATIAL RESOLUTION OF FOCAL EPILEPTIFORM DISCHARGES BY DENSE ARRAY EEG RECORDINGS

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Rationale: Evaluating the location and distribution of scalp EEG-recorded interictal epileptiform discharges is an important part of the

evaluation of medically refractory localization-related epilepsy. In some cases this information is useful in predicting the zone of seizure onset. This project was undertaken to determine if additional information can extracted from the scalp EEG by employing dense-array (256-channel) EEG, when compared to that obtained by conventional scalp EEG (19-channel) recordings.

Methods: Eleven patients with refractory partial seizures, all surgical candidates for whom outcome data is available, underwent preoperative 256 channel EEG recordings. Epileptiform discharges in all cases were recorded. Localization of the spike components of discharges was accomplished by source analysis techniques. These findings were then visualized on standard MRI models. Results obtained using all 256 channels in the analysis were compared to results obtained by subsampling the dense-array data to simulate the information that would be gained from conventional EEG.

Results: When compared to standard EEG recordings, increasing the spatial sampling of scalp EEG up to 256 channels improved the detection of discharges, reduced the margin of error in source analysis calculations, and enhanced the reliability of spike localization.

Conclusions: The noninvasive spatial resolution of epileptiform discharges may be greatly improved by dense array scalp EEG recordings. This enhanced capability may have implications in studies that examine the utility of dense-array EEG studies in predicting interictal activity recorded by intracranial electrodes, the extension of dense-array recording to 24-hour monitoring, and the accuracy of both interictal and ictal dense array EEG in localization of the seizure onset zone in relation to surgical outcome

1.171

INDEPENDENT COMPONENT ANALYSIS (ICA) IN THE DISTINCTION BETWEEN FOCAL AND MULTIFOCAL EPILEPSY

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Rationale: Independent component analysis (ICA) is a novel system that finds independent sources in recorded signals. One of its capabilities is probably to separate epileptiform activity of different origin. The goal of this study was to probe that ICA is useful for differentiating focal and multifocal epilepsies

Methods: We analyzed with ICA 120 samples of 12 patients with unifocal (temporal (n = 3), frontal (n = 3) or multifocal epilepsy (bitemporal (n = 3), extratemporal (n = 3)). Each sample contained at least 2 spikes. The samples were recorded digitally with a 32-channels Lamont amplifiers and Harmonie 5.2b program. ICA was applied using the JADE algorithm implemented in a Matlab platform. The components were identified visually. The EEG and the isovoltage map of the suspected components were reconstructed to probe the nature and location of each spike.

Results: In multifocal epilepsies, the spikes were separated in different components in all cases. In unifocal epilepsies ICA found in a single component all the spikes of the same location. In some of these cases, other components were responsible for small parts of the spikes. Frontal spikes were separated very often in several components, but if they were unifocal a single component included part of all the spikes. The components of the waves were separated in different components both in the unifocal and in the multifocal samples.

Conclusions: ICA separates in different components multifocal spikes while includes in a single component spikes of the same focus. ICA might be a useful tool to distinguish between unifocal and multifocal epilepsies. (Supported by the "UTE project CIMA" and by the Government of Navarra, grants for research in Health 12/2003 and 16/2003. Dr Urrestarazu is a Research Fellow supported by a grant for research of the Department of Education of the Basque Government.)

1.172

A RELATIONAL DATABASE FOR NEUROPHYSIOLOGY REPORT GENERATION AND RESEARCH

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Rationale: Electronic medical records for neurophysiology reports come in many forms. Many are sold with EEG equipment; others are customized by each epilepsy center or neurophysiology lab for prospective research projects. We report our experience with a multi-user, password protected customized relational database and discuss benefits and pitfalls encountered.

Methods: In 1997 we developed a relational database using Microsoft Access for large multi-hospital epilepsy center and neurophysiology labs. Currently there are over 13,000 unique patients listed. The database was constructed to include demographic information, EEG report data to meet criteria specified by the American Clinical Neurophysiology Society guidelines, standardized classification of EEG abnormalities, classification of epileptic and nonepileptic events modified from the ILAE proposed classifications and other pertinent patient characteristics needed for epilepsy evaluations. The database can generate EEG reports, video-EEG reports and other neurophysiology reports such as the Wada test and evoked responses.

Results: Advantages of this database include easy report generation, compact data storage compared to text or word processing files, networked data availability for clinical management, ability to create queries for research and ease for database modification when needed for clinical care, research, or regulatory changes such as HIPAA.

Since the database stands independent of a specific neurophysiology equipment vendor, the use of multiple neurophysiology equipment vendors with their database incompatibilities is avoided and changing EEG equipment does not result in data retrieval inconvenience.

Problems encountered include obtaining network connectivity among affiliated institutions where different internet protocols exist, the desire of some hospitals to maintain separate databases, arrangements for database backups, training for database use vs. report retrieval, integration of reports into institutional electronic medical records that are insensitive to research requirements, and constantly evolving privacy rules and security for electronic records.

Conclusions: For an academic epilepsy center using multiple equipment brands at multiple hospitals and neurophysiology laboratories, a customized neurophysiology database for EEG and other epilepsy program related data allows long term data collection and report retrieval that is more effective than databases supplied by equipment vendors. (Supported by Parkland Health and Hospital Systems, Children's Medical Center of Dallas, University of Texas Southwestern Medical Center.)

1.173

INDEPENDENT COMPONENT ANALYSIS (ICA) IN THE STUDY OF THE EPILEPTIFORM DISCHARGES

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Rationale: Independent component analysis (ICA) is a system that finds independent sources in many types of signals. One of its capabilities is to study the epileptiform discharges to probe the similar or different origin of its components. The goal of this study was to discover how ICA analyse the spike-and-wave discharges of several types of epilepsies, and to use this information to know more about the origin and propagation of the interictal discharges.

Methods: We analyzed 60 spikes of 16 patients (3 temporal epilepsy (n = 15), 3 centrotemporal (n = 15), 4 frontal (n = 15) and 6 with generalized epilepsies (n = 15)). Most of them were followed by a slow wave (spike-and-wave discharge). The samples were recorded digitally with a 32-channels Lamont amplifiers and Harmonie 5.2b program. ICA was applied using the JADE algorithm implemented in a Matlab platform. The components were identified visually. The suspected components were selected and the EEG of these components by itself and together were reconstructed. The topography in each component of the discharge was compared with the original using the BESA program in the same period.

Results: In the focal discharges, ICA separated the spike from the wave components, getting a close but not similar topography. The spikes of the focal discharges were separated in one or two components at

maximum. The topography of these components was very similar but not identical. Each component of the spike or wave in these focal epilepsies accounted very well for the EEG in the correspondent time.

In the discharges of the generalized epilepsies the patterns were more variable. The spikes were divided in up to 4 components (only in a small percentage in one or two), having very often a variable topographic distribution. The majority of the components were asymmetrical. In the same burst of spike-and-wave discharges, the components of the spikes may vary and even new components may appear.

Conclusions: ICA differentiates several components in the epileptiform discharges. In each patient the way of decomposition of the discharge was very similar. In most of the discharges, the spike and the wave had different components suggesting different origin. The generalized discharges had more complexity than the discharges in focal epilepsies, and even in the same patient the variability was higher. (Supported by the UTE project CIMA and by the Government of Navarra, grants for research in Health 12/2003 and 16/2003. Dr Urrestarazu is a Research Fellow supported by a grant for research of the Department of Education of the Basque Government.)

1.174
SOURCE ANALYSIS OF INTERICTAL SHARP WAVES IN FOCAL EPILEPS

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Rationale: Mapping of interictal epileptiform discharges is typically based on analysis of the highest amplitude to a non-active reference. Particulalry when electrodes other than the typical 10–20 system are maximal it is often difficult to grasp the location of the maximal EEG activity. Dipole modeling assumes that a scalp EEG field is generated by one or a small number of dipolar sources. This technique can be applied for the analysis of interictal epileptiform discharges. The goal of this study was to retrospectively evaluate whether dipole source analysis using 32 electrode during surface video-EEG could be useful in the presurgical work up of focal epilepsy.

Methods: We analysed retrospectively the interictal sharp waves of 10 patients that underwent epilepsy surgery. EEG was aquired digitally with 32 channels with the 10–20 EEG system and with additinal temporal electrodes. Sphenoidal recordings and EKG were disregarded in the analysis. The interictal sharp waves were analysed using BESA 5 software. Homogenous samples of typical sharp waves were averaged to improve signal-to-noise ratio and decrease artifacts. A semi-automated dipole modeling technique was then then applied to these waves to solve inverse problem, yielding the most likely intracranial source of the observed surface activity. A blinded reader classified the resultant dipole location into one of the following regions: anterior, middle, posterior, mesial vs.non-mesial temporal, mesial, basal frontal or other frontal areas, and parietal regions. The region of the dipole was correlated with data obtained from conventional EEG, MRI, and invasive EEG.

Results: Four patients had mesial temopral sclerosis, 2 patients had other lesional temporal epilepsy, 1 patients had non-lesional temporal epilepsy, and 3 patients had lesional extra-temporal epilepsy. Surgeries consisted of temporal lobectomy in 5 cases, lesionectomy with intraoperative electrocorticography in 2 patients, and subdural grids in 3 patients. Dipole Source Analysis (DSA) evaluation revealed that in the 7 patients with temporal lobe epilepsy, the independent analysis was accurate in localizing the epileptogenic region. In 3 out of 7 cases, the DSA was limited in differentiating mesial vs neocortical epileptogenic foci. The DSA findings correlated accurately with the MRI and invasive EEG data in the 3 extra-temporal lesional patients.

Conclusions: Our study revealed that the use of EEG source analysis of interictal sharp waves can provide useful data in the presurgical work up for patiens with focal epilepsy. In our patients, DSA allowed accurate localization of the interictal discharges to specific affected brain regions. The DSA visual display allows also recognition of brain regions, for professionals not familiar with EEG electrode nomenclature.

Clinical Epilepsy—Adult 1

1.175
SEIZURES IN THE ELDERLY: VIDEO-EEG MONITORING ANALYSIS

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Rationale: Recently there is remarkable increase in seizures in the elderly due to growing size of this segment of the population. In the literature there is little information about the characteristic presentation of epileptic and non-epileptic events in the elderly.

Therefore we report the results of Video EEG recordings in patients aged 60 or older who were admitted over 2 consecutive years to the epilepsy monitoring unit.

Methods: We examined the records of all patients admitted to EMU between 12/1999 and 12/2001. All patients underwent continuous CCTV/EEG monitoring with cable telemetry using 64 channels Nicolet BMSI system, and scalp electrodes were placed according to international 10–20 system. Based on reasons for admission Video EEG reports were categorized into 1) diagnosis of events, 2) characterization and localization of seizures, 3) adjustment of medication, 4) status epilepticus (nonconvulsive).

Results: Fifty-eight patients were admitted to the EMU, 26 women between the age of 60–91 years and 32 men between the ages of 60–84 years. The main reasons for admission were diagnosis of events (57% of patients), followed by characterization and localization of events (36% of patients). There were 6 patients with PNES, 5 were women and 4 of them >70 yrs old. All PNES patients presented with motor symptoms except for an 87 yrs old male who presented with abdominal spasm. Two of these 6 patients were suspected to have PNES before admission. Two patients were admitted with suspicion of SE, but none of them proved to have SE. The Most frequent diagnosis was NES (26 patients; 45%). Seven (27%) of these 26 patients were on AEDs, which were discontinued after the diagnosis. CPS was the most frequent seizure type, occurring in 22 patients and 6 of them (27%) had both CPS and secondary generalization.

Conclusions: In the elderly, Video-EEG results in definite diagnosis in the majority of cases and leads to the discontinuation of unnecessary medication with its deleterious effects. PNES can occur in elderly, which needs to be recognized and managed properly.

1.176
IS TELEMEDICINE A VIABLE OPTION FOR EPILEPSY CARE?

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Rationale: Telemedicine utilizes a communication technology in delivery of health care when the patient and the physician are separated by space. Since there are very few epileptologists in western Canada, patients have to travel long distances to attend their appointments. This leads to significant traveling costs, lost time from work for the patient and family and considerable inconvenience. We sought to determine if video tele-consultation was a viable option for epilepsy care.

Methods: Seven out-of-province referrals were booked for teleconsultation. Consultation was sought for diagnostic and therapeutic interventions. Ages ranged from 22 to 59 years. There were four new patients and three follow-ups. The traveling distances ranged from 790 km to 1497 km with a mean of 1220 km. Consultations were done with video conferencing. Four patients had other family members attend the sessions. Approximate travel and lodging costs were calculated to determine cost savings. A consultation report with recommendations was mailed to the referring physician.

Results: There were no major technical difficulties in conducting the consultations with the exception of minor difficulties in one consult from Winnipeg. Neurological examination was limited but provided by the referring neurologists. The average traveling and accommodation cost per patient was $726 (excluding costs for the travel attendant). The

patients and families expressed satisfaction with the consultation and had the opportunity and time to inquire about specific issues. On an average an additional 15 minutes of the specialist time was utilized for each patient.

Conclusions: Teleconsultation in epilepsy is a viable option where major commute is necessary to attend the epilepsy clinic. It may lead to significant cost savings for the patient and health care region, and serve as a means of health delivery within one's own community. However, it requires some additional time commitment from the treating physician. Further research is needed to compare teleconsultation with conventional clinics in terms of patient satisfaction, doctor satisfaction, quality of health delivery and cost impact. [Supported by Medical Services Delivery Innovative Fund (MSDIF); a joint initiative of Alberta Health and Wellness and the Alberta Medical Association.]

1.177
CEREBROVASCULAR DISEASE AND EPILEPSY: A RETROSPECTIVE STUDY ON MORE THAN 2000 PATIENTS

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Rationale: Cerebrovascular disease is a well-recognized cause of late onset epilepsy, but the true frequency, risk factors and prognosis are not well established.

Methods: We studied all consecutive patients with cerebrovascular disease and/or epileptic seizures who were seen in our department between January 2000 and June 2003. The diagnosis was established by history, clinical examination, EEG, laboratory findings, ultrasound studies and neuroimaging including MRI. Seizures were classified according to the international classification of epileptic seizures.

Results: Ischemic cerebrovascular disease was diagnosed in 1029 patients; 1114 patients had one or more epileptic seizures during the study period. Ischemic disease was identified as the cause of one or more seizures in 121 patients. Sixty-six patients (55%) had only one seizure, 55 patients (45%) went on to develop epilepsy with recurrent seizures during the observational period. In 71 patients the exact time span between the acute ischemic event and the first seizure could be determined. In 27% of patients the first seizure occurred within the acute phase of the cerebrovascular event (early seizures), in 73% of patients the first seizure occurred more than 2 weeks after cerebral ischemia (late seizures). Nearly 20% of patients with a major stroke had at least one seizure during the study period as opposed to only 5% after a transient ischemic attack (TIA) and 2% after a reversible ischemic neurologic deficit (RIND). Within the group of patients with cardiac emboli as pathogenic mechanism 13% of patients had one seizure and half of them developed epilepsy with recurrent seizures. Focal epileptogenic changes could be seen in the same number of patients with early or late seizures, but 95% of patients with cerebral ischemia and an epileptogenic focus had at least one seizure, 30% during the acute phase, 70% later during follow-up. High age at onset of cerebral ischemia and smoking as vascular risk factor lowered the risk for early or late seizures after stroke.

Conclusions: In our present study, 12% of all patients with cerebral ischemia developed one or more seizures. The data emphazise a higher rate of seizures and epilepsy in patients with major stroke as compared to patients with transient ischemic events and in patients with focal epileptogenic changes at EEG. On the other hand, old age at onset of ischemia as well as smoking as vascular risk factor were associated with a lower risk of developing epilepsy after a cerebrovascular event. These results can have major therapeutic implications considering antiepileptic medication at an relatively early stage after stroke in patients at high risk for developing epilepsy after stroke.

1.178
TREATMENT OF EPILEPSY IN THE ELDERLY "VETERANS ADMINISTRATION COOPERATIVE STUDY 428": ANALYSIS OF HOSPITALIZATIONS

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Rationale: Hospitalization is not infrequent in the elderly population. We analyzed a group of veterans with newly diagnosed epilepsy with respect to there hospitalizations during the study. Demographics were analyzed including relationship to the study.

Methods: Data was retrospectively obtained. We focused on our Denver population. This was a multi-center Veterans Administration Cooperative Study of new onset seizures in the elderly. No patients were profoundly demented or had known fatal illnesses. Concomitant medical diseases were permitted.

Results: Fifty charts were retrospectively reviewed from our Denver site. Thirty-three patients competed at least three months of the study. We found a total of 24 hospitalizations, 17 total patients. Five patients were intractable (greater than one seizure per month) with respect to their epilepsy. The mean age was 70.4 years old. There was no significant difference between those not hospitalized. Diagnosis for hospitalization include: Neurological/Psychiatry (progressive dementia and depression) two patients, Cardiac nine patients, Pulmonary four patients, four scheduled Surgeries, two Orthopedic patients, two Gastro-Intestinal bleeds, and one tracheal repair. All but two hospitalizations lead to a return to previous function. Six patients discontinued the epilepsy study because of the hospitalization. No hospitalization was related to the study drug.

Conclusions: Hospitalization of patients enrolled in the VA Cooperative study #428 was common. The hospitalization did not appear to be related to the patients epilepsy or study medication. The most common diagnoses were Cardiac, Pulmonary and scheduled Surgeries. The hospitalizations would be expected in the elderly population such as ours.

1.179
THE EFFICACY OF PREGABALIN AS ADD-ON TREATMENT OF PARTIAL SEIZURES DOES NOT APPEAR TO BE LIMITED BY DURATION OF EPILEPSY DIAGNOSIS AND NUMBER OF CONCOMITANT ANTIEPILEPTIC DRUGS

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Rationale: Pregabalin is a novel compound that binds to the alpha$_2$-delta subunit protein of voltage-gated calcium channels, and it has demonstrated anticonvulsant, analgesic, and anxiolytic activity. This report describes analyses performed to determine whether time since diagnosis of epilepsy (epilepsy duration) or number of concomitant AEDs (both of which can be indicators of epilepsy severity) influenced the degree of patient response to add-on treatment with pregabalin. Pooled data here reported were from three randomized, double-blind, placebo-controlled, add-on trials, each consisting of 8-week baseline and 12-week double-blind phases.

Methods: Patients were refractory to 2 AEDs at maximally tolerated doses, experienced $\geq$6 partial seizures during baseline with no 4-week seizure-free period, and were currently receiving 1–3 AEDs. Data from the three trials were pooled across dose regimens. Patients were randomized to placebo or 50, 150, 300, or 600 mg/day pregabalin (PGB). The primary population was intent-to-treat (ITT) defined as all patients randomized to treatment and who received at least one dose of study medication. Efficacy was assessed by seizure-frequency reduction from baseline. Seizure reduction was analyzed by dose using ANCOVA, with refractoriness measured by duration of epilepsy in years or number of concomitant AEDs as explanatory variables to determine if efficacy varied with refractoriness.

Results: Duration of epilepsy ranged from 0.6 years to 71 years (mean 25 years). Interaction between duration of epilepsy by dose was not statistically significant ($P = 0.8968$), suggesting that the treatment effect is similar regardless of epilepsy duration. Approximately 27% of patients were on one AED, 50% on two, and 23% on three AEDs. Interaction between number of concurrent AEDs and dose was also not significant ($P = 0.7651$), indicating that number of AEDs does not affect seizure reduction within doses of pregabalin.

Conclusions: In this population of patients with epilepsy refractory to treatment, pregabalin's efficacy was not a function of epilepsy severity

as measured by epilepsy duration and number of concomitant AEDs. (Supported by Pfizer, Inc.)

1.180
LATE-ONSET TEMPORAL LOBE EPILEPSIES LINKED TO ANTI-THYROID ANTIBODIES

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Rationale: Among temporal lobe epilepsies, some authors have defined a so-called mesio-temporal lobe epilepsy syndrome (MTLE), based on electro-clinical, radiological and pathological criteria. In a cohort of non-tumoral adult patients with temporal lobe epilepsies not filling the criteria of MTLE, we have assessed the possibility of an autoimmune component.

Methods: All patients underwent neuropsychological examination, long-term video-EEG monitoring, high-resolution MRI and laboratory analysis including anti-thyroid antibodies and exhaustive screening of autoimmunity.

Results: We have identified twenty patients with high levels of autoantibodies to thyroid peroxydase and/or thyroglobulin (33 times higher than the upper limit of normal range). They differed from classical MTLE : female predominance (90%), no history of febrile seizures (95%), age at onset above 18 years-old (95%, average 37 years, range 15–71 years), bilateral independent seizures or EEG abnormalities (50%). 65% of patients had other marks of autoimmunity (i.e. antinuclear antibodies...). Two patients could be classified as Hashimoto's encephalopathy. MRI highlighted unilateral ($n = 6$) or bilateral ($n = 2$) hippocampal sclerosis, multiple cortical and/or sub-cortical bilateral lesions ($n = 3$), transient focal abnormalities ($n = 2$) and was normal or non specific in the remaining 7 patients. Seven patients (35%) had a drug-resistant epilepsy and some of them were treated with corticosteroids ($n = 4$) or immunoglobulins ($n = 1$).

Conclusions: In late-onset non tumoral temporal lobe epilepsies, detection of anti-thyroid antibodies should be considered, with the aim to assess corticosteroids in case of antiepileptic drug-resistance, since steroids were reported to be valuable in the most serious cases like Hashimoto's encephalopathies. The prevalence of autoimmune marks during focal epilepsies and their pathological significance remain to be studied.

1.181
NONCONVULSIVE STATUS EPILEPTICUS (NCSE) IN THE ELDERLY POPULATION: A CASE-CONTROL STUD

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Objective: To evaluate risk and associated factors of NCSE events in the 75-year-old and older population.

Background: Mental status changes are very common in elderly patients. NCSE, a potentially treatable disorder, is one important underdiagnosed etiology usually associated with a history of epilepsy, acute medical disease, and use or withdrawal of different medications. Nevertheless, there are no clinical trials focusing on NCSE and its associated factors in the elderly population.

Design: Case-control study

We retrospectively evaluated the clinical manifestations and EEG findings in 19 consecutive elderly patients presenting with 20 NCSE events (group 1, mean age 83.3 years old). NCSE was characterized as at least 30 minutes long mental status changes (confusion or depressed level of consciousness) and continuous EEG epileptiform activity.

We compared patients in group 1 with those of a similar age control group (Group 2, n:28 patients; mean age: 83.3 years) with at least 30 minutes long acute confusion or depressed level of consciousness without obvious cause but without EEG status epilepticus criteria.

The criteria compared included presence of brain lesions on CT or MRI, number of concomitant chronic active diseases, previous neurological disorders, number of medications at the onset of the mental disturbance, frequency of metabolic disorders, withdrawal of medications, and outcome (mental status improvement vs. lack of improvement or death)Statistical analysis was performed using Chi Square and Fisher's exact two-tailed tests.

Results: Of the 20 NCSE events, 8 occurred prior to admission while 12 occurred after admission. Etiology was epilepsy in 2, acute medical problems in 14 (unrelated to surgery in 9, post-surgery in 5) and cryptogenic in 4.

A history of epilepsy was common in patients with NCSE ($p = 0.017$) although it was only present in 30% of patients in this group. The use of opiates for analgesia ($p = 0.001$) and a worse outcome ($p = 0.0003$) were significantly more common in patients with NCSE. The percentage of patients who developed new onset mental status changes during hospitalization was higher in group 1 ($p = 0.05$).

There were no statistical differences between both groups regarding: frequency of chronic active disease, dementia or cerebrovascular accidents, metabolic disorders, cortical lesions on CT or MRI. The number of patients on antibiotics or anti-depressive drugs, or on withdrawal of psychoactive medications was similar in both groups.

Conclusions: NCSE is an important etiology of mental status changes among the elderly population. Most of these patients lack a history of epilepsy, and the use of opiates was associated with the onset of NCSE. Elderly patients with mental status changes with and without NCSE cannot be differentiated clinically, and only the prompt use of EEG can determine the diagnosis.

1.182
TREATMENT CHANGES ASSOCIATED WITH REMISSION IN A REFRACTORY ADULT EPILEPSY POPULATION

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Rationale: In a recent evaluation of 246 well-defined refractory adult epilepsy patients identified at the University of Pennsylvania Epilepsy Center, we found an approximately 5% per year six-month terminal remission rate. We wished to determine what treatment changes or additions lead to remission in our patients.

Methods: From the 3224 charts at the University of Pennsylvania Epilepsy Center, we identified 246 patients followed from 2000 who met the following criteria: 1) were having at least one seizure per month and 2) had failed at least two antiepileptic drugs (AEDs) at the index date. Records were reviewed to identify current and previous drug therapy, and therapeutic interventions that occurred over the 3 yearobservation period. Changes in therapeutic strategy (surgery, drug addition/removal or dose change) and alterations within three-months of onset of seizure freedom were identified.

Results: Overall, 38 of the 246 patients (15.5%) attained six-month terminal remission. Of the 21 patients referred for surgery, 11 attained six-month terminal remission, one after subsequent drug addition. None of the 27 patients with Lennox-Gastaut syndrome (LGS) attained terminal remission, despite an average of 9 drug changes/person. Six month terminal remission in the remaining 198 patients occurred in 13.6%. New antiepileptic drugs were added 320 times, and removed 274 times. Forty-four patients had no addition or removal of medication over the period of observation. The following drugs were added most frequently: levetiracetam: 146; zonisamide: 51, lamotrigine: 24, oxcarbazepine: 21, topiramate: 19. Addition of levetiracetam was associated with the attainment of terminal remission in 14 patients, lamotrigine in 4, and zonisamide in 1. In four patients a combination of levetiracetam plus either zonisamide, valproic acid, topiramate, or lamotrigine were added prior to remission. In four patients, there had not been a change in antiepileptic drug at any time in the three years prior to development of seizure freedom although 3 had dosage changes. In the three months prior to remission, a new antiepileptic drug had been initiated in 14 patients, a dose change was made in 7, and no change in regimen or dose was made in 6.

Conclusions: Levetiracetam was the most frequently newly prescribed drug over this three-year period, since its launch occurred proximate to the index date. Assessment of the rate of remission related to rate of initiation of specific drugs yielded the following results:

levetiracetam: 18/146 (12.3%), lamotrigine 5/24 (20.8%,) topiramate 1/19 (5.3%), valproic acid 1/9 (11.1%), zonisamide 2/51 (3.92%). The small number of cases for some of the drugs precludes definitive interpretation. Further prospective studies are recommended.

1.183
LOW INCIDENCE OF SPONTANEOUSLY REPORTED ADVERSE EVENTS ASSOCIATED WITH DIAZEPAM RECTAL GEL USE IN ELDERLY PATIENTS

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Rationale: New challenges for safe and effective treatment of patients with epilepsy emerge as medical care improves and patients live longer. Elderly patients generally have a greater number of comorbid medical conditions and require more concomitant medications than younger patients. In addition, patients' response to a medication alters due to age-related pharmacokinetic and pharmacodynamic changes. Although diazepam rectal gel, a rescue medication for the treatment of breakthrough seizures, has demonstrated an excellent safety and efficacy profile in children and adults, few data regarding safety evaluations specific to the geriatric population are available. As the segment of elderly patients grows to represent an increasing percentage of the epilepsy population, the need for these data will assume increasing importance. To evaluate the safety of diazepam rectal gel use in elderly patients, postmarketing reports of adverse events were reviewed.

Methods: We evaluated the number and type of adverse events occurring in elderly patients that were spontaneously reported to the MedWatch program of the Food and Drug Administration. Patients aged 61 years and older were included. Projected, age-specific numbers of patients using diazepam rectal gel were estimated from the NDC Health Market Focus Reports.

Results: Approximately 6000 patients at least 61 years of age were estimated to have used diazepam rectal gel between 1999 and 2002, inclusive. Of these patients, an estimated 3800 were at least 71 years of age. Among the 40 MedWatch reports for this time period, only 1 adverse event was spontaneously reported in an elderly patient. This patient was an 85-year-old man with a history of diabetes, Parkinson disease, and 2 strokes. Beginning approximately 1 day following a single 10-mg dose of diazepam rectal gel, the patient experienced confusion, disorientation, and forgetfulness for at least 1 week.

Conclusions: The absence of any reports of respiratory adverse events, hypotension, or falls with fractures in geriatric diazepam rectal gel users is an important observation. While these data do not capture all adverse events, the relative absence of reported adverse events among patients over the age of 60 provides evidence for the safety of diazepam rectal gel use in elderly patients. (Supported by Xcel Pharmaceuticals.)

1.184
MRI AS A PROGNOSTIC FACTOR IN EPILEPSY

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Rationale: The aim of the study was to analyze prognostic factors in epileptic patients in relation to the response to the pharmacological treatment.

Methods: We studied 378 patients with a previously defined epileptogenic zone who have been submitted to MRI studies. They were classified into 2 groups: Refractory (G1) and Non Refractory (G2) to the drug therapy. We analyzed the variables: age, age at onset (AO), epileptogenic zone, MRI results (normal or abnormal) and the predictive value of the MRI.

Results: G1: n = 171, average age 30.8 ± 12.1 years, AO 10.7 ± 10.2 years. Temporal 93 (54.4%); Extratemporal 69 (40.3%); Generalized 9 (5.3%). Abnormal MRI: 113 (66.1%).

G2: n = 207, average age 34 ± 15.8 years, AO 19.2 ± 16.7 years. Temporal 66 (31.9%); Extratemporal 93 (44.9%); Generalized 48 (23.2%). Abnormal MRI: 72 (34.8%).

There were differences in age ($p < 0.02$) and AO ($p < 0.01$) less in G1. Generalized epilepsy was more frequent in G2 ($p < 0.01$) and temporal lobe epilepsy (TLE) more frequent in G1 ($p < 0.03$). Abnormal MRI was more frequent in G1 (Odds Ratio: 3.65 [2.33–5.73], $p < 0.001$). The positive predictive value of the MRI was 61.1%. The negative predictive value of the MRI was 69.9%.

Conclusions: Younger age and TLE were related to a bad response to the pharmacological treatment. Generalized epilepsy was related to a good outcome. MRI seems to be the most powerful tool to define a prognosis in epilepsy patients. (Supported by Secretaría de Ciencia y Técnica Ministerio de Salud de la Nación.)

1.185
IMPROVED MOOD STATES WITH THE ADDITION OF LAMOTRIGINE TO OTHER ANTIEPILEPTIC DRUGS

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Rationale: To determine the effect of lamotrigine (LTG) on mood states when added to other antiepileptic drugs (AEDs).

Methods: LTG was added to other AEDs in a study of adjunctive therapy. Patients were evaluated for changes in mood states with the Profile of Mood States (POMS) and QOLIE-31 at baseline, after addition of LTG as adjunctive treatment, and after withdrawal of other drugs to LTG monotherapy. POMS scores include six subscales (Tension, Depression, Anxiety, Vigor, Fatigue, Confusion) and a total. Physicians' ratings of global change were used to determine minimal clinically important changes (MCIC) in POMS scores.

Results: POMS scores were clinically and statistically significantly improved with LTG. MCIC changes in POMS scores were: Tension 17%, Depression 38%, Anger 39%, Vigor 21%, Fatigue 25%, Confusion 34%, Total 43%, based on physicians' detection of overall patient improvement. Among all patients completing Adjunctive LTG (N = 155, effect sizes 0.35–0.65) all scale scores were improved (all $p < 0.0001$). Tension, Vigor and Fatigue subscales met MCIC, with Total scores improving 39% (effect size 0.58). Among patients completing both Adjunctive and Monotherapy LTG (N = 51), all POMS scores were statistically improved ($P < 0.003$) with effect sizes 0.48–0.94. Subscale scores at the end of Adjunctive and Monotherapy LTG were: Tension 28, 26%, Depression 36, 37%, Anger 39, 36%, Vigor 31, 43%, Fatigue 36, 42%, Confusion 30, 27%, respectively. Total scores improved 47% (effect size 0.82) at end of Adjunct LTG, and 50% (effect size 0.84) at end on Monotherapy LTG. At the end of monotherapy, all scores remained significantly better than baseline (all $p < 0.003$, effect sizes 0.48–0.94), but none were significantly different from end of the adjunctive phase. POMS scores correlated highly with the QOLIE-31 Emotional Well-Being subscale($r = 0.698$), a known measure of mood, but not with seizure reduction.

Conclusions: POMS score changes were defined as clinically important improvements with the addition of LTG to other AEDs, and withdrawal to monotherapy. The improvements in all measured aspects of mood states likely were not a synergy between LTG and other AEDs because they remained stable after withdrawal of the other AEDs. (Supported by GlaxoSmithKline.)

1.186
SIGNIFICANT AND UNIQUE INFLUENCE OF DEPRESSION AND PERSONALITY (NEUROTICISM) ON QUALITY OF LIFE IN TEMPORAL LOBE EPILEPSY

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Rationale: Health-related quality of life (HRQOL) after temporal lobectomy is dependent on a complex interaction of variables (demographics, clinical epilepsy characteristics, degree of seizure-freedom, psychological variables). It is now recognized that HRQOL is influenced by factors previously thought to be of little consequence (e.g., depression and anxiety). Depression is commonly seen in 30–50% of temporal lobe cases, and recent studies report clear links between quality of life and these mood states. Personality could also potentially influence HRQOL.

Neuroticism, a personality dimension characterized by chronic negative emotions and behaviors) has been related to poorer QOL. This study investigated the separate and combined contributions of depression and neuroticism to HRQOL.

Methods: Subjects were 57 patients (26 males) with carefully documented temporal lobe epilepsy as reported in Wiebe et al. (2001), who randomized patients to the surgical or medical arm of an RCT. In the present study, measures were collected at baseline, during inpatient epilepsy unit monitoring, and six months later. Wiebe et al. report characteristics of the sample and procedural details. Dependent measures in the present study include the QOLIE-89, and a measure of depression (CES-D). Neuroticism was evaluated with the negative affect scale of the PANAS. Analyses included product-moment correlations among variables at each assessment time. Multiple regression analyses were performed, with depression and neuroticism as individual and combined predictors of follow-up QOLIE-89.

Results: The CES-D and PANAS were significantly correlated ($r = .77$, $p = .0001$). Although sharing a large degree of variance (approximately 50%), they appeared sufficiently independent. Depression was significantly correlated with overall QOLIE-89 at baseline ($r = -.45$, $p < .01$), suggesting greater pre-operative depression is associated with poorer QOL. The correlation between depression and overall QOL at follow-up remained significant, but the association was not as strong ($r = -.38$, $p = .05$). Comparisons of Neuroticism with the QOLIE-89 overall scores were also significant, both at baseline ($r = -.41$, $p = .001$) and to a lesser extent at the 6-month follow-up ($r = -.18$, $p = .05$). Step-wise linear regression analyses suggested depression and neuroticism contribute significant but unique variance to 6-month HRQOL outcomes.

Conclusions: This study sought to advance our understanding of the complex interaction of factors comprising HRQOL ratings. It is clear depression and neuroticism are related, but retain sufficient independence to be considered different. In addition to seizure frequency, there are important factors beyond depression that affect quality of life for these patients. Neuroticism has an important influence on quality of life and on depression.

1.187
THE IMPACT OF VIDEO-EEG MONITORING ON DIAGNOSTIC CERTAINTY AND THERAPEUTIC DECISION MAKING

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Rationale: Video-EEG monitoring is becoming a favored diagnostic tool for the differential diagnosis of seizure-like events and to optimize epilepsy treatment through medication or surgical therapies. However, payers are requesting that approvals for video EEG monitoring be justified by improved clinical outcomes. We therefore characterized the patients utilizing this resource by determining the primary reason for admission and assessed whether video EEG monitoring contributed to clinical care as demonstrated by a change in medication or referral for epilepsy surgery.

Methods: Sequential patients admitted in 2001 to the Epilepsy Monitoring Unit (EMU) at New York Presbyterian Hospital, Columbia Campus were evaluated. Columbia is an urban Level IV Epilepsy Center. We retrospectively reviewed discharge summaries and EMU reports for specific criteria including reason for admission, change in therapeutic regimen and referral for epilepsy surgery.

Results: Data was acquired from 50 patients (18 male, 32 female) with a mean age of 40.4 years (range 18–87). The primary reason for admission to the EMU included; diagnosis of paroxysmal spells (40%), characterization of known seizures (32.7%), presurgical evaluation (11.5%), evaluation of subclinical seizures or non-convulsive status epilepticus (9.6%) and medication adjustment or toxicity (5.8%). As a result of their evaluation, 84% of patients had a change in therapeutic regimen and 21% were discharged with a referral for epilepsy surgery.

Conclusions: Timely diagnosis and optimal treatment has a positive impact on patient outcome and quality of life. Determination of the nature of seizure-like events through video-EEG monitoring is truly helpful in guiding appropriate care to maximize therapeutic options including adjustment or change in drug regimen, determination of appropriate surgical referrals and initiation of proper treatment of paroxysmal events that are nonepileptic. Video EEG monitoring may also minimize unnecessary medical services by establishing a clear diagnosis.

1.188
LEVETIRACETAM IN THE TREATMENT OF PARTIAL STATUS EPILEPTICUS OR FREQUENT PARTIAL SEIZURES

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Rationale: Levetiracetam (LEV) is an antiepileptic drug (AED) approved as add-on therapy in the treatment of partial onset seizures in adults with epilepsy. It has a rapid onset of action, though its effectiveness in the treatment of repetitive seizures or status epilepticus is unknown. This study reports the acute use of LEV in hospitalized, EEG monitored patients with recurrent seizures.

Methods: We retrospectively identified adults who underwent continuous scalp EEG monitoring at Washington University from 1/02 to 5/04, were diagnosed with nonconvulsive, partial status epilepticus or frequent seizures (>1/hour) and were given LEV during the recording. Patients who previously had taken LEV were not included. The mean age at the time of monitoring was 54.8 years (range: 19–81 years).

Results: Seventeen patients were identified who were given LEV for acute treatment of seizures. Sixteen (94.1%) were given benzodiazepines including lorazepam and midazolam. Fourteen (82.4%) were treated with phenytoin (PHT) and 7 (41.2%) with valproate (VPA). Three patients received LEV as a primary AED during EEG monitoring without PHT or VPA. These cases are reported.

Case 1: A 77-year old woman with a history of dementia and seizures on carbamazepine (CBZ) monotherapy was admitted with new aphasia, disorientation and right sided weakness. Neuroimaging was unrevealing, and EEG showed left temporal seizures occurring initially every 3–6 minutes without clear changes in baseline behavior. Rapidly escalating doses of LEV to 2000 mg BID were started initially with maintenance CBZ. Increasing seizure free periods were noted, and by hospital day #4, the patient remained seizure free.

Case 2: A 60-year old man presented with a 4 day history of confusion and difficulty speaking. A seizure was witnessed after outside hospital admission, and he was treated with lorazepam and PHT loading. He was transferred because of continued confusion, and EEG initially revealed posterior onset seizures every 10–40 minutes. He was started on LEV to a dose of 1500 mg BID and given 2 total doses of lorazepam after which the seizures did not recur and mental status returned to baseline.

Case 3: A 60-year old woman with a history of subarachnoid hemorrhage and PHT allergy had been admitted with sepsis. She was maintained on a ventilator with intermittent midazolam for agitation. She had a witnessed generalized tonic-clonic seizure, and EEG revealed ongoing right frontopolar electrographic seizures. She was treated with lorazepam and started on LEV to a dose of 1000 mg BID with resolution of seizures on EEG and no clinical recurrence.

Conclusions: LEV may be an effective treatment as adjunctive therapy in the acute management of patients with frequent partial seizures or partial status epilepticus.

1.189
SENSITIVITY AND SPECIFICITY OF CATAMENIAL PATTERNS OF SEIZURE EXACERBATION IN PREDICTING OVULATION

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Rationale: Cyclic changes in neuroactive steroid concentrations may induce variation of seizure frequency. Herzog et al. (*Epilepsia* 1997;38:1082–8) have provided statistical evidence for the occurrence

of 3 patterns of catamenial seizure exacerbation (CSE): 1) perimenstrual (C1: Day −3 to 3), and 2) periovulatory (C2: Day 10 to −13) in ovulatory cycles, and 3) luteal (C3: Day 10 to 3) in anovulatory cycles. They also determined mathematically based levels of seizure exacerbation for designation of CSE for each of these patterns. Sensitivity and specificity of these 3 patterns as predictors of ovulation, however, remain to be established.

Methods: 87 women, 13–45 years of age, with refractory localization-related epilepsy recorded seizures and menses during 3 cycles. A midluteal progesterone level < 5 ng/ml was used to designate anovulatory cycles. The menstrual cycle was divided into 4 phases: menstrual (M) = −3 to +3, follicular (F) = 4 to 9, ovulatory (O) = 10 to −13 and luteal (L) = −12 to −4. Average daily seizure frequency (ADSF) for each phase was compared among phases. Comparisons were carried out separately for ovulatory and anovulatory cycles. CSE designation was made if seizure exacerbation exceeded predetermined levels: C1 - ADSF during the M phase relative to the F and L phases in ovulatory cycles ≥ 1.69; C2: ADSF during the O phase relative to the F and L phases in ovulatory cycles ≥ 1.83; and C3: ADSF during the O, L and M phases relative to the F phase in anovulatory cycles ≥ 1.62. The frequency of each pattern in relation to ovulatory and anovulatory cycles was tabulated and proportions were compared using χ^2 analysis.

Results: The distribution of catamenial patterns in relation to ovulatory and anovulatory cycles is presented in Table 1.

	C1 &/or 2	C3	Total
Ovulation	112	24	136
Anovulation	5	16	21
Total	117	40	157

$\chi^2 = 29.8$; $p < .0001$

Sensitivity and specificity values for catamenial patterns 1 and/or 2 in predicting ovulation and pattern 3 in predicting anovulation are presented in Table 2.

	Sensitivity	Specificity
C1 &/or 2	82.4%	95.7%
C3	76.2%	40.0%

Ovulatory cycles that showed the C3 pattern had higher midluteal estradiol/progesterone ratios than those that showed C1 and/or 2 patterns: 12.5 ± 5.6 vs 8.0 ± 3.7 (p = .01).

Conclusions: Catamenial patterns of seizure exacerbation differ significantly between ovulatory and anovulatory cycles. C1 and 2 patterns are both highly sensitive and specific for ovulatory cycles. C3 is quite sensitive, but lacks specificity, for anovulatory cycles because it relates to high E/P ratios regardless of ovulation. (Supported by NIH RO1 NS39466.)

1.190

PREGABALIN ADD-ON TREATMENT IN PATIENTS WITH PARTIAL SEIZURES: FIXED- AND FLEXIBLE-DOSE REGIMENS

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Rationale: Randomized controlled trials (RCT) rarely resemble behaviors in clinical practice. We compared the efficacy, tolerability, and AE profiles exhibited by pregabalin (PGB)–an α_2-δ ligand with anticonvulsant, analgesic, and anxiolytic properties–administered using a flexible-dose regimen, similar to clinical practice, against profiles exhibited when using a fixed-dose regimen, commonly employed in RCTs.

Methods: Data from two 12-week, placebo-controlled, double-blind, randomized, trials were used to identify differences in efficacy, tolerability and AE profiles observed when PGB is used as add-on therapy administered via fixed- and flexible-dose schedules. All randomized patients experienced refractory epilepsy and were on 1–3 anti-epileptic drugs (AEDs). In the fixed-dose group, patients were randomized to 1of 3 effective dosages of PGB: 150, 300, or 600 mg/day (BID) or placebo (PBO). In the flexible-dose group, patients received: 150–600 mg/day PGB (BID) which was adjusted at regular intervals depending on treatment efficacy/tolerance; or PBO. The effect of dosing regimen on PGB anticonvulsant treatment was assessed using measurements of: seizure frequency (% change), incidence of patients experiencing a ≥50% seizure-frequency reduction (responders), adverse events, and tolerability.

Results: A total of 794 patients were enrolled in both studies (PBO: 173; PGB: 621). The average patient suffered epilepsy for 25 years and experienced approximately 9 seizures/month (median) before PGB add-on treatment. Approximately, 75% of patients were on 2 or more concurrent AEDs. The primary population was intent-to-treat (ITT) defined as all patients randomized to treatment and who received at least one dose of study medication. All PGB treatment arms were superior to PBO. Patients receiving 600 mg/day PGB in both studies with a fixed-dose schedule experienced significant reductions in seizure frequency (fixed dose: 54% and 49% vs. flexible dose: 35%) versus PBO and significant increases in responder rates (fixed dose: 51% and 45% vs. flexible dose: 31%) versus PBO. The AE profiles were similar for both studies with most common AEs being: dizziness, somnolence, ataxia, asthenia and weight gain. PGB was well tolerated by all treatment groups, however, greater tolerability was exhibited by patients on the flexible-dose regimen as evidenced by discontinuation rates due to AEs (fixed dose: 23.6% and 32.8% vs. flexible dose: 12.2%).

Conclusions: PGB is an effective and well-tolerated add-on treatment for patients with partial seizures. Patients receiving PGB via both fixed- or flexible-dose regimens benefited from significant reductions in seizure frequency. In addition, flexible-dosing provided improved tolerability. (Supported by Pfizer, Inc.)

1.191

RECTAL VERSUS INTRAVENOUS ADMINISTRATION OF MEDICATION: PATIENT PERCEPTIONS OF DIAZEPAM RECTAL GEL USE

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Rationale: The safety and efficacy of diazepam rectal gel, a portable rescue medication for the at-home treatment of breakthrough seizures, has been demonstrated in patients of various ages with a broad range of seizure types. Despite the benefits that diazepam rectal gel can provide, some physicians and patients may feel wary about its rectal route of administration in the adult population. Rectal delivery modalities are well accepted in the pediatric population. Physicians with negative perceptions of rectally administered medications may convey these feelings to their patients and, in turn, bias patients against trying this option. However, alternate choices for emergency seizure treatment—emergency department (ED) visits and intravenous/intramuscular injections—present other challenges for the patient. Visits to the ED are time consuming and costly. Use of needles with an actively convulsing patient is inherently hazardous. However, patients transported by ED ambulance usually have intravenous access established as part of the emergency protocol. Needle phobia is a frequent concern for many outpatients. A study was conducted with a survey to assess patients' fear of treatment with needles versus rectal administration of medication and other quality of life factors pertinent to patients with epilepsy.

Methods: A multiquestion survey was administered to patients with epilepsy concerning preferences and concerns about rectal versus intravenous administration of medications. Information was also sought regarding ED visits and preferences for at-home treatment or ED visits for breakthrough seizures. Other quality of life information was obtained using the Quality of Life in Epilepsy-10 (QOLIE-10) Survey.

Results: A pilot study of 12 patients with seizure exacerbation or prolonged seizures completed the survey. All patients in this study preferred

at-home management of breakthrough seizures to treatment in the ED, which is often time consuming and costly. In addition, these patients did not view rectally administered medication as a barrier to use. In fact, it was preferred to receiving a needlestick, which would be required for establishing IV access. Additional patients will be surveyed to extend these results to a larger sample.

Conclusions: These results indicate that patients with epilepsy view rectal administration positively and prefer this route of administration in the outpatient setting to needlesticks. (Supported by Xcel Pharmaceuticals.)

1.192

MAGNETIC RESONANCE EVIDENCE OF MESIAL TEMPORAL SCLEROSIS IN SPORADIC "BENIGN" MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Sporadic "benign" mesial temporal lobe epilepsy (BMTLE) is a rather common epileptic syndrome with typical onset in adulthood, in which genetic factors seem to play a major etiopathogenetic role. Its relationship with severe mesial TLE is far more complex, but evidence has emerged that BMTLE and severe pharmacoresistant TLE might lie on a biological continuum. In this study, we wished to determine the occurrence of magnetic resonance imaging-detected mesial temporal sclerosis (MTS) in patients with sporadic BMTLE.

Methods: The study group consisted of consecutive 98 unrelated patients (50 female, mean age 49.7 years, SD $\pm$ 18.1; range 5 to 81) with BMTLE, who rarely or never had seizures at long-term (< 2years) follow-up. The diagnosis of TLE was mainly based on typical temporal auras and/or interictal EEG discharges with a maximum over the temporal lobes. A familiar history of febrile convulsions or epilepsy was observed in 37% of the patients. Twenty-two% of the patients had a personal history of febrile convulsion, which were simple in almost all of them. The mean age at seizure onset was 28.7 years (SD $\pm$ 24.7), the mean duration of epilepsy was 17.1 years (SD $\pm$ 15.7). In all patients, brain MR images were obtained using sequences and slices to optimize visual detection of mesial temporal structures.

Results: Thirty-six percent (35/98) of the patients had MRI evidence of MTS. In detail, 18 had left MTS, 16 had right MTS, while in the remaining patient there was evidence of bilateral MTS. Hyperintense FLAIR and T2 signal with or without mesial temporal atrophy was observed in 22 of these 35 individuals. MRI abnormalities correlated with the epileptogenic focus defined by lateralized EEG discharges, with or without lateralized seizure features.

Conclusions: These results indicate that MRI evidence of MTS is often encountered in BMTLE. In this way, our findings reinforce the belief that MTS is not necessarily related to seizure severity, and that other factors, both genetic and environmental, play an important role in determining seizure severity in patients with TLE.

1.193

DIAZEPAM RECTAL GEL AND EFFECTIVE BREAKTHROUGH SEIZURE TREATMENT IN ADULT PATIENTS

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Rationale: Seizures in adult patients with epilepsy are often well controlled by antiepilepsy drugs (AEDs) though the risk of breakthrough seizures persists. As many as 35% of patients with epilepsy experience inadequate seizure control. The unpredictable nature of breakthrough seizure activity requires a patient to have a rescue medication as part of a comprehensive treatment plan. Diazepam rectal gel is effective in terminating breakthrough seizures with minimal adverse effects, establishing both efficacy and tolerability. Effective control of breakthrough seizures without the necessity of medical intervention may encourage renewed feelings of confidence and empowerment in epilepsy patients. This study examines the ability of diazepam rectal gel to establish effective breakthrough seizure control and tolerability in adult patients with prolonged seizures or seizure clusters.

Methods: A chart review was conducted to identify adult epilepsy patients who had used diazepam rectal gel for breakthrough seizures in the previous 18 months. Information was collected regarding several aspects of treatment including diagnoses, dose, frequency of use, reasons for use, safety, and efficacy. To assess treatment effectiveness, efficacy in stopping breakthrough seizures in relation to reported adverse events was evaluated.

Results: Forty-seven patients received at least 1 dose of diazepam rectal gel. The patient cohort comprised 23 men and 24 women; the mean patient age was 34.7 years (range, 18–59). Diagnoses consisted of partial epilepsy (25 patients), generalized epilepsy (18), multifocal epilepsy (3) and nonepileptic spells (1). Among the patients with generalized epilepsy, 9 were diagnosed with Lennox-Gastaut syndrome. The patient with nonepileptic spells had used rectal diazepam gel before the diagnosis was established, following video-electroencephalogram (EEG) monitoring. The mean diazepam rectal gel dose was.20 mg/kg; the mean total dose was 15.6 mg (range, 10–20 mg). Reasons for use included seizure clusters (26 patients), prolonged seizures (12 patients), or both (9 patients).The frequency of use ranged from once every 4 months to weekly in poorly controlled seizures. Diazepam rectal gel was effective in stopping seizures in 43 patients (91.4%). Somnolence was reported in all patients, although this may partially be due to characteristics of the postictal state. No other AEs and no serious AEs were reported.

Conclusions: Diazepam rectal gel demonstrates efficacy and tolerability as a seizure rescue medication for adult patients with a variety of seizure types. Breakthrough seizures were controlled in most patients and repeat use suggests acceptance of mild AEs in favor of effective seizure control. Effective at-home treatment that results in well-controlled seizures suggests the potential for improved patient confidence, ability to expand the activities of daily living, and enhanced quality of life. (Supported by Xcel Pharmaceuticals.)

1.194

REFRACTORY SEIZURE UNRESPONSIVE TO ANTICONVULSANTS IN IDIOPATHIC HYPERTROPHIC PACHYMENINGITIS: RESPONSE TO STEROID

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Rationale: Idiopathic intracranial hypertrophic pachymeningitis (IIHP) is an uncommon disorder that causes a localized or diffuse thickening of the dura mater and at the onset most of the patients have chronic daily headache, associated with or without neurologic manifestation such as cranial nerve palsies, cerebellar ataxia, and neuro-opthalmic complications. To our knowledge, there are no reported cases of IIHP with intractable seizures unresponsive of conventional anticonvulsants. We describe two men with refractory seizures which remitted after steroid therapy.

Methods: 2 case reports

Results: A 45-year old man admitted 6-year history of chronic daily headache and facoal seizure of left arm. MRI revealed diffuse thickening and enhancement of the right frontotemporal dura mater. Histopathological study provided reactive gliosis and chronic inflammation. Carbamazepine was tried, but seizure control was failed. The patient showed a good response to steroid therapy, seizure was controlled. Later, when steroid tapered, he developed aggravation of seizure. A 62-year old man presented recurrent complex partial seizures and left hemiparesis. MRI showed a linear contrast enhancement on the gyral surfaces of right temporoparietal region. Interictal electroencephalogram((EEG) showed left temporal (T3) sharp waves. Seuzures were not response to Valproic acid and Carbamazepine. But steroid resulted in seizure control.

Conclusions: IIHP has been linked to medically intractable partial seizure and refractory seizure is also controlled by steroid therapy as other clinical signs. Pathophysiological mechanisms seem to be inflammatory perivascular infiltration that plays an important role in cortical irritative symptomatology. Therefore, Corticosteroid should be considered in the treatment of seizures which underlying mechanism is inflammatory proccess.

1.195

HIPPOCAMPAL SCLEROSIS AND REFRACTORY EPILEPSY: A POPULATION-BASED MRI STUDY

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Rationale: Hippocampal sclerosis (HS) is the lesion most frequently described in temporal lobe epilepsy. HS can be detected in-vivo using magnetic resonance imaging (MRI). The presence of HS is believed to predict an increased risk of medically refractory epilepsy. Most studies of HS deal with patients under pre-surgical evaluation, and consequently probably reflect the more serious cases.The few existing studies on broader patient groups rely on qualitative MRI. We performed a retrospective study of quantitative MRI findings in partial epilepsy, in order to dertermine the frequency of HS and its impact on seizure control.

Methods: We analysed data from 784 consecutive MR-scans performed at the MR-Center, Skejby Sygehus, as part of the investigations for partial epilepsy in the period 1995–2003. Patients were aged 15–50 years and had been referred from the Department of Neurology, Aarhus University Hospital, or from a private neurologist in the County of Aarhus, the only local sites for investigation of newly-diagnosed epilepsy. All MR-scans (1.5 T) included volumetry and T2-relaxometry of the hippocampal region. Patients were categorized into 5 groups according to MRI-findings: 1. HS (atrophy and ipsilateral raised T2 signal), 2. Unilateral hippocampal atrophy only, 3. Unilaterally raised T2 signal, 4. Bilaterally raised T2 signal, and 5. Normal MRI.

Clinical information regarding age of onset, duration, and seizure frequency was extracted from Epibase, a prospective database in which all epilepsy patients have been systematically registered since 1999. Results are based on this preliminary information, and information on all patients is currently being extracted from medical records.

Results: Seven hundred-fifty-three persons were scanned. 31 patients had two scans. Mean age was 31 years. Hippocampal changes were found in 27% of scans. HS was detected in 40 (5%), unilateral atrophy alone in 33 (4%), unilaterally raised T2 signal in 99 (13%) and bilaterally raised T2 signal in 41 scans (5%). Left HS was more common than right (26 vs.14 scans, $p = 0.04$). The age of onset tended to be lower (13 vs. 18 years, NS), and the duration of epilepsy was longer in the HS group compared to patients with other unilateral changes (group 2 and 3)(21 vs 14 years, $p < 0.05$). Seizure-freedom was rarer in patients with HS than in the groups with other unilateral changes (24% vs. 45%, $p < 0.05$), and more patients with HS had frequent seizures compared to patients with other unilateral change and to normals (62% vs. 36% and 33%, $p < 0.05$).

Conclusions: HS, defined as atrophy and raised T2 signal on the same side, was found in 5% of our patients with partial epilepsy. Overall, unilateral hippocampal changes were present in 22%. Hippocampal sclerosis shown by quantitative MRI was associated with lower age of onset and a greater risk of severe, intractable epilepsy. (Supported by Aarhus University Hospital, The Danish Epilepsy Society.)

1.196

PAROXETINE IN THE TREATMENT OF DEPRESSION AND ANXIETY IN PATIENTS WITH EPILEPSY

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Rationale: The purpose of this study was to asses the efficacy and safety of the selective serotonin-reuptake inhibitor (SSRI) paroxetine in depressed and anxious epileptic patients.

Methods: We evaluated 31 epileptic patients (18 female, 13 male), who suffered from interictal depressive disorder, additionally 22 of these had symptoms of interictal anxiety disorder (generalised anxiety disorder and panic disorder). Before treatment the diagnoses were verified with MINI International Neuropsychiatric Interview. Patients were evaluated using HAMD17 and HAMA scales before paroxetine treatment and after 4 and 8 weeks of treatment. The dose of paroxetine was fixed, 10 mg/day for one week followed by 20 mg/day from week 2. During paroxetine treatment there were only minor changes in antiepileptic therapy, in all patients epilepsy was stabilized. The presence of depressive and anxiety symptoms were not related to epileptic seizures in time.

Results: During paroxetine treatment we found HAMD 17 total score to have decreased from 20.5 ± 3.7 (range 14–28) pre-treatment to 14.1 ± 2.8 (range 9–20) ($p < 0.001$) after 4 weeks and to 9.1 ± 2.0 (range 4–13) ($p < 0.001$) after 8 weeks of treatment. During treatment we found in 22 patients with comorbid anxiety disorder a decrease in HAMA total score from 26.0 ± 6.6 (range 16–37) pre-treatment to 17.8 ± 4.9 (range 10–27) ($p < 0,001$) after 4 weeks and to 10.1 ± 2.3 (range 6–16) ($p < 0.001$) after 8 weeks of treatment. The number of responders, related to depressive symptoms, (>50% decrease in HAMD 17) was 6 (19.3%) and 20 (64.5%) patients after 4 and 8 weeks of treatment respectively.

The number of responders, related to anxious symptoms, (>50% decrease of HAMA 17) was after 4 weeks of treatment: 4 patients (19.3%) from those with a positive diagnosis of anxiety disorder ($n = 22$), after 8 weeks of treatment: 17 patients (77.3%). Nausea was the most common adverse event, occurring in 8 patients (25.8%) during the first treatment month, in 2 patients (6.4%) continuing during the second month. Sexual function problems (decreased libido, loss of ability to achieve orgasm) related to the situation pre-paroxetine treatment was reported in 3 (10%) male patients during the whole treatment period. The frequency of seizures was unchanged.

Conclusions: Paroxetine is a safe and effective antidepressant in the treatment of depressed and anxious epileptic patients.

1.197

PERFUSION PATTERNS IN SEIZURES DUE TO MTS COMPARED TO SEIZURES OF MEDIAL TEMPORAL ONSET OF OTHER ETIOLOGIES

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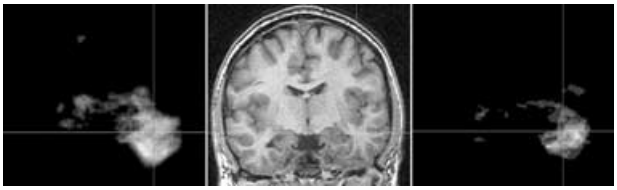
Rationale: Mesial temporal lobe epilepsy (MTLE) due to mesial temporal sclerosis (MTS) is a unique clinical syndrome, which may produce specific ictal perfusion patterns. To investigate this possibility, we compare a group of patients with MTLE due to MTS with a group of patients with MTLE due to other etiologies.

Methods: We retrospectively reviewed consecutive intractable partial epilepsy patients who had ictal and interictal SPECT images performed at Saint Louis University Hospital. Patients with video-EEG recordings and MRI findings consistent with seizures of mesial temporal lobe onset were included in the series. We recorded the time sequence of all seizure semiology and injection of radiotracer. Subjects were determined to have MTS using MRI-based hippocampal volumetric asymmetery and/or post-operative pathological results. Using a previously validated technique, we created composite SISCOM images of the MTS and non-MTS groups. To compare all subjects, the subjects with right-sided onset of seizures were inverted, so that perfusion changes are depicted on the left side of the final template composite images.

Results: There were 17 subjects in the MTS group, and 14 subjects in the non-MTS group. For the MTS group, mean seizure duration was 90 s, and mean injection time was 32 s. For the non MTS group, mean seizure duration was 96 s, and mean injection time was 34 s. Regions of perfusion significance were set at $P \leq 0.012$ for the MTS group, and $P \leq 0.016$ for the non-MTS group. A gradient shading scale was then used to show the regions of significant perfusion change for the MTS and non-MTS groups. Figure 1 shows the perfusion changes of the MTS group (left image) and non-MTS group (right image). The middle image is the coregistered template MRI. Cross-hairs show the same reference in space of all images. The regions of perfusion changes were similar between the two groups, showing the anterior temporal region, basal ganglia, and insula as the most commonly perfused regions in both groups.

Conclusions: Regional hyperperfusion patterns in MTLE due to MTS are similar to hyperperfusion patterns of seizures of medial temporal onset due to other etiologies. This is suggestive that activation of neuronal networks in seizures of medial temporal onset is more dependant on neuro-anatomical localization of seizure onset than the underlying neuropatholocial etiology of the epileptic seizures.



1.198
PURE ICTAL DIZZINESS: A CASE OF ICTAL ASYSTOLIA
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Rationale: Cardiac changes during seizures may be important complications, because the possibility of producing syncope or even sudden death. However, ictal asystolia is an infrequent seizure manifestation, and most of times it follows complex partial seizures. We present a case in which the seizures were symptomatic exclusively due to the ictal asystolia: dizziness and weakness were the ictal symptoms.

Methods: The patient is a right-handed 47-year-old woman with focal motor seizures since the age of 42. She had focal seizures with loss of consciousness and hemicorporal convulsions on the left side. An EEG and MRI were unremarkable. In these years she tried carbamazepine and valproate, and the frequency of these episodes was very low (one every 3–6 months). The new complain during the last year was that, approximately once a month, she may present episodes of dizziness, generalized weakness, slow speech, occasionally followed by partial disconnection. They lasted 1–2 minutes, and after the episode the patient was very weak and pallid. She was send to our center for video-EEG.

Results: She underwent a video-EEG monitoring study with a digital video-EEG system (Harmonie, Stellate, Montreal). During wakefulness she presented one typical spell. On the EEG, around 40 seconds before the abnormal sensation, rhythmic activity develops on the electrodes T4-T6, and less clearly on T2. However the symptoms appeared very late, corresponding to the time when the EKG shows bradycardia and periods without QRS complexes of 3, 4, 7 and 3 seconds. She recognised the spell as typical for the last year, being different from the initial motor seizures.

Conclusions: Pure dizziness or weakness can be a peculiar manifestation of a focal ictal event associated to ictal asystolia. The manifestations can be related to the ictal phenomenon but in some cases they are provoked by the cardiac changes that follow the focal seizure.

1.199
UTILIZATION OF A SOFTWARE PROGRAM TO CHARACTERIZE HOSPITALIZATION RATES FOR INDIVIDUALS WITH EPILEPSY OR SEIZURE DISORDERS
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Rationale: Individuals admitted to urban hospitals with admitting diagnosis of seizure/epilepsy are more difficult to care for. Barriers to seizure control may include more severe disease, personal habits, failure to comprehend medication instructions or communicate health care needs. This can result in increased readmission rates for recurrent seizures, medication toxicity or other seizure related injury.

Methods: CareScience Care Management System(tm) (CSM) software was utilized to identify 305 individuals admitted to our urban, tertiary care hospital from 7/02–6/03 with a primary diagnosis of seizures (SZ) or epilepsy (EPD). Data included morbidity, mortality, complications, length of stay (LOS), payor mix, admission source and disposition. Readmission rates within 30 days for any cause, but specifically for epilepsy related causes were compared to a group of 1159 individuals also suffering from epilepsy but admitted during same time period for conditions other than epilepsy.

Results: Readmission rate for epilepsy as primary diagnosis was 9.2%. (28 of 305). Readmission for an epilepsy related cause was 11/28. In contrast, among individuals with epilepsy admitted to hospital for other diagnoses (Epilepsy as secondary diagnosis ESD) had a readmission rate of 21.1% with only 2% (20 of 1159) readmissions attributable to epilepsy or associated morbidity. EPD subjects had a mean age of 47.6 years and LOS 3.7 days. In contrast the ESD group had mean age of 53.8 years and LOS of 8.4 days. The ESD group was a sicker population with 3.2 fold morbidity rate and 2.4 fold complication rate compared to EPD population.

While 84% of the EPD group was admitted from the emergency ward, mean travel distance was 15.5 miles, hence this group is represents the metropolitan region. 77% of the subjects were discharged home, 7.2% left against medical advice. Mean time until the second hospitalization was 16.6 days for recurrent seizures and 15.8 days for AED toxicity. In the EPD group, co-morbid alcohol or drug abuse identified in 23% of cases and was not associated with increased risk for readmission.

Conclusions: CSM(tm) was useful in formulation of optimum treatment protocols to improve clinical quality in epilepsy care. It identified a trend towards recurrent hospital use for individuals hospitalized for seizures. Most of the initial hospitalizations are brief, but complete control of seizures is not accomplished during that hospitalization given the rate of readmission and the incidence of AED toxicity.

Issues that are likely to contribute to readmission may be missed by this software include cost and access to medicine. Most readmissions occur 10–26 days after discharge, before subjects have outpatient follow-up. Based on this data, our institution will develop care plans that address factors leading to incomplete seizure control.

1.200
THE EFFECTS OF HIPPOCAMPAL SCLEROSIS REVEALED BY MAGNETIC RESONANCE IMAGING ON THE PHARMACORESISTANCE OF MESIAL TEMPORAL LOBE EPILEPSY
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Rationale: Hippocampal sclerosis is known to strongly correlate with the medical intractability of mesial temporal lobe epilepsy. However, it is possible that the informations about this has been biased due to the improper selection of the sampling obtained from severe cases of tertiary epilepsy center and surgical epilepsy field. We tried to investigate the influence of hippocampal sclerosis on the pharmacoresistance in mesial temporal lobe epilepsy by group comparison study.

Methods: The fifty patients with complex partial seizures of temporal lobe origin, and temporal spike on electroencephalography and/or hippocampal sclerosis on brain magnetic resonance imaging were selected. Follow-up period of them were more than 2 years. The patients who had seizure or seizures during the last 1-year period and had already been in the adequate doses of two or more antiepileptic drugs were considered to be the poorly controled epileptics.

Results: Five of 17 patients without hippocampal sclerosis (29.4%) and 24 of 33 patients with hippocampal sclerosis (72.7%) were poorly controled by medication and the difference was significant ($p = 0.003$, chi-square). Other factors, including sex, age of onset, febrile convulsion, secondary generalization, familial history of epilepsy, duration of disease, and delay of initial therapy had no significant effects on medical response ($p > 0.05$). The only independent predictor of intractable epilepsy after multiple logistic regression analysis was also hippocampal sclerosis ($p = 0.005$).

Conclusions: The medical response in mesial temporal lobe epilepsy was significantly associated with hippocampal sclerosis. The hippocampal sclerosis on brain magnetic resonance imaging itself may be a crucial factor determining the pharmacoresistance of mesial temporal lobe epilepsy.

1.201

CLINICAL CHARACTERISTICS OF RECURRED SEIZURE AFTER SURGERY FOR MEDIAL TEMPORAL LOBE EPILEPSY

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Rationale: The prognosis of surgery for medial temporal lobe epilepsy (MTLE) has been well reported. However, the clinical characteristics of recurred seizure had not been studied. We examined semiology, time, cause and fate of recurred seizure after anterior temporal lobectomy for medial temporal lobe epilepsy (MTLE).

Methods: We reviewed the medical records of 79 patients who had recurred seizure, out of 227 patients who received anterior temporal lobectomy for MTLE between October 1994 and October 2000. MTLE was defined when hippocampal sclerosis is detected on MRI in the absence of other structural lesion.

Results: The types of recurred seizures were similar to the previous seizures in most patients except two. Seizure recurrence happened within the postoperative one month in 33.8%, between one month and one year in 38.2%, during second year in 14.7%, after more than two years in 13.2%. Seizure recurred during the withdrawal phase of antiepileptic medication in 75% of the patients who had recurrence after one month. In one patient, seizure was provoked by alcohol intake, after two year seizure-free period. Last one-year outcome after recurrence was as follows: seizure free without medication-9.52%; free of disabling seizure-52.4%; rare disabling seizure-21.4%; worthwhile improvement-2.38%; no worthwhile improvement-14.3%. Two patients received re-operation.

Conclusions: Most seizure recurrence happened during immediate postoperative period or the withdrawal phase of medication. In considerable patients, seizure recurred after 2 year seizure free period. Final outcome after recurrence was generally favorable.

1.202

IDENTIFYING RISK FACTORS FOR NONCONVULSIVE STATUS EPILEPTICUS: TRACKING SEVERITY OF SUBCLINICAL EPILEPTIFORM DISCHARGES SUGGESTS A THRESHOLD EFFECT

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Rationale: Nonconvulsive status epilepticus (NCSE) is diagnosed when cognitive and/or behavioral impairments unaccompanied by significant motor behavior are the principal clinical manifestation of prolonged or repetitive electrographic seizures lasting $\geq$ 30–60 minutes. This major subtype of status epilepticus (comprising $\sim$25% of the 60,000–150,000 cases of status/year) can last weeks, months or longer as early diagnosis is hampered by the subtle and often nonfocal nature of clinical deficits. Identification of patients predisposed to develop NCSE could facilitate earlier detection through closer clinical monitoring, improving quality of care and outcome.

Methods: We reviewed records of adult patients previously identified between 1987 and 2002 as part of an ongoing study of cognitive deficits from recurrent frontally predominant subclinical seizures in Veterans with epilepsy. Severity of underlying subclinical epileptiform discharges (SEDs) was defined as% of time/EEG with SEDs (ictal + inter-ictal), permitting comparisons of records independent of EEG duration. Inclusion criteria included: recurrent SEDs on $\geq$ 1 EEG and $\geq$ 18 months of followup with serial EEGs. Patients with $\geq$ 1 EEG with $>$ 10% SEDs were rated *High%SED* and the rest were rated *Low%SED*. The cutoff of 10% was based on prior observations that suggested a minimum level of impairment with $<$10% SEDs. Fishers exact test was used to compare proportions of patients receiving treatment for NCSE in the High and Low% SED groups. Statistical testing was conducted at the 0.05 level (two-sided).

Results: Nine of 11 male patients (82%) met inclusion criteria. Five were classified High% SED and four as Low% SED. Average age at onset or diagnosis of epilepsy did not significantly differ between the groups. The most common seizure types were (usually primary) generalized tonic-clonic seizures and absence-like events. Clinical seizures were infrequent in later years (average: 0–2/year). Comparing High% vs. Low%SED groups: Three patients (60%) in the High%SED group were treated for NCSE compared with 0/4 (0%) in of the Low% SED group ($p = 0.17$). No patient with a Low% SED was treated for NCSE.

Conclusions: Although statistical significance was not obtained due to small sample sizes, power calculations indicated a sample size of only 12 patients/group would have shown statistical significance at 80% power and a 0.05 significance level (2-sided). Verifying that $>$10% of time/EEG as SEDs predisposes patients to develop NCSE would provide a valuable objective marker to help clinicians identify patients who might benefit from more frequent cognitive testing.

1.203

CLASSIC JME VERSUS CAE EVOLVING TO JME: FAMILY RISKS

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Rationale: Juvenile myoclonic epilepsy (JME) accounts for 4 to 11% of all epilepsies. Previous analyses of 258 JME probands revealed classic JME or cJME (73%) and childhood absence evolving to JME or CAE/JME (17%) as the two most common subsyndromes. Here, we calculate and contrast the risks of having epilepsy in relatives of both subsyndromes.

Methods: Each class/degree relative was examined separately for history of epilepsy. Offspring were analyzed separately. For risk calculations, we used the lifetime prevalence of having epilepsy reported by the Rochester study considering a frequency of familial history of epilepsy of 3%. An estimated prevalence of 0.00045 for JME and 0.00066 for childhood absences was used for the risk calculations.

Results: The risk of having seizures was 3 times higher in CAE/JME when compared to general population and cJME. In CAE/JME, this risk is high for all relatives in first, second and third degree (3.1 to 3.8). In cJME, the relative risks for JME exhibit a genetic pattern with risks decreasing with increasing distance of relationship. In cJME, the relative risk of developing JME in both nuclear members and second degree relatives is higher that of the general population. In cJME, parents and siblings have 69 to 136 times higher risk of having JME and 11 to 20 times of having absence compared to general population. However the risk of developing absences for second-degree relatives is not more than the risk for absences in the general population. These suggest a major gene for cJME. Parents and second degree relatives of families with CAE/JME, have 15 to 36 times the risk of having JME compared to general population. Frequency of myoclonic seizures was higher in JME when compared to CAE/JME (39.5% vs. 6.3%). The risk for JME in relatives was 2 times higher in JME families compared to families with CAE/JME. In contrast, frequency of absences was higher in CAE/JME compared to those of cJME (40.5% vs. 6.8%). When the prevalence of CAE in general population was used, the risk for absences in relatives were considerably higher in CAE/JME. The risk of tonic-clonic seizures was similar in both groups (30.2% in JME and 27.8% in CAE/JME). The risk of having a mother with seizures was increased (1.9 in CAE/JME and 1.5 in JME families) but the risk of affectedness in the father was not increased (relative risk of 1 in both subyndromes).

Conclusions: Separate genes (more than one), responsible for the complex inheritance of cJME and CAE/JME are influenced by maternal genes. (Supported by NINDS: 5RO1NS042376-03.)

1.204

QUANTIFIED ANALYSIS OF WRIST AND TRUNK MOVEMENTS DIFFERENTIATES BETWEEN HYPERMOTOR AND AUTOMOTOR SEIZURES

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Rationale: To evaluate the movement characteristics of hypermotor and automotor seizures based on an observer independent objective method.

Methods: We included EEG and video recorded automotor (n = 10) and hypermotor seizures (n = 10) of 17 patients considered for resective epilepsy surgery, in whom the camera position was perpendicular to the trunk facing the camera in an upright position and wirst and trunk movements were continously visible on the video recordings. The movements were quantifed from the videos by analyzing all video frames during the entire seizure (25/s). Seizure duration, movement angular speed, movement extent and predominant frequencies (power spectral analysis) of the movements were analyzed (Wilcoxon rank sum test).

Results: Maximum speed (median 902 pixel/s vs. 223 pixel/s, $p<0.001$) and extent (median 45597 pixel^2 vs 2304 pixel^2, $p<0.001$.) of the wrist movements were significantly faster and greater in hypermotor seizures than in automotor seizures. The extent of trunk movement was significantly greater in hypermotor seizures (median 4458,5 pixel^2) than in automotor seizures (median 412,5 pixel^2) ($p<0.001$). The analysis of wrist movement extend separated all automotor from hypermotor seizures. The analysis of maximum angular speed of the wrist movement showed that only one automotor seizure (585 pixel/s) was above the lowest maximum angular speed of wrist movements of hypermotor seizures (553 pixel/s). The predominant repetition rate of the automatisms in automotor seizures was ca. 1/s, whereas no predominant frequency of movements was observed in the hypermotor seizures. The duration of the automotor seizures (median 81 $\pm$ 41s) was longer than that of the hypermotor seizures (69 $\pm$ 54s) ($p<0.04$).

Conclusions: The quantitative analysis of wrist and trunk movements provides objective measures for the differentiation of hypermotor and automotor seizures. This information is helpful for the classification of seizure types in patients considered for resective epilepsy surgery.

1.205
EPILEPSY MANAGEMENT IN PREGNANT WOMEN

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Rationale: Pregnancy in women with epilepsy presents with multiple issues that are not encountered in the general population, notably increase risk of seizures, maternal complications, and higher risk of adverse fetal outcome. Much is known about changes in plasma levels in highly protein bound agents during pregnancy, increase in seizure frequency in pregnancy, as well as the risk of teratogenicity related to the older "standard "anticonvulsants. Limited information regarding teratogenicity is available about the "newer" agents in pregnancy.

Methods: Over the last eight months, 17 pregnant women with epilepsy presented for consultation to the epilepsy clinic. Two women became pregnant twice during this time frame. Each patient was followed by a neurologist during the pregnancy. Attempts were made to collect plasma levels of anticonvulsant medication on a monthly basis,and adjusted according to either drop in level or increase in seizure frequency. When possible, plasma levels are collected from cord blood. Levels are also collected in the immediate postpartum.

Results: Of the 19 pregnancies, there have been to date 10 live births, 2 miscarriages. 15 women are on monotherapy,10 of which are on newer agents and 4 on polypharmacy.

7 of 8 women to date continued to experience seizures during pregnancy, 2 with an increase in seizures. To date, one patient has had a breakthrough seizure during pregnancy.

All women have shown alterations in plasma levels and in most, an increase in dosage was necessary.

The 10 live births had normal fetal outcomes. One patient developed lateral sinus thrombosis during pregnancy. Data pertaining to the remaining pregnancies as well as any future consultations are being collected.

Conclusions: Monitoring of both seizure frequency and plasma levels are indicated in pregnancy. Information about the newer agents their effects in pregnancy. Is the efficacy of the newer agents during pregnancy better, is teratogenicity less, is there variation in plasma levels during pregnancy between the protein bound and renally excreted drugs. This cohort of women is too small to answer any of these questions, yet may serve as a stepping stone. Outcome pregnancy data are important as they may or may not lead to changes in the future treatment of women with epilepsy of childbearing potential.

1.206
DIAZEPAM RECTAL GEL FOR SEIZURE EMERGENCIES IN ADULT PATIENTS WITH REFRACTORY SEIZURES

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Rationale: Despite adherence to a medication regimen, many patients with epilepsy continue to experience breakthrough seizures that result in time consuming and costly visits to the emergency department (ED). These case reports examine the effectiveness of diazepam rectal gel in reducing the number of ED visits for adult patients with refractory seizures.

Methods: Patient charts were reviewed from 1999 to present to compare the number of ED visits before and after starting diazepam rectal gel for treatment of breakthrough seizures.

Results: Prior to receiving diazepam rectal gel, 5 patients visited the ED a total of 37 times. Patient 1, a 32-year-old woman with recurrent seizures, continued to have breakthrough seizures necessitating ED visits despite trying multiple medications and implantation of a vagus nerve stimulator. She had 4 ED visits in 2001 and 6 visits in 2002. Patient 2, a 41-year-old man, has experienced seizures since childhood, which are inadequately controlled on his current regimen of carbamazepine and levetiracetam. He visited the ED twice in 2000 and 3 times in both 2001 and 2002. Patient 3 is a 55-year-old man taking carbamazepine and lamotrigine for postencephalitic seizures. This patient visited the ED twice in 1999 and 2000 and 4 times in 2001. Patient 4, a 39-year-old woman taking oxcarbazepine and zonisamide for her idiopathic seizures, visited the ED 3 times in 2001. Following the use of diazepam rectal gel for breakthrough seizures beginning in 2003, none of these patients has visited the ED. One additional patient, a 24-year-old man, visited the ED 3 times in 2000, once in 2001, and 4 times in 2002 when carbamazepine and levetiracetam failed to control posttraumatic seizures. Since starting diazepam rectal gel in 2003, this patient has visited the ED only once. Mild sedation was the only reported adverse event.

Conclusions: Diazepam rectal gel effectively treated breakthrough seizures in these patients. Use of diazepam rectal gel is associated with dramatic reduction in the combined total number of ED visits from 37 to 1 and entirely eliminated the need for ED visits in 4 of 5 patients. (Supported by Xcel Pharmaceuticals.)

1.207
QUANTIFICATION OF IPSILATERAL AND CONTRALATERAL HEAD MOVEMENTS DURING SEIZURES IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: To evaluate quantitatively the lateralizing significance of ipsilateral and contralateral head movements during seizures in patients with temporal lobe epilepsy.

Methods: We included only EEG and video recorded seizures of patients with temporal lobe epilepsy, in whom the camera position was perpendicular to the head facing the camera in an upright position and bilateral head movements were recorded. Head turning in a reaction to outside stimuli was excluded. A total of 12 seizures in 10 patients, in whom both, contralateral and ipsilateral head movements were recorded with high quality video were investigated. Nine patients have had unilateral temporal lobe epilepsy. One patient has had bilateral temporal lobe epilepsy with ictal EEGs of the two seizures showing independent seizure onset from either side. Ipsi- and contralateral head versions were defined

according to the side of ictal EEG seizure patterns. Head movements were quantifed for speed analysis on the videos by selecting the movement of the nose in relation to a defined point on the trunk (25/s) in the inner 90° angle facing the camera. The analysis of the duration was independent of the camera angle. The angle, the duration, and the angular speed of the ipsilateral and contralateral head movements were computed. Inter- and intrasubject analysis was performed (Mann-Whitney-Test).

Results: The positive predicting value was 100% for both, the ipsi- and contralateral head movement with regards to the ictal EEG pattern. Ipsiversion always preceded contraversion. The duration of the contralateral head version was significantly longer than that of the ipsiversion (7.4 $\pm$ 3.2s vs. 4.6 $\pm$ 2.9s, $p<0.036$). The angular speed of the contralateral head version was similar to the ipsilateral version (11.5 $\pm$ 7.8 vs. 11.1 $\pm$ 8.6 deg/s).

Conclusions: Ictal head versions have a high lateralizing significance in temporal lobe epilepsy. The quantitative analysis of ipsilateral and contralateral head versions shows that the duration of head version and the occurrence in the seizures evolution is important for the correct lateralization.

1.208
DERMATOGLYPHIC VARIATIONS FOR DIGITAL AND PALMAR PATTERN TYPES IN EPILEPTICS

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Rationale: Epilepsy is a heterogeneous disorder caused by genetic,intrauterine and other causes.The study of dermatoglyphic variations in epileptics and undertaken to determine whether chracteristic variations of dermatoglyphic traits exist in relation to epilepsy.

Methods: Finger and Palmar prints were obtained from 400 epileptic patients(200 idiopathic,200 symptomatic) attending Neurology OPD, PGIMER, Chandigarh. A sample of 100 healthy individuals was studied as a control group. The prints were obtained on a drawing sheet with the help of printers black ink.

Results: The comparison of finger ball pattern type revealed statistically significant differences between idiopathic and symptomatic epileptics for digits 1,3 and 5; between idiopathic epileptics and controls for digits 1,2,4 and 5; while between symptomatic and control for digits 1,2 and 4.Pattern Intensity Index(PII) was higher in epileptics than controls.The comparison of palmar pattern types revealed significant differences between symptomatic and controls for right second interdigital area and left hypothenar area. No significant differences were observed for other palmar areas pattern types.

Conclusions: Digital pattern frequencies are better indicators than palmar pattern frequencies in determining association between dermatoglyphics and epileptic seizures caused by different etiological factors. There seems to be no differences between idiopathic and symptomatic types of Epilepsy for dermatoglyphic variations. The group deviations are observed between Epileptics and controls suggesting a possible genetic predisposition in the origins of both symptomatic and idiopathic types of Epilepsy

1.209
GELASTIC SEIZURES OF TEMPORAL LOBE ORIGIN

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Rationale: Gelastic seizures (epileptic laughter) occur most commonly in conjunction with hypothalamic harmartomas, which present in childhood, with or without associated endocrine dysfunction. Gelastic seizures occur less commonly with lesions in other parts of the limbic system. We evaluated two patients with gelastic seizures, characterized their clinical events, and compared them with similar cases which have been previously described in an effort to better characterize gelastic seizures of non-hypothalamic origin.

Methods: We recorded prolonged video-EEG (VEEG) in two women, each of whom had been previously diagnosed to have a psychiatric disturbance because of episodes of inappropriate laughter. MRI brain imaging with standard seizure protocol was performed in each case. Review of previously published cases of gelastic and dachrystic seizures of non-hypothalamic origin was accomplished to ascertain and compare reported clinical manifestations, demographic features, prognosis, and approaches to treatment.

Results: Case 1: A 42 year old woman suffered a closed head injury in an equestrian exercise. One year later, she began having episodes of staring and loss of contact, associated with automatisms invariably accompanied by laughter. She also had generalized tonic-clonic seizures.

MRI: right mesial temporal sclerosis. EEG: right anterior and mesiobasal temporal lobe spikes. VEEG: laughter a prominent component of 10/10 recorded complex partial seizures. Six of ten events were localized to right temporal lobe by scalp and sphenoidal EEG. Ictal SPECT demonstrated increased uptake in right temporal lobe. She awaits right amygdalohippocampectomy.

Case 2: A 48 year old woman developed symptoms of depression, followed by episodes of brief staring and inattentiveness precipitated by psychological stress. She had rather mirthless laughter as a part of these episodes. She experienced a generalized tonic-clonic seizure, prompting neurological evaluation.

Interictal EEG: normal. MRI brain scan: normal. Prolonged VEEG, with sphenoidal leads: interictal left anterior and mesiobasal temporal spikes. Rhythmic theta activity began in left mesiobasal temporal lobe during ictal recording of typical episode. Her events have been controlled with a combination of phenytoin and levetiracetam.

Literature review: We located 62 cases of gelastic or dachrystic seizures of non-hypothalamic origin, including temporal, cingulate, and frontal lobe foci. Gelastic seizures disproportionately took origin from right cerebral hemisphere, whereas dachrystic seizures overwhelmingly orginated in left cerebral structures. In a few instances, gelastic and dachrystic seizures occurred in the same person.

Conclusions: 1. Epileptic laughter may be a prominent feature of temporal lobe seizures.

2. Gelastic seizures are more likely to occur in seizures of right temporal or frontal lobe lobe origin, whereas dachrystic seizures are much more likely to orginate in the left cerebral hemisphere.

1.210
INSULAR SEIZURES IN SPORADIC AND FAMILIAL NOCTURNAL FRONTAL LOBE EPILEPSY

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Rationale: Nocturnal hypermotor seizures (NHS) are considered highly suggestive of a frontal lobe onset, and more specifically of a mesial frontal origin. This is even more true when such an epileptic pattern affects several members of the same family, suggesting the syndrom of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Electrophysiological evidences of the frontal origin of such seizures are scarce, however. We report in this study three patients with either sporadic NHS or ADNFLE in whom invasive monitoring demonstrated the insular origin of seizures.

Methods: We identified the three patients presented in this study among the 486 patients who underwent a stereoelectroencephalography (SEEG) procedure in the epilepsy surgery departments of Grenoble and Lyon, and reviewed their detailed clinical and intra-cranial EEG findings. 14 to 15 intracranial electrodes were stereotactically implanted in all three patients, and mainly targeted the mesial and lateral frontal lobe structures. Based on electroclinical evidences, most electrodes were placed in the same hemisphere, with one exploring the anterior part of the insula ipsilateral to the suspected epileptogenic zone in all patients.

Results: All three patients presented with predominantly nocturnal seizures which started between three and nine years of age. No remarkable past history was noted in two patients, whereas the third one presented with a typical familial history of ADNLFE. All three patients exhibited prominent ictal motor activity, consistent with the

diagnosis of hypermotor seizures, including bicycling, pelvic thrusting, and turning over. Shouting, grimacing, and facial expression of fear were also commonly observed during seizures, the latter being usually of short duration without post-ictal confusion. In the two sporadic cases, SEEG data clearly identified a very active and focal interictal focus as well as the origin of ictal discharges in the anterior insula *(either right or left-sided)*. In the patient with ADNFLE, seizures originated almost simultaneously from the left anterior insula and the ispilateral frontal operculum. Seizures always rapidly propagated to the mesial frontal lobe, concommitantly with the onset of hypermotor activities.

Conclusions: Sporadic cryptogenic epilepsy characterized by nocturnal hypermotor seizures, as well as ADNFLE, can be associated with an ictal onset zone located within the insula rather than within the frontal lobe proper. Taking into consideration previous observations from our groups in temporal plus epilepsy, it appears that depending on the portion of the insula where seizures arise, the latter can alternatively mimick temporal or frontal lobe epilepsy.

1.211

JUVENILE MYOCLONIC EPILEPSY: ANALYSIS OF FACTORS IMPLIED IN DELAYED DIAGNOSIS AND PROGNOSIS AFTER CLINICAL AND ELECTROENCEPHALOGRAPHC CHARACTERIZATION

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Rationale: Although considered a common epileptic syndrome, corresponding to 2.8–11.9% of all epilepsies and presenting distinct clinical characteristics, Juvenile Myoclonic Epilepsy (JME) is still not well diagnosed, a fact that may bring about important deleterious consequences. Valproate (VPA) is considered the drug of choice in control of the seizures in this syndrome. The aim of this study was to characterize the factors implied in the delay of diagnosis and the response after adequate therapeutic institution in JME patients.

Methods: A series of 41 JME patients has been attended to by two MD in our outpatient clinic since October 2000 and continues to be so up to now. We analyzed the initial diagnosis, the delay and the factors implied in it as well as the prognosis after establishment of adequate treatment since most of the patients were receiving antiepileptic drugs (AED) other than VPA.

Results: At the time of admission only 8 out of the 41 patients (19.5%) had had syndromic diagnosis while 33 (80.5%) had not yet had the diagnosis of JME being more frequently labeled as indeterminate epilepsy. The diagnosis was established in a mean of 8.2 yr. (15 days to 34 yr.) after clinical onset. The electroclinical data of these patients agree with the classical description of this syndrome as follows: the age of onset of the epilepsy varied between 7 and 24 yr, presence of myoclonic seizures in all patients, generalized tonic-clonic seizures also present in 92.7% and absences in 43.9%. Only 4.9% had only myoclonic seizures. The main factors identified in the delay of diagnosis were: omission in 4 (9.7%) and asymmetry in 12 (29.3%) of the myoclonic jerks; normal first EEGs at the time of the institution of drug therapy (41%); some normal EEGs in the series of recordings in 73.2%; presence of focal abnormalities in the EEGs in 35.9% and asymmetry of the generalized paroxysms in 33%. The mean in years for the establishment of the diagnosis was 11.6 for the group with asymmetric compared to 8.5 in those with symmetric paroxysms. The institution of treatment with VPA associated with avoidance of precipitant factors (APF) led to seizure control in 92.5% of all patients in the first year. This rate dropped to 41.3% in the third year of follow-up. The main factor that implied in this drop was non-compliance.

Conclusions: JME continues to be misdiagnosed and the response to VPA + APF in one year is excellent suggesting pharmacosensitivity although it has not continued to do so over the years. Despite all the instructions it is very difficult for the JME patients to rigorously follow them over the years. [Supported by FAPESP (Fundação de Amparo a Pesquisa do Estado de São Paulo), CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).]

1.212

COMPLEX DERANGEMENT OF CHROMOSOME 5 PRESENTING WITH ADULT-ONSET EPILEPSY AND UNUSUAL IMAGING FINDINGS

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Rationale: To report an epileptic disorder in a patient with a previously undescribed chromosomal abnormality with novel imaging findings

Case Report: A 40 year old, Irish man, with mild learning difficulty presented with focal status epilepticus, with secondary generalisation. He had dense aphasia, right hemiplegia and right homonymous hemianopia.

Results: Brain MRI showed high signal in the cortex of the posterior frontal perisylvian region, thalamus, temporal, parietal and occipital lobes on FLAIR sequences which has been described previously in the literature with seizure-related MRI changes. However, these areas also demonstrated high signal on T1-weighted images, a finding not previously described. A comprehensive evaluation failed to reveal a definite biochemical, metabolic, infectious or structural cause. The patient has two chidren with a known chromosome 5q34 duplication but no epilepsy. Genetic analysis of the patient showed a previously undescribed, complex derangement of chromosome 5.

Discussion: Known chromosome 5 syndromes such as deletions, duplications and ring forms are not known to be associated with epilepsy. However, childhood epilepsy has been described in a patient with 5p tetrasomy (1). The distal part of the long arm of chromosome 5 carries a cluster of $GABA_A$ receptor genes at locus 5q34 (2). Mutations in $GABA_A$ receptor genes have a role in the pathogenesis of several epilepsy syndromes (3).

Conclusions: The genotype of this complex derangement of chromosome 5 and the clinical phenotype of adult onset epilepsy with unusual and unexpected imaging findings is unlikely to be a fortuitous association. We hypothesise that the abnormal genotype contributed to both the clinical presentation and the unusual imaging findings in our patient.

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1.213

PATTERN-MATCH REGULARITY STATISTICS: A MEASURE QUANTIFYING THE CHARACTERISTICS OF EPILEPTIC SEIZURES

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Rationale: Quantitative analyses of intracranial EEG recordings from epileptic patients with temporal lobe epilepsy indicate that ictal and preictal states can be distinguished from seizure-free states for the applications of detection and prediction of seizures (*IEEE Trans Biomed Eng* 2003; 50(5):549–58, 2003; *Lancet Neurol* 2002; 1(1):22–30). These findings suggested that it is possible to develop an implantable device for diagnostic and therapeutic purposes. In this study, we propose a new measure of signal regularity, pattern-match regularity score (PMRS), for the detection of EEG state changes, especially seizures. The measure is based on the estimation of signal pattern similarity. A major advantage

of this measure is the ability to interpret it in both stochastic and chaotic models. This study tests the hypothesis that PMRS can distinguish state changes in intracranial EEG recordings.

Methods: Intracranial EEG recordings obtained from 6 patients with a total of 81 medically intractable partial seizures were analyzed to test the hypothesis. PMRS was calculated for each EEG channel for each sequential 10.24-second non-overlapping data segment. The algorithm involves state space reconstruction, search for the pattern matched state vectors, and the estimation of pattern-match probabilities. The paired-T statistic was employed for each 10-minute sliding overlapping window to test the mean difference of PMRS values between two electrode sites. Electrode pairs were considered not entrained during any 10-minute period if the mean PMRS values were significantly different ($p<0.05$). The PMRS and T-index curves were generated for the 1-hour time interval before and after each seizure. Significant changes observed in both PMRS and T-index curves were used for the detection of epileptic state changes in EEG recordings.

Results: Significant decrease of PMRS values during the ictal periods was observed in 91.4% of seizures. 87.7% of the preictal periods were detected by the presence of entrainment transition (gradual decrease in T-index values), and 87.7% of the seizures showed the postictal disentrainment with a rapid increase of T-index values after the end of a seizure.

Conclusions: The results suggest that epileptic state changes can be detected by pattern-match regularity statistical analysis of EEG recordings from intracranial electrodes. Thus, it may be possible to predict and detect a seizure with this measure for clinical applications. (Supported by NIH grant RO1EB002089 and Department of Veterans Affairs.)

1.214
TRIAL OF LEVETIRACETAM IN ADULTS WITH EPILEPSY AND DEVELOPMENTAL DISABILITIES

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Rationale: Levetiracetam, as an add-on therapy, has been found to be safe and effective in patients with partial epilepsy. This study seeks to evaluate the safety and efficacy of Levetiracetam in patients with intractable epilepsy and Developmental Disabilities (DD) already tried on 2–3 antiepileptic drugs (AEDs).

Methods: The charts of 35 patients from the out patient neurology clinic at The Westchester Institute for Human Development were reviewed. These patients were tried on Levetiracetam as add on therapy due to intractable epilepsy or discontinuation of previous antiepileptic drugs due to adverse effects. The patients mostly have mixed seizure disorder. Data was checked 6 months before and 6 months after starting Levetiracetam. There were 18 males and 17 females.

Results: Dose of Levetiracetam ranged from 1000–5000mg/day. Age ranged from 19–63 years (mean 43.2years). The level of mental retardation (MR) was borderline-1, moderate-15, severe-7, and profound-12. The number of patients having more than 10 seizures per 6 months was reduced from 14 to 10, and those with less than 10 seizures per 6 months decreased from 18 to 13. Ten patients became seizure free. No improvement in seizures noticed in one patient and one patient was lost to follow up. One patient displayed increased behavior problem at 3250mg/day of Levetiracetam and behavior stabilized on lowering the dose to 3000mg/day. In several patients concomitant AEDs were discontinued.

Conclusions: Individuals with DD and refractory mixed seizures benefited significantly from addition of Levetiracetam with minimal side effects.

1.215
VIDEO-EEG EXPERT SYSTEM: SOFTWARE TO COMPUTE SEIZURE FOCUS LATERALIZATION AND LOCALIZATION PRIOR TO EPILEPSY SURGERY

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Rationale: The object is to develop the Video EEG Expert System (VES), a computer program to analyze patient data with the goal of finding anatomic seizure focus in the context of epilepsy pre-surgical evaluation. The system behavior is intended to model the decision making process of the epilepsy patient evaluation team which typically consists of neurologists, neurosurgeons, neuropsychologists, and nurses.

Methods: Patient data included clinical information, MRI, PET, SPECT, and video EEG. The system is written in Lisp and a logic programming module, Prolisp, that supports hypothesis-driven rules. Benchmark files (controls) and corresponding anatomic localization hypothesis trees were created. A numeric instrument (called the confidence factor) for representing uncertainty was employed to encode data quality (e.g., a mildly suggestive MRI finding was assigned the value 0.6 instead of 1.0). An explanation facility was written to display the rules and confidence factors that were important to each diagnostic result. 23 experimental files obtained from charts were used to test correctness in localizing seizure focus. The principle developer was blind to these files.

Results: The system selected the correct localization for 100% of benchmark files (which is expected since these files were created with data clearly associated with a specific localization). For experimental files, VES selected the correct lateralization in 23/23 (100%), the correct localization in 18/23 (78%), and localization and lateralization in 18/23 (78%). First place ties were computed in 13%, and incorrect localizations were found in 9%. Analysis of incorrect results revealed some incomplete knowledge concerning temporal lobe localization. The explanation facility provided feedback on the decision analysis in a clear manner.

Conclusions: VES performed well at identifying seizure focus. The tools developed for VES, especially Prolisp, should serve future neurological expert system development. Confidence factors provided an adequate mechanism for truth representation. Further work is planned to incorporate Bayesian statistical methods into the rule analysis thereby providing software users with probabilistic guides for seizure focus lateralization and localization.

1.216
SLEEP-ONSET MESIAL TEMPORAL SEIZURES ARISE FROM LIGHT NREM SLEEP

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Rationale: Most sleep-onset partial seizures occur during NREM sleep, possibly due to neuronal hypersynchrony facilitated by the same thalamocortical networks that modulate sleep spindles during normal Stage 2 NREM sleep. Previous studies of sleep-onset partial seizures have lacked precise localization of the epileptogenic focus. We studied sleep stage prior to seizure onset in well-localized mesial temporal epilepsy, hypothesizing that sleep-onset seizures would predominantly occur during Stage 2.

Methods: We identified consecutive seizure-free patients following anterior temporal lobectomy (ATL) from 1993–2001 with video-EEG captured seizures in both wakefulness and sleep. We analyzed each seizure for sleep stage at onset. Sleep stage was determined by standard Rechtshaffen and Kales criteria modified as follows: no chin EMG, frontopolar leads for eye movement determination, bipolar montage for slow wave amplitude, and NREM stages 3 and 4 grouped together as slow wave sleep. We excluded all simple partial seizures without accompanying ictal EEG change and seizures not containing an adequate montage for visual sleep staging.

Results: 40 patients were seizure-free following ATL. 23 (10 men and 13 women) patients had seizures in both sleep and wake states. The mean number of seizures recorded per patient was 13 (range: 5–43). There were a total of 335 (176 right and 159 left) temporal onset seizures. 106 (32%) arose from sleep. Sleep seizures were evenly distributed between Stages 1 (54 seizures) and 2 (51 seizures) NREM sleep, with a single seizure from slow wave sleep and none in REM.

Conclusions: Sleep-onset seizures in mesial temporal lobe epilepsy occur almost exclusively in light NREM sleep, and only rarely from slow wave sleep. REM onset seizures were not seen. Limitations of our methodology imposed by typical video-EEG recording specifications including lack of electrooculogram leads and chin electromyography could

have lead to errant staging of tonic REM sleep as Stage 1 NREM sleep. Also, slow wave sleep could have been underestimated due to utilization of bipolar montages for delta slow wave amplitude instead of central leads referenced to the alternate ear as required by Rechtschaffen and Kales criteria. We conclude that mesial temporal lobe sleep-onset partial seizures occur predominantly in light NREM sleep. Future prospective studies utilizing video-EEG polysomnography techniques would allow for more accurate sleep staging prior to seizure onsets.

1.217
THE SEMIOLOGY OF "NOSE-WIPING": ICTAL, POST-ICTAL, OR RELEASE?
Barbara E. Swartz and Richard Kim (The Epilepsy Center, Hoag Hospital Memorial Presbyterian, Newport Beach, CA)

Rationale: Post-ictal nose-wiping is considered highly lateralizing in temporal lobe epilepsy (using the hand contralateral to the focus). Like many automatisms, its origin is not completely understood. It could represent a "release" phenomenon if it occurred either ictally or post-ictally. There is some reason to believe this behavior to be ictal, rather than post-ictal, as vibrissae rubbing occurs in one stage of kindled seizures in rats. One report of nose-wiping during absence seizures is more consistent with a release phenomenon. We therefore report on intracranial recordings during "nose wiping" on two patients.

Methods: Two patients with history of nose and face wiping underwent implantation of an 8x8 grid, hippocampal depth and sutemporal stip electrodes to locate epileptogenic zones. The first was on the left, the second on the right. The electroclinicical and neuroanatomical correlates of nose-wiping were collated across all seizures.

Results: Patient No. 1 had 5 of 7 seizures with face and/or nose rubbing. This occurred at 61, 59, 34, 74, and 26 sec after D-EEG onset, during ictus. The ictal activity was basal and lateral temporal cortex at the time. All were CPS except one which secondarily generalized. The hands used were ipsilateral on the 1st and ipsilateral to bilateral on the 2nd seizures, bilateral on the other three. Only the last event generalized. Patient No. 2 had ipsilateral nose wiping on 3 of 5 seizures. Those without it secondarily generalized. It began 110, 106, and 149 sec after onset of the seizure, during ictus, but persisted after the D-EEG activity stopped in two. The ictal activity was perisylvian at the time of onset.

Conclusions: The fact that seizures with nose-wiping rarely generalized (1 of 8) and the persistence of nosewiping after cessation of ictus suggests that this behavior is a release type phenomenon, but not specifically post-ictal. When nose-wiping was an isolated automatism the focus was ipsilateral but when it occurred in the context of other facial wiping, lateralizing value was lost. The literature will be reviewed and further cases will be sought for evaluation. Video clips will be presented.

1.218
CASE MANAGEMENT IN EPILEPSY: AN IMPACT STUDY
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Rationale: Case management (CM) coordinates patient care services in a cost-effective fashion in an effort to improve the quality of the services rendered. The objective of this pilot study was to address the initial impact of an epilepsy case management program

Methods: A total of 737 patients entered a dedicated case-management program provided by a single not-for-profit, state-supported epilepsy service provider for a 4-county area in west central Florida. Initial and follow-up survey forms from 171 new consecutive patients were compared after 1 year of CM. Standardized forms supplied by the Florida Department of Health were administered in self-reported survey format upon admission. Prospective follow-up survey information was obtained and corroborated with medical record review. Changes in demographics, epilepsy measures, and QoL were assessed. All patients were managed by case managers that had obtained at least a college level education. The initial analysis of the first 30/171 patients was performed between 2002–2003. Ongoing analysis is in progress and will updated from this preliminary report.

Results: Twenty-one males and 9 females were evaluated for outcome measures after the initial year of case management. Twenty-seven completed the survey independently and three required assistance. Twenty-one of 30 (70.0%) reported ED visitation (total visits = 50) the year prior to intake, while only 2/30 (6.7%) had a total of 2 visits after CM. Both the number of patients on "new" AEDs developed after 1993 (13/30 vs 6/30), and those reporting seizure control (26/30 vs 12/30) more than doubled. During this time available income rose in 11/30 (36.7%) with 5/30 (16.7%) newly employed. The number without depression did not change, and only 10–20% reported improvement in their energy level or being angry. However, more than 80% reported some improvement in their relationships (26/30), independence (27/30), self-appreciation (25/30) and improved QoL (27/30).

Conclusions: Case management appears to be an effective paradigm for outpatient epilepsy patients with improved health care over several self-reported measures of income status, seizure control, and QoL. The significant reduction of ED visits before and after CM represents a potential cost savings.

1.219
ASSOCIATION AMONG TEMPORAL LOBE EPILEPSY WITH MESIAL TEMPORAL SCLEROSIS AND PSYCHOSIS
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Rationale: To study the association among temporal lobe epilepsy (TLE) with mesial temporal sclerosis (MTS) and psychosis.

Methods: Evaluation of clinical data in a group of patients with TLE with MTS and associated psychosis.

Results: Out of 46 patients with epilepsy associated with psychosis, we have selected 23 with MTS diagnosis. Average age of onset of epilepsy was 7,8 years old (DP = 5,83), 28 years old (DP = 11,2) for psychosis, with an average difference of onset for both diagnoses of 20,1 years (DP = 11,38), 82,6% had interictal psychosis and 30,4% posictal. There were no case of ictal, pre-ictal or alternating psychosis. Most patients presented schizophreniform presentations.

Conclusions: TLE with MTS is a frequent epileptic syndrome, specially important for its clinical refractoriness, while psychosis is one of the most important psychiatric conditions associated with epilepsy. The elevated number of posictal cases evolving to interictal psychosis in these patients points to the need of incisive treatment of this epileptic syndrome.

1.220
PRE-ICTAL HEADACHE IN INTRACTABLE PARTIAL EPILEPSY
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Rationale: Headache (HA) associated with epilepsy may be pre-ictal, ictal, post-ictal or inter-ictal. Pre-ictal headache (PIHA) has not been emphasized. Our purpose was to study clinical characteristics of PIHA in a group of patients with intractable partial epilepsy.

Methods: We used a standardized interview in 100 consecutive patients undergoing comprehensive presurgical evaluation including video-EEG telemetry for medically intractable partial epilepsy. PIHA was subdivided into prodromic (prodPIHA: 24 hours-30 minutes prior to seizure onset) and early pre-ictal (earlyPIHA: within 30 minutes prior to seizure onset). For each HA type, subsequent questions inquired about HA lateralization, location, quality and severity of pain assessed by the visual analogue scale (VAS). Migrainous character of the HA and family history of recurrent HA or migraine were documented.

Results: Out of 100 patients, 11 (11%) had PIHA. Four had prodPIHA and 7 earlyPIHA.

Ten of these patients had temporal lobe epilepsy (TLE) and one had frontal epilepsy. Lateralization of HA was ipsilateral to the epileptic focus in 9 TLE patients and contralateral in 2 (one with TLE). All patients

had frontotemporal PIHA. HA spread occurred in 3 patients with prodPIHA (ipsilateral 2, contralateral 1). Average intensity of PIHA was 6.8 in earlyPIHA and 7.5 in prodPIHA. Migrainous features were found in 4 patients. Family history of recurrent HA or migraine was found in all patients in prodPIHA and 1 patient in earlyPIHA.

Conclusions: Frontotemporal pre-ictal headache is mostly ipsilateral to the seizure focus in TLE patients and has migrainous characteristics in about one third of patients. It may be a useful clinical lateralizing sign in patients undergoing presurgical evaluation.

1.221
CLINICAL FEATURES OF PATIENTS WITH UNILATERAL MESIAL TEMPORAL SCLEROSIS (MTS) WITH PERSISTENT SEIZURES FOLLOWING ANTERO-MESIAL TEMPORAL RESECTION

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Rationale: Despite careful selection of patients with unilateral MTS for temporal lobe resection, most centers report persistent seizures in 20–40% of patients postoperatively.

Methods: We reviewed records from 195 patients who had anteromesial temporal resections for epilepsy surgery and identified 17 patients with suspected mesial temporal sclerosis by MRI and no other risk factors for seizures but had an Engel outcome Class of II-IV (15 Class II, 1 Class III, 1 Class IV). All patients had extensive presurgical evaluations that included angiogram/Wada, neuropsychological evaluation, noninvasive interictal and ictal scalp AV/EEG, and intracranial EEG(14 of 17) and were determined to be good temporal lobectomy candidates by a multidisciplinary team. We compared historical and presurgical data from this group to 20 consecutive class I outcome patients with MTS (control group).

Results: The mean age of onset at the time of first non-febrile seizure was 12 years (range, 6 months-31 years) and duration of epilepsy was 26 years (range, 6–47) for the study group. Mean age of seizure onset was 9 years (range 1–26) and duration of epilepsy was 21 years (range 4–38) for the control group. Mean age at time of surgery was 38 years (range, 12–65) for the study group and 30 years (range 14–43) for controls. Febrile seizures occurred in 5 of 17 patients (29%) compared with 11 of 20 (55%) of controls.

Conclusions: These data suggest that older age at time of surgery, longer duration of epilepsy before surgery, and absence of febrile seizures may be associated with persistent seizures following antero-mesial temporal resection in otherwise well-selected MTS patients.

Clinical Epilepsy—Pediatric 1

1.222
RECOVERY OF CONSCIOUSNESS FOLLOWING EPILEPTIC SEIZURES IN CHILDREN

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Rationale: Impairment of consciousness following epileptic seizures is commonly seen. However, there is no research data on the duration of this period, or the factors which effect it. Impairment of consciousness following a seizure may be due to an underlying acute encephalopathy rather than a post-ictal phenomenon.

Methods: Children aged 1–16 years attending the accident and emergency department, and in-patients who had suffered seizures involving impairment of consciousness, were studied. Hourly modified paediatric coma scores were performed, until a coma score of 15 was obtained. The Poisson regression model was used to determine which factors influence recovery time.

Results: One hundred and ten children were studied: 42 male, 68 female, median age was 6 years. Median time for full recovery of consciousness was 38 minutes (0.63 hours, range 0.05–17.0 hours). Median recovery time from febrile seizures was 18 minutes (0.3 hours, range 0.05–9.0 hours), which was significantly shorter than seizures of other aetiology ($p < 0.05$). Median recovery time from idiopathic seizures was 1.35 hours (range 0.07–13.13 hours), from remote symptomatic seizures was 1.25 hours (range 0.07–12.10 hours), and from acute symptomatic seizures was 4.57 hours (range 0.25–17.0 hours). Median recovery time following the use of benzodiazepines was 3.46 hours (range 0.08–14.25 hours), which was significantly longer for seizures not treated with benzodiazepines; median 0.47 hours (range 0.05–17.00 hours). Age, gender, number of seizures and type of seizure did not significantly affect recovery time. There was no significant correlation between recovery time and seizure duration.

Conclusions: This results show that the majority of children suffering from febrile seizures recover within $^1/_2$ hour. An acute symptomatic aetiology should be considered if recovery takes longer than 1 hour and warrants further investigation. Administration of emergency anti-epileptic drugs in the treatment of seizures has also been shown significantly prolong recovery and should be considered.

1.223
EPILEPSY AFTER STROKE IN CHILDHOOD

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Rationale: In daily clinical practice parents and the patients themselves want to know soon, what the long-term prognosis after a stroke is. Whether epilepsy develops after stroke or not very often plays a major role for the quality of life later-on. Most published data on risk factors for the development of epilepsy after stroke in childhood are from the pre-MRI-area. We were interested in the question to which extent modern neuroimaging will be able to estimate better the individual risk for the development of epilepsy in children who have suffered a stroke.

Methods: 98 patients (46 female, 52 male; average age 7 7/12years, standard deviation 5,15) treated in our rehabilitation department after childhood stroke in the time between 1986 and 2003 were included in this study. Children suffering from perinatal or traumatic insults resembling stroke in childhood were excluded. 46 of our patients had an MRI which was examined focused on localization and extent of damage once more. The following variables were taken into account: type of damage (hemorrhage vs. ischemia), localization and extent of damage, age at damage, age at seizure-onset. Seizures occurring $\leq$ 2 days after the stroke were labeled as "early seizures; " seizures occurring 2 days after the stroke and later-on were labeled as "late onset seizures." Minimumfollow up was 2 years.

Results: N = 25 (25,5%) of all the patients developed epilepsy. Onset of epilepsy occurred often within the first 2 years of life; N = 10 (45,5%). N = 15 (60%) of the patients who developed epilepsy had "early seizures." There was no significant difference between the "hemorrhage-group" (27,7% epilepsy) and the group of patients with ischemia (23,5% epilepsy). 100% of the patients who developed epilepsy had cortical scars; 10 of 25 patients (40%) with cortical scars developed epilepsy. Patients with lesions restricted to basal ganglia or cerebellum did not develop epilepsy. The risk for the development of epilepsy was higher when the territories of 2 or more vessels were damaged.

Conclusions: The over-all risk for the development of epilepsy after childhood stroke is around 25%. It is not surprising that epilepsy develops only in cases with cortical damage. However, not all patients with cortical scars develop epilepsy. In contrast to series dealing with stroke in adulthood, early seizures are a major risk-factor for epilepsy. There is no difference between hemorrhagic- vs. ischemic insults with respect to the development of epilepsy.

1.224
EVIDENCE BASE FOR EVALUATION IN PRIMARY CARE OF PEDIATRIC EPILEPSY

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Rationale: A key feature of optimal health care delivery is the dissemination of comprehensive "best practice" models that are readily

applicable to the average clinician's practice. However, in pediatric epilepsy care the evidence base for "best practice" standards is largely uncharacterized. Our objective was to analyze the evidence for elements of pediatric epilepsy care including: behavioral/psychosocial issues, cognitive issues, use and monitoring of antiepileptic drugs (AEDs), and diagnostic issues.

Methods: We searched medical databases and reference lists of seminal review articles published in English between 1980 and 2003. We selected primary data studies for children with a principal diagnosis of epilepsy. Three neurologists reviewed and rated eligible studies for evidence quality using classification criteria adopted by the American Academy of Neurology.

Results: Searches yielded 733 eligible studies which were reviewed and classified. Of these, 31 (4%) articles were rated as highest quality (Class I), 191 articles each were rated Class II and III, and the remaining articles were rated Class IV. There was consistent Class I and II evidence recommending a waiting period before treatment initiation and identified evidence-based risk factors that indicate early treatment is necessary. Established recommendations based on substantial Class II evidence supports discontinuation at twelve or twenty-four months seizure-free; specifying seizure types, syndromes, and other necessary factors for consideration in decision making. Notably, five Class I and 51 Class II (13% of all studies) articles addressed cognitive and behavioral problems; all supported screening at diagnosis. Cognitive correlates included seizure type, syndrome classification, and pre-existing status, but not AED use. Evidence on AED side effects, monitoring, and factors influencing diagnostic testing or specialist referral was limited in breadth, and lacked sufficient consistent Class I and II evidence.

Conclusions: Despite the vast literature regarding the diagnosis and management of pediatric epilepsy, few data meet rigorous standards of study design or analysis for evidence-based practices. This study identified gaps where additional studies are necessary. Support for some elements of care may lead to recommendations for practice that are not currently part of the primary management of pediatric epilepsy. (Supported by a cooperative agreement from the Centers for Disease Control and Prevention through the Association of American Medical Colleges, grant number U36/CCU319276-02-3, AAMC ID number MM-0531–03/03. Publication and report contents are solely the responsibility of the authors and do not necessarily represent the official views of the AAMC or the CDC.)

1.225
OUT-OF-HOSPITAL TREATMENT FOR CONVULSIVE STATUS EPILEPTICUS (CSE) IN CHILDHOOD

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Rationale: Adequate emergency pre-hospital treatment reduces seizure duration and thus the probability of children having a seizure lasting at least 30 minutes (CSE). Therefore, we hypothesize that in the general paediatric population those children that fail to respond to an adequate initial dose of pre-hospital treatment will be more likely to have refractory CSE than those that receive inadequate or no treatment. From an ongoing prospective population-based study, the North London convulsive STatus EPilepticus in childhood Surveillance Study (NLSTEPSS), we report on the effect of pre-hospital treatment of CSE.

Methods: The methods for ascertainment of cases and data collection have been previously described (AES 2003). Data on choice and dose of antiepileptic drugs(AED) were compared to the Advanced Paediatric Life Support treatment guideline for CSE(3rd Ed). A Kruskal-Wallis ANOVA was used to investigate whether the median duration of CSE was different in children that received adequate, inadequate or no treatment. Chi-square testing was carried out to examine relationships between pre-hospital treatment in incident and non-incident cases, and the relationship to admission to PIC.

Results: 110 incident and 81 non-incident cases of CSE, of out of hospital onset, have been enrolled. Pre-hospital treatment was administered in 49(45%) incident and 62(77%) non-incident cases ($p < 0.001$). Rectal (PR) diazepam was the first AED administered in 116(95%) cases. In those children treated with PR diazepam the dosage was adequate in only 15(33%) incident and 10(17%) non-incident cases ($p = 0.02$). The median duration of CSE was similar in all treatment groups ($p = 0.33$), however those that received adequate pre-hospital treatment were more likely to require admission to PIC than those that received no or inadequate pre-hospital treatment ($p = 0.05$). There was no evidence for increased respiratory insufficiency in those children adequately treated ($p = 0.95$).

Conclusions: Children with a first time episode of CSE are less likely to receive pre-hospital treatment than those with a recurrent episode, although those with first time events are more likely to receive an adequate dose. Pre-hospital treatment in children that ultimately have a seizure lasting at least 30 minutes does not reduce overall seizure length. However, children who fail to respond to adequate pre-hospital treatment are more likely to require PIC admission, suggesting that these children are more likely to have refractory CSE than those inadequately or not treated. Conversely, children inadequately or not treated in the pre-hospital setting are likely to respond to treatment in the hospital setting and not require PIC, suggesting that seizure duration would have been shorter in a large number if the initial dose were adequate.

1.226
PUSHING THE LIMITS OF CORTICAL PLASTICITY: REHABILITATION OF POST-HEMISPHERECTOMY CHILDREN

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Rationale: Functional and clinical outcomes of hemispherectomy have recently become an area of intensive research. Understanding the potential of the remaining hemisphere and the mechanisms of functional recovery is crucial in designing rehabilitation strategies for this population. We investigated the effects of intervention in children with hemispherectomy performed as long as 10 years ago by studying training-induced neuroplasticity of the intact hemisphere, employing functional magnetic resonance imaging (fMRI).

Methods: Twelve children (4 females and 8 males) who underwent hemispherectomy as part of the UCLA Pediatric Epilepsy Surgery Program between 1986 and 2001 were offered intensive therapy to improve their gait and walking speed. Their age ranged from 10 to 19 years (median 12 years). The postsurgery period ranged from 2 to 10 years (median 6 years). Etiology classification, inclusion criteria and hemispherectomy technique were similar to those reported in de Bode, 2004. Each participant received the Body Weight Support Treadmill Training provided by trained therapists in two sessions a day, 5 days a week for 2 weeks. The fMRI activation study of ankle dorsiflexion (active and passive) was performed before the BWSTT intervention and following its completion two weeks later.

Results: To monitor functional changes associated with training the following measures were collected pre- and posttraining: the Fugl-Meyer motor index for the lower extremity, walking speed (normal and fast pace) and the single limb stance time (i.e., the time a child could stand unassisted on her affected leg). Three of the four measures showed statistically significant changes indicating improvements. Functional changes correlated with the evolution of cortical maps observed with fMRI. The two main trends of activation changes were noted: in children with limited ability to actively dorsiflex their ankle cortical maps evolved from wide-spread into focal and localized areas as their ability to move an ankle improved; in children with relatively spared ability to voluntarily move an ankle, locations of cortical activations remained unchanged but intensity of the signal in these areas statistically increased.

Conclusions: The goal of our study was to use the intensive practice of a well-defined locomotor therapy to demonstrate that functional improvements associated with cerebral representational plasticity are possible in children whose surgery was 1–10 years ago. An intensive pulse of physical therapy seemed to improve walking and reduce impairments associated with hemiplegia. Furthermore, cortical plasticity induced by training suggests that the potential of the remaining hemisphere may not be fully utilized without specific intervention. [Supported by the NRSA in Neurological Rehabilitation (NS 07479) to B. Dobkin, the Rehab-Net West grant to S. de Bode and R01 NS 38992 to G.W. Mathern.]

1.227
AGE AT SEIZURE ONSET AMONG CHILDREN WITH PVL
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Rationale: Children with cerebral palsy (CP) secondary to periventricular leukomalacia (PVL) often present with recurrent unprovoked epileptic seizures. To better understand the nature and source of these seizures, it is necessary to explore the distributions of and interplay between key clinical factors, most notably PVL severity and the age at onset of first seizure.

Methods: All children at the regional CP treatment center having clinical patterns associated with PVL (spastic diparesis, triparesis, leg-dominant quadriparesis) were screened for epilepsy and radiological evidence of PVL. The extent and distribution of the PVL was rated radiologically in a blinded fashion, from PVL1 to PVL3, in order of increasing severity; those with additional focal cortical or subcortical pathology were scored as PVL4. Descriptive analyses were conducted on this sample, with special attention to severity grade of PVL and subjects' age at first onset of seizures.

Results: Of 218 subjects with appropriate CP patterns, 157 had radiologically confirmed PVL and 130 had CT±MRI studies available for scoring, with 37/130 having epilepsy; 22, 60, 40 and 8 patients were scored with PVL severity 1–4 respectively, while 5, 10, 17 and 5 had epilepsy. Among the patients with epilepsy, the mean age at onset of first seizure was 35.4 months (SD = 41.4) and the median was 30.0 months (IQR = 34.0). For those of PVL severity 1–4 respectively, the mean age at seizure onset was 34.0 (SD = 4.9), 37.6 (SD = 7.7), 31.3 (SD = 12.3) and 56.6 months (SD = 34.1). Age at onset was weakly inversely correlated with PVL severity (Spearman's rho = -0.302, p = 0.05).

Conclusions: In patients with PVL who develop epilepsy, there is some evidence of a weak relationship between PVL severity and the age at onset of first unprovoked seizure.

1.228
COMMON EEG CHARACTERISTICS BETWEEN BENIGN CHILDHOOD EPILEPSY, SYMPTOMATIC FOCAL EPILEPSY, AND EEG GENETIC TRACE WITHOUT EPILEPSY
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Rationale: EEG is an important tool for the diagnose of Benign Childhood Epilepsy (BCE) making other expensive tests, such as MRI, non-mandatory, but some Focal Symptomatic Epilepsies (FSE) can be overlooked when the diagnose is only based on clinical and EEG data. Also, epileptiform paroxysms (EP), typical of BCE, can occur in non-epileptic children, as a genetic trace (GT), a source of misdiagnose. We tried to identify EEG characteristics more specific of BCE as compared to FSE and GT.

Methods: EEG recordings of children with normal background activity and EP suggestive of BCE, registered in our lab along 1993 and 1994, were blindly collected and lately confronted with clinical and neuroimaging data of the patients (follow-up of 3 to 13 years). We carried out a conventional analysis of the following characteristics of the EP: number and location of the foci, electrical fields, presence of tangential dipole, association of the spikes with a slow wave, presence of pseudo-slowing, EP with double-spike, sleep activation, presence of bisynchronous spikes and/or generalized spike-wave.

Results: We reviewed 173 EEG from 145 children, diagnosed as BEC (80), GT (38), FSE(25) and Landau-Kleffner Syndrome (2). Among BEC, we found 65 (81.3%) with Rolandic Epilepsy, 9 (11.2%) with Occipital Panayotopoulos-type Epilepsy, 4 (5%) with Occipital Gastaut-type Epilepsy, 1 (1.2%) with BEC with Affective Symptoms and 1 with Infantile Benign Focal Epilepsy. None of the EEG characteristics studied were significantly more common in BEC as compared to the other two groups.

Conclusions: There seems to be superposition of the EEG characteristics between some FSE and BCE, which makes accurate clinical and neuroimaging tests necessary for their differentiation in some cases. Our results suggest that the morphology, location, field distribution (including tangential dipole) and sleep activation, among other aspects of the EP, under a normal background EEG activity, are not always enough to discriminate those syndromes. (Supported by FAEPA, Support Foundation to Teaching, Research and Assistance of Ribeirao Preto Medical School, University of Sao Paulo.)

1.229
INTRACTABLE PEDIATRIC EPILEPSY: DO MECHANISMS OF ACTION MATTER?
Monisha Goyal (Pediatric Neurology, Rainbow Babies & Children's Hosp., Case University, Cleveland, OH)

Rationale: What constitutes intractable epilepsy remains controversial. The prevailing consensus is failure of seizure control after trial of 2 or more antiepileptic drugs. Though it is widely felt that "rational" therapy should be employed, previous studies have not specifically looked at the impact of mechanism of action of antiepileptic drugs in helping further define and characterize intractability.

Methods: A review of the database of all active pediatric epilepsy patients followed at our center between January 2003 and April 2004 was made. Patient charts were reviewed for further information.

Results: At the time of this abstract submission, 511 pediatric patients were on seizure medication or had been weaned off during the data collection period. Two hundred and four patients (40%) were on a stable dose or being titrated on the first AED. One hundred and four patients (20%) were on a second AED, and 33 (6%) were on a third AED. Thirty-five patients (7%) had a second drug added. Twenty-seven patients (5%) were on a second and third drug combination.

Seizure freedom was defined as no seizure for more than one year. One hundred and sixty-two of 511 patients (32%) were seizure free. Of these, 82 (50%) achieved seizure freedom after institution of the first drug, 44 (27%) after the second AED, 5 (3%) after the third, and 8 (5%) with the fourth AED. For patients on combination therapy, 11 (7%) were seizure free on the first two AEDs, and 5 (3%) achieved seizure freedom on a second and third drug combination.

Of the 44 patients who were seizure free on the second AED, 15 were on the second drug because of poor seizure control and 9 due to side effects. The others had only transient exposure or were weaned from their first AED. Conversion from a narrow spectrum drug (phenytoin, carbamazepine) to a broad spectrum drug (eg. topiramate, lamotrigine) or the converse did not influence seizure freedom in the 15 patients who were on a second drug due to incomplete efficacy. In fact, 4 of 15 were placed on oxcarbazepine from carbamazepine, both considered narrow spectrum drugs.

Conclusions: Seizure freedom in 32% of pediatric patients is less than reported previously in prospective studies. This may in part be due to our data collection process which includes both retrospective and prospective data, thus incorporating longer seizure histories.

Similar to previous studies, our results show a dramatic decline (<5%) of achieving seizure freedom by the time a third drug is utilized.

Though rational polytherapy is encouraged, our data analysis does not substantiate this rationale. This may in part be due to incomplete data analysis at the time of this abstract submission.

1.230
TIME TO FIRST SEIZURE IN PEDIATRIC PATIENTS WITH NONCONVULSIVE SEIZURES ON CONTINUOUS EEG MONITORING
Nathalie Jette, John Wittman, Jan Claassen, Ronald G. Emerson, and Lawrence J. Hirsch (Neurology - Comprehensive Epilepsy Center, Columbia University College of Physicians and Surgeons, New York, NY)

Rationale: The use of continuous EEG monitoring (cEEG) is essential for the detection of subclinical/nonconvulsive seizures. However, how long to monitor patients in order to rule out nonconvulsive seizures is unclear.

Methods: The Columbia Comprehensive Epilepsy Center cEEG database was reviewed to identify pediatric patients with nonconvulsive seizures and to determine time to first seizure on cEEG.

Results: 189 pediatric patients were monitored, the majority in the ICU, with ages ranging from day one of life to 18 years (mean 5). 56 patients (29.6%) had nonconvulsive seizures, while 24 patients (12.7%) had convulsive seizures on cEEG. Of the 56 patients with nonconvulsive seizures, seizures occurred immediately upon hookup in 9 patients (16.4%), in $\leq$ 1 hour in 53%, $\leq$ 12 hours in 83%, $\leq$ 24 hours in 87%, $\leq$ 48 hours in 93%, and $>$ 48 hours in the remaining 7%.

Conclusions: Nonconvulsive seizures are common during cEEG monitoring in the pediatric population but only half are detected in the first hour of recording, and 13% are not recorded until >24 hours of monitoring. This confirms the importance of prolonged EEG monitoring for critically ill pediatric patients in order to detect nonconvulsive seizures.

1.231

INTRACTABLE SEIZURES IN CHILDREN WITH BRAIN TUMOR

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Rationale: Seizures are reported in 20–45% of brain tumor patients, most frequently in patients with supratentorial tumors. Studies suggested that seizures related to brain tumors are more refractory to antiepileptic drugs (Schaller B, Epilepsia 2003). The goal of this study is to identify the incidence of seizures in children with brain tumors, and specifically the incidence of intractable seizures.

Methods: Retrospective record review of 199 hospitalized pediatric patients with brain tumors treated at Schneider Children's Hospital between 1998 and 2003.

Results: Out of 199 patients, sufficient information was obtained from the records of 164 patients. Thirteen patients with optic gliomas, cavernous angiomas and metastatic tumor were excluded. The remaining 151 patients constituted the study population. Eighty-nine had infratentorial tumors, 62 had supratentorial tumors. Eleven percent (10/89) of patients with infratentorial tumors had seizures, mostly related to acute hydrocephalus and to surgical or non-surgical treatment complications. Forty eight percent (30/62) of the patients with supratentorial tumor had seizures, mostly (20/30, 67%) as part of the initial presentation. Thirty percent (12/40) of all seizure patients had used 3 or more antiepileptic drugs and 12.5% (5/40) patients met the criteria for intractable seizures defined as failing 2 antiepileptic drugs and more than 1 seizure per month for 18 months. All 5 patients with intractable seizures had either residual tumors or tumor recurrence requiring 2 or more surgical intervention (Table1).

Conclusions: The intractable epilepsy rate of 12.5% in this population is similar to the rate reported in non-tumor epilepsy children (Berg AT, neurology 2001). Our data did not support the hypothesis that brain tumor patients have higher risk for medically refractory seizures (95% confident interval 2.3%-23%). Seizures in infratentorial tumors are mostly related to hydrocephalus or treatment. Significant proportion of the patients with supratentorial tumor had seizures as their initial presentation.

1.232

AGE EFFECTS ON CLINICAL CHARACTERISTICS OF STATUS EPILEPTICUS IN THE FIRST TWO YEARS OF LIFE

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Rationale: Clinical studies of pediatric epilepsy focus on effects of seizures occurring in the first years of life. Rat pup studies have indicated significant differences in long term effects, including epileptogenicity, of prolonged convulsions induced at different ages. Clinical human studies typically focus on seizures and episodes of status epilepticus (SE) occurring in the age category of "greater than one month and less than one year." Conclusions vary, although statistics are consistent. Clinical experience and review of refractory pediatric SE cases indicated a high proportion of children with no co-morbid factors and low morbidity who presented with febrile SE around one year of age. Review of previoudsly reported cases to ascertain a peak incidence for benign febrile SE was undertaken.

Methods: Previously reported cases from the Greater Richmond Metropolitan Area prospective collection of all first SE cases were re-examined. SE and seizure types were defined as described previously (*Neurology* 1996; 46:1029). All cases with ages between one month and 17 years of age were reviewed. More detailed examination of incidence was undertaken, with cases grouped by age categories covering three month increments for those four years of age or younger. Subsequently, cases of febrile status were segregated. (These cases had fever or infection, but not meningitis or encephalitis, listed as an etiology. There were no co-morbid features *e.g.* prior seizures, cerebral palsy, genetic abnormalities, delayed development, prior or ongoing neuorlogic insults.)

Results: Review of cases indicated a bimodal distribution of SE in the first two years of life. A large group of children with febrile status accounted for the second peak (as well as 21% of all cases of SE in the one month to 17 yr age group.) This group had no associated mortality. 61% of febrile status occurred in the 9 month - 18 month age group.

Conclusions: Febrile SE in children with no co-morbid features and low associated morbidity peaks around 9 to 18 months. This group may have particular susceptibility to acute convulsions, but may be less prone to long term sequelae. In recent articles, epidemiologic information is

TABLE 1. *Patients with more than 3 AEDs and/or intractable seizures*

Age	Histology	Location	Intractable SZ	AEDs⟨3	Treatment	Complication	SZ as initial presentation
8Y	Astrocytoma	B/L thalamus, brainstem	Yes	Yes	Partial resect, RT, chemo		No
8Y	Astrocytoma	Brainstem & L hemisphere infiltrative	Yes	Yes	Biopsy, RT		Yes
16Y	DNET	L front, temp	Yes	Yes	Surgx3		Yes
4Y	DNET	L front	Yes	Yes	Partial resect		Yes
14Y	Ependymoma	L ventricle	Yes	Yes	Surgx2, RT	Multiple seeding, Stroke	No
10M	Astrocytoma	Insular	No	Yes	Gross total	Development regression	Yes
5Y	Astrocytoma, pilocytic	Cerebellar	No	Yes	Gross total	Comatose, mutism	No
12Y	GBM	Front	No	Yes	Surgx2		No
7Y	Well diff neoplasm of uncertain histogenesis	L temp	No	Yes	Gross total		Yes
12Y	Ganglioglioma	L temp	No	Yes	Lobectomy, chemo		Yes
22Y	PXA	L front, temp	No	Yes	Surg x3, RT		No
12Y	Craniophrengioma	suprasella	No	Yes	Partial, RT	Stroke	No

DNET: dysembryoplastic neuroepithelial tumor GBM: glioblastoma multiforme PXA: Pleomorphic Xanthoastrocytoma RT: Radiation therapy.

Febrile and other SE by Age							
1–3 mos	3–6 mos	6–9 mos	9–12 mos	12–15 mos	15–18 mos	18–21 mos	21–24 mos
x*	OOOO	OOOO	OOOO	OOOO	OOOO	OOOO	OOOO
X*	OOOO	OOOO	OOOO	OOOO	OOOO	x	x
x*	x*	x*	OOOO	OOOO	OOOO		x
x*	x*	x^	OOOO	OOOO	OOOO		
x	x	x	OOOO	OOOO	OOOO		
x	x	x	OOOO	OOOO	x		
x	x	x	OOOO	OOOO	x		
x	x	x	OOOO	OOOO	x		
	x		OOOO	OOOO	x		
	x		OOOO	OOOO	x		
	x		OOOO	x^	x		
	x		OOOO	x	x		
	x		OOOO		x		
	x		x^		x		
	x		x				
	x		x				
	x		x				
	x		x				
	x		x				
			x				
			x				
			x				
			x				
			x				
			x				

OOOO = febrile SE; x = other SE; * = died within 30 days of SE; ^ = died later.

typically stratified into a "less than one year" category. Future studies of seizures and SE in the very young may yield more prognostic information if the age category of "over one month but less than six months" is utilized. (Supported by NIH PO1-NS25630.)

1.233

POLYSPIKE AND WAVE DOES NOT PREDICT GTCS IN CHILDHOOD ABSENCE EPILEPSY

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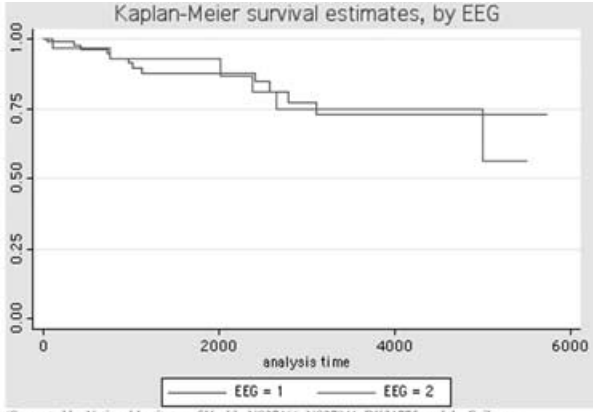
Rationale: About 40% of children with Childhood Absence Epilepsy (CAE) develop generalized tonic-clonic seizures (GTCS) but the clinical and electrophysiological factors predicting this evolution are not well defined. Some clinicians believe that polyspike and wave (PSW) pattern on the EEG marks the later development of GTCS when seen in CAE patients. However, there is no firm epidemiological evidence for this proposition. We therefore tested the hypothesis that PSW predicts GTCS in typical CAE patients.

Methods: We used a cohort design to measure the incidence of GTCS in CAE patients after diagnosis and to assess predictive factors. We identified 115 patients (60% female) with typical CAE (defined by the ILAE 1989 criteria) who first visited our outpatient epilepsy clinic between 1992–2003. We obtained longitudinal data on the incidence of GTCS by a combination of chart review, postal questionnaire and telephone interview. Final response rate was 84%. Using survival analysis, we compared the incidence of GTCS in CAE patients with either simple 3Hz spike and wave or PSW patterns on EEG. We looked at the effect of age, sex and family history of epilepsy on GTCS incidence by multivariate analysis using a Cox proportional hazards model.

Results: The mean age of CAE onset was 6.5 years; mean duration of follow-up was 5.3 years; 30 (26%) patients had PSW on their EEG. Incidence rate of GTCS was 8 per 100,000 person-days of follow-up. The incidence rate ratio (RR) for GTCS in patients with PSW compared with simple 3Hz EEG pattern was 0.99 (95%CI:0.37–2.64): Fig. 1 shows GTCS incidence since onset of CAE (days) by EEG (1 = 3Hz, 2 = PSW). In multivariate analysis, only age of onset after 8 years significantly increased risk of GTCS: Hazard Ratio 3.6, 95%CI:1.2–10.1, adjusted for sex, family history of epilepsy and EEG pattern (PSW or 3Hz).

Conclusions: There was no evidence that PSW predicted GTCS development in CAE patients, GTCS incidence was identical for CAE patients with simple 3Hz vs PSW. A later age of onset was the best and only independent predictor of GTCS in CAE patients; PSW was not more common in older onset CAE. These results have implications for the choice of first-line AEDs, especially if valproic acid is being chosen because of PSW on the EEG.



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1.234

NONEPILEPTIC EVENTS IN PEDIATRIC POPULATION

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Rationale: Non-epileptic events are characterized by seizure-like behaviors without any associated EEG changes. Psychogenic seizures make the majority of the non-epileptic events in adults; however, the spectrum is much wider and includes both psychogenic and organic etiologies in pediatric population. Although, there is numerous literature on non-epileptic events in adults, limited data is available in pediatric population.

Methods: We reviewed the data on the pediatric patients (age <18 years) who underwent at least 24-hours long-term video-EEG monitoring (LTM) at the University of Michigan Hospitals. Patients with possible simple partial seizures without any EEG correlation and with uninterpretable EEGs were excluded. All EEGs and video events were first reviewed by an EEG fellow then by an attending physician board certified in clinical neurophysiology. Predominantly motor-behavioral events without any EEG correlation were classified as stereotyped movements in children < 1 year old and as behavioral events in children older than 1 year with some degree of mental retardation.

Results: A total of 156 children were admitted for LTM during 12 month period. Out of these, 39 (25%) patients had non-epileptic events. Twenty patients were male (56%) and the mean age was 8.4 years (range 2 months-17 years). Four patients (10%) also had concomitant epilepsy. Psychogenic seizures were most common and occurred in 13 (33%) patients. Majority of patients (10 patients, 77%) with psychogenic seizures were adolescents (age >12). Behavioral events were the second most common type of non-epileptic event seen in 9 patients (23%). All patients with behavioral events had mild-to-moderate degree mental retardation. Other diagnostic categories include parasomnias (10%), stereotyped movements (8%), daydreaming (5%), non-epileptic myoclonus (5%), and hand tremor, breath holding spells, presyncope, paroxysmal non-kinesigenic choreoatetosis, nocturnal enuresis, gastroesofageal reflux disease were seen in one patient each (3%).

Conclusions: Non-epileptic events occurred in about one-quarter of our pediatric patients. Psychogenic seizures were the most common diagnosis in this population and occurred mostly in adolescents warranting psychologic counseling in this age group. Therefore, LTM is important in the pediatric population with paroxysmal events in order to prevent misdiagnosis because of various etiologies of the events.

1.235
ORAL KETAMINE IN THE TREATMENT OF PAEDIATRIC NON-CONVULSIVE STATUS EPILEPTICUS

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Rationale: Non-convulsive status epilepticus (NSCE) is not an uncommon problem in paediatric patients with refractory epilepsy. Standard treatments include steroids, benzodiazepines and the ketogenic diet but response to these treatments is variable and side effects common. A recently published small case series report suggested ketamine, a non-competative NMDA receptor antagonist, may have a role in the treatment of NSCE. We report our prelimenary findings in the use of oral ketamine for NSCE.

Methods: Subsequent to the recently published paper we are carrying out a prospective audit in our use of oral ketamine. Patients were selected on the basis of clinical and electrophysiological findings, all had an unequivocal diagnosis of NSCE prior to starting therapy. Oral ketamine was prescribed (0.75mg/kg twice daily for 5 days), the first dose being administered under supervision. All patients had a clinical and EEG re-evaluation on day 5 of treatment.

Results: A total of 7 pateints (2 male) with a mean age of 7.4 years fulfilled the criteria. Diagnoses were different in all 7 patients and included Lennox Gastaut Syndrome, unclassified myoclonic epilepsy, symptomatic generalised epilepsy and Landau Kleffner varient with recurrent epileptic encephalopathy. 7/7 had previously had episodes of NSCE (range 1–8 episodes) and all had received at least one course of steroids in the past with variable response. 1 patient developed a steroid myopathy following repeated steroid administration and 2 patients reported significant mood and behavioural disturbances. 4/7 patients had an excellent clinical and EEG response to following ketamine administration with a rapid improvement in cognitive function and an improvement in EEG findings. 2 patients relapsed back into NSCE immeadiately after ketamine was discontinued at day 5. Both showed a clinical and electrophysiological improvement after ketamine was re-introduced. 2 patients did not show any response to ketamine. There were no reported adverse during or after ketamine administration including 2 patients maintained on ketamine for longer than 2 months.

Conclusions: Ketamine appears to be an effective and well tolerated alternative to steroids and benzodiazepines in the management of non-convulsive status epilepticus. Further studies are required to assess its efficacy and safety compared with standard treatments.

1.236
THE DISTRIBUTION OF EPILEPSY SYNDROMES IN CHILDREN WITH INTRACTABLE SEIZURES ADMITTED TO AN EPILEPSY MONITORING UNIT

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Rationale: Epilepsy Monitoring units (EMUs) have become increasingly important in the diagnosis and management of epilepsy. In spite of this role, very limited information is available about the distribution of epilepsy syndromes in children with intractable epilepsy, which is expected to be rather different from the general epilepsy population. In this study, we analyzed the distribution of epilepsy syndromes in children with intractable epilepsy who were admitted to an EMU.

Methods: A total of 1430 patients were admitted to the EMU at Montefiore Medical Center between January 1991 and December 1998. Among them, 859 patients were under 12 years old of which 483 patients were children with intractable epilepsy admitted for diagnostic and/or therapeutic purposes. These 483 children are the subject of this retrospective chart review. Children who were admitted for the first time for diagnostic purposes without clear history of clinical seizures were excluded from the study. Classification of seizure types and epilepsy syndromes were made using an algorithm based on the ILAE classification.

Results: To date, we have reviewed 150 cases. The etiology of epilepsy syndromes was idiopathic in 14 (9%), cryptogenic in 42 (28%), and remote symptomatic in 94 (62%). Epilepsy syndromes were generalized in 83 (55%) children, localization related in 51 (34%), and undetermined whether focal or generalized in 15 (10%). Among children with generalized epilepsy syndromes, those of cryptogenic or symptomatic etiology (infantile spasms, Lennox-Gastaut and myoclonic astatic epilepsy) accounted for the majority of cases (80%). In children with localization related epilepsy, the majority (85%) met the criteria for symptomatic epilepsy by virtue of either localization or etiology. Of the 150 children, 75(49%) were either developmentally delayed or had abnormalities on their neurological examination. Neurodevelopmental abnormalities were present in 59 (71%) of 83 children with generalized epilepsy syndromes compared with 16 (31%) of the 51 children with partial epilepsy ($p < 0.0001$). Thirty-four (22%) children had multiple admissions including 18 (22%) with generalized epilepsy and 11 (22%) with localization related epilepsy.

Conclusions: The distribution of epilepsy syndromes in children admitted to EMUs is skewed towards nonidiopathic generalized epilepsy syndromes and symptomatic localization related epilepsy. A high proportion of children, particularly those with generalized epilepsy are neurologically abnormal. The remainder of this cohort is being reviewed. Follow up study is underway to assess the long-term seizure outcomes, neurodevelopmental status and school progress of these children.

1.237
ICTAL SCALP EEG IN TEMPORAL LOBE EPILEPSY IN THE PEDIATRIC POPULATION

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Rationale: The purpose of this study is to identify specific ictal electroencephalographic (EEG) patterns associated with temporal lobe epilepsy(TLE) in the pediatric population. The localization of temporal lobe foci (mesial versus neocortical) in adults has been well described.

It is important to observe whether any age related maturational changes, or other variables related to the developing brain, have any impact on the ictal scalp EEG recordings.

Methods: We reviewed the ictal scalp EEG in 9 epilepsy surgery candidates (age 7–17 years). Mean age at seizure onset was 10 years (range 5–16). 7 patients were male. A total of 33 seizures were recorded. The ictal EEG features during the first 40 seconds were included in the analysis. Several patterns were identified. The location of the seizure focus was confirmed in 5 patients, that either became seizure free or only had auras after temporal lobectomy(TL) and with a minimum of 1 year postoperative follow up. The remaining 4 patients either just underwent TL (n = 1) or are completing the presurgical evaluation.

Results: The seizure semiology in all patients was consistent with TLE seizure semiology. The most common sequence noted consisted of an aura of fear, rising epigastric sensation, followed by loss of consciousness, staring, automatisms such as lip smacking, unilateral dystonic posturing, unilateral or bilateral hand automatisms. All patients had brain MRI lesions that either involved the mesial structures only (n = 4), the neocortex (n = 2) or both. The abnormalities identified on the imaging studies were suggestive of hippocampal sclerosis (n = 3), malformations of cortical development (n = 2), dual pathology (n = 2), low grade tumor (n = 2). The ictal EEG patterns fell into one of the following types: bifronto-central theta to alpha range activities, followed within 10–20 seconds(s) by unilateral temporal theta(UTT) activity; bifrontal delta activity, followed within 10–25 s by UTT rhythm or first by unilateral delta then theta activities; unilateral temporal delta(UTD)activity, followed within 5–15 s by UTT; less commonly, delta intermixed with theta activity from onset to offset.

Conclusions: The most common ictal EEG pattern was represented by the UTD activity, followed within 5–15 s by UTT. This is also the most common pattern previously described in adult patients with mesial TLE. 1 patient with bifrontal delta pattern at onset, followed by UTD, then UTT, became seizure free after surgery. 1 patient with bifronto-central theta to alpha range activities, followed by UTT activity, has auras only postoperatively. A larger series of pediatric patients with TLE is needed to further identify the various ictal scalp EEG patterns within this age group, and distinguish any particularities in pediatric versus adult patients with mesial TLE, if any.

1.238
MORTALITY FOLLOWING A FIRST UNPROVOKED SEIZURE IN CHILDHOOD

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Rationale: There is a known increased mortality rate in patients with epilepsy. In children most of the excess risk is in those with remote symptomatic epilepsy. The risk following a first seizure has not been well studied. We report the mortality rates and causes in a cohort of 407 children who initially presented with a first unprovoked seizure.

Methods: In a prospective study, 407 children with a first unprovoked seizure were identified and followed for a mean of 14 years. Seizure etiology, seizure type and epilepsy syndrome were classified in accordance with the ILAE criteria.

Results: There were 9 deaths in the cohort. Two deaths were entirely unrelated (one meningitis in an infant, one gunshot wound in a 20 year old) and occurred in normal children who only had one seizure and were never treated. Three deaths were related to the underlying neurological disorder. Two of these children, both with severe neurological disability died more than 3 years after the initial and only seizure. Neither was taking medication. The third died due to the underlying disease 14 years after the initial seizure and was >2 years seizure free at the time. In the remaining four cases, the deaths were possibly or definitely related to the seizure disorder. All 4 of these children were on AED therapy at the time of death. Two were severely neurologically abnormal and died suddenly more than 2 years after initial presentation without a witnessed seizure and are considered possible SUDEP. The other two were probable SUDEPs. One was 11 years old with intractable daily seizures and progressive neurologic decline who was found dead one morning. The other was an adolescent with primary generalized epilepsy (random grand mal). He was treated after his second seizure 4 months after the initial seizure. He died 2.5 years later in association with his ninth seizure.

Conclusions: There is an increased mortality in children who present with a first unprovoked seizure. Delaying treatment until after the second or third seizure would not have altered mortality in this cohort. While a small risk can not be excluded, there are also risks associated with AED therapy. These data provide further support for the recent practice parameter of the American Academy of Neurology (Neurology 2003; 60:166–175) that treatment following a first seizure in children does not alter prognosis. Concern about mortality risk should not be a major issue in decision regarding treatment after an initial seizure. (Supported by NIH grant NS 26151 from NINDS.)

1.239
EPILEPSY AND MOVEMENT DISORDERS IN SUCCINATE SEMIALDEHYDE DEHYDROGENASE (SSADH) DEFICIENCY: RELEVANCE TO HUMAN GAMMA-HYDROXYBUTYRATE (GHB) TOXICITY

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Rationale: SSADH deficiency is a disorder of GABA catabolism characterized by supraphysiologic levels of GABA and GHB, the latter an endogenous GABA metabolite. Drop attacks, cataplexy, tremors, and myoclonus have been reported in human GHB intoxication. The latter is a growing problem in the US population. We report the seizure data, EEG findings, and movement disorders observed in our expanding patient database of SSADH deficiency.

Methods: We have a database of 81 patients with SSADH deficiency, comprised of 40 patients in our practice population or in whom we have collected systematic questionnaire data, and 41 patients with detailed published case reports. We analyzed this data for presence of seizures and seizure type(s), EEG abnormalities, and extrapyramidal movement disorders.

Results: Of 81 patients, 40 (50%) had seizures: 15 tonic-clonic; 10 absence; 7 myoclonic; 2 partial; 1 atonic; 1 ALTE; 18 unclassified. Of 40 patients with EEG data, 28 (70%) were abnormal: 17 with background slowing; 11 generalized epileptiform discharges; 6 focal discharges; 2 photoparoxysmal response. Of 81 patients, 8 patients (10%) had prominent extrapyramidal manifestations (chorea, athetosis, dystonia, myoclonus). The mean age of onset in this cohort was 2.2 yrs (median 12 mos), vs 4.2y in the total group. In 4, the clinical course was consistent with a progressive encephalopathy, with regression or decompensation. In contrast, seizure onset was widely variable, from infancy to early adulthood, and most patients followed a static appearing course.

Conclusions: Our expanding SSADH deficiency database enables a wider and more accurate description of the phenotype of this hyper-GABAergic disorder. Half of SSADH deficient patients have seizures, which are usually generalized when classifiable. Nearly 75% of patients will have abnormal EEGs, with background slowing, generalized>focal spikes, and occasionally photosensitivity. Patients with prominent movement disorders appear to have a more severe phenotype, and manifest some features seen also with acute GHB intoxication. Treatment strategies for seizures and movement disorders in SSADH deficiency may have therapeutic relevance to the growing problem of illicit GHB use. (Supported by NIH: NS40270, Epilepsy Foundation of America, Pediatric Neurotransmitter Disease Association.)

1.240
NEUROLOGICAL OUTCOME OF PRETERM AND TERM NEONATES WITH NEONATAL SEIZURES

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Rationale: Neonatal seizures are considered an acute manifestation of brain injury and they are classified as undetermined epilepsies with both generalized and focal seizures.

Our goal was to evaluate neonatal risk factors, EEG findings and ictal semeiological characteristics of our newborns with neonatal seizures in order to identify which clinical variables were the most early predictive factors of poor neurodevelopmental outcome and of epilepsy.

Methods: During a period of 6 years, thirty-five preterm (PT) and forty-one term infants (FT)consecutively admitted to the NICU of University of Parma, Italy, were recruited for this study according to the following criteria: presence of EEG-confirmed repetitive neonatal seizures and/or neonatal status epilepticus, need of chronic anticonvulsant therapy, more than three EEG performed during the neonatal period, several cerebral ultrasound examinations, at least one neuroimaging exams (cerebral CT and/or cerebral MRI) and neurological follow-up longer than nine-months. Independent variables considered included mood of delivering, gestational age, birth-weight, Apgar score at 1^{st}, 5^{th} and 10^{th} minute, needs for resuscitation and assisted ventilation for more than one minute soon after birth, aetiologic factors, onset, duration and type of seizures, ictal and interictal EEG activity. Clinical seizures without EEG correlates were not considered. Neurodevelopmental outcome was assessed at 44 weeks of post-conceptional age, and at the corrected age of 1, 3, 6, and 9 months. The neurodevelopmental outcome was classified as favorable or adverse. A favorable outcome was defined as normal neurologic development, whilst adverse outcome was identify as involvement resulting in death, cerebral palsy, developmental delay, epilepsy. The Student's t test for unpaired date was used to compare means of subcategories of patients, while nominal data were analysed using χ^2 test and, if significant, Fisher's exact test for 2-by-2 comparison was used. In all instances, a p value of less than 0.05 was considered to be significant.

Results: Ten of the 35 PT subjects and 6 of the FT infants had neonatal status epilepticus. Among the PT infants (one lost during follow-up): five were normal, nine had CP, seven presented CP and epilepsy, one had only epilepsy while twelve died. Twenty-two FT infants had a normal outcome, nine had cerebral palsy, 2 presented cerebral palsy and epilepsy, five were epileptic and three died.

Conclusions: From our data severely abnormal background EEG activity ($p < 0{,}01$), low Apgar scores ($p < 0{,}008$), severely abnormal neurological examination at birth ($p = 0{,}013$) and abnormal cerebral ultrasound scans ($p < 0{,}001$) were the most significant predictors of poor neurodevelopmental outcome. Furthermore, none of the infants with status epilepticus presented a normal outcome and they had a greater risk of subsequent epilepsy.

1.241
NONLESIONAL FRONTAL LOBE EPILEPSY (FLE) OF CHILDHOOD: CLINICAL PRESENTATION, RESPONSE TO TREATMENT, AND IMPACT ON LEARNING, BEHAVIOUR AND COGNITION

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Rationale: Few studies have looked at the long-term epileptic and cognitive outcome of frontal lobe epilepsy in children and most of them are limited by the inclusion of both lesional and non-lesional patients.

Goal: To define the epileptic and functional outcome of children with non-lesional FLE.

Methods: We reviewed medical and neuropsychological records of patients with FLE diagnosed between 1994–2004. We included children with either focal EEG findings or regional EEG changes and focal functional imaging abnormalities. We reviewed their charts for seizure and neuropsychological outcome.

Results: We retrieved 21 children, including 14 boys. Mean age at seizure onset was 6.7 ± 3.9 years and mean follow-up 9.4 ± 3.5 years. Cerebral CT/MRI were normal by definition in all children. Ten of 16 with a specified seizure frequency (62.5%) presented with daily seizures. Seizures were nocturnal in 7/21, secondarily generalized in 5/21, adversive in 5/21, and focal motor in 5/21. The initial therapy was Carbamazepine (10), Phenytoin (2), Phenobarbital (1) and valproic acid (3). Although initial seizure control was poor (14/21 failed the initial drug), long-term seizure control was still achieved in 9/21 patients after several months of treatment (14.6 +/- 22.3). Early development was normal in 12/21 children but at latter formal neuropsychological evaluation only 3 of the 12 still had a normal profile. The majority of children had learning difficulty requiring special help prior to seizure onset (52.4%). But a clearly defined regression after seizure onset was observed in only 3 patients. A detailed neuropsychological evaluation was performed in 18/21 patients. The majority exhibited attention deficit and hyperactivity or impulsivity (14/21), behavioural problems (7/21) and cognitive impairments (7/21 low average IQ). Early seizure control was associated with a better outcome

Conclusions: Non-lesional FLE is associated with poor seizure, cognitive and behavioural outcomes. Whether this is secondary to MRI-silent developmental lesions or the repercussion of seizures on frontal lobe functions remains uncertain. A prospective study with early neuropsychological assessment could help confirm the latter.

1.242
TREATMENT OF BIPOLAR AND EXPLOSIVE MOOD DISORDER COMORBID WITH PEDIATRIC EPILEPSY

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Rationale: Anticonvulsant drugs are commonly used as first line treatments for both bipolar mood disorders and epilepsy. We sought to identify medications commonly used in pediatric epilepsy patients with comorbid bipolar disorder or explosive mood symptoms, and assess whether single drug therapy was effectively used in treatment of both conditions.

Methods: A retrospective chart review was conducted in a tertiary care pediatric facility. Records sufficient to confirm diagnoses of mood disorder and epilepsy, and to assess treatment responses were included. Psychiatric diagnoses, symptoms, and treatment responses were rated independently by two mental health clinicians, one of whom was a board certified child psychiatrist. A board certified child neurologist specializing in epileptology confirmed epilepsy diagnoses and treatment ratings. Divalproex sodium and lamotrigine were highlighted by virtue of having FDA indications for treatment of partial seizures in adults and children, and for bipolar disorder in adults. Clinical improvement was noted if Clinical Global Impression Improvement (CGI-I) ratings were 1, 2, or 3 (1–7 scale).

Results: Thirty-eight (21 male, average age 10.4) patients were selected. Thirty had complex partial seizure disorder and eight had primary generalized seizure disorder. Half met DSM-IV criteria for Bipolar I Disorder; the other half had nonspecific mood disorder that included altered mood states but insufficient criteria for a Bipolar I diagnosis. Common mood disorder symptoms included impulsivity (37), psychomotor agitation (37), and explosive rage (28). Forty-two medication treatment trials with 11 different anticonvulsants were identified and rated. CGI-I ratings for seizure control did not significantly differ between drugs. Monotherapy was attempted in 30 instances. In the 20 cases where lamotrigine, divalproex sodium, or carabamazepine were used, CGI-I ratings for psychiatric symptoms were better than for the other 10 cases ($p = 0.03$). Use of divalproex sodium (15) or lamotrigine (6) either in single or combination treatment was associated with psychiatric improvement ($p = 0.016$). Divalproex sodium used either as monotherapy or adjunctive therapy was associated with greater clinical improvement as compared to all other medications ($p = 0.03$).

Conclusions: In children with epilepsy and bipolar mood disorder symptoms, use of anticonvulsants with adult bipolar FDA indications were associated with greater psychiatric improvement with no apparent difference in seizure control. Divalproex sodium, either as monotherapy or as adjunctive therapy was associated with greater psychiatric improvement as compared with other medications. In some cases, single anticonvulsants appeared to simultaneously treat both epilepsy and mood disorder symptoms. (Supported by grant from Abbott Laboratories, Inc.)

1.243
EFFECT OF INTRATHECAL BACLOFEN ON SEIZURE FREQUENCY IN CHILDREN WITH CEREBRAL PALSY

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Rationale: Intrathecal baclofen has been associated with the occurrence of epileptic seizures and status epilepticus in patients with multiple sclerosis (Schuele, 2004) and traumatic head injury (Kofler, 1994). Children with cerebral palsy (CP) are at increased risk for epileptic seizures and a recent study in 54 children with CP reported the new onset of seizures in 14% of children after initiation of oral baclofen therapy (Hansel, 2003). The goal of our study was to investigate the effect of intrathecal baclofen (ITB) therapy on seizure frequency in children with CP.

Methods: Data were obtained from the Pediatric Neurosurgery ITB database. The database contains records of all patients since 1996 with a diagnosis of CP who had an ITB pump implanted for the treatment of spasticity or dystonia. Patient who had no follow-up at our institution after the implantation were excluded (n = 5).

Results: Forty-two consecutive children, 30 male and 12 female, underwent implantation of a baclofen pump between 1996 and 2003 and were subsequently followed for a median of 38 months (range 5 to 89 months). Mean age at pump implantation was 10.8 years. Fourteen patients (33%) had a diagnosis of epilepsy prior to pump implantation with a median seizure frequency of 2 per year (<1/year to 5/day). Two patients had new events after initiation of ITB therapy: an 8 year old boy had an isolated seizure in the context of a febrile illness and a 9 year old girl with a past history of neonatal convulsions had two unprovoked seizures 6 and 11 months after pump implantation. These events were felt to be unrelated to the ITB therapy. No new seizure or increase in seizure frequency was seen in the remaining patients.

Conclusions: In our series of 42 children with cerebral palsy treated with intrathecal baclofen, we did not observe an increase in seizure frequency during a observation period of three and a half years. In patients with cerebral palsy, intrathecal baclofen does not appear to increase the risk of seizures as compared to oral baclofen.

1.244
QUALITY OF LIFE FOLLOWING HEMISPHERECTOMY FOR INTRACTABLE EPILEPSY

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Rationale: Given the elevated incidence of behavioral and adjustment problems in epilepsy relative to other chronic pediatric disorders, health-related quality of life (QL) is an important domain to assess. Furthermore, the use of surgical interventions to improve QL through reduced seizure frequency makes it a pertinent outcome to measure. Though QL has been evaluated following focal resection surgery in some samples, it has not been investigated in children receiving hemispherectomy or hemispherotomy (HE). When reported, cognitive and psychosocial outcomes appear mixed, but previous studies have used neither standardized measures of QL nor appropriate control groups. This study describes post-operative QL in a sample of HE patients using standardized instruments with established reliability and validity and appropriate surgical and non-surgical epilepsy controls.

Methods: Participants in the current study included a group (N = 14) of hemispherectomy/hemispherotomy (HE) patients, groups of temporal (N = 16) and frontal (N = 10) resection patients, as well as non-surgical pediatric epilepsy cases (N = 84). Parents of all participants completed the Impact of Childhood Illness Scale (ICI) and the Hague Restrictions in Epilepsy Scale (HARCES), at least 1 year post-operatively for surgical patients. On these scales, a lower score signifies a higher QOL.

Results: Generally speaking, temporal lobe resection patients had the lowest ICI and HARCES scores. HE patients had lower HARCES scores than frontal resection and non-surgical control patients, but all three groups showed similar ICI scores. In all surgical groups, post-operative seizure frequency (Engels classification) was moderately correlated with ICI scores and HARCES scores.

Conclusions: HE patients in our study had similar ICI QL scores to surgical and non-surgical controls, and *fewer* physical difficulties on the HARCES than non-surgical and frontal resection patients. This suggests that parents of HE patients perceive their children to have similar QL to other children with epilepsy. For all surgical patients, residual seizure frequency emerged as an important correlate of poor QL, and for all patients (including non-surgical cases), duration of illness was related to worse QL. These findings suggest that continued seizure activity has a significant negative impact on QL. (Supported by B.C. Medical Services Foundation and the Vancouver Foundation grants to the second author.)

1.245
LESION ON MRI IN CHILDREN WITH NEW-ONSET TEMPORAL LOBE EPILEPSY PREDICTS EPILEPSY SURGERY FOR REFRACTORY SEIZURES

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Rationale: There is a paucity of prospective data on outcome for children with new-onset temporal lobe epilepsy (TLE), particularly regarding intractability and the need for epilepsy surgery.

Methods: We previously characterized a cohort of 63 children with new-onset TLE (Neurology 1997; 49:960–8) and followed them prospectively. Age at seizure onset was 0.2–14 (median 6.4) years and mean delay from onset to recruitment was 1.2 years. MRI was performed at recruitment in 58 children; only CT in the remainder. Lesions on MRI were present in 23 children, presumptive diagnoses including tumor in 8, hippocampal sclerosis (HS) in 13, dysplasia in 1 and arachnoid cyst in 1. Three children with HS had dual pathology, additional lesions being porencephaly in 1, caudate atrophy in 1 and parieto-occipital atrophy in 1. Eighteen children had significant antecedents, including complicated febrile convulsions in 5 and cerebral infection in 5, 12/18 having HS. FSIQ ranged from 48–145 (mean 100). Seizure frequency at recruitment was daily in 9, weekly in 15, monthly in 26 and quarterly or less in 13. Children were reassessed approximately 5 and 10 years following recruitment, recognizing that refractory patients were more extensively reevaluated.

Results: 20/63 (32%) children had undergone epilepsy surgery. These children were aged 1.5–13 (median 7) years at seizure onset and 5.7–21 (median12) years at surgery. TLE duration prior to surgery was 0.3–14 (median 5.9) years. Nineteen children had lesions on MRI at recruitment; 1 child with apparent normal MRI at recruitment was diagnosed with tuberous sclerosis on repeat imaging. Surgery was temporal lobectomy in 13 and corticectomy or lesionectomy in 8. Histologically-confirmed lesions were HS in 7, DNET in 3, ganglioglioma in 2, astrocytoma in 2, cortical dysplasia in 6 and Rasmussen encephalitis in 1.

In the non-surgery group, only 4/42 had lesions on MRI ($p < 0.001$), all having refractory seizures. There were no significant differences between the surgery and non-surgery groups with respect to patient demographics, age at seizure onset, pretreatment seizure frequency or FSIQ.

Conclusions: Lesion on MRI predicts surgical treatment for seizure intractability in new-onset TLE in childhood. Demographic, seizure and intellectual factors are not predictive. (Supported by Neurological Foundation of New Zealand.)

1.246
SEIZURE FREEDOM IN LENNOX-GASTAUT SYNDROME

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Rationale: Lennox-Gastaut syndrome (LGS) is an epilepsy syndrome of childhood characterized by intractable generalized seizures, mental retardation, and slow spike-wave EEG findings. LGS is typically associated with poor neurologic outcome, however recent data suggest that some patients do well. To assess the prognosis of LGS we investigated the proportion of LGS patients who become seizure free and the duration of seizure freedom.

Methods: 46 patients were identified from the UVA Epilepsy Database who were coded as LGS and were confirmed to have generalized seizures, mental retardation, and slow spike-wave on at least one EEG. The database was queried to determine maximum, minimum and current seizure frequency for all seizure types including atonic, tonic,

atypical absence, and generalized tonic clonic (GTC) seizures. For those with current seizure frequency of zero, the duration of seizure freedom was obtained from chart review.

Results: The average age of the 46 patients meeting LGS criteria is 26.5 years. Average age of seizure onset is 3.22 years. Male:female ratio is 1.88:1. Etiology of LGS is symptomatic in 34.8% and cryptogenic in 65.2%. Mean current seizure frequency for all seizure types is 62.5 per month. Eight of the 46 LGS patients (17.4%) are currently seizure free. Average length of seizure freedom in these patients is 33.8 months (range 3–157 months), and 5 have been seizure free for greater than one year. Average age of the seizure free patients is 28.0 years and 62.5% are cryptogenic. The youngest seizure free patient is 7 years. For all LGS patients in the database, maximal atonic seizure frequency is 84.0 seizures per month and current frequency is 2.57 seizures per month ($p = 0.0008$). For tonic seizures, maximal seizure frequency is 191.1 seizures per month and current frequency is 24.1 seizures per month ($p = 0.0015$). For atypical absence seizures, maximal seizure frequency is 383.4 seizures per month and current frequency is 46.7 seizures per month ($p = 0.0114$). For GTC seizures, maximal seizure frequency is 40.3 seizures per month and current frequency is 3.25 seizures per month ($p = 0.0003$).

Conclusions: The frequency of seizures in LGS diminishes substantially over time in some patients with many patients becoming seizure free for long periods. The data suggest that the natural history of LGS is not uniformly severe.

1.247
LONG-TERM USE OF LEVETIRACETAM IN SEVERE CHILDHOOD ONSET EPILEPSY

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Rationale: There are only a few studies on the long-term use of levetiracetam (LEV), in children in particular. We report on 101 patients with severe childhood onset epilepsy who were treated with LEV and followed up at least 24 month.

Methods: 101 patients (ages 6 month to 36,8 years, mean age 11,2 years; 68 male) with intractable seizures were treated with LEV as add-on ($n = 95$; 94%) or mono-therapy ($n = 6$; 6%). 62 Patients (61%) had focal epilepsy, 30 (30%) had generalized epilepsy and 9 (9%) had an epilepsy which could not be classified. Average dose of LEV was 39,1 mg/kg/d (range 6- 70 mg/kg/d), concomitant anticonvulsants (AED) ranged from none to four and number of prior AEDs ranged from one to fifteen (median six). Seizure frequency was determined six weeks before therapy with LEV, and three month, six month and two years after starting the therapy with LEV. Responder were defined as a reduction of seizure frequency >50% in comparison to four weeks before starting the therapy with LEV and a lasting effect for at least five month

Results: Responder at six month were 43 (43%), of which 13 (30%) had side effects. After 24 month the responder in our group of patients with highly intractable childhood epilepsy were 13% ($n = 13$), of which seven patients (54%) had a focal epilepsy, five patients (38%)had a generalized epilepsy and there was one patient with a not classified epilepsy. Side effects occurred in 48 (48%) patients and were mainly sleepiness, aggressive behaviour and worsening of seizures. All side effects were reversible by discontinuing the therapy and this occurred mainly within the first three month($n = 34$; 34%).

Conclusions: The long-term retention rate of LEV in this group with difficult to treat childhood onset epilepsy was similiar to our experience with lamotrigin, topiramat and felbamat, but better than with tiagabin, gabapentin and vigabatrim in similiar patient groups (Zsótér A., Kluger G.,Holthausen H, Neuropediatrics 2004 data in print). LEV seems to be a safe drug and is easy to handle in this group of patients. (Supported by Ucb- Group.)

1.248
NEUROPATHOLOGICAL STUDY AND MRI FINDINGS IN A 17-MONTH-OLD PATIENT WITH ACUTE PRESENTATION OF HEMICONVULSION-HEMIPLEGIA EPILEPSY: A REPORT WITH VALUABLE PATHOPHYSIOLOGICAL IMPLICATIONS

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Rationale: The mechanisms underlying the Hemiconvulsion-Hemiplegia-Epilepsy (HHE) are unclear. The current proposed pathogenic mechanism is a neuronal injury induce by venous thrombosis and/or hypoxia. Previous abnormalities of the brain were suggested as underlying mechanism. We report a patient with HHE who presented acutely. Unfortunately, the patient died. With the data of neuroimaging and neuropathological studies, we discuss the possible pathophysiology of the HHE and possible therapeutic implications

Methods: A 17-months-old girl with 2 days history of fever and treatment with acetaminophen presented a prolonged status epilepticus. She had no particular medical history. The day of her referral, she was found by her mother to be unresponsive and having left hemiconvulsion. The patient was found in the morning (6 hours without surveillance). She was given diazepam, phenytoin, phenobarbital and thiopental who permitted to stop the seizure. She was intubated and transferred in pediatric intensive care unit. Initial EEG showed right predominant periodic spikes and slow spikes (1 Hz). Routine laboratory investigations and CSF analysis were normal. Cranial CT the day of admission revealed neither edema nor abnormal tissue densities. At day 2, a right hemiplegia was noted. The EEG revealed right pseudoperiodic spike-wave complexes. MRI performed 5 days after admission displayed an abnormally high signal in the right hemispheric white matter in the diffusion-weighted and T2-weighted images. At day 5, EEG was characterized by a progressive decrease of cortical activity. At day 6, the patient presented a decrease of blood pressure, an areactive coma without bulbar reflexes. The EEG confirmed the cerebral dead. A neuropathological study was performed (immunochemistery, ultrastuctural analysis)

Results: The neuropathological studies confirmed a right homogenous hemispheric edema. There were neither thrombus nor cellular inflammatory response. There was no malformation in limbic or cortical structures. We observed axonal damages in the right thalamus

Conclusions: The abnormalities in diffusion-weighted imaging indicate cytotoxic edema of the epileptic hemisphere confirmed by the neuropathological studies. The neuropathological studies suggest that the edema is responsible of neuronal death. In HHE, we suggest cell damages induce by edema as possible pathophysiological mechanism. The thalamic dysfunction induced by cell damages can be responsible of an disrutpion of thalamo-cortical circuit and can play a role in the latter epilepsy. In acute presentation, the use of anti-edema therapy should be discuss to prevent the cell injury.

The neuropathological studies will be presented in details.

1.249
RISK FACTORS FOR PSYCHOGENIC NON-EPILEPTIC SEIZURES IN CHILDREN AND ADOLESCENTS WITH EPILEPSY

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Rationale: Frequency of non-epileptic seizures in adults ranges between 17–30% (Lancman et al. 2001). Golden et al. (1985) found that 19% of adolescents with new-onset seizures had non-epileptic events. Several studies demonstrated two peaks: during adolescence and early adulthood. However, it must be emphasized that there is lack of data on children with psychiatric disorders, suggesting that children with non-epileptic events remain underdiagnosed. This study aimed to evaluate patients with psychogenic non-epileptic seizures (PNES) considering type, frequency and risk factors in order to enable early diagnosis and treatment, consequently avoiding iatrogenic complications.

Methods: All patients were referred to the Unit for Research and Diagnostic of Epilepsy and Psychiatric Disorders in Childhood. Seizures and epileptic syndromes were classified according to ILAE criteria. Patients were evaluated with a structured psychiatric anamnesis and classified according to DSM IV, CID 10 and KIDDIE-SADS. Risk factors such as head trauma; emotional, physical and/or sexual abuse; psychiatric

diagnoses and previous history of epilepsy were investigated by review of medical records and/or follow-up interviews.

Results: From a group of 69 patients (53.6%, male),with ages from 4 to18 years, we prospectively identified 20 (29%) children and adolescents under 18 years with a diagnosis of PNES, 12 of whom diagnosed by VEEG, and the remaining by direct observation of non-epileptic events. Ten patients were female. Two patients were under 6 years, 9 between 7 and 13 years, and 11 over 13 years. Mean age was of 12.8 years (SD 4.32). As to psychiatric diagnoses, 14 patients (70%) presented mood disorders (depression-anxiety), of which four with other associated diagnoses (3 with oppositional disorder and one with personality disorder), 3 (15%) with pure dissociative disorders, 2 (10%) with ADHD and one (5%) with oppositional disorder. History of abuse occurred in 3 cases. Eighteen patients (90%) had epilepsy (7 symptomatic, 9 cryptogenic, and 2 idiopathic) and eight patients(40%) had family history of epilepsy.

Conclusions: It is assumed that children have a lower risk for PNES than adults (Sahlholdt et al. 1993), leading to under diagnosis and consequent inadequate therapeutic approaches. Among our 20 patients with PNES the most common psychiatric diagnosis was depression. Personal and family history of epilepsy were strongly related factors. Patients in late childhood and adolescence had a higher risk for NES than younger children, although the latter could not be excluded. These features may identify a population in need of adequate therapy and may point out a risk for a long lasting pathology.

1.250

SCALP-RECORDED INTERICTAL PAROXYSMAL FAST ACTIVITY AS A SURROGATE MARKER OF EPILEPTIC CORTEX IN PEDIATRIC EPILEPSY AND EPILEPSY SURGERY

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Rationale: Recognized as an abnormal electroencephalographic EEG characteristic, paroxysmal fast activity (PFA) is typically a bilateral non-localizing finding associated with generalized tonic seizures in the Lennox-Gastaut Syndrome. The significance of focal PFA as a marker of epileptogenesis is not known. The purpose of this study was to determine if interictal PFA is a non-invasive surrogate marker of the epileptic cortex in pediatric epilepsy.

Methods: All video EEG (VEEG) of children were reviewed for the 2001 calendar year at UCLA (n = 260), and the location of interictal PFA and seizure onsets determined. In addition, whether PFA was capable of identifying new or previously unknown cortical regions of independent seizure generation was examined by investigating the relationship of contralateral PFA and post-hemispherectomy seizure outcome for all children at our institution from 2000 to 2003.

Results: Interictal PFA occurred exclusively in the sleep state. Interictal PFA was bilateral, focal, or multifocal, and co-localized with the seizure onset zone within the same VEEG, with a sensitivity of 90%, a specificity of 67%, and an accuracy of 83%. In post-hemispherectomy children, the presence of preoperative PFA contralateral to the side resected predicted post-surgery epilepsy, with a sensitivity of 83%, specificity of 80%, and accuracy of 81%.

Conclusions: We found a strong association between the locations of interictal scalp-recorded PFA and seizure onset zones. Furthermore, PFA in the contralateral hemisphere predicted, preoperatively, who was at risk for post-operative epilepsy in our post-hemispherectomy children. Both of our findings validate the potential of interictal PFA as a non-invasive surrogate marker of the epileptic cortex in pediatric epilepsy and epilepsy surgery patients. (Supported by RO1 NS38992 to G.W.M.)

1.251

MALFORMATIONS OF CORTICAL DEVELOPMENT AND EPILEPSY: EVALUATION OF 101 CASES

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Rationale: Patients with malformations of cortical development (MCD) present with a wide spectrum of clinical manifestations ranging from asymptomatic cases to those with epilepsy and developmental problems. Advanced neuroimaging studies have been helpful in better defining MCD. We evaluated the clinical, EEG and neuroimaging features in patients with MCD.

Methods: We studied 101 patients with MCD between 01.01.2002–01.11.2004 at Hacettepe University Children's Hospital Department of Pediatric Neurology. All patients underwent neurological evaluation with detailed medical and family history, and neuropsychological evaluation. Routine EEG, and MRI were obtained.

Results: Age at the time of evaluation ranged between 1 month and 19 years of age (mean: 6.1± 4.4 years). Mean age at the time of the diagnosis was 4.3±4.0 years. Fifty-four patients were diagnosed with polymicrogyria (PMG), 23 with lissencephaly, 12 with schizencephaly, and 12 with heterotopia. Parents were relatives in 31.7% of the cases; consanguinity was most common in lissencephaly, and in MCDs with diffuse/bilateral involvement. Initial clinical presentation was seizures (61.4%), developmental delays (12.9%), and microcephaly (9.9%). Neurological evaluation revealed most severe abnormalities in patients with lissencephaly, and relatively better outcome in patients with heterotopias. 71.3% of patients had epilepsy; overall 32.7% of patients had generalized seizures, 25.7% had complex partial seizures, and 11% had secondarily generalized seizures. Mean age at the onset of seizures was 2.7±3.4 years. The onset of epilepsy tended to be younger in patients with lissencephaly, and older in patients with heterotopias. Patients with heterotopias and PMG achieved better seizure control in comparison with other groups. 79.2% of the cases had abnormal EEG (56.3% epileptiform abnormality, 22.9% non-epileptiform abnormalities such as background slowing, focal features and asymmetry). 49.9% of the cases without epilepsy had an abnormal EEG. Mental retardation was seen in 68% of the cases, and was most severe in patients with lissencephaly. Patients with heterotopias were better compared to other groups with respect to cognitive functions.

Conclusions: Initial presentation and clinical course of patients with MCD is variable and seems to be correlated with the extent of cortical involvement. Epilepsy and mental retardation are most common problems. Most severe clinical outcome was seen in patients with lissencepahly. Better clinical delineation of patients with MCD may guide genotype-phenotype correlation studies. (Supported by by NIMH ICORTHA Fogarty International Mental Health and Developmental Disabilities (MH/DD)Research Training Program (D43TW05807) at Children's Hospital Boston, (D.Y.); PI: Kerim Munir, MD, MPH, DSc.)

1.252

INITIATION OF THE KETOGENIC DIET WITHOUT THE TRADITIONAL FASTING PERIOD

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Rationale: In 1921, R.M. Wilder, MD theorized that the ketosis and acidosis resulting from minimal caloric intake produced an anticonvulsant effect. In recent years the ketogenic diet has become a common therapy for children with intractable seizures. The classic ketogenic diet involves an initial period of starvation that is followed by a diet consisting of a 3:1 or 4:1 ratio of fat to carbohydrate and protein. During the fasting period, children may become hypoglycemic and hyperketotic leading to nausea, vomiting and irritability. These complications frequently impair the child's ability to consume the diet successfully, often requiring additional days in the hospital. At least one death has been reported during the fasting period. For these reasons, the ketogenic diet is initiated under inpatient supervision at our facility without the traditional fasting phase.

Methods: On the morning of admission, the child is allowed to eat his/her usual breakfast at home. Upon admission to the hospital, the child is fed ketogenic meals totaling 1/3 of his/her total daily caloric diet goal. On day 2 of admission, the child is fed 2/3 of his/her total daily caloric goal. Full calories are provided on day 3.

The medical charts of 50 consecutive children who consume their diets orally (vs. via feeding tube) were reviewed and the levels of urine

ketones registered for each of the three days was recorded. Ketone levels were measured with urinalysis reagent strips and indicated as negative, trace, small, moderate or large.

Results: By day 3 of ketogenic diet initiation, 100% (50) of the children had registered large ketones on urinalysis reagent strips. Complications including hypoglyemia and/or emesis occurred in less than 20% of children. The average inpatient stay for these 50 children was 3.2 days.

Conclusions: Our non-fasting protocol has allowed a smooth transition to the ketogenic diet while minimizing complications and inpatient hospital days.

Clinical Epilepsy—All Ages 1

1.253
LEVETIRACETAM, A SUBSTITUTE FOR ANTIEPILEPTIC RELATED RASH

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Rationale: Antiepileptic drugs (AEDs) with aromatic ring structures such as phenytoin, carbamazepine, and oxcarbazepine are known to cause allergic rashes in 4–10% of patients within the first month of treatment. Although the rash of a serious hypersensitivity reaction occurs in 1–4 in 10,000, rash is a major reason for discontinuing these drugs. Lamictal introduced in the 1990s has also been associated with a rash in the first few months. The incidence however has declined with slow titration and a serious hypersensitivity reaction is also uncommon.

Since the introduction of levetiracetam, this broad spectrum AED offers an effective substitute for those who develop benzene ring related rashes as well as lamictal rashes. Levetiracetam is well tolerated, is rarely associated with a rash, and avoids hepatic metabolism and multiple drug-drug interactions. In addition, it can be utilized effectively for sudden oral loading.

Methods: Adult and pediatric patients who developed benzene ring or lamictal associated rashes, were loaded with levetiracetam as a substitute AED to prevent breakthrough seizures and avoid worsening rash while limiting pharmacologic and metabolic complications.

Results: We report 2 adults and 3 children who developed AED associated rashes. These medications were abruptly stopped and levetiracetam was immediately introduced at a full maintenance dose without seizures occurring; 3 grams in the adult cases and 1 gram in the pediatric cases. One young adult remains seizure free three years later after having a drug rash to phenytoin and oxcarbazepine. The other young adult tolerated levetiracetam substituting for lamictal for partial onset epilepsy with infrequent breakthrough seizures. The three children had partial onset epilepsy and rashes to oxcarbazepine (2) and carbamazepine (1). One patient remained seizure free on the initial dose, while two patients required a dosage adjustment to 1500 mg per day and now are seizure free for greater than one year.

Conclusions: In conclusion, we propose that levetiracetam is an effective broad spectrum medication which may be substituted for AED related rashes. Levetiracetam offers a means for rapid oral loading without fear of worsening rash or harmful pharmacological or metabolic interactions.

1.254
TOLERABILITY OF RAPID INITIATION AND TITRATION OF VAGUS NERVE STIMULATION (VNS)

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Rationale: There is currently no standard protocol for initiation and titration of VNS. In published literature, titration is often completed over multiple outpatient visits spanning up to several months. However, slow titration may delay effective therapy and may increase costs. We have traditionally performed more rapid titration over one visit and report our experience.

Methods: We performed a retrospective chart review on 64 patients who had initial ramp-up of a first VNS device. Replacement VNS was excluded. Patients were separated into two groups, those whose stimulus had not yet been turned on and those whose stimulus was turned on to 0.25 mA in the operating room. Data collected from each chart included gender, age at implant, time between each 0.25 mA increase in stimulation, adverse effects reported during steps of ramp-up, whether the device was titrated back due to adverse effects, the final discharge stimulus and the total amount of time spent for the visit.

Results: There were 36 men and 28 women, with a mean age of 33 ± 13 years (median 31, range 8–68). All patients received standard parameter settings of 500 μs pulse width, 30 s on, 5 minutes off. Forty-six patients who started with 0.00 mA achieved a final output current of 0.76 ± 0.28 mA (median 0.75, range 0.25–1.50), accomplished over 37 ± 45 min (median 19, range 1–213). Two of the patients did not have total programming time recorded but were discharged at 1.00 mA in one visit. The mean interval was 9 min for the 2nd increase (0.50 mA), 23 min for 3rd increase (0.75 mA) and 34 min for the 4th increase (1.00 mA). Eighteen patients who started with 0.25 mA stimulation reached a mean final output current of 0.89 ± 0.32 mA (median 1.00, range 0.25–1.50), accomplished over 62 ± 78 min (median 50, range 1–270). This included one patient without documented total programming time who achieved a final output current of 0.50 mA at the end of one session. Fifteen (23%) of the patients experienced symptoms requiring backward titration during ramp-up; the causes included cough (7), throat discomfort (4), facial discomfort (1), choking (1), ear pain (1), feeling scared (1). In 14 patients, reducing stimulus by 0.25 mA controlled the symptoms; in the remaining case the stimulus was reduced by 0.50 mA.

Conclusions: Our patients tolerated well the rapid titration of VNS and many achieved stimulation parameters within a desirable range in a single visit. Rapid titration may be beneficial to patient therapy with VNS, by achieving therapeutic stimulation levels without unnecessary delay and programming costs. This may be particularly useful for patients who must travel long distances for VNS programming.

1.255
CORRELATION OF ICTAL EEG LATERALIZATION AND THE LOCATION OF HYPOTHALAMIC HAMARTOMAS

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Rationale: Hypothalamic hamartomas (HHs) are rare developmental abnormalities that cause various types of seizures including gelastic seizures. These seizures are often refractory to medical treatment, and patients undergo extensive evaluations in order to identify definite seizure foci. Surgical resection of HH has proven to be highly effective, especially when the lesion is completely disconnected from the attached hypothalamus. It is also found that the HHs are predominantly attached to one side of hypothalamus. Thus, it is important to identify the location of hamartomas in order to achieve successful seizure control with HH surgery. Ictal EEG data on patients with HHs was reviewed in order to determine whether video-EEG monitoring can reliably predict the attachment side of HHs.

Methods: From our database, 41 patients with HH who previously underwent surgical treatment were reviewed. Among these patients, data on presurgical video-EEG monitoring and brain MRI scans were evaluated when available. Information on ictal EEG changes, seizure localization, seizure outcome, and location of the HH was reviewed retrospectively.

Results: Twenty-three of 41 patients had previous video-EEG monitoring and all 41 patients had brain MRI scans. Detailed monitoring reports were available in 20 patients. Of these cases, 12 hamartomas were attached to the left hypothalamus and eight to the right. Ictal onset was infrequently lateralized to the same side of HH attachment (10%), and majority of seizures were non-lateralizing (75%). The remaining 15% had alternating sides of ictal onset. No difference in seizure outcome was noted regardless of HH location or seizure lateralization.

Conclusions: Scalp video-EEG monitoring does not provide useful information in the presurgical evaluation of HH resection. Our study indicates that in 90% of the cases, ictal onset was either non-lateralizing or falsely lateralizing. Thus, ictal video-EEG monitoring has limited utility and should not influence the side of surgical resection and/or disconnection of the HH.

1.256

EPILEPSY IN SOUTH AMERICA: A SYSTEMATIC REVIEW OF ITS INCIDENCE AND PREVALENCE

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Rationale: Epilepsy is the most common serious neurological condition in the world. It is a very important cause of mortality and disability in developing countries. Because epidemiological and clinical characteristics of epilepsy vary according to regional factors, it is imperative to know the peculiarities of epilepsy in South America.

Methods: We used MEDLINE and LILACS (The Latin-American and Caribbean biomedical database) to search and identify community-based studies including information on epilepsy in South America. Community-based studies were included if data were collected through standardized questionnaires and if raw population numbers were available for data confirmation. Age adjustments were described as originally reported.

Results: Twenty-six papers provided information on the epidemiology of epilepsy. Community-based studies showed crude epilepsy prevalence rates ranging from 3.7 (in urban areas) to 33.0 (in rural areas) per 1000 and annually incidence rates from 11.3 to 19 per 1000. Colombia and Brazil are the countries with most of the epidemiological information. Information does not exist for Paraguay, Peru, Venezuela, and the Guyanas.

Conclusions: Even though, epilepsy has been poorly studied in some areas of South America, and infectious diseases, especially parasitic diseases are most common in this region of the globe, available data suggest that the prevalence and incidence of epilepsy in some countries are not too dissimilar to the ones in developing countries.

1.257

CHARACTERIZATION OF GLIONEURONAL LESIONS ASSOCIATED WITH CHRONIC INTRACTABLE EPILEPSY USING CD34: A NOVEL DIAGNOSTIC MARKER

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Rationale: The spectrum of glioneuronal lesions underlying intractable epilepsies includes malformative pathologies like focal cortical dysplasia (FCD); and neoplastic lesions like gangliogliomas (GG) and dysembryoplastic neuroepithelial tumours (DNET). These glioneuronal lesions may occur either singly or as dual lesions having the presence of both malformative and neoplastic elements simultaneously. However, lacunae in knowledge exist in terms of the relationship between the malformative and neoplastic glioneuronal lesions. Recently CD34, a stem cell marker transiently expressed during early neuralation, has been identified in these tumours. We undertook this study to (i) evaluate the role of CD 34 as a diagnostic marker for glioneuronal lesions of epilepsy (GG, DNET and FCD), and (ii) to attempt to define the relationship and origin of various glioneuronal lesions associated with epilepsy, using CD 34 as a marker.

Methods: In the present study, we have examined tissue resected from twenty-six ($n = 26$) patients with medically intractable epilepsy associated with glioneuronal lesions (GG, DNET and CD). Immunohistochemical (IHC) staining was done with antibodies against CD34 antigen.

Results: Dysplastic neurons, which could not be identified on routine haematoxylin and eosin (HandE) staining, were highlighted by CD 34-immunostaining. FCDs showed solitary or small clusters of CD34-immunoreactive cells in 40% cases (2 out of 5). While isolated GGs showed immunoreactivity for CD 34 in only 25% (1 out of 4) cases, prominent immunoreactivity was observed in dual lesions (GG with FCD), with 80% (8 out of 10) cases showing positivity in GG areas and all 10 cases showing positivity in FCD areas. However, cases of DNET were largely negative for CD 34-immunoreactive cells, with only 33% (1out of 3) cases of dual lesions (DNET with FCD) showing positivity in the FCD areas. None of the adult control tissues and none of the specimen obtained from the developing brain, contained CD34-immunoreactive neural cells.

Conclusions: CD34 may, thus, represent a valuable marker for the diagnostic evaluation of neoplastic and/or malformative pathological changes in intractable epilepsy patients. The CD34 immunoreactivity of these lesions indicates an origin from dysplastic or undifferentiated neural precursors. Based on these findings, we propose a common origin of GG and FCD, from a bipotent precursor that undergoes abnormal glioneuronal development, while the cases of DNET possibly have a different origin.

1.258

THE EFFECT OF THE EPILEPSY SYNDROME ON THE ELECTROCLINICAL FEATURES OF TYPICAL ABSENCE SEIZURES

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Rationale: The electro-clinical features of typical absence seizures have been reported to differ according to the epilepsy syndrome in which they occur. Systematic studies of absence seizures in newly presenting untreated patients with IGE have not been performed, nor have confounding factors affecting the semiology been scrutinised.

Methods: 70 consecutive untreated children (aged 2–16 years) with newly presenting absence seizures were studied using video-EEG. Detailed electro-clinical analysis of the semiology and the ictal EEG was performed. A statistical model was used to correct for the confounding effects of state (awake, drowsing, sleep), provocation (hyperventilation, intermittent photic stimulation), epilepsy syndrome, age and seizure duration.

Results: 509 seizures were analysed in 70 children [Childhood absence Epilepsy (CAE) 37, CAE+photoparoxysmal response (PPR) 10, Juvenile Absence Epilepsy (JAE) 8, Juvenile Myoclonic Epilepsy (JME) 6, unclassified 9]. The epilepsy syndrome had a direct effect on the duration of the absence seizure, the number of spikes per wave and the presence of fragmentation of the discharge, but had no independent effect on the level of awareness of the child, the presence of eye opening or the presence of abnormal eyelid movement during the absence seizure. The age of the child, independent of the epilepsy syndrome, had an effect on the level of awareness, presence of eye opening and presence of fragmentation but not on the presence of abnormal eyelid movement, the duration of the seizure, or the maximal number of spikes per wave. The state or provocation the seizure occurred in as well as specific (unmeasured) features of the child, independently influenced the duration of the seizure, the level of awareness, the presence of eye opening, the presence of abnormal eyelid movements, the presence of fragmentation, and the maximal number of spikes per wave.

Conclusions: This study demonstrates that the electro-clinical features of typical absence seizures in an individual are influenced by a complex interaction of age, epilepsy syndrome, state in which the seizure occurred, provoking factors and other unique features of that individual that are genetically and environmentally determined. This suggest that the seizure semiology and electrographic features per se are of limited value in distinguishing between the different common idiopathic absence epilepsy syndromes.

1.259

SEIZURE AND EPILEPSY IN THE HOSPITALIZED PATIENTS OF TRENTO, ITALY: PREVALENCE AND CLINICAL FEATURES DURING FIVE YEARS

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Rationale: Patients presenting a first seizure are commonly hospitalized in order to achieve a better diagnosis. Moreover, even patients affected by chronic active epilepsy may be occasionally admitted for therapy changes, intractable seizures, and so on. The main purpose of this study was to determine the characteristics of patients with a discharge diagnosis of seizure and epilepsy. To also establish the period prevalence of seizure and epilepsy according to age groups.

Methods: We conducted a descriptive and retrospective study based on the discharge code registry of patients with a diagnosis of isolated and recurrent seizures who were attended in all Hospitals of the area between January 1998 and December 2002. Moreover, we reviewed in detail all medical discharge reports of patients with seizures admitted in our Clinic between 1998 and 2002. Patient's demographic data were screened and patients residing outside the Trento Province were excluded. The population census of 2002 was used to calculate the period prevalence of epilepsy.

Results: A total of 15 Trento Province Hospitals were involved in the study. Between 1998 and 2002, 2412 (1302 females and 1110 males) patients were hospitalized and discharged with a diagnosis of seizure and epilepsy. Age of patients ranged from 2 months to 98 years old (mean: female, 59 yrs; men, 56 yrs). In more than one half (58.8%) patient age was > 50 year old. Age at seizure onset varied from 2 months to 95 years old. Epilepsy was partial in 71.5% and generalized in 25.5% cases. In 3% of patients a well-defined epilepsy diagnosis was not possible. A poor correlation between actual epileptic events and related medical discharge report codes was found in our hospitalized patients. The period prevalence rate of epilepsy in 2002 (January to December) is 1.3 in 1000.

Conclusions: The prevalence rate of epilepsy in this Italian population was lower than what reported in other developed countries. It is likely that our study could represent an underestimation of the true epilepsy prevalence in Trento. One of the reasons of this underestimation may be due to the methodological approach (single method). However, other reasons need to be considered, such as a poor attention on discharge coding procedures for epidemiological purpose.

1.260

HEMISHERIC LANGUAGE DOMINANCE IN PATIENTS WITH FOCAL EPILEPSIES: DISTRIBUTED SOURCE VERSUS SINGLE DIPOLE MODEL FROM NEUROMAGNETIC FIELDS

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Rationale: Previously, we described using magnetoencephalography (MEG) as a non-invasive tool for determination of hemispheric language dominance (HLD)using a single dipole model [1]. This study further investigated HLD with MEG in 24 right-handed pts with medically intractable focal epilepsies. We separately calculated the Laterality Index (LI) based on dipole counting and Dynamic Statistical Parametric Maps (dSPM) with a visual language paradigm.

Methods: 24 pts aged 13–52 years were studied using 306-channel MEG and 70-channel EEG (Elekta-Neuromag). Some pts were included in a previous report [2]. Visual word stimuli were presented. Equivalent Current Dipoles (ECD) on a spherical head model were fitted using sequential single dipole fitting with a time range of 150ms–600ms and 1ms steps. Only dipoles with a goodness of fit (GOF) >70% were displayed for analysis. The LI was calculated using for each pt using the formula: LI = (L-R)/(L+R).

Minimum norm estimates (MNE) and dSPM [3] were constrained to cortical surface, with loose orientation constraint and noise normalization. The LI was calculated using: LI = (L-R)/(L + R), where L & R = area of activated cortex.

Results: ECD: 15/24 pts (62.5%) showed left HLD. Three pts showed right HLD (12.5%). 6 pts (25%) showed a Bilateral(LI = -0.1-+0.1) HLD. One pt with right HLD suffered from left HE and 2 suffered from right HE.

Using dSPM the results were comparable, but were highly dependent upon the thresholding used for the statistical analysis. 11/24 pts had the WADA test preformed 8 were left dominant result and 5 showed left HLD with MEG analysis (Fig. 1).

Three of the Bilateral HLD pts had the WADA test preformed and the results were all left. One pt had a right WADA test result and the MEG was also Right HLD.

10/15 left HLD pts suffered from left hemisphere epilepsy (HE), five from right HE. 1/10 pts with Left HE and a Left LI with MEG showed an inconclusive WADA test result.

Conclusions: ECD counting and dSPM current summation are promising methods in determination of HLD. The dSPM method requires the calculation of statistics with the use of a properly chosen statistical threshold.

REFERENCE

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FIG 1a

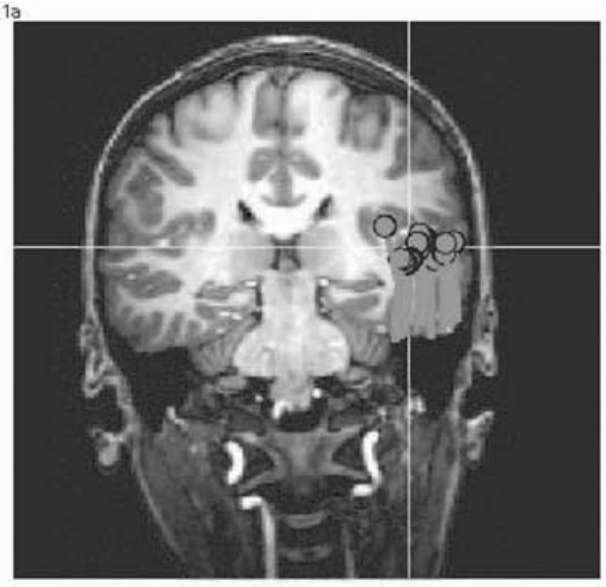
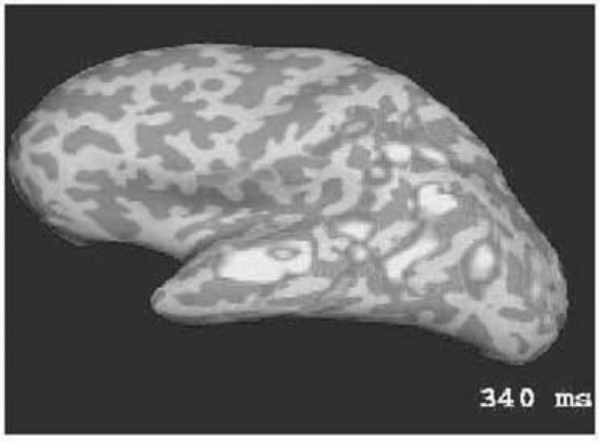


FIG 1b



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1.261
TENUOUS PHOTOSENSITIVITY IN IDIOPATHIC GENERALIZED EPILEPSY
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Rationale: Photosensitive patients may constitute an underreported number of cases. This fact can be due to the ineffectiveness of appropriate testing during EEG. We report 4 patients with a very peculiar photosensitivity pattern recorded only with partial environmental illumination.

Methods: We report 4 patients who were referred consecutively in a period of 1 month for routine EEG in a secondary care university center and presented generalized discharges precipitated by eye closure in partial environmental illumination.

Results: Four healthy female patients aged 12–16yr., who presented new-onset epileptic fits, characterized by generalized tonic-clonic seizures in three and typical absence seizures in one, were referred for EEG examination. All of them had generalized discharges consisting of irregular spike-wave activity predominating in occipital areas after eye-closure in partial illuminated environment. Only one, who was taking phenobarbital, had photoparoxystic response and the other three were not receiving antiepileptic drugs, including one that was in the puerperal period. No discharges were elicited after eye closure in total darkness.

Conclusions: Although photosensitivity is rare, the increase of sensibility of the EEG with single tasks such different intensity light stimulation, may grow the number of reported cases, improve diagnostic approach and select patients for genetic studies. Seasonal factors may play a role in precipitation seizures in some photosensitive patients.

1.262
RELATIVE IMPACT OF THE SOURCE OF STUDY POPULATION ON THE REPORTED INCIDENCE OF SUDEP: A SYSTEMATIC REVIEW
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Rationale: The mortality of individuals with epilepsy is 2–3 times that of the general population. This is attributable to underlying diseases and to epilepsy itself. Sudden unexpected death in epilepsy (SUDEP), an important epilepsy-related cause of death, has recently aroused interest. The reported incidence varies substantially among studies.

Objective: To analyze the importance of the source of study population, as compared to other variables, on the estimates of incidence of SUDEP, using a rigorous systematic review process.

Data Sources: An expert in library resources and electronic databases searched the Medline, Index Medicus, and Cochrane databases. We also searched bibliographies of pertinent review and original articles, book chapters and expert consultation. **Study selection.** Two reviewers independently applied the following inclusion criteria: retrospective and prospective cohort studies without age limitation, containing extractable information about incidence. We excluded duplicate publications. We assessed the methodological quality of individual studies using established principles for epidemiological research. Two investigators independently extracted data, and resolved disagreements through discussion.

Results: Of 404 initial articles, 74 potentially eligible studies were reviewed in full text, and 31 fulfilled eligibility criteria. There was substantial between-study variability in the methodology, source of study populations, and definition of SUDEP. The annual incidence of SUDEP ranged from 0.09:1000 to 10:1000. Source of study population strongly correlated with incidence, which was higher in studies from epilepsy clinics and referral centers (1.2:1000 to 10:1000) than in those from the general population (0.09:1000 to 1.3:1000). The incidence ranged from 1:1000 to 10:1000in patients with mental retardation, and from 0:1000 to 0.1:1000 in children. Risk factors for SUDEP were inconsistent among studies.

Conclusions: Although there is substantial variability in the incidence of SUDEP among different patient populations, common themes emerge. SUDEP was rare in children On the other hand, SUDEP was more frequent in epilepsy clinics or surgery programs than in coroners reports and general population, suggesting that patients with more intractable and more severe epilepsy may have a higher risk of SUDEP. The role of methodological differences and study populations is explored.

1.263
PREDICTORS OF COGNITIVE SIDE EFFECTS IN PATIENTS WITH EPILEPSY
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Rationale: Cognitive side effects (CSEs) occur in many patients taking antepileptic drugs (AEDs). The predictors of these side effects, however, are unknown.

Methods: As part of the Columbia AED database, we reviewed patient background, medical history, medication, efficacy, and side effects for 1286 patients with epilepsy. We reviewed the incidence of cognitive side effects in the 1222 patients on 8630 AED regimens for which we have detailed information since January 1, 2000. CSEs included were aphasia, poor concentration, poor memory, psychomotor slowing, cognitive slowing, confusion/disorientation, or word finding difficulty. Using univariate chi-square tests, we analyzed the association of 91 variables in predicting the incidence of CSEs and the occurrence of CSEs that led to a medication or dosage change. Significance was set at $p < 0.01$.

Results: Of 1222 patients, 285 (23.3%) experienced CSEs and 144 (11.8%) experienced CSEs that led to a dosage or medication change. The two most significant risk factors for cognitive side effects were use of topiramate ($p < 0.001$) and a history of CNS infection ($p < 0.01$). Less significant risk factors included simple partial seizures and use of oxcarbazepine, phenytoin or zonisamide. The factors that were most associated with a decreased risk of CSEs were juvenile myoclonic epilepsy ($p < 0.01$) and use of lamotrigine ($p < 0.01$); static encephalopathy was also associated with a decreased risk of CSEs.

Conclusions: Patients with epilepsy are most likely to experience cognitive side effects if they have a history of CNS infection or if they are receiving topiramate. Patients are least likely to experience CSEs if they have juvenile myoclonic epilepsy or if they are receiving lamotrigine. (Supported by The Columbia AED Database is supported by Elan, GlaxoSmithKline, Ortho McNeill, Pfizer, and UCB Pharma.)

1.264
INTRANASAL MIDAZOLAM USE FOR MANAGING STATUS EPILEPTICUS IN THE COMMUNITY
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Rationale: Status epilepticus remains a medical emergency. Deinstitutionalisation and inclusion means people with epilepsy are more likly to have seizures in public. For 2 years we have trialled the use of intranasal midazolam (INM) to manage prolonged seizures in the community. The training package and protocols developed will be described. Evaluation of parent/carer preferences and perceptions of effectiveness with the use of both rectal valium (RD) and INM will be reported.

Methods: A protocol was developed to trial INM managing prolonged seizures in the community, initially in educational settings. Incorporating a formal seizure management training package, it was soon adopted by adult services in the community, parents and carers. Dose 0.2–0.3 mg/kg. The protocol specified INM would not be given in the community if the person had not safely had a previous dose of midazolam by any route. Plastic 5mg/1ml ampoules only, as drops could be administered directly into the nostrils from the inverted ampoule. An initial survey was distributed to parents and carers to determine acceptance of the use of INM, and perceived effectiveness of both RD and INM. Results of a more comprehensive evaluation will be available before the Annual Meting.

Results: Over 100 children and adults have now had prolonged seizures successfully managed with INM. In an initial survey of parents and carers trained to give INM, 37 had actually administered INM. Of 23 who had administered both RD and INM to manage prolonged seizures, 78.4% considered INM very effectice, compared with 39.1% for RD. Perceptions of time to take effect, within 2 minutes (32.4% INM, 8.7% RD). More than 10 minutes (17.4% RD, 0 INM). Preference, 74% INM, 4% RD, 22% either. Reasons given for preference for INM were ease of administration, and less intrusive.

Conclusions: RD and INM must be administered with caution, especially in the community. Status epilepticus carries significant morbidity not controlled within 30 minutes of onset. Even if access to ambulance services is fairly prompt, there is no guarantee an ambulance will arrive in time to control the seizure within 30 minutes, so relying on ambulance support alone may result in morbidity. There are also cost benefits. In our opinion, INM is a safe means of controlling prolonged seizures, providing the safeguards we have developed are followed - training in first aid and seizure management, a test dose before giving INM in the community, only using a 5mg in 1 ml plastic ampoule, and having the medical order clearly documented for all to follow.

1.265

EPILEPTIC FEATURES OF PATIENTS WITH UNILATERAL AND BILATERAL SCHIZENCEPHALY

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Rationale: The extent of cortical maldevelopment may correlate with the severity of clinical manifestation such as cognitive delay or motor dysfunction. The objective of this study was to investigate clinical features of epilepsy in patients with unilateral and bilateral schizencephaly.

Methods: We studied all patients with schizencephaly diagnosed by MRI in our University Hospital. The following data were assessed: presence of epilepsy, occurrence of status epilepticus and cluster of seizures, treatment with AED (monotherapy x polytherapy), seizure control, EEG abnormalities, and diagnosis of epileptic encephalopathy (mental retardation + uncontrolled seizures). Statistical analysis was performed using the chi-square and t-Student test.

Results: Forty-four patients were studied, 24 with unilateral cleft (GI) and 20 with bilateral clefts (GII). Age ranged from 1 to 37 years (mean = 10.6). Epilepsy was present in 15 (63%) patients of GI and in 11 (55%) of GII; history of status epilepticus occurred in 2 (13%) patients of GI and in 3 (27%) of GII; history of cluster of seizures occurred in 6 (40%) patients of GI and in 5 (45%) of GII; 8 (53%) patients of GI and 6 (50%) of GII were in monotherapy; 10 (67%) patients of GI and 7 (64%) of GII had seizures controlled with AED; EEG abnormalities occurred in 75% of the patients in GI and in 85% of GII; epileptic encephalopathy was diagnosed in 47% of the patients of GI and in 82% of GII. Statistical analysis showed no difference between the two groups.

Conclusions: The extent of the cortical maldevelopment in patients with schizencephaly does not correlate with the severity of the clinical and electrographic features of epilepsy.

1.266

RISK-TAKING BEHAVIOUR IN PATIENTS WITH EPILEPSY IN JUNIOR AND SENIOR HIGH SCHOOL IN NORWAY (THE AKERSHUS COUNTY HEALTH PROFILE FOR CHILDREN AND YOUTH STUDY)

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Rationale: Epilepsy in children and youth can be associated with psychosocial problems. Most studies have been performed in selected groups with difficult-to-treat-epilepsy. The aim of the present study was to assess risk-taking behaviour like drug abuse and tendency to criminal behaviour among children and youth with epilepsy in a population-based study.

Methods: The study was cross-sectional and based on questionnaires. The questionnaires were completed at school during a lesson. 10.924 questionnaires were administered to junior high school (age 13–16) and 13.420 to high school (age 16–19). Response rate was 86% in junior high school and 79% in high school.

Results: 241/19985 (1.2%) reported having epilepsy. Risk taking behaviour was more common in children with epilepsy compared to children without. We found significant higher use of cannabis (15.5% compared to 9.2%, $p < 0.001$), narcotic tablets (10.5% compared to 5.8%, $p = 0.003$) and narcotics intravenously (5% compared to 1%) among adolescents with epilepsy. We also found a significant increased tendency to criminal behaviour like breaking an entry to steal, in patients with epilepsy (11.2% compared to 5.5%, $p < 0.001$).

Conclusions: : In our population based study we found increased risk taking behaviour among children and youth with epilepsy compared to those without epilepsy. To explore this finding we are performing a more detailed analysis of the relation between different factors in relation to the epilepsy group and other groups of patients.

1.267

CHARACTERISTICS OF REFRACTORY JME

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Rationale: Juvenile myoclonic epilepsy (JME) is a relatively benign idiopathic generalized epilepsy with well-described clinical and EEG features. Good response to treatment is considered one of its hallmarks with various cohorts reporting 82–97% of patients with good seizure control and only 10–15% as refractory. We examined the proportion of refractory JME patients in our clinic and hypothesized that there are clinical and EEG traits that are associated with refractoriness.

Methods: Patients with JME were identified from the 1702 cases in the University of Virginia epilepsy database and presence of generalized poly-spike wave and generalized seizures were confirmed from medical records. Demographic, clinical and EEG data were collected. Patients were classified as non-refractory (NR) if they had been seizure free for at least one year at the time of their last visit and as refractory (R) if they continued to have seizures of any type despite having tried valproate. They were subdivided into those with a history of high versus low monthly seizure frequency. History of a maximum monthly seizure frequency >10 was deemed high for myoclonic (MYO) and absence (ABS) seizures and >3 for generalized tonic-clonic seizures (GTC). If a specific seizure type was not present they were deemed null. Other features analyzed were age of epilepsy onset, seizure types present, EEG features, psychiatric comorbidity, evolution from other syndromes, and family history of seizures.

Results: A diagnosis of JME was identified in 75 patients out of 239 with idiopathic generalized epilepsy (31% of all IGE). Mean age was 32 ± 12 and 40 (53%) were women. Mean age of onset was 14 ± 5. Despite AED use, 32 patients continued to report seizures. Questionable compliance or inadequate AED use was found in 8, leaving 23 (30%) who were truly refractory. Prior history of high monthly seizure frequency was more frequent in R than NR patients for MYO seizures (69.6% vs 36.5%, $p = 0.017$) and GTC seizures (52.2% vs 21.1%, $p = 0.03$). Other features including photoconvulsive response, family history of seizures, psychiatric comorbidity and combinations of seizure types present were not statistically different between groups.

Conclusions: We found a relatively high proportion of JME patients (30%) that continued to have seizures despite use of the most accepted drug for their syndrome. Although some referral bias is likely, this emphasizes that some patients with JME are refractory. A history of high frequency of MYO or GTC seizures increased the chances of being refractory later. In contrast to previous reports, we did not find that psychiatric comorbidity or seizure type combinations increased the chance of refractoriness. We did not find features that helped predict responsiveness to treatment. Further studies are warranted to investigate whether genetic or neurophysiologic factors account for a lack of response to treatment.

1.268

SOURCE ANALYSIS OF SIMULTANEOUS EEG-MEG RECORDINGS: INTERICTAL VERSUS ICTAL ACTIVITIES

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Rationale: Monitoring of spontaneous seizures with video-EEG is regarded as an important aspect of the pre-surgical workup of epilepsy patients. This study investigated the differences in the informational content of ictal versus interictal EEG-MEG data, recorded simultaneously, using dipole localization and brain source montages in the non-invasive delineation of epileptogenic areas.

Methods: Data were obtained from two Neuromag(tm) systems that allowed for co-registration of 306/122 MEG with up to 60 EEG channels. Seizures and interictal spikes were recorded in four patients during one hour sessions. Two patients had confirmed temporal and two extra-temporal lobe epilepsy. Brain source montages were derived using individual dipole analysis (BESA) to monitor the on-going brain activity in different brain regions independently for EEG and MEG. The region of initial seizure activity in source montages was compared to the dipole localizations during spike and seizure onset for EEG and MEG.

Results: EEG and MEG showed consistent focal unilateral onset in the right and left temporal-basal source channels in cases 1 and 2, respectively. This was confirmed by temporal-basal dipole sources that were localized consistently using either the interictal EEG or MEG. Seizure onset was more difficult to determine in the two extratemporal cases. The MRI of patient 3 showed a cortical dysplasia in the left posterior insula. During combined EEG-MEG recording (cortical lesion in left posterior insula) one seizure was observed with rhythmic 2.4 Hz onset discharges. MEG localized the 2.4 Hz activity to the border zone of the lesion. In EEG it appeared in the left parietal source montage, but dipole localization was imprecise. In the forth patient, seizure onset was seen with EEG flattening followed by mid-frontal 3.4 Hz discharges. After averaging, initial MEG and EEG dipoles localized to the left mid-frontal cortex. Interictal MEG and EEG activity was unclear in case 3 and confirmatory in case 4.

Conclusions: Video-monitored EEGs of seizures do not always provide precise electro-clinical correlates and are frequently contaminated by muscle and movement artifact. Brain source montages applied to the scalp EEG can substantially improve the visibility of focal spike and seizure activities. But cases remain when the EEG is difficult to interpret, provides only a partial picture of epileptogenesis, and may, thereby, give potentially misleading information. Detailed work-up of co-registered EEG-MEG can provide information which is not available from either modality alone and helps in determining how many different areas of potential epileptogenicity exist in a patient.

1.269

DIAZEPAM RECTAL GEL FOR THE TREATMENT OF BREAKTHROUGH SEIZURES IN PATIENTS WITH INTRATHECAL BACLOFEN PUMPS

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Rationale: Many patients experiencing spasticity associated with brain and spinal injuries, cerebral palsy, and multiple sclerosis may also have epilepsy diagnoses. Breakthrough seizures, if left untreated, may pose a serious health risk, potentially causing long-term neuronal damage. For patients living in rural or medically underserved areas, a one-way trip to the clinic could take from 2 to 5 hours. Therefore, a rescue alternative is critical for seizure emergencies. Diazepam rectal gel, a portable rescue medication, has demonstrated efficacy in the at-home management of breakthrough seizures for various populations who experience seizures. Our clinic also uses it as part of a rescue protocol for pump refill and pump failure emergencies in patients with intrathecal baclofen (ITB) pumps. Diazepam rectal gel may play a critical role in providing effective treatment for both seizure and pump emergencies for this group of patients. The current study investigated the efficacy of diazepam rectal gel in treating breakthrough seizures in patients who have ITB pumps.

Methods: We reviewed the charts of patients with ITB pumps, identified patients with a diagnosis of epilepsy, and examined their use of diazepam rectal gel treatment for seizure emergencies.

Results: In this primarily pediatric population, of 80 patients treated with ITB, 24 also had epilepsy diagnoses. Ten patients were female, 14 male; mean patient age was 14.3 years (range, 7–23 years). Among these patients with head injury, cerebral palsy, and static encephalopathy, seizure diagnoses were generalized tonic-clinic (17 patients), complex partial (6), and absence (1). Eighteen of the 24 patients experienced seizure emergencies and were treated with diazepam rectal gel. For all 18 patients, diazepam rectal gel successfully terminated the seizure. No adverse events were reported.

Conclusions: Diazepam rectal gel effectively terminated breakthrough seizures in this patient population. Because it may be administered at home by nonmedically trained caregivers, diazepam rectal gel provides an especially valuable management option for breakthrough seizures in these patients. Given that many of the patients live in rural and medically underserved communities where travel to the nearest hospital may take several hours, a portable rescue medication for seizure emergencies is vitally important. (Supported by Xcel Pharmaceuticals.)

1.270

CREATING AN EVIDENCE-BASED PROTOCOL FOR STATUS EPILEPTICUS MANAGEMENT

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Rationale: Rapid termination of status epilepticus (SE) significantly impacts SE outcome. Despite several recent large trials for SE treatment, there are no evidence based guidelines using a systematic analysis for best initial SE therapy. This is important because medical practitioners are often unaware as to which initial AED is best for terminating SE in adults and children.

Methods: Medline, Index Medicus, CINAHL, EMBASE databases were searched along with hand searching for published abstracts in both English language and non-English journals for trials involving randomization of patients with newly diagnosed SE into various medication regimens as initial treatment. Refractory SE (RSE) Trials were excluded and trials were divided by age so that separate analyses could be performed for adults and children. Three reviewers independently extracted data and assessed trial quality. Relative risk (RR) with 95% confidence intervals (CI) were calculated for each trial. Summary RR and 95% CI for dichotomous data were tabulated using a random effects model. A test of statistical heterogeneity was conducted for each pooled RR calculation. Three analyses were performed: use of any benzodiazepine (BZD) versus no BZD; lorazepam versus diazepam; and diazepam and phenytoin versus phenobarbital as initial treatment. A number needed to treat (NNT) analysis with 95% CI were performed as a subanalysis for adult patients.

Results: Of 2024 articles found in the initial search, 13 papers were identified as studies. 8 trials met inclusion criteria; 4 in adults and 4 in children. The four trials in adults represented 758 patients with newly diagnosed SE and randomization to lorazepam, diazepam, diazepam and phenytoin or phenobarbital. Not surprisingly, the use of any BZD resulted in greater success than not using a BZD (RR = 0.78; 95% CI, 0.66 to 0.92). The NNT was 8 for BZD. Lorazepam is better at terminating SE than diazepam (RR = 0.68; 95% CI, 0.49 to 0.96) The NNT was 7 favoring lorazepam suggesting that for every 7 SE patients in which lorazepam is used, one case of failing to stop SE by diazepam is prevented. There was no significant difference between diazepam and phenytoin versus phenobarbital. (RR = 1.02; 95% CI, 0.81 to 1.28)

The 4 pediatric trials represented 237 patients randomized to rectal or IV diazepam, IM midazolam or buccal midazolam; however there was significant heterogeneity between the studies ($p = 0.01$). Therefore combining data from these trials is inappropriate. However, there were no reported significant differences between any of the benzodiazepines in terminating SE.

Conclusions: Lorazepam followed by either phenytoin or phenobarbital are the best initial choice for SE management in adults. Any choice of rectal, IV diazepam or buccal, IM midazolam is useful initially in children with SE. A trial for RSE is needed to complete an evidence based protocol for SE. Guidelines need to be disseminated to all medical practitioners who manage SE initially. (Supported by Mayo School of Continuing Medical Education.)

1.271
STATIONARY AND RECURRENT SOURCE DISTRIBUTIONS IN THE HIPPOCAMPUS DURING SLEEP
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Rationale: Depending on the vigilance state different brain areas are active. Normally, an exact localization is possible only from short (few ms) averaged segments by means of computational demanding methods such as dipole fitting. In contrast to this, we used principle component analysis (PCA) and independent component analysis (ICA) to approximate the global source distribution, i.e., the origins of the postsynaptic potentials, from stationary segments (20 seconds) of the EEG. We analyzed intracranial EEG recordings of six patients with mesial temporal lobe epilepsy. The obtained map of the source landscape is then assigned to a distinct vigilance state. We investigated whether a constant and recurrent distribution of the sources in the hippocampus can be found for the same vigilance state. Furthermore, we tried to identify differences between the focal and non-focal side.

Methods: We used PCA and ICA to transform a multi-channel recording, e.g., EEG, into principle and most independent components, respectively. The matrix obtained from this transform contains the information about the source distribution. Subsequently we derived a similarity measure which shows the change of this transform matrix over time and therefore reveals the temporal activations of the source. We calculated these similarity values between all segments (from different times) resulting in an image which exhibits typically a chess pattern. Edges of the squares in these images correspond to a change in the vigilance state.

Results: We applied the algorithms on intracranial EEG of six patients with unilateral mesial temporal lobe epilepsy which were recorded continuously during night. A sleep stage classification was carried out by an expert EEG reader using a simultaneously recorded surface EEG. In the obtained images we found:

a.) pronounced blocks (many segments) with constant source distributions
b.) beginning and ending of these blocks correspond to a change of the sleep stage
c.) same sleep stages show the same source distributions during the whole night

As for the comparison of PCA and ICA we obtained similar results for both techniques. However, because ICA is a more sophisticated approach the data must fulfil also more assumptions what is not always provided. So PCA is normally preferred.

Conclusions: Our method provides a very fast and robust way to identify changes of the vigilance state from the analysis of multi-channel EEG. For all patients we found stationary and exactly recurrent source distributions which were strongly correlated with the sleep stages obtained from surface EEG. This means that always the same sources are active in the same sleep stages. Furthermore, we found predominately stronger correlation of our results with the sleep stages classification for the left hemisphere. Aspects of further investigations should concern the identification of vigilance stages during the day and the possible differences between focal and non-focal hemisphere.

1.272
MRI-COMPATIBLE EEG ELECTRODE SYSTEM USE IN EPILEPSY MONITORING UNIT
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Rationale: To evaluate the efficacy of an Magnetic Resonance Imaging (MRI) Compatible EEG recording system in the Epilepsy Monitoring Unit.

Methods: Comparison of EEG recorded seizure data in 50 Epilepsy Monitoring Unit (EMU) patients with MRI compatible electroencephalogram (EEG) recording electrodes and 50 EMU patients without MRI compatible EEG recording electrodes. Only patients who underwent MRI after Epilepsy Unit EEG technologist scheduled work hours met criteria.

Results: 17/50 (34%) patients with MRI compatible recording electrodes had recorded clinical seizures, larval seizures or non-epileptic seizures, 9/17 (53%) had first recorded event. Of the 33/50 (66%) that did not have recorded seizures, 28/33 (85%) had no previous seizures recorded during EMU stay, 5/33 (15%) had previous seizures recorded. 13/50 (26%) had new information recorded apart from seizures. 19/50 (38%) patients without MRI compatible recording electrodes had seizures not recorded during MRI time frame, 5/19 (26%) had their first recorded event not recorded. 31/50 had no seizures missed, 17/31 (55%) had no previous events recorded and 14/31 (45%) previous events recorded. Only 1 patient (2%) had first and only seizure during EMU stay with EEG electrodes off for MRI scanning. The average length of stay for patients with MRI compatible recording electrodes was 9 days and patients without MRI compatible electrodes was 11 days.

Conclusions: MRI compatible recording electrodes allow an artefact-free recording in a 1.5 T MR scanner with average SAR less than or equal to 1.6 W/Kg. MRI compatible recording electrodes reduced the average length of stay, reduced patient's anxiety if electrodes to be removed for duration of time for MRI while on reduced anti-epileptic medications and captured 34% of clinical seizures, larval seizures or non-epileptic seizures which previously would have not been recorded. No seizures were missed on patients with MRI compatible recording electrodes and 26% of patients with MRI compatible recording electrodes had new data recorded during the MRI time frame. Patients requiring electrodes to be removed for MRI purposes with collodion remover/acetone and their reapplication immediately afterwards can result in painful abrasions of the scalp and/or infection.

1.273
ACIDOSIS AND STATUS EPILEPTICUS: ASSOCIATIONS AND EFFECTS
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Rationale: Animal studies suggest that acidosis is a metabolic consequence of convulsive status epilepticus (SE). This study examines the factors associated with acidosis in human SE cases, and its effect on mortality.

Methods: The population-based Richmond, Virginia, SE Database was used, and 455 SE cases with metabolic profiles during SE were identified. Acidosis was defined as serum bicarbonate level of <20 mEq/L. Multivariate analyses were performed to identify the predictors of acidosis, and to determine whether acidosis predicts mortality in the presence of the other variables. Parameters were: age, sex, race, SE type, etiology, location of SE onset, mortality, and the duration of seizure activity at the time the blood sample was drawn (time to lab). Similar analyses were performed on a subset of cases ($N = 296$) for which pH during SE was available.

Results: Time to lab was not associated with degree of acidosis. Acidosis (bicarbonate <20 mEq/L) occurred significantly more often in the setting of generalized convulsive SE (GCSE) (44%) compared with partial SE (17%) or nonconvulsive SE (26%) ($p < 0.002$). Mortality was significantly higher in acidotic cases (43%) than nonacidotic cases (35%) ($p < 0.05$). In the multivariate analysis, these were the only two variables that remained significantly associated with acidosis (Odds Ratio (O.R.) = 3.2 for GCSE vs. partial SE, and O.R. = 1.8 for fatal vs. nonfatal cases). In the analysis of mortality, acidosis remained a significant predictor (O.R. 2.0), along with etiology (hypoxia/anoxia), and age (O.R. = 1.5 per year of increasing age). Low pH (<7.2) was not an independent predictor of mortality associated with SE.

Conclusions: A minority of GCSE cases were acidotic, but acidosis was significantly more common in GCSE than in other types of SE. Low bicarbonate level independently predicted mortality in SE cases. (Supported by NIH P01-NS25630.)

1.274
THE COMORBIDITY OF EPILEPSY: A CANADIAN POPULATION HEALTH SURVEY
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Rationale: Experienced clinicians understand that patients with epilepsy have substantial comorbidity of chronic conditions. However, apart from psychiatric or psychological ailments, few data exist on the prevalence of chronic health conditions associated with epilepsy. We assessed the prevalence of self-reported chronic conditions associated with epilepsy in two omnibus population health surveys in Canada.

Methods: We analyzed data from the National Population Health Survey (NPHS, 49,000 respondents) and the Community Health Survey (CHS, 130,882 respondents). Both surveys used probabilistic sampling of the entire Canadian population and explored the presence of 19 common chronic conditions. These were ascertained through personal interviews asking one question. In the case of epilepsy the question was "Do you have epilepsy diagnosed by a health professional?" (NPHS), and "Do you have epilepsy?" (CHS). We obtained a risk ratio of the prevalence of chronic conditions in epilepsy versus that in the general population, calculated 95% confidence intervals around the risk ratios, and compared findings from both surveys

Results: Of 19 chronic conditions explored, 13 (68%) occurred significantly more frequently in epilepsy patients than in the general population (Risk ratio >1, with 95% CI excluding the null value). The chronic conditions with the highest prevalence in epilepsy patients (Risk ratio ≥ 2) were peptic ulcer disease, gastrointestinal illnesses, stroke, urinary incontinence, bowel disorders, chronic fatigue syndrome, migraine, chronic bronchitis and emphysema, and heart disease.

Conclusions: The self reported prevalence of chronic health problems is high in patients with epilepsy in the general population. In keeping with existing notions, stroke and migraine were more prevalent in patients with epilepsy than in the general population. However, we also found some associations not reported previously, such as a higher frequency of cardiac and pulmonary problems, chronic fatigue syndrome and gastrointestinal illnesses. We discuss methodological issues, interpretation and validity of findings.

1.275
OXCARBAZEPINE WITHDRAWAL SEIZURES DURING EPILEPSY MONITORING
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Rationale: It has been established that carbamazepine withdrawal is associated with more severe seizures than withdrawal of other classical antiepileptic drugs. Oxcarbazepine (OXC) has structural and some functional similarities to carbamazepine. It is not known if OXC is similar to carbamazepine in associated withdrawal seizures.

Methods: We identified all epilepsy patients admitted to the epilepsy monitoring unit (EMU) on OXC monotherapy between 2000 and 2004. As a control group, we identified all patients who were admitted to the EMU on phenytoin (PHT) monotherapy in the same period of time. AEDs were usually discontinued on day 1 or 2 of admission. For each patient we recorded pre-admission seizure frequency for each seizure type, as well as the number and type of seizures recorded in the EMU. We calculated seizure frequency for complex partial seizures (CPS) and generalized tonic clonic seizures (GTCS) before admission and during monitoring, and calculated the relative change in frequency for each seizure type. We compared the OXC and PHT groups for the above parameters.

Results: Twelve epilepsy patients were admitted to the EMU on OXC monotherapy and 11 on PHT monotherapy. Five patient in the OXC group had no prior history of GTCS; one of these had one during monitoring. Seven had prior GTCS and 4 of them had GTCS in the EMU. For the whole group there was a 59 fold relative increase in frequency of GTCS during monitoring. The average frequency of complex partial seizures surprisingly did not change. In the phenytoin group, there were 2 patients who never had GTCS. Only 3 patients had GTCS in the EMU, all of them with prior history of GTCS. Overall, there was a 10.6 fold relative increase in GTCS frequency and a 6.5 fold increase in CPS frequency in the EMU.

Conclusions: Oxcarbazepine withdrawal appears to be associated with a greater increase in GTCS frequency than phenytoin withdrawal. Oxcarbazepine withdrawal in the EMU should be handled with caution.

Human Imaging—Adult 1

1.276
DIRECTIONALLY ENCODED COLOR (DEC) MAPPING OF THE HIPPOCAMPAL FORMATION IN TEMPORAL LOBE EPILEPSY
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Rationale: Diffusion Tensor Imaging (DTI) has been recently used for detecting focal abnormalities in temporal lobe epilepsy (TLE). Tractography and directionally encoded color (DEC) mapping are derivatives of DTI and may allow 3-dimensional characterization of the structural changes of neuronal networks. We conducted this study to evaluate the relative role of DEC mapping in lateralizing the seizure focus and mapping the structural changes in TLE.

Methods: Sixteen patients with TLE being evaluated for epilepsy surgery were recruited for this study. All patients had unilateral TLE based on clinical history, routine EEG and unilateral ictal EEG recording. DTI was performed on a 1.5T Vision MR scanner using a single shot echo planar diffusion weighted imaging sequence. To determine the diffusion tensor fully, we collected diffusion-weighted images along six different directions with a b value of 1000 sec/mm^2 as well as an image acquired without diffusion weighting ($b = 0$, B_0 image). Seventeen coronal slices were acquired to cover the entire temporal lobes. The imaging parameters included: TR = 6000ms, TE = 100ms, FOV = 240 mm, 98 x 128, and 4 acquisitions. The maps of mean diffusivity and fractional anisotropy (FA) were calculated from the diffusion-weighted images using software written in IDL (Interactive Data Language, USA). DEC FA-weighted images were calculated using statistical parametric mapping software (SPM'99) and were assigned different colors (red, blue, & green) along the three principle directions Left/Right, Superior/Inferior, Anterior/Posterior respectively. We performed visual inspection of the DEC FA-weighted images in both patient and control groups and identified any abnormal color patterns in the HF in the patient group.

Results: High-resolution brain MRI revealed unilateral HF abnormality in 12 of 16 patients while 4 of 16 had no abnormalities. DEC imaging mapping revealed unilateral defects in the color maps of the HF in 11 of 16 patients and the abnormal HF DEC maps lateralized to the temporal seizure focus in all patients. In addition, in 5 patients with either subtle HF signal abnormality or negative high-resolution MRI, a unilateral and widespread abnormal HF DEC pattern was detected and lateralized to the epileptogenic temporal lobe.

Conclusions: DEC can detect the abnormal and/or epileptogenic HF in unilateral TLE. The loss of anisotropy and the HF color map defects ipsilateral to the seizure focus in TLE may reflect disruption of the structural organization, drop in neuronal count and gliosis in mesial temporal sclerosis. In addition, the DEC mapping may detect changes related to 3-dimensional structure of the neuronal networks connected with the seizure focus when such changes produce only subtle or no changes on high-resolution MRI.

1.277
THE ROLE OF THE THALAMUS IN BILATERAL SYNCHRONY: CORTICAL AND THALAMIC EEG-fMRI RESPONSES IN FOCAL EPILEPSY
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Rationale: We recently reported cortical and thalamic fMRI BOLD responses in patients with idiopathic generalized epilepsy (*Agha Khani et al. Brain:127; 1127–1144*). In order to better understand the role of

the thalamus in spike synchronization and propagation, we investigated patients with focal epilepsy and compared the BOLD responses in the thalamus and cortex in those with or without bilateral synchrony (BS).

Methods: We used combined EEG-fMRI in 64 patients with focal epilepsy who had active interictal spiking during routine or telemetry recording. Twenty-one Ag/AgCl electrodes were applied using the 10–20 system (EMR32 amplifier, Schwarzer, sampling rate 1000Hz, EEG processed off-line to filter out the scanner artifact). MR images were obtained with a 1.5T scanner (Vision), and at the start of each study an anatomical MR was performed (T1, 256x256 sagittal, 160 slices, 1 mm thick, slice gap of 0.2 mm). fMRI images were motion corrected and smoothed using in-house software (25 BOLD EPI 64x64 axial slices, voxel size 5x5x5 mm, TE 50 ms, flip angle 90°). Study duration varied between 90 to 120 min. We performed statistical processing of the images using the method of Worsley et al. in order to find the areas that changed in response to the epileptiform discharges. A response could either consist of an activation (positive BOLD) or of a deactivation (negative BOLD).

Results: Forty patients had spikes during fMRI scanning. Twenty-nine had uni- or bilateral independent temporal or extratemporal spikes without BS (group 1), and 11 showed BS (group 2). Forty fMRI spike analyses were performed in group 1 with significant BOLD responses in 18 (45%). In the second group, all the patients showed a significant BOLD response. A thalamic response was found in 55% of the patients with BS compared to 25% with focal discharges only. The cortical BOLD responses were also more widespread in patients exhibiting BS. Cortical activation was the dominant response and had a better correlation with spike distribution in patients without BS, while those with BS showed both widespread positive and negative BOLD responses.

Conclusions: We demonstrated metabolic and hemodynamic evidence of thalamic involvement in patients with focal epilepsy. Activation and deactivation in the thalamus and the cortex were more frequently observed in patients with BS and the cortical fMRI responses were more widespread compared to patients with focal spikes only. These findings support the role of the thalamus in the synchronization and propagation of spikes between the two hemispheres. The similarities in hemodynamic response between patients with BS and those with generalized epilepsy suggest a common underlying synchronizing mechanism. (Supported by CIHR MOP 38079.)

1.278
COMBINED EEG-fMRI USING Z-SHIMMING IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

Andrew P. Bagshaw, Leili Torab, Eliane Kobayashi, Colin Hawco, François Dubeau, G. Bruce Pike, and Jean Gotman (Montreal Neurological Institute and Hospital, McGill University, Montréal, QC, Canada)

Rationale: Functional magnetic resonance imaging (fMRI) studies of the temporal lobes are hampered by signal loss caused by magnetic field inhomogeneities. Z-shimming is a technique whereby multiple images are acquired with different acquisition parameters optimised for the regions suffering from signal loss. A final image is created by combining these individual images. This study used z-shimming in an attempt to increase the signal intensity in patients with temporal lobe epilepsy (TLE) with the goal of detecting the generators of interictal epileptiform activity more reliably.

Methods: Four patients with a clinical diagnosis of TLE underwent continuous EEG-fMRI monitoring using a z-shimming protocol (Constable and Spencer 1999). The fMRI images were acquired in a 1.5T MR scanner (Sonata, Siemens, Germany) using an echo-planar imaging sequence (voxels 5x5x5mm, 12 slices, TE = 50ms, TR = 3.3s, flip angle 75°). An angulation along the long axis of the temporal lobes was used to cover as much of the posterior temporal lobes as possible. Three z-shim levels were used (100%, 80% and 120% of the nominal Gz) and composite images formed by taking the sum of squares at each voxel. An anatomical scan was also acquired. EEG data were recorded using a BrainAmp amplifier (BrainProducts, Germany) from 21 MR compatible Ag/AgCl electrodes. The signal intensity in the composite images was compared with that in the nominal images (i.e. those acquired with the nominal Gz), both throughout the brain and specifically in the temporal lobes. For the latter comparison, the temporal lobes were marked bilaterally on the anatomical scan and the corresponding voxels in the functional scan were identified.

Results: The overall signal intensity increase in the brain for the composite functional images, averaged across all patients, was 22.7±0.4% [range 22.2–23.1%]. Within the temporal lobes, the increase in signal was 42.3±3.8% [range 37.4–45.7%]. The average increase in the number of voxels above a brain intensity threshold was 295±42 [range 253–343]. An average of 109±30 voxels [range 75–143] were added to the temporal lobes, corresponding to 10.2±1.6% of the total number of marked temporal lobe voxels.

Conclusions: Using the z-shimming technique leads to a considerable increase in the signal intensity in the temporal lobes. This increases the probability of detecting subtle changes in the fMRI signal as a result of interictal epileptiform activity generated in the temporal lobes.

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1.279
THE RELATIONSHIP BETWEEN CEREBRAL BLOOD VOLUME AND OXYGENATION FOLLOWING BIPOLAR STIMULATION OF THE HUMAN CORTEX: EVIDENCE FOR AN INITIAL DIP

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Rationale: Human brain mapping has undergone a revolution in recent years as a result of advances in imaging techniques such as fMRI and optical recording of intrinsic signals (ORIS). Both techniques are based on the coupling and uncoupling between electrophysiological activity, cerebral blood flow and hemoglobin oxygenation. Controversy exists regarding events which occur in the first few hundred milliseconds following neuronal activation. While some investigators demonstrate an initial dip in oxygenated hemoglobin (HbO2), others report no such event. We investigated the change in deoxygenated hemoglobin (Hbr; 605/630nm) as well as changes in cerebral blood volume (CBV; 546 nm) with high resolution, high speed ORIS in the human brain following bipolar cortical stimulation.

Methods: Bipolar cortical stimulation was delivered to 8 patients undergoing craniotomy for resection of medically intractable epilepsy as biphasic trains of 1 msec pulses at 60 Hz for 2–3 seconds (1–4 mA). A sterile glass footplate was placed on the surface of the brain to reduce cortical pulsation and a CCD camera was draped sterilely and suspended over the brain. Changes in light reflectance at each incident wavelength were calculated by dividing each image (10 Hz framerate) by an image prior to the onset of cortical stimulation. Experiments consisted of 6–12 trials at each incident wavelength.

Results: Bipolar stimulation induced a highly reproducible change in light reflectance which could be seen after only a single trial. Intertrial 2-dimensional correlation coefficients were highly significant ($r = 0.75$; $p < 0.001$). At 605 and 630 nm, a clear dip in oxygenation was seen within 200 ms after stimulation that peaked at ~2 s. This signal was highly focal, compared with the inverted signal that appeared later in the draining veins consisted with a less well-localized BOLD signal. The signal recorded at 546 nm (CBV) was monophasic and was also apparent as early as 200 ms after stimulation. Although highly localized in the first 2 s, the CBV signal then spread to adjacent gyri and peaked at (5–8 s. The average amplitude of the peak of the monophasic signal recorded at 546 nm (CBV: 9.69%) was larger than the initial dip (3.46%) and BOLD signal (-8.48%). Stimulation at increasing amplitudes revealed a nonlinear increase in the ORIS.

Conclusions: We find a clear decrease in oxygenation as early as 200 ms after bipolar stimulation of the human cortex. This initial dip is highly localized compared with a later increase in oxygenated hemoglobin (BOLD signal). Changes in CBV occur more rapidly after cortical stimulation than expected and are also highly localized in the first 2 s. However, this rapid increase in CBV may influence the magnitude of the optical

signal recorded at 605/630nm since an overall increase in CBV may raise Hbr as well as HbO2. [Supported by NIH (NINDS), Dana Foundation, CURE Foundation.]

1.280
VECTOR FIELD ANALYSIS OF HIPPOCAMPAL HIGH-DIMENSIOINAL MAPPING IN MESIAL TEMPORAL EPILEPSY

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Rationale: More precise techniques, such as HDM-LD mapping of the hippocampus, may assist in detecting subtle abnormalities in MTS. We compare groups of patients with well-defined MTS with controls, to determine influences of normal hippocampal right/left asymmetries on results, and document the ability of HDM-LD-defined hippocampal changes to predict MTS. In this study, we objectively quantitate shape variations in patients with right and left mesial temporal epilepsy (MTLE) as compared to controls, using large deformation high dimensional mapping (HDM-LD) vector analysis.

Methods: Subjects were identified retrospectively from consecutive cases from the epilepsy surgery series at Saint Louis University. All epilepsy subjects had post-surgical confirmation of MTS. Using a previously described technique, the right and left MTS groups were compared independently with the control group, resulting in eigenvector fields describing differences within the populations. This technique accounts for normal asymmetries of the right and left hippocampus, and results in a subset of eignevectors which maximally discriminate MTS groups from controls. A leave-on-out (jackknife) procedure comparing eigenvector-defined shape differences between MTS groups and controls was used to predict the side of MTS.

Results: The mean coefficient associated with the first nine shape eigenvectors for each group showed that the first three eigenvectors were large, and accounted for most of the differences between groups. The largest difference among the two MTS groups was found in the second eigenvector, while the MTS groups were rather similar in the first and third eigenvectors. This suggested that the laterality of the MTS was largely symmetric in the diseased side hippocampus and was characterized by eigenvector 2. When comparing the left MTS group with the controls, eigenvectors 1,2,3 were selected by a logistic regression procedure (Likelihood Ratio: $2 = 32.0$, $df = 3$, $p < .0001$). A leave-on-out procedure correctly predicted group classification in 14 out of 15 (93.3%) MTS subjects and in 14 out of 15 (93.3%) control subjects. When comparing the right MTS group with the controls, eigenvectors 1,2,3 were selected by a logistic regression procedure (Likelihood Ratio: $2 = 41.3$, $df = 3$, $p < .0001$). The leave-on-out procedure correctly predicted group classification in all 15 MTS and 15 control subjects.

Conclusions: HDM-LD eigenvector analysis shows MTS affects the right and left hippocampi in a nearly identical pattern, after accounting for normal right/left hippocampal shape differences. Shape analysis also predicts the hippocampus which is affected by MTS.

1.281
INTERRATER AGREEMENT FOR MRI INTERPRETATION OF EPILEPSY SURGERY PATIENTS

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Rationale: To determine agreement levels between two independent radiologists interpreting MR images of intractable seizure patients.

Methods: As part of a multicenter study of epilepsy surgery, 2 radiologists independently evaluated 512 preop MR scans. A standard data form was used. Quantitative measurements were not performed.

Hippocampal size, signal, and hippocampal sclerosis (HS) diagnosis were assessed on a 5-point scale (definitely normal = 1, probably normal = 2, equivocal = 3, probably abnormal = 4, definitely abnormal = 5). Presence of periventricular heterotopia, cortical thickening, sulcal morphologic changes, focal volume loss, & temporal lobe encephalocele were assessed on a 3-point scale (no, equivocal, yes), along with lesion location and diagnosis. Weighted Kappa assessed interrater agreement.

Results: MRI lesions occurred in 70%: HS 44%, dual path 11%, atrophy 5%, development 4%, tumor 4%, vascular 3%. In the STUDY group, number of abnormalities both raters agreed were present: hippocampal changes = 222; volume loss = 34; cortical thickening = 9; sulcal changes = 5; heterotopia = 4; encephalocele = 0.

Interrater agreements were excellent for hippocampal volume, hippocampal signal changes and MR diagnosis of HS (wKappas 0.80–0.83); but rater bias was present with rater 2 scoring higher than rater 1 on the 5-point scale in 76.5% of the disagreed cases ($p < .0001$; Table 1). For all 5-point assessments, categories of Definitely Normal or Abnormal produced excellent wKappas, while Probable categories produced good-fair wKappas, and Equivocal category produced poor wKappas. Good agreement occurred for cortical thickening and location (wKappas 0.70–0.72). Agreement was fair for volume loss and heterotopia and poor for sulcal changes and encephaloceles.

Interrater Reliability (wKappas)		
Hippo Atrophy	Hippo Signal	MR diagnosis HS
0.80	0.83	0.82

$p < 0.0001$					
Brain location	Focal volume loss	Cortex thick	Encephalocele	Sulcal changes	Heterotopia
.72	.57	.70	.17	.20	.53

$p < 0.02$ (Agreement: Poor <.40; Fair.40-.59; Good.60-.74; Excellent.75–1.00)

Conclusions: There was excellent inter-rater agreement for hippocampus abnormalities and rater bias did not preclude this robust agreement. Kappas for other assessments ranged from good to poor, in part due to the relatively rare occurrence of these abnormalities, lack of a focused region of brain (unlike the hippocampus) and the subjective nature of these observations. With a 5-point scale, ratings at the ends of the scale were more robust than in the scale's center and changing to a 3-point scale would mask this phenomenon. In summary, qualitative assessment of MR images of epilepsy patients using a systematic approach can reliably detect and localize hippocampal and other brain lesions. This is crucial for surgical planning, which demands robust preoperative measures. (Supported by NIH grant IR01 NS32375–01.)

1.282
FOCAL REFRACTORY NONCONVULSIVE STATUS EPILEPTICUS AND ABNORMALITIES ON SEQUENTIAL MRI

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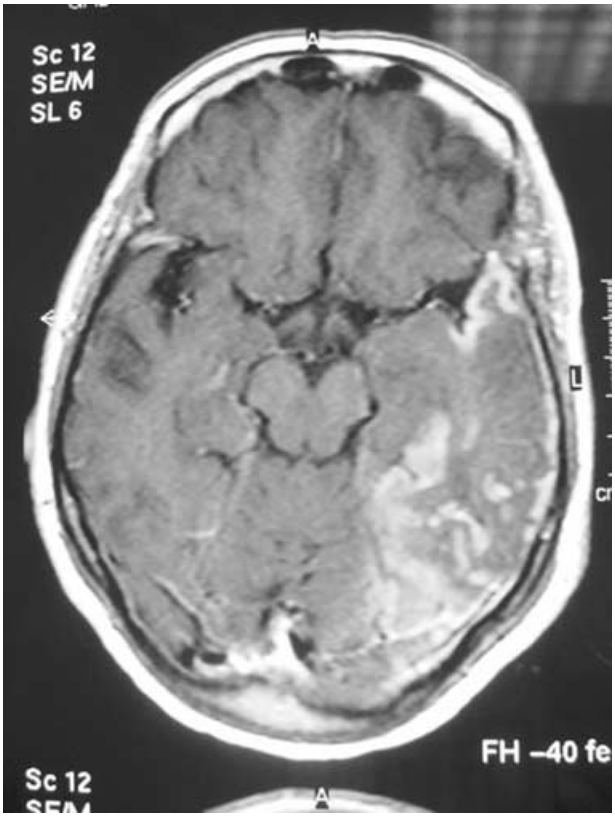
Rationale: A series of transient alterations have been registered on MRI scanning studies of focal refractory nonconvulsive status epilepticus. We report a case and the abnormalities observed on sequential MRI.

Methods: A 63-year-old female patient with a familial history of a sister and cousins suffering from epilepsy is admitted with confusional symptoms starting 72hrs before. Two similar episodes of 5 minutes each had occurred in the previous two years, which had recommended a cardiologic study, EEG and cranial MRI, all with normal results.

A new EEG was consistent with left temporal status epilepticus and the MRI scanning showed diffuse T2-weighted and FLAIR hyperintense images in the left temporal lobe without mass effect as well as

gadollinium uptake areas in leptomeninges and cortex. CSF showed no cells and hyperproteinorrachia of 1 gr/dl. The symptoms continued for 10 days and the patient did not respond to antiepileptic drugs until the administration of steroids.

Results: A new MRI performed 10 days after resolution of symptoms showing a marked regression of the lesion following the administration of steroids (Fig. 1). A new MRI performed after 3 months yielded normal results.



Conclusions: The case reported here supports the few previous reports on the occurrence of MRI abnormalities consistent with cytotoxic-vasogenic edema secondary to neuronal damage and rupture of the hematoencephalic barrier, respectively in relation with focal refractory nonconvulsive status epilepticus. Sequential MRI scanning, hyperproteinorrachia and the response to anti-edema therapy support our findings. Steroids may be a suitable therapeutic option in cases of refractory status epilepticus.

1.283

BILATERAL LIMBIC ABNORMALITIES DEMONSTRATED WITH DIFFUSION TENSOR IMAGING IN PATIENTS WITH UNILATERAL MESIAL TEMPORAL SCLEROSIS

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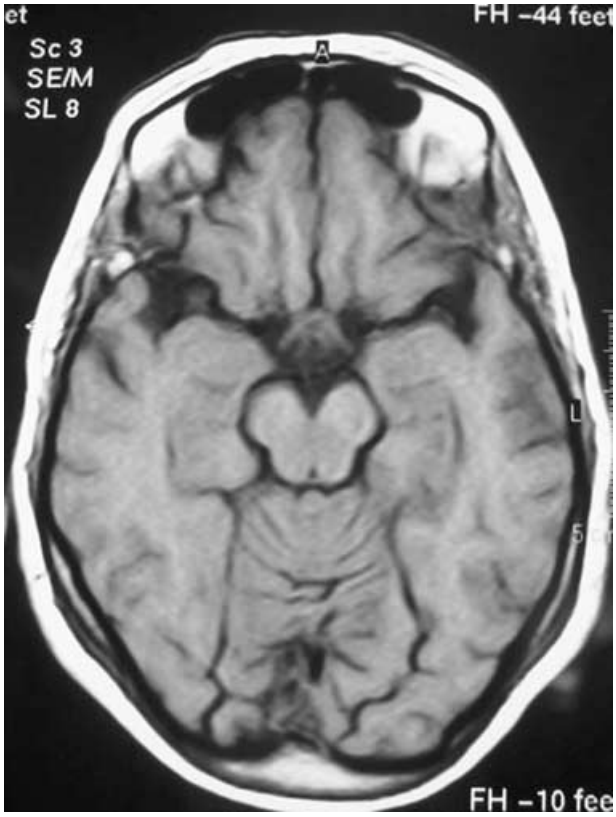
Rationale: Magnetic Resonance Diffusion Tensor Imaging (DTI) provides information on the micro-structural state of white matter based on the diffusion of water molecules. DTI tractography uses the directionality of water movement to virtually dissect the fiber tracts, otherwise not discernible with conventional imaging methods. The fornix and cingulum are two of the most prominent fiber bundles of the limbic system. They have been visualized with tractography in healthy individuals, but not in patients with Temporal Lobe Epilepsy (TLE). The objective of this study was to determine whether evidence of axonal degeneration could be detected in vivo within the fornix and cingulum in a series of epilepsy patients with unilateral Mesial Temporal Sclerosis (MTS).



Methods: We performed DTI derived tractography of the fornix and cingulum and subsequent quantitative analysis of water diffusion behaviour in a series of eight patients with medically intractable TLE and clinical imaging evidence of unilateral MTS and nine healthy controls.

Results: We found bilateral and symmetrical reduction in fractional anisotropy (FA) in the fornix of patients with TLE as compared with controls ($FA = 0.48 \pm 0.02$ and $FA = 0.53 \pm 0.02$, respectively, $p < 0.0001$ for both sides), along with an increase in water mobility perpendicular to the axis of the fibers and a small, yet significant, reduction in diffusion parallel to the fibers. The mean FA for the cingulum in the control group was 0.50 ± 0.03, while the patients had a mean FA value of 0.44 ± 0.02 in the cingulum ipsilateral to MTS ($p < 0.001$) and a mean FA value of 0.46 ± 0.02 in the contralateral side ($p = 0.005$). The rest of the findings in the cingulum were similar to our observations in the fornix with the exception that while the fornix had no change in bulk diffusivity (regardless of directionality), this measurement was significantly increased in the cingulum.

Conclusions: Reduced diffusion anisotropy in association with an increase in water mobility perpendicular to the axis of fibers is consistent with axonal degeneration within the fornix and cingulum. Our findings of strikingly symmetrical bilateral abnormalities of axonal integrity in the fornix and cingulum in a series of patients with unilateral MTS, strongly suggest that TLE with unilateral MTS is in fact associated with extensive bilateral limbic system pathology. (Supported by The Savoy Foundation, AHFMR, CIHR, Promep, the Canada Foundation in Innovation, Alberta Science and Research Authority, and the University Hospital Foundation. Fiber tracking software provided by Drs. Susumu Mori and Hangyi Jiang.)

1.284

ANTIEPILEPTOGENIC DRUG EFFECTS IN fMRI LANGUAGE MAPPING

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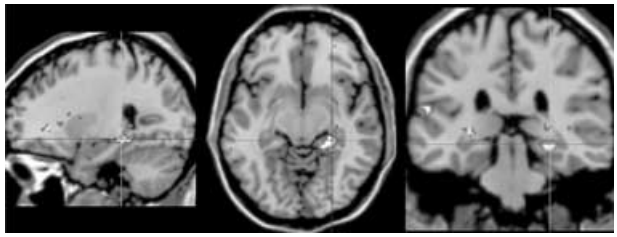
Rationale: It is becoming increasingly recognized that baseline brain state must be considered when evaluating fMRI results. Antiepileptogenic medications are known to alter baseline flow and metabolism. Functional MRI, produces signal changes dependent upon a complex interaction between blood flow, oxygenation, volume, oxygen extraction fraction, and oxygen consumption, some of which may be influenced by medications. This work examined 37 patients with language mapping, to investigate the influence of antiepileptogenic meds on the activation patterns.

Methods: Imaging was performed on a 1.5T GE Signa. Patient population consisted of patients with intractable epilepsy who were candidates for surgical intervention (37 patients (23F, 14M), mean age 34.8y, mean duration of epilepsy 16.9y). Patients presented with the following meds: 13 Carbamazepine, 9 Phenytoin, 13 Lamotrigine, 3 Oxcarbamazepine, 8 Valproate, 3 Gabapentin, 4 Topiramate, and 15 Levitiracetam. Drugs were grouped according to mechanism (ion channel, multiple mechanisms, and unknown) and a general linear model was run on the% signal change activation maps across subjects. This allowed hypothesis testing for a main effect of drug in the activation maps. Effects of age at onset, FSIQ, and patient age were also included in the GLM. Functional imaging was performed using previously published language paradigms (Constable et al, *NeuroImage* 2004).

Results: The ion channel blockers led to increased activation in left posterior STG and bilateral insula in the auditory sentence task and increased posterior cingulate and right insula in the reading task (Fig. 1). The multiple mechanism drugs had little impact in sentence-reading, and led to increased right STG and right insula in the auditory task. The Levitiracetam led to increased activation in left IFG during reading and increased caudate and hippocampal activation (shown below) in the auditory task. Age at onset was associated with increased activation in medial PFC, whereas FSIQ was positively correlated to activation in both the left IFG and STG.



Conclusions: The results provide evidence of drug effects in fMRI. The results are modality dependent, indicating drug effects may be regional in nature. A targeted study of these effects could reveal not only what drug effects occur, but with a larger in-magnet behavioral task battery, it would be possible to associate specific changes in activation patterns with specific changes in the performance across a number of different tasks. (Supported by NIH NS40497, NS38467, EB00473.)

1.285

EEG-FMRI RESPONSES IN TLE FREQUENTLY EXTEND BEYOND THE TEMPORAL LOBE

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Rationale: Simultaneous EEG and functional MRI (fMRI) allow evaluation of BOLD responses related to interictal spikes. Our objective was to investigate the extension of EEG-fMRI responses related to spikes in TLE patients.

Methods: We performed two-hour continuous EEG-fMRI recordings using 21 MRI compatible electrodes and amplifier. BOLD-EPI fMRI acquisition parameters were: 5x5x5 mm voxel, 25 slices, 64x64 matrix, TE = 50 ms, TR = 3 s, flip angle 90°. EEGs were filtered to remove the scanning artefact and spikes were marked using FEMR or Vision Analyser softwares. Maps of the t statistic (t-maps) were created with the timing of spikes as events in the fMRI analysis. At each voxel, the maximum t value was taken from four t maps created with hemodynamic response functions peaking at 3, 5, 7 and 9 seconds. BOLD-fMRI responses were defined as positive (activation) and negative (deactivation), for voxels exceeding a corrected $p = 0.01$. Localization of responses was determined by co-registration of anatomical and t-maps.

Results: We studied 28 patients with lesional and seven patients with non-lesional TLE. The lesional group included patients with hippocampal atrophy (n = 5), atrophy/gliosis of TL neocortex (n = 3), developmental mesial temporal abnormalities (n = 5), and other TL lesions (n = 9). Eight patients had no spikes during the scan, and eight others had independent bitemporal spikes, which were analysed separately, giving a total of 35 EEG-fMRI studies. Twelve studies showed only activation, 14 both activation and deactivation, and three only deactivation. Eighteen studies had TL activation: 12 were bitemporal, four ipsilateral to EEG spiking and two contralateral. Associated extra-temporal activation was seen in 16 of them. Eight studies showed only extra-temporal activation.

Eight studies showed TL deactivation: four bitemporal, two ipsilateral and two contralateral. Nine studies showed only extra-temporal deactivation, and all eight studies with TL deactivation also showed extra-temporal deactivation. TL responses were more frequently neocortical, with or without concomitant mesial involvement. Extra-temporal responses were either ipsilateral or bilateral. Basal ganglia and thalamic responses were seen in five studies, while cingulate responses were observed in nine studies.

Conclusions: EEG-fMRI responses were observed in most TLE patients and were in general more widespread than expected, involving also the TL contralateral to the spikes, and some extra-temporal areas, including the thalamus. fMRI responses in the TLs were predominantly neocortical and bilateral, even in patients with unilateral spikes. These results point to a potential effect of epileptic spikes beyond their place of generation. (Supported by grant MOP 38079 of the Canadian Institutes of Health Research. E.K. receives a Preston Robb fellowship from the Montreal Neurological Institute.)

1.286

PRECISE REGISTRATION OF PREOPERATIVE MRI WITH HISTOPATHOLOGY AFTER TEMPORAL LOBE RESECTIONS

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Rationale: Conventional and novel MRI techniques can detect cerebral abnormalities in patients with refractory focal epilepsies. Correlation of preoperative MRI data and neuropathological analysis of the neocortex is not straightforward. Per-operative neuronavigation and placement of markers on tissue is of limited use in temporal lobe resections. MRI scanning of the resected specimen for registration with in-vivo MRI is complicated by anisotropic deformation of tissue after resection. We have developed a method to facilitate precise registration of preoperative MRI with the resected specimen and enable accurate correlation of MRI findings with histopathology.

Methods: Ten temporal lobe resections undertaken for refractory temporal lobe epilepsy were studied. *En bloc* neocortical resections were performed followed by amygdalo-hippocampectomy. The middle temporal gyrus was marked with ink in the operating room, and the orientation of the specimen noted. The specimen was fixed in formalin for a week and then cut coronally using a specially manufactured cradle with parallel blades at 5 mm intervals to ensure evenly thick slices in the same orientation. The posterior face of each tissue block was photographed. Volumetric T1-weighted preoperative MRI were reformatted and sliced coronally in the same orientation as the fixed lobe. Consecutive MRI slices (0.94 mm) were compared to photographs of the 5 mm thick tissue blocks by two observers (SHE and SLF) separately and then together for a consensus.

Results: In eight cases hippocampal sclerosis seen on MRI was confirmed. There were 4–6 slices of temporal neocortex per case. In eight cases, one or more tissue block could be confidently matched with MRI slices, from which correlation of the remaining slices could be estimated. In two cases finding corresponding slices were more difficult, but there were one or two probable matches, from which the

remaining correlations could be estimated. Matching was usually easiest 1.5–2 cm posterior from the temporal pole, where distinct anatomical features could be distinguished. Simultaneous review of postoperative MRI scans was useful, ensuring that all matched MRI slices were included in the resection. In all cases, consensus was reached by the two observers and the proposed MRI-pathology matches were plausible.

Conclusions: Careful labelling, postoperative handling and the new method of orienting and slicing resected specimens ensured histopathological tissue blocks of uniform thickness and slicing angle. In 80% of cases confident and precise matching of MRI and blocks was possible, enabling MRI-pathological correlations. This technique can be applied to a range of MRI datasets, enabling exploration of the pathological basis of abnormalities on conventional and novel MRI. (Supported by The Wellcome Trust, UK.)

1.287

ANTERIOR TEMPORAL LOBE fMRI ACTIVITY IN NORMAL CONTROL SUBJECTS AND PATIENTS WITH TLE

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Rationale: Testing the functional integrity of mesial temporal lobe (MTL) structures in temporal lobe epilepsy (TLE) especially in presurgical planning, needs information about physiological functions within the to-be-resected anterior MTL. The amygdala and the anterior MTL itself are known to be involved in visual processing, memory and emotional assessment.

Methods: A new visual paradigm presenting scenes with animated fearful faces from commercial movies alternating with landscape scenes was investigated using functional MRI. 12 healthy subjects and 3 patients with right sided TLE were scanned using a 1.5 T MRI (blocked design, coronal EPI, voxel size 3.9x3.9x5 mm3). The scans were analysed using SPM99 (Wellcome Dept., UCL London, UK) to test for individual and group effects ($p = 0.05$ corr).

Results: We found highly significant activations of the left and right amygdala, hippocampus and MTL cortex in individual and in group analyses. In the control subjects, there was a symmetrical activity pattern in the amygdala (left-right ratio of activated voxels 1.07). In 3 patients with right TLE, fMRI activity was strongly lateralized to the healthy MTL (left-right ratio 2.42).

Conclusions: The new paradigm seems to be a powerful method to induce anterior MTL fMRI activity. Future measurements and clinical correlations will answer the question whether the procedure is of further clinical use (e.g. whether it predicts individual postsurgical outcome).

1.288

PARADOXICAL IMAGING FINDINGS IN LESIONAL EPILEPSY

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Rationale: Lesional epilepsy is due to cerebral gliomas in 10–15% of cases. The therapeutic management and prognosis in such patients depend on the reliable distinction between high- and low-grade gliomas.

MRI is an excellent tool for tumor localization. When MRI is scored based on multiple criteria (heterogeneity, cyst formation or necrosis, hemorrhage, tumor crossing the midline, edema and/or mass effect, definition of border, flow void, degree of contrast enhancement, heterogeneity of contrast enhancement), the accuracy of the grading of gliomas can reach 88%.

FDG-PET is thought to be another useful tool for the evaluation of the degree of malignancy of cerebral gliomas. In one study, 86% of the patients with hypometabolic FDG-PET had low grade gliomas, and 94% of the patients with hypermetabolic FDG-PET had high-grade gliomas. Therefore, combining these two noninvasive neuroimaging techniques may be considered highly accurate for preoperative grading of gliomas. However, hypermetabolism may also be present if the scan is obtained during a seizure (ie, an ictal scan).

Methods: We recently encountered two patients with tumors in our epilepsy surgery program who exhibited paradoxical findings on both MRI and FDG-PET scans. Both patients presented with medically intractable epilepsy. Both patients underwent MRI brain and FDG-PET scans, EEG-Video Monitoring, and Neuropsychological evaluations.

Results: Patient #1 presented with a 2 year history of temporal lobe epilepsy. MRI scan revealed a right medial temporal homogenous, nonenhancing lesion involving the right amygdala and uncus. FDG-PET showed hypometabolism in the right medial and lateral temporal lobe structures. Video EEG monitoring showed seizure onset in the right medial temporal region. The patient underwent a right temporal lobecotmy including amygdalohippocampectomy. Postoperative histopathology showed a glioblastoma multiforme (grade IV).

Patient #2 presented with a 7 year history of left sided sensory seizures. MRI scan revealed a 4cm intraaxial mass involving the right posterior parietal region. This tumor had minimal mass effect, heterogeneous signal on T1 and T2-weighted images, cyst formation, a large area of surrounding edema, and moderate enhancement with contrast. FDG-PET revealed increased glucose uptake in the region of the lesion, and simultaneous EEG was normal. Subsequently, the patient underwent intracranial subdural grid placement, motor/sensory mapping, and resection of the lesion as well as the surrounding epileptogenic cortex. Postoperative histopathology showed an oligodendroglioma (grade II) without anaplastic features.

Conclusions: The combination of MRI and FDG-PET is a useful tool for the noninvasive preoperative grading of gliomas, but rare exceptions do occur. Caution should be taken when planning epilepsy surgery and when interpreting and discussing these studies with patients.

1.289

THE ROLE OF THE THALAMUS IN SPONTANEOUS PARTIAL SEIZURES AND SEIZURES INDUCED BY ECT: AN [^{11}C] DIPRENORPHINE PET STUDY

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Rationale: Little is known about mechanisms of seizure cessation and the neurotransmitters involved. [^{11}C] diprenorphine (DPN) PET images all subtypes of opioid receptors. We have previously shown involvement of endogenous opioids in absence seizures provoked by hyperventilation, and in reading-induced seizures in reading epilepsy. Here, we investigate spontaneous complex partial seizures (CPS) in patients with temporal lobe epilepsy (TLE) and compare changes (compared to controls) with changes in patients having a first-ever secondarily generalized tonic-clonic seizure (2°GTCS) following electroconvulsive therapy (ECT) for depression.

Methods: We studied eight TLE patients 1.5–22h after the last spontaneous CPS and interictally. Four patients with severe depression were scanned prior to and four hours after their first 2°GTCS following ECT. Eighteen healthy controls were studied for comparison, and test-retest variation established in fourteen. All had high resolution MRI and quantitative [^{11}C] DPN PET on a Siemens/CTI ECAT HR++ scanner. Spectral analysis and metabolite-corrected arterial plasma input functions were used to produce parametric images of DPN volume-of-distribution (Vd). Individual parametric images were spatially normalised to a DPN template in standard stereotaxic space, using Statistical Parametric Mapping (SPM99) software, and group comparisons performed correcting for global Vd.

Results: In the TLE patients, postictal decreases of [^{11}C] DPN Vd were seen in both thalami ($Z = 3.55$, $k = 6968$, $p_{uncorr} < 0.05$) and medial frontal lobes ($Z = 3.24$, $k = 16397$, $p_{corr} < 0.07$). Depressed patients showed decreases of [^{11}C] DPN Vd following ECT in the thalamus bilaterally ($Z = 3.67$, $k = 6208$, $p_{uncorr} < 0.03$) and in both insular

cortices (right, Z = 4.29, k = 24615, $p_{corr} < 0.004$; left, Z = 3.55, k = 10470, $p_{corr} < 0.14$).

Conclusions: Our data is compatible with a release of endogenous opioids during both spontaneous CPS and electrically induced 2°GTCS in the thalamus bilaterally, consistent with animal studies and case reports in humans of reduced seizure activity following intermittent electrical stimulation of the thalamus.

Endogenous anti-convulsant mechanisms may modulate abnormal network activity through thalamic release of opioids. Medial frontal changes in TLE patients could be a common endpoint for seizures starting in different parts of the temporal lobe and are compatible with previous SPECT studies of ictal blood flow. Changes in the insulae in ECT patients could be due to the site of onset of the electrically induced seizures. (Supported by Medical Research Council, National Society for Epilepsy.)

1.290

REPRODUCIBILITY OF HIPPOCAMPAL 1H SPECTROSCOPY

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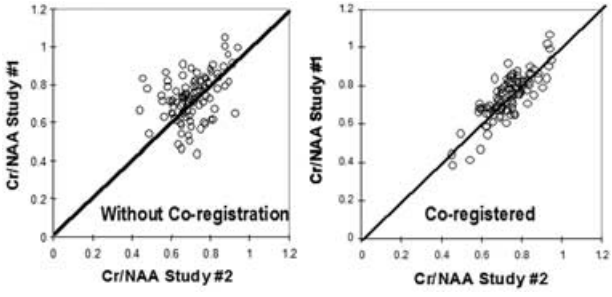
Rationale: 1H spectroscopic imaging (SI) of N-acetyl aspartate (NAA) has proven to be highly useful in the identification of neuronal injury in patients with MTLE. Despite its excellent success in seizure lateralization, there are few studies evaluating its accuracy and reproducibility. This issue is of major importance, as NAA is increasingly used for longitudinal studies and therapeutic planning. Previous work reported a range of coefficients of variation (CV, 17–41%) for single pixel measurements of NAA/creatine (NAA/Cr). These variations are due to the large heterogeneitites in metabolite content that normally occur along the hippocampus. To overcome this problem we developed an automated co-registration approach that reduces the study-to-study CV by (50%, reaching 9% for individual pixels and 3.5% over the entire hippocampus.

Methods: Spectroscopic images were acquired using a single plane spectroscopic imaging sequence, 24x24 encodes 0.64cc/voxel (19min).To provide for reproducible voxel selection and reconstruction, an automated co-registration, selection and reconstruction routine was used. The images were co-registered by maximizing the overlap between two tissue-segmented structural images. Five non-overlapping voxels from each hippocampus (10 per study) were automatically reconstructed by translating along the hippocampal midline with the central voxel placed at the level of the aqueduct.

Results: We acquired two hippocampal SI studies in 10 control subjects (mean separation, 34 days), analyzing each dataset two ways. In approach A, we selected 5 voxels from each hippocampus using the SI determined grid following the contours of the hippocampi (no co-registration). In approach B, the automated voxel coregistration and reconstruction was used to evaluate 5 voxels along the mid-line of the hippocampal formation. Approach B demonstrated (50% reduction in CV for individual pixels, 9.0%, versus 17.1% from approach A. Use of the coregistration method B increased the correlation coeffcient between the two studies from R = 0.39 to R = 0.82 (Figure). Also, approach B reduced the CV of the entire hippocampus (all 5 voxels averaged) by 3 fold, with CVs of 3.5% vs 10.7% (respectively methods B, A).



Conclusions: Compared to conventional voxel selection routines, these methods reduce the study-to-study CV of Cr/NAA along the hippocampus by 47%. The CV of 9% is (1/5 of mean difference between controls and patients with intractable TLE. This approach should improve longitudinal studies of TLE patients as well as the accuracy of the hippocampal measurement. (Supported by NIH P01-NS-39092, R01-EB000473, Dana Foundation.)

1.291

FOCAL TRANSMANTLE CORTICAL DYSPLASIA: A PARTICULAR MRI-BASED DIAGNOSTIC TYPE OF FOCAL CORTICAL DYSPLASIA

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Rationale: MRI is the method of choice to detect and characterize developmental malformations of the cerebral cortex. One of these particular entities is focal cortical dysplasia (FCD). Its diagnostic characteristic, based on the MRI findings, is loss of differentiation between grey and white matter, without oedema or mass effect. A diagnosis of Focal Transmantle Cortical Dysplasia (FTCD) is made when the focal lesion extends from subarachnoid space to ventricular wall.The aim of this study was to determine if FTCD, a MRI-based diagnostic entity, could be considered a particular type of FCD.

Methods: We selected those patients with a diagnosis of FCD based on MRI findings from our Epilepsy Centre. They were divided into two groups; A) Focal Transmantle Cortical Dysplasia (FTCD): with focal lesion extending from the superficial cortex to the ventricular wall and; B) non-FTCD (NFTCD): with focal lesion not extending to the ventricular wall. We analyzed average age (AA), sex, age of onset of epilepsy (AOE), developmental delay (DD), history of pregnancy or perilabour trauma (PT), annual seizure frequency (ASF), family history (FH) and epileptogenic zone (EZ).

Results: Group A: (n = 10; 4 men); AA: 38 ± 14 years; AOE: 12.1 ± 8.9 years; DD: 1; PT: 1; ASF: 238.6 ± 279.9; FH: 2; EZ Temporal in 4. Group B: (n = 13; 9 men); AA: 32.3 ± 15.1 years; AOE: 16.6 ± 17.4 years; DD: 0; PT: 7; ASF: 81.7 ± 119.2; FH: 4; EZ Temporal in 6. PT was significantly more frequent in NFTCD group (p = 0.038 Fisher exact test).

Conclusions: FTCD seems to be a different type of FCD involving less acquired factors in its genesis and affecting less frequently the temporal lobe than NFTCD. MRI characteristics allowed to define a particular subset of FCD.

1.292

EFFECT OF CHRONIC DEEP BRAIN STIMULATION (DBS) OF THE SUBTHALAMIC NUCLEUS (STN) IN FRONTAL LOBE EPILEPSY: SUBTRACTION SPECT ANALYSIS

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Rationale: Experimental data and case reports of intractable epilepsy patients treated with DBS of STN suggest the considerable anticonvulsant effect. But, no satisfactory mechanisms of the action have been elucidated yet. We investigated its therapeutic mechanism from the perfusion changes measured by subtraction SPECT image of pre-insertion state from that of the chronic post-insertion period.

Methods: Case 1: A 23-year-old female patient who had previous resective surgery on right frontal cortex with anterior callosotomy four years ago was selected for DBS of STN. She showed frequent bilateral asymmetric tonic seizures (left > right) with rare drop attacks and her seizure frequency was 15/month in the pre-insertion period. Interictal spikes were seen in the bilateral frontal areas with right dominance (F2, FC2, F4 maximum, 149 per 3 minutes). Her AED medication was VPA 1200mg, CBZ 400mg, TPM 300mg, Oxcarbazepine 600mg/D. After starting STN DBS, the number of seizures was slowly decreased. At the moment of 18 months after stimulation on, she experienced only two seizures per month (86.7% reduction), with decreased severity and

duration and interictal spikes was also decreased (48.6% reduction). Valproate and oxcarbazepine was successfully discontinued as well. Case 2: A 22-year-old male patient was admitted for DBS of STN. He had also right cortical resection with invasive study from the frequent brief, hypermotor seizure with fencing posture originated from right supplementary motor area (SMA). But he showed unsatisfactory outcome after incomplete resection of extensive epileptogenic zone. The seizure frequency was 2.5/day under six AED regimen. Six months after STN DBS, he showed only two seizures a week (88.6% reduction) and slight reduction of AED dosage was permitted. After chronic STN DBS [18 months after (case 1) and 6 months (case 2)], SPECT subtraction with volumetric MRI coregistration was performed using Analyze 5.0 software.

Results: In case 1, the brain perfusion was increased in bilateral frontal areas (bilateral SMA with right dominance and right dorsolateral frontal area) after STN DBS. Case 2 showed unexpected hyperperfusion on right insular cortex and inferior temporal areas as well as definite perfusion increase in right SMA.

Conclusions: We demonstrate that the cerebral perfusion increase at the irritable zones of epilepsy patients is associated with the favorable seizure reduction after STN DBS in two cases of frontal lobe epilepsy. Although its exact mechanisms remain unknown, it suggests that the perfusion changes after STN DBS in frontal lobe epilepsy patients is quite different from those in subjects with Parkinson's disease. This preliminary data suggests the relevance to assessing their post-procedural outcome as well as the characteristics of perfusion patterns in other epilepsy syndromes.

1.293

POSTICTAL MR-PERFUSION IMAGING IN PATIENTS WITH FOCAL EPILEPSY

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Rationale: To investigate the interiktal and postiktal perfusion changes in patients with focal epilepsies.

Methods: Six patients with temporal lobe epilepsy (n = 5) and parietal lobe epilepsy (n = 1) (3 male, 3 female, age range 23 to 47 years) with complex partial seizures (n = 6), additional secondary generalyzed seizures (n = 4) and simple partial seizures (n = 2) participated in this study. Three patients had a hippocampus sclerosis and one patient had a posttraumatic atrophy in the lateral temporal cortex. MR perfusion measurement with bolus application of 0,2 mol/kg Gd-DTPA and echo planar imaging was performed interiktally, and postiktally after 1 to 12 min, 13 to 30 min, 30 to 60 min and 60 to 100 min, respectively, as part of a presurgical evaluation. Bolus-to-peak-ratio was measured in the hippocampus, parahippocampal gyrus, thalamus, cortex and white matter. An asymmetry index (AI) reflecting hyperperfusion (AI>1) and hypoperfusion (AI < 1) of the ictogenic vs. the non-ictogenic side was calculated.

Results: Interiktally perfusion was increased in the hippocampus of the ictogenic side (AI>1) in 5 patients. In 4 patients the AI decreased in the first half hour postiktally (25–39%) and returned to baseline in the later measurements. In the parahippocampal gyrus the AI was elevated interiktally and showed a further increase in the early postiktal measurements (8–24%). In the late postiktal measurements the AI decreased. The thalamus showed little perfusion change postiktally (8–24%). In the white matter the AI increased in the first half hour in the patients with hippocampal sclerosis and decreased in the late measurements. In the cortex perfusion changes were parallel to the hippocampus showing a decrease in the early (10–26%) and an increase in the late measurements.

Conclusions: Our patients with temporal lobe epilepsy showed in initial drop and a delayed increase of perfusion postiktally in the affected hippocampus and a reverse pattern in the adjacent parahippocampal gyrus. The postiktal perfusion changes were minor in the thalamus and non-uniform in the cortex and white matter. This may be due to the spread of the iktal activity from the hippocampus to the adjacent lateral areas while the remote areas are less involved.

1.294

METABOLIC CHANGES AFTER SELECTIVE TEMPORO-MESIAL RADIOSURGERY VERSUS AMYGDALO-HIPPOCAMPECTOMY IN MESIO-TEMPORAL LOBE EPILEPSY

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Rationale: The purpose of our study was to compare the metabolic consequences of two selective surgical procedures in medial temporal lobe epilepsy (MTLE): selective amygdalo-hippocampectomy (SAH) and gamma-knife radiosurgery (GK).

Methods: We included 18 patients with drug resistant MTLE associated with unilateral hippocampal sclerosis. 10 patients were treated by SAH (group 1) and 8 by GK (group 2). A positron emission tomography (PET) scan using 18-fluorodeoxyglucose (18FDG) and a magnetic resonance imaging (MRI) were performed twice for each patient, before SAH and GK and at least one year after. Group analysis of 18FDG-PET imaging were performed using statistical parametric mapping software (SPM99) and a group of 10 control subjects.

Results: The comparison between preoperative and postoperative FDG-PET scans demonstrated a statistically worsening of the hypometabolism after both SAH and GK. As expected in group 1, we found, a worsening of the hypometabolism in the medial temporal lobe structures ($p < 0{,}001$) that have been surgically removed, but also in the ipsilateral temporal pole ($p < 0{,}001$), in the caudate nucleus and in the thalamus, that have been anatomically spared. In group 2, we only reported a worsening of the hypometabolism in the medial temporal lobe structures ($p < 0{,}01$) and in the ipsilateral temporal pole ($p < 0{,}007$). The comparison of metabolic data after both procedures shows a similar hypometabolism worsening in the ipsilateral temporal pole, even if it was more severe after SAH than after GK on the medial temporal structures ($p < 0{,}001$).

Conclusions: Our study demonstrated a less important hypometabolism worsening after GK than after SAH in the medial temporal structures, but a similar worsening in the ipsilateral temporal pole that has been anatomically spared by the surgery. This suggests that functional consequences are more serious after SAH than after GK on medial temporal structures and some distanced structures. These results have to be correlated to seizure outcome and with neuropsychological outcome after surgery.

1.295

VOXEL-BASED MORPHOMETRY IN LATERALIZED TEMPORAL LOBE EPILEPSY

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Rationale: Voxel-based morphometry (VBM) can be used to compare regional differences in gray or white brain matter volume between groups. Applied as an automated method, the technique can elucidate differences that might not otherwise be apparent on normal appearing MR images. Previously, this technique has been used to characterize abnormalities in gray matter (GM) in subjects with temporal lobe epilepsy (TLE). However, few investigations have investigated white matter (WM) in TLE using VBM. This study seeks to use VBM to characterize both GM and WM abnormalities in subjects with lateralized TLE.

Methods: 25 subjects with unilateral TLE (13 left, 12 right) were selected using the following criteria: 1) age 14 to 60 years; 2) ictal EEG confirmation of unilateral temporal lobe seizure onset; 3) absence of MRI abnormalities other than atrophy; 4) no other neurological disorder. Healthy controls were friends or family members of the TLE subjects. The SPM2 software (Wellcome Department of Cognitive Neurology,

University College, London) was used for VBM analysis. VBM was performed with methodology similar to Good et al. (Neuroimage 14, 2001). This includes study-specific-template creation, 12-mm FWHM image smoothing, and the volume-preserving modulation step. Results were corrected for multiple comparisons at FDR < 0.05.

Results: *Gray Matter:* Volume reduction was present in the ipsilateral hippocampus of both left and right TLE groups. Significant volume decreases were also detected in the ipsilateral thalamus of both left and right TLE groups. *White Matter:* A strong WM volume decrease was present in the temporal pole ipsilateral to seizure onset. Volume loss was detected extratemporally in bilateral prefrontal white matter of the left TLE group. Additionally, voxels located in the corpus collosum of both left and right TLE groups and the fornix of the right TLE group indicated significant volume decrease.

Conclusions: Previous region-of-interest based quantitative MRI studies, as well as prior VBM studies using slightly different techniques (concentration changes rather than volume changes as in this study), have reported abnormalities in the hippocampus and thalamus. In the context of these gray matter changes, this investigation detected significant abnormalities in white matter that preferentially affected the ipislateral temporal pole, with secondary effects in the frontal lobes, corpus callosum and fornix. The relationship between these VBM-defined volumetric changes and clinical seizure features such as onset, duration, and seizure frequency/severity will be explored further using VBM. [Supported by NIH NS 2RO1–37738 and MO1 RR03186 (G.C.R.C.)]

1.296

ETIOLOGIES OF STATUS EPILEPTICUS ASSOCIATED WITH MRI CHANGES

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Rationale: Magnetic resonance imaging (MRI) changes due to status epilepticus (SE) have been documented in both animal models and humans. The etiology of MRI changes due to seizures is unknown, although MRI effects are often suggestive of a combination of cytotoxic and vasogenic edema. It is not yet apparent why only certain patients have MRI changes and whether the etiology of the seizure influences the MRI manifestations.

Methods: Using a research patient database, the records of all patients who were admitted to Brigham and Women's Hospital or Massachusetts General Hospital for SE from 1/1999–7/2003 and who also received MRI were reviewed for etiology of SE and MRI changes attributed to seizures.

Results: Eighty-six patients were identified. Ten patients had MRI abnormalities that were likely due to seizures. These consisted of focally increased T2 signal with reversible restricted diffusion in the hippocampus corresponding to the seizure focus (5 cases), increased T2 signal and variable restricted diffusion in the splenium (1 case), and a larger gyral pattern of restricted diffusion corresponding to the apparent seizure focus (4 cases).

In the 5 cases of reversible restricted diffusion in the hippocampus ipsilateral to the side of seizure onset, 3 had epilepsy (2 with extratemporal vascular malformations, 1 with hippocampal sclerosis), and in the other two SE was their initial seizure presentation (1 each with malignant glioma and multiple sclerosis). The patient with focal edema of the splenium had elevated levels of clozapine, and MRI became normal after discontinuation of clozapine and initiation of anticonvulsants. All 4 patients with a gyral pattern of restricted diffusion had possible hypoperfusion and/or hypoxia associated with their seizures; 2 patients had acute myocardial infarctions requiring intubation, 1 had multiple metabolic derangements with episodic hypotension, and 1 had ipsilateral subclavian steal syndrome. Two of these 4 patients died, 1 clinically resolved but did not receive follow-up imaging, and one showed resolution of T2 hyperintensity but developed diffuse atrophy.

Conclusions: In this series of 86 patients in SE, the incidence of MRI changes attributed to seizures was 11.6%. A gyriform pattern of restricted diffusion in the cortical gray matter was seen in patients with possible hypoperfusion in the region of seizure origin. When this pattern is seen in patients with SE, ischemic and/or hypoxic injury should be suspected. The pattern of reversible restricted diffusion in the hippocampus was seen in patients with either hippocampal sclerosis or extratemporal structural lesions, and may demonstrate selective vulnerability of the hippocampus in these situations to seizure induced edematous changes. (Supported by Brigham and Women's Hospital Translational Neuroscience Grant.)

1.297

DEPRESSION IN TLE SURGERY PATIENTS: RELATIONSHIP TO PATTERNS OF EXTRATEMPORAL HYPOMETABOLISM ON FDG-PET IMAGING

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Rationale: Depression is a common and important co-morbidity in patients with medically refractory temporal lobe epilepsy (TLE). In particular, at least 30% of patients who undergo surgery for medically refractory TLE develop clinical depression in the first three months following the surgery. The reasons underlying the association between depression and TLE is uncertain, with both neurobiological and psychosocial explanations postulated. FDG-PET shows hypometabolism in the frontal lobes of depressed non-epileptic patients, and many patients with TLE have hypometabolism involving frontal regions. We studied the patterns of FDG-PET hypometabolism in patients undergoing surgery for medically refractory TLE to determine whether patients who had clinical depression pre-operatively and/or post-operatively demonstrated differences from non-depressed patients.

Methods: A cohort of 23 patients who underwent an anterior temporal lobectomy for medically refractory TLE, had an FDG-PET scan performed as part of their pre-operative evaluation, and had a formal pre- and post-operative psychiatric assessment, were studied. Statistical parametric mapping (SPM-99) was used to compare the patterns of hypoperfusion on FDG-PET between patients who were depressed pre-operatively ($n = 9$) and those who were not ($n = 14$), as well as between those who developed post-operative depression ($n = 13$) compared to those who did not ($n = 11$). The level for determining a significant region of hypometabolism was set at $p < 0.001$ for a cluster of at least 20 contiguous voxels.

Results: Pre-operatively depressed patients showed a focal region of hypometabolism in the region of the ipsilateral orbitofrontal cortex compared with those who were not ($t = 4.64$ $P < 0.001$). Patients who developed depression post-operatively also showed a similar region of significant hypometabolism in the ipsilateral orbitofrontal frontal region ($t = 5.10$, $P < 0.001$).

Conclusions: These results demonstrate a focal region of relative hypometabolism in the ipsilateral frontal lobe on FDG-PET scans in TLE patients who are depressed post-operatively and those who develop depression following temporal lobe surgery. This suggests that this region my play in a role in the neurobiological mechanisms predisposing TLE patients the depression commonly seen in this epilepsy syndrome.

1.298

LOCALIZING EPILEPTIC FOCI USING VARIABLE RESOLUTION ELECTROMAGNETIC TOMOGRAPHY (VARETA)

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Rationale: Source-analysis techniques have been applied to localize cortical generators of scalp-recorded epileptic spikes and rhythmic ictal potentials. However, source analysis of the EEG background itself has seldom been attempted in partial epilepsy. Variable Resolution Electromagnetic Tomography (VARETA) allows frequency-domain

source-localization of background EEG potentials. We sought to determine the value of VARETA in localizing epileptic foci by applying this technique to scalp-recorded EEG from patients with partial epilepsy.

Methods: We obtained samples of standard digital EEG recordings from 6 adult patients who later underwent invasive intracranial EEG localization of their epileptic foci. We selected two-minute-long samples of artifact-free EEG for analysis. Our analysis first transforms the time-domain EEG data into the frequency-domain. The source generators of the EEG at each frequency is then computed using VARETA and registered in MNI brain coordinates. The magnitude of the generator at each voxel is compared to values based upon a normative EEG database of 305 normal adult subjects and Z-score deviations from norm are computed and displayed. The analysis is repeated at several different EEG frequencies. We applied this method blinded to clinical data from each patient, and compared the results of VARETA analysis to localization based on invasive intracranial EEG, visual analysis of the EEG sample, and 2-D topographic spectral maps generated by conventional Q-EEG techniques.

Results: Lateralization and localization of seizure foci to a lobe based on VARETA analysis in the delta and theta range was concordant with the results of intracranial recordings in all of the 6 patients studied. The presence of bi-temporal dysfunction in one instance, and bi-hemispheric extra-temporal dysfunction were correctly predicted by VARETA analysis. By comparison, visual inspection of the EEG samples correctly localized dysfunction to a hemisphere in 5 patients, but was able to localize epileptic dysfunction to a lobe only in 1 of the 6 patients. Visual inspection of the 2-D topographic spectral maps lateralized the focus in 2 patients, while localization to a lobe was possible only in 1.

Conclusions: Source localization of background EEG activity using VARETA can potentially lateralize and localize epileptic dysfunction to a lobe. The EEG signal frequencies at which VARETA analysis yielded the best results were in the theta and delta range. At these frequencies, VARETA may provide a novel technique for imaging epileptic foci even in the absence of population-based normative EEG data. (Supported by F.A.C.E.S Foundation, New York, U.S.A.)

1.299

INVIVO MRI BASED STEREOLOGICAL ESTIMATION OF THE ISOPERIMETRIC RATIO IN TEMPORAL LOBE EPILEPSY

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Rationale: The folding or gyrification of the cerebral cortex is a developmental process, which allows for an increase in cortical surface area and inter-neuron connectivity without a disproportionate increase in cranial size relative to body size. Cortical developmental malformations (CDM) may give rise to disruption in the folding process. The isoperimetric ratio (IR), a measure of the degree of cortical folding, is defined as the ratio of the total cortical surface area (SA) to the total volume (V) of the cerebrum to the power of two thirds. With the advent of MRI, CDMs are increasingly recognised as a cause of epilepsy. An abnormal IR may be a surrogate for subtle CDMs. This measurement has not previously been reported for an epilepsy population.

Stereology is a tool used to estimate geometric information of a three-dimensional object based on two-dimensional information of that object. Stereological estimates are based on the rules of geometric probability and are considered to be mathematically unbiased, in addition they are routinely robust and time-efficient. Stereological estimates are generated by counting the number of intersections a test probe has with the geometric structure of interest. For isoptropic, uniform, randomly orientated test probes with respect to the object, the number of intersections generated is proportional to the geometric property of interest.

Methods: High resolution 3D SPGR MRI brain image data was acquired from five normal control subjects and five temporal lobe epilepsy (TLE) patients. For each individual the IR was derived from stereological estimates of cerebral volume and surface area.

Results: The mean and standard deviation of cerebral surface areas for the control group was 1595cm^2 (32.14), and for the TLE group was 1686cm^2 (192.22). Mean (SD) cerebral volumes were 1143cm^3 (53.27) and 1146cm^3 (66.29) for the control and TLE groups respectively. For the control group the mean (SD) IR was 15.03 (0.59) and for the TLE group was 16.11 (1.45). Three out of five TLE patients demonstrated increased IR measuring greater than 2 standard deviations above the mean of the control group.

Conclusions: This preliminary study demonstrates the application of stereological techniques for the *in-vivo* quantification of the degree of gyrification of the human cerebrum based on the IR. Volume, surface area and IR measurements in this study are in agreement with previously reported studies in literature. Results support the concept of IR as a surrogate for subtle CDMs, which may not be readily identifiable under routine visual inspections of MRI data. The identification of CDMs may facilitate a fuller understanding of the influencing factors of the epileptic brain. A larger study is planned to apply the IR to a homogeneous group of epileptic patients as well as a group of age, handed and sex-matched controls. (Supported by the Brain Research Foundation and the Irish Institute of Clinical Neuroscience.)

1.300

MULTIPLE SPATIAL NETWORKS SUBTEND GENERALISED SPIKE-WAVE ACTIVITY DURING HUMAN ABSENCES: AN ICA STUDY OF SIMULTANEOUSLY ACQUIRED ICTAL EEG/FMRI DATA

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Rationale: To determine whether the spatial networks underlying generalised spike-wave activity during human absence seizures are identifiable using fMRI data alone.

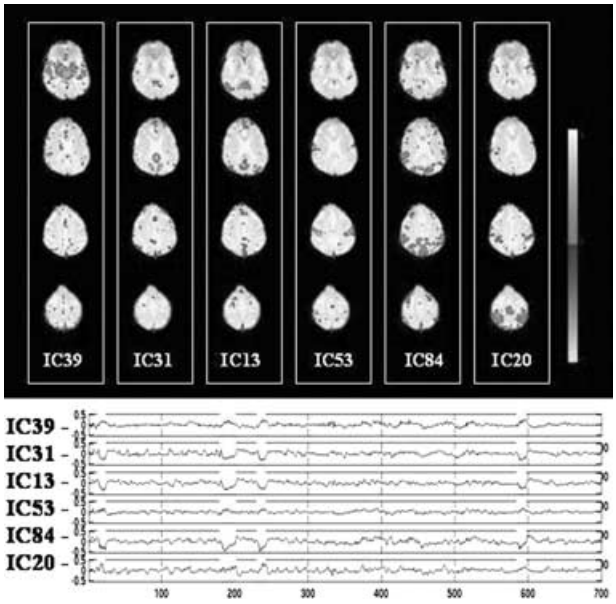

Fig. 1. Five thresholded IC maps (alternative hypothesis test at $p > 0.5$) are shown with their corresponding timecourses underneath. Four absence seizures are indicated with gray shading.

Methods: Spatiotemporal Independent Component Analysis (ICA) was performed using MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) version 2.0, part of the FSL software package (FMRIBs Software Library, http://www.fmrib.ox.ac.uk/fsl), on ictal fMRI data acquired previously from a patient with intractable Idiopathic Generalised Epilepsy[1].

Pre-processed data (masked, mean corrected and variance normalised) was whitened and projected into a 111-dimensional subspace using probabilistic Principal Component Analysis where the number of dimensions was estimated automatically. The observations were decomposed into a

set of time-courses and spatial maps by optimising for non-Gaussian spatial source distributions using a fixed-point iteration technique. Estimated Component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity values (probabilistic ICA). All time-courses were ranked according to degree of correlation with seizure onset and the corresponding spatial components contrasted with the results of a General Linear Model (GLM) analysis.

Results: At least ten independent components were identified as contributing to the previously reported pattern of thalamic activation and cortical deactivation, each with a timecourse mirroring the ictal EEG activity (see Fig. 1).

Conclusions: Our observations indicate that a weighted mixture of several *independent* spatial networks may simultaneously subserve the generation of generalised spike-wave activity in man. A mechanism is therefore provided, whereby subject or syndrome-specific changes in this blend, could account for a number of apparent discrepancies in the EEG/fMRI literature[1–3].

Our results also support the notion that the haemodynamic consequences of prolonged spike-wave activity may be identifiable using fMRI alone.

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1.301
CEREBRAL PERFUSION CHANGES IN PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY: SPM ANALYSIS BETWEEN SPECT IMAGES OF PATIENTS AND CONTROLS

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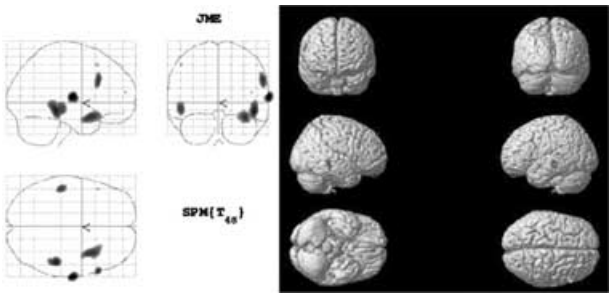
Rationale: Patients with juvenile myoclonic epilepsy (JME) show normal brain MRI. To investigate the abnormality of cerebral perfusion in patients with JME, statistical parametric mapping (SPM) was performed between SPECT images of patients and controls.



Methods: ^{99m}Tc-ethyl cysteinate dimer brain SPECT was performed in 25 JME patients (21.1 ± 5.0 years) and 25 age & sex-matched 25 controls (23.0 ± 4.4 years). For SPM analysis, all SPECT images of patients and controls were spatially normalized to the standard SPECT template, then smoothed with 14-mm full width at half maximum gaussian kernel. The *t*-test was performed for comparison between two groups. The height threshold was set to uncorrected $P < 0.005$, and extent threshold was set to $K_E > 50$.

Results: The JME group showed singificant interictal hypoperfusion in right superior temporal gyrus (x,y,z:68,-12,8, BA = 42, $P = 0.004$; x,y,z:36,10,-20, BA = 38, $P = 0.001$), right fusiform gyrus (x,y,z:48,-34,-12, BA = 37, $P = 0.001$), right middle frontal gyrus (x,y,z:60,22,30, BA = 9, $P = 0.001$), and left middle temporal gyrus (x,y,z:60,22,30, BA = 9, $P = 0.001$) but there was no brain regions showing interictal hyperperfusion (Fig. 1).

Conclusions: JME patients showed decresaed cerebral perfusion in right frontal lobe and bilateral temporal lobes. Absence of interictal hyperperfusion suggesting neuronal irritability may be related to the use of antiepileptic drugs in most of the patients. [Supported by a grant (no. HMP-03-PJ1-PG3-21300-0033) of the Good Health R&D Project, Ministry of Health & Welfare, Republic of Korea.]

1.302
PILOT STUDY OF THE UTILITY OF DIFFUSION TENSOR MRI IN LATERALISING NONLESIONAL TLE

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Rationale: Approximately 40% of patients with medically refractory non-lesional Temporal Lobe Epilepsy (TLE) are not lateralised with current structural MRI techniques including volumetric analysis and T2 mapping. Diffusion tensor (DT) MRI is a relatively new MRI technology that has potential to detect functional abnormalities in patients with normal structural MRI.

Aims: To perform a pilot study to assess the potential for DT MRI to lateralise non-lesional TLE.

Methods: Seven patients with non-lesional TLE (four with hippocampal sclerosis (HS) and four without HS on structural MRI), and well lateralised seizures on ictal-EEG were studied with DT MRI (1.5 Tesla, GE system) performed in 25 directions with b value: 1500 s/mm^2. The tensor signal was quantitated for voxels placed over the hippocampus and anterior temporal pole bilaterally and the side-to-side ratios correlated with the ictal EEG lateralisation.

Results: The tensor signal was higher on the epileptogenic side for the hippocampal voxels in 4/7 (71%) of patients, and for the anterior temporal voxels in 4/7 (51%) of patients.

Conclusions: Fractional anisotropy shows a trend to be decreased in the hippocampus ipsilateral to the EEG lateralization. Quantitation of ADC with DT signal in the hippocampal region shows promise for lateralising non-lesional TLE in this pilot study, but further patients and correlation with surgical outcome is required before its role is established.

1.303
COMPARISON OF ICTAL AND INTERICTAL SPECT ANALYSIS USING ANALYZE® AND AFNI

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Rationale: Single Photon Emission Computed Tomography (SPECT) has been used to assist in localizing the ictal onset zone in patients with intractable epilepsy. Several methods including visual analysis, difference analysis, and subtraction ictal SPECT co-registered with MRI (SISCOM), have been used to analyze SPECT images in an effort to identify the ictal onset zone. However, visual and difference analyses are subject to interobserver variability in interpretation of results. We used Analysis of Functional Neuroimaging (AFNI), a powerful software tool, to analyze ictal and interictal SPECT studies, to lessen subjectivity in the analysis, and to compare results with ANALYZE.

Methods: We analyzed pre-operative ictal and interictal SPECT studies done on nine patients who underwent epilepsy surgery and were subsequently seizure free for six or more months. Ictal and interictal scans were obtained by injecting Tc-99m ECD (ethyl cysteinate dimer, Neurolite). ANALYZE analysis included anatomic registration of ictal and interictal SPECT studies, and normalization of the scans to the mean intensity. Regions more than two standard deviations over the mean in the difference image between normalized ictal and interictal scans were calculated and identified. AFNI analysis involved registration of the interictal and template anatomy with the ictal SPECT scans using FLIRT (Functional Magnetic Resonance Imaging of the Brain's Linear Image Registration Tool), calculation of the mean and normalization of the

scans to mean intensity, converting the anatomy image to Talairach coordinates, calculation and identification of brain voxels more than 2 standard deviation above the difference mean, and finally calculation of the voxel volume for both the ictal CBF increases and decreases and identification of the Talairach coordinates for the mean voxel volume location.

Results: We were able to visually compare the results from Analyze and AFNI. The regions of ictal CBF relative hyperperfusion and hypoperfusion evident on difference images were similar in ANALYZE and AFNI in all nine subjects. We were also able to obtain the voxel volumes and the Talairach coordinates for both hyperfused and hypoperfused regions using AFNI.

Conclusions: Using AFNI, we obtained results nearly identical to those generated by ANALYZE. The voxel volume and Talairach coordinates of the largest regions of CBF increases and decreases were readily obtained. Simultaneous visualization of both the ictally hyperperfused and hypoperfused regions could be easily accomplished using AFNI as compared to ANALYZE, where this required a separate session of image processing. Using AFNI, active thresholding of the difference scans assisted in further evaluating regions of blood flow from 1–4SD above or below the mean, which is an advantage compared to ANALYZE. SPECT image analysis using AFNI can potentially assist in further localizing and characterizing seizure-induced perfusion changes in patients with intractable epilepsy.

1.304

THE EXTENT OF RESECTION OF THE HYPOMETABOLISM ON FDG-PET IS ASSOCIATED WITH OUTCOME FOLLOWING SURGERY FOR TEMPORAL LOBE EPILEPSY

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Rationale: A significant minority of patients undergoing surgery for medically refractory non-lesional TLE continue to have seizures, and the reasons for this are uncertain. Flurodeoxyglucose positron emission tomography (FDG-PET) shows hypometabolism in a majority of patients with non-lesional TLE, even in the absence of hippocampal atrophy. It is controversial whether the surgical resection of the region of temporal hypometabolism influences outcome. We examined whether the extent of resection of the area of hypometabolism on the pre-operative FDG-PET scan influenced outcome following surgery for non-lesional TLE.

Methods: 24 patients who underwent temporal lobectomy for medically refractory TLE with at least 6 months follow-up were studied. The pre-operative FDG PET was compared with 20 non-epileptic controls using SPM-99 to identify regions of significant hypometabolism ($p < 0.0005$, cluster > 200). This image was then co-registered to the post-operative MRI scan using Analyze 7.55 (Mayo Foundation). The volume and brightness area product (BAP) of the FDG-PET hypometabolism that lay within the area of the resected temporal lobe was calculated and expressed as a percentage of the volume and BAP of hypometabolism.

Results: Mean follow-up was 3.01 yrs (range 0.7 – 5.4 yrs). Patients with an excellent outcome had a greater proportion of the FDG-PET hypometabolism volume resected than those with a non-excellent outcome (24.2% vs. 12.0%, $p = 0.04$). Similarly, the percentage of the BAP resected was higher in the excellent outcome group (25.2% vs. 10.6%, $p = 0.04$). Logistic regression demonstrated that the extent of resection of the hypometabolism was significantly correlated with outcome independent of the presence of hippocampal sclerosis ($b = 8.1$, $p = 0.047$ and $b = 1.5$, $p = 0.22$).

Conclusions: The extent of resection of the region of hypometabolism on the pre-operative FDG-PET is predictive of outcome following surgery for non-lesional TLE, independent of the presence of hippocampal sclerosis.

1.305

^{1}H MRS, ^{18}F-FDG PET AND ICTAL SPECT IN PRE-OPERATIVE EVALUATION FOR EPILEPSY SURGERY: A RECENT META-ANALYSIS

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Rationale: To assess the predictive diagnostic added value of MRS, PET and ictal SPECT in the pre-operative evaluation of candidates for epilepsy surgery an extensive meta-analysis from January 1992 to July 2003 was performed.

Methods: From a PubMed search 78 studies presenting detailed diagnostic test results and a classified outcome of the patients were included. Studies exclusively reporting on patients with brain tumors or on children were excluded.

Results: MRS ratio decrease ipsilateral to surgical resection revealed a predictive value of 82% for good outcome (Engel Class I and II) in an unspecified population. The odds ratio of unilateral versus bilateral MRS abnormalities for seizure freedom was 4. 891 [1. 965–12. 172]. Ipsilateral PET hypometabolism showed a predictive value of 86% for good outcome. In patients with normal MRI the predictive value was 80%, and in patients with non-localized ictal scalp EEG 72% respectively. PET did correlate well to the other non-invasive diagnostic tests, but none of the odds ratios of any test combination was significant. The attempt failed for ictal SPECT due to insufficient literature data. Also heterogeneity among the studies and weakness regarding their study design were observed. Besides in 2 studies the additional new information for localizing the epileptogenic zone achived by MRS, PET or SPECT was not stated in the studies. The studies addressed mainly epilepsy patients of temporal lobe origin.

Conclusions: Our data confirm that MRS, PET and ictal SPECT may be an indicator for good post-operative outcome in presurgical evaluation of drug-resistant temporal lobe epilepsy, but under cost-effectiveness aspects their role and value remained questionable and unclear. They should not be used in patients localized by ictal scalp EEG and MRI. Prospective studies limited to patients with non-localized ictal scalp EEG or to MRI-negative patients are required for validation.

Antiepileptic Drugs—Adult 1

1.306

SAFETY AND TOLERABILITY OF DIFFERENT TITRATION RATES OF THE NOVEL AED RETIGABINE

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Rationale: Retigabine (RGB) is currently under development as an adjunctive therapy for the treatment of partial-onset seizures. This study was designed to compare 3 different rates of dose titration to achieve the target dose of 1200 mg/day when administered to patients with partial onset seizures who were already taking one or two other anti-epileptic treatments.

Methods: This randomized, double-blind study consisted of starting the patients on 300 mg/day of RGB administered in 3 divided doses. A total of 73 patients were randomized to one of 3 titration groups: 24 in the 150 mg/2 days group, 25 in the 150 mg/4 days group, and 24 in the 150 mg/7 days group achieving the target dose of 1200 mg/day on day 13, 25 and 43, respectively. The discontinuation rates in the fast- and medium-titration groups were compared with the discontinuation rates in the slow-titration group as a measure of the tolerability of different titration rates.

Results: The discontinuation rates due to adverse events (AEs) were 13.0% in the slow-titration group, 31.8% in the medium-titration group and 43.5% in the fast-titration group. Overall, the most common AEs leading to discontinuation were somnolence, speech disorder, ataxia, dizziness, and asthenia. Significantly more patients discontinued due to AEs in the fast-titration group compared with the slow-titration group ($p = 0.024$; odds ratio $= 5.1$). The incidence of patients discontinuing due to AEs in the medium-titration group was not significantly different from the slow-titration group ($p = 0.124$; odds ratio $= 3.1$). There were

no clinically significant changes in ECGs or laboratory parameters at any of the titration rates.

Conclusions: The titration rate of 150 mg/7 days appears to be best tolerated.

1.307

IMPACT OF LEVETIRACETAM AND TOPIRAMATE ON OUTCOMES OF CARE AND ADVERSE EVENTS INCIDENCE IN A COMMERCIALLY INSURED SETTING

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Rationale: To investigate the difference in outcomes and compare the incidence of adverse events (AEs) in a commercially-insured epileptic patient population initiating levetiracetam (LEV) or topiramate (TPM).

Methods: A retrospective cohort analysis of patients diagnosed with epilepsy was conducted using a large US medical and pharmaceutical claims database. Patients without any LEV or TPM prescription during a 6-month baseline period were classified into mutually exclusive treatment groups based on their first LEV or TPM medication prescription. A minimum 3-month duration of follow-up was required. All relevant claims between July 2001 and September 2003 were considered. Patients were matched on a 1:1 basis by seizure type, mono versus adjunctive therapy and propensity score adjusted for clinical and demographic characteristics. Differences in outcomes (medications, outpatient and inpatient care) were tested by univariate techniques. The risk of adverse events at one year of follow-up was compared across treatment groups using Cox proportional hazards models controlling for confounding covariates.

Results: A total of 1454 and 1297 patients receiving LEV and TPM respectively met the study inclusion criteria. Matching resulted in the selection of 822 patients in each LEV and TPM group. Both groups were comparable with respect to clinical and demographic characteristics: mean age ~31 years, ~64% female, 70% generalized seizures, 66% adjunctive therapy, mean propensity score = 0.53. During follow-up period, LEV was prescribed more often than TPM (mean/patient/year: 12.1 vs 8.5). Furthermore, the annualized mean number of physician office visits was significantly lower in LEV than in TPM (15.3 vs 18.6, $p = 0.004$) as well as the mean number of medications (excluding antiepileptic drugs) per patient per year (19.5 vs 25.9, $p < 0.001$). LEV also showed lower use of other outpatient visits, while use of diagnostic tests and inpatient services was lower in TPM. The rate of patients who did not experience any AE during the follow-up period was 52.6% for LEV versus 47.3% for TPM. Time to first AE was significantly longer for LEV than for TPM (Hazard Ratio: 0.83, $p = 0.006$). Mean duration to first AE was 85 days for LEV versus 73 days for TPM.

Conclusions: In a commercially-insured setting, treatment with LEV was associated with a significantly lower use of common health care services compared to TPM. Data suggest better adherence to treatment with LEV. In addition, LEV patients were significantly less likely to experience AEs than TPM patients. (Supported by UCB Pharma S.A.)

1.308

USE OF LEVETIRACETAM PLASMA LEVELS MONITORING IN THE MANAGEMENT OF PATIENTS WITH EPILEPSY

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Rationale: The aim of this study was to evaluate if monitoring levetiracetam (LEV) plasma levels can be useful in the management of patients with epilepsy.

Methods: This study includes 30 patients with epilepsy, 20 females and 10 males, mean age 39.4 yrs, 25 with Focal Epilepsy and 5 with Generalized Epilepsy, all already treated with two or more appropriate AEDs. LEV was used as adjunctive treatment of refractory seizures in 28 patients; in the remaining 2, already seizure free, LEV was added with the goal of successively reducing concomitant AEDs. After stabilization of the new therapeuthic regimen, with LEV daily oral dosages ranging between 2–3 g, LEV plasma concentrations were evaluated before carrying out further changes of AED treatment. LEV quantitation was performed by a HPLC method (ES/IS) and detected using a PDA. Plasma levels between 10–40 μg/mL were considered in therapeutical range. Patients were considered responders to add on LEV therapy when a reduction of seizures $\geq$50% in respect to baseline was observed.

Results: *At the time of LEV plasma levels evaluation:* 5 patients were seizure free; they were candidate to reduction of concomitant AEDs, which caused side effects in most cases. In 3 of these subjects LEV plasma levels were at the mid of the therapeutical range, and withdrawal of concomitant AEDs was started without any change of LEV oral dosage. In the other 2, in whom LEV plasma levels were at the lowest end of the range, withdrawal of concomitant AEDs was accompanied by an increase in LEV oral dosages. All these 5 patients remained seizure free after reduction/withdrawal of concomitant AED therapy. 13 patients were responders with a $\geq$50% reduction of seizure frequency. In most of them LEV plasma levels were at the lowest end of the therapeutical range, with the remaining showing plasma levels at the mid/high end of the range. In all these 13 subjects LEV oral dosages were increased, resulting in a further reduction of seizure frequency in 8 patients (3 becoming seizure free and 5 reaching a $\geq$75% seizure reduction). 12 patients were non responders, having shown no change or a $<$ 50% reduction in seizure frequency. In 2 of them LEV plasma levels were found below the therapeutical range: these patients admitted non compliance to LEV therapy. In the remaining, LEV plasma levels were at the lowest end of the therapeuthical range in 8 and at the mid/high end in 2. In these 10 patients LEV oral dosage was increased, resulting in $\geq$50% reduction of seizure frequency in 5 cases.

Conclusions: In our sample of polytherapy patients, in whom further increase of LEV oral dosage or tapering of concomitant AEDs could have been problematic, evaluation of LEV plasma levels was extremely useful, resulting in increase of responders.

1.309

POPULATION PHARMACOKINETICS OF TOTAL VALPROIC ACID (VPA) CONCENTRATIONS IN ELDERLY NURSING HOME RESIDENTS

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Rationale: Very little information is available on antiepileptic drug pharmacokinetics in elderly nursing home residents. Contemporary population pharmacokinetic approaches enable the use of sparse data to characterize pharmacokinetics and relate them to patient-specific covariates. The objective of this study was to identify covariates that affect VPA clearance in elderly nursing home residents.

Methods: Data were collected from June 1, 1998 to December 31, 2000. Entry criteria included residency in a nursing home for at least two months, aged 65 years or older, a stable dosing regimen of VPA for at least 4 weeks, VPA concentration(s), and complete dosing information including time, date, and dose of the last four VPA administrations. Apparent oral VPA clearance (CL/F) was analyzed by NONMEM. A one-compartment model with first-order absorption and elimination was used. Both volume and absorption rate constant were fixed (14 L and 1 hr^{-1}, respectively). Information on 23 covariates was available for testing. Dichotomous covariates present in less than 10% of the population were not included, leaving 15 covariates tested. Covariates were tested by forward-inclusion and backward-elimination. Interindividual variability in clearance was estimated using an exponential error model and expressed as a coefficient of variation (CV%). Residual error was estimated using a combined additive and constant CV error model. An objective function decrease of 7.9 (χ^2, $p < 0.005$) for forward-inclusion and increase of 10.8 (χ^2, $p < 0.001$) for backward elimination were used to determine significance.

Results: The study consisted of 405 observations from 146 (52 men, 94 women) elderly nursing home residents. The population CL/F was 0.843 L/hr with CL/F being 1) 27% lower in female residents; 2) 41% greater when the resident was on concomitant carbamazepine (CBZ) or

phenytoin (PHT) co-therapy; and 3) 25% greater when syrup formulation was used. Therefore, the final model was CL/F (L/hr) = 0.843 × 0.729 (if female) × 1.41 (if on CBZ or PHT co-therapy) × 1.25 (if formulation is syrup). Variability in CL/F was 32.9%. CV and standard deviation of the residual error were 18.2% and 10.6 mg/L, respectively.

Conclusions: The mean population CL/F of VPA is lower in elderly nursing home women than in men. Patients taking a metabolic inducer (CBZ or PHT) along with VPA or taking the syrup formulation have a higher clearance than patients without CBZ or PHT co-therapy. The increased CL/F in patients taking VPA syrup may be due to a decreased bioavailability rather than an increased CL. This could be associated with pathology requiring use of syrup rather than an inherent property of the drug formulation. (Supported by NIH NINDS P50-NS16308.)

1.310
NONCONVULSIVE STATUS EPILEPTICUS IN TWO PATIENTS RECEIVING LEVETIRACETAM TREATMENT

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Rationale: Levetiracetam (LEV) is a new antiepileptic drug licensed for add-on treatment of patients with partial seizures with or without secondary generalization. In several placebo-controlled clinical studies its efficacy as well as tolerability has been demonstrated. Although the mechanism of action of LEV has not been fully elucidated, the drug does not appear to act at any recognized site of antiepileptic drug activity implying a potentially unique mechanism of action. So far, only few patients with increase of seizure frequency have been reported under LEV medication which can occur with every antiepileptic drug treatment.

Methods: We report two patients with intractable epilepsy with partial seizures who developed a nonconvulsive status epilepticus on treatment with LEV. Both patients never had a status epilepticus in their medical history.

Results: Patient 1: 71 year old male patient with symptomatic epilepsy with complex partial seizures after radiotherapy of a frontal astrocytoma 1985. Seizure frequency 1–3 seizures per month with carbamazepine (CBZ) monotherapy. Add-on LEV in a dosage of 2000 mg/day since end of 2001. In april 2003 emergency admission in nonconvulsive status epilepticus by means of clinical status and EEG pattern. After intravenous administration of clonazepam the manifestations ceased. CBZ monotherapy was started.

Patient 2: 30 year old male patient with epilepsy with primary complex partial seizures due to mesial temporal lobe sclerosis. Seizure frequency on treatment with valproic acid (VPA) and CBZ was 1–2 seizures per month. Following presurgical monitoring with only one seizure after drug withdrawal LEV monotherapy was started with dosage up to 2000 mg/day. After a 4-week seizure free interval the patient was admitted in nonconvulsive status epilepticus with complex partial seizures. Diagnosis was made on clinical presentation and EEG changes. Status ceased under intravenous treatment with clonazepam. LEV was tapered off and lamotrigin started. Te patient was again admitted in nonconvulsive status epilepticus while still on 500 mg LEV per day. Status ceased again on intravenous clonazepam, LEV was discontinued.

Conclusions: In both patients first-ever nonconvulsive focal status epilepticus occurred on treatment with LEV monotherapy in a dosage of 2000 mg/day. Patient 2 even had status recurrence under 500 mg LEV. We postulate a correlation between occurrence of nonconvulsive status and treatment with LEV in these two patients.To our knowledge, apart from singular mentally retarded patients with status epilepticus under high dosages of LEV this has not been described before. Seizure aggravation as well as a possible paradoxical effect have to be considered as underlying mechanism.

1.311
PREVALENCE OF PARKINSONISM IN A COHORT OF PATIENTS EXPOSED TO ANTIEPILEPTIC DRUGS

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Rationale: Following reports of a syndrome of reversible parkinsonism with normal β CIT –SPECT in patients exposed to sodium valproate(VPA) the authors wished to establish the prevalence of this symptom in people taking anti-epileptic drugs(AEDs) by means of a validated 11 item screening questionnaire for parkinsonism

Methods: Three hundred and fifty six consecutive patients with epilepsy attending a tertiary epilepsy clinic(Hope Hospital) and a district general neurology clinic(Leigh Infirmary) were recruited. Patients with learning difficulties, progressive neurological conditions, history of previous head injury were excluded. Patients were asked to complete an 11 item validated questionnaire(sensitivity 84.4%, specificity 86.3%) designed to screen for parkinsonism. Forty-two controls were recruited from healthy relatives accompanying patients to the clinic and from hospital staff. Twenty-one patients diagnosed as having Parkinson's Disease(PD) (Presence of at least 2 of the following; resting tremor, bradykinesia, rigidity) were recruited.

Results: 356 patients completed the questionnaire, 75 were found to be taking/or have taken psychotropic or anti-emetic medication and were excluded from further analysis.

One hundred and thirty-two patients took one anti-epileptic(AED) drug only. There were no significant differences between the VPA, Carbamazepine(CBZ) or Lamotrigine(LTG) groups for age at time of study or duration of epilepsy. There were no significant difference for age between epilepsy patients and controls. Patients with PD were significantly older. A further 38 patients took VPA plus one other AED, 22 took LTG plus one other AED, 33 took CBZ plus one other AED.

Chi-square test of the three monotherapy groups showed no significant difference in the number of individuals with positive questionnaires suggesting the presence of parkinsonism between the three groups or when compared with the control group. Chi –square became significant when the Parkinsons Disease group PD was added to the analysis. When the duel therapy groups were combined with the monotherapy groups for the purpose of analysis there were no significant differences between the groups.

Conclusions: Previous studies of the prevalence of parkinsonism in patients taking VPA suggest a rate of 6 per hundred as opposed to the age adjusted prevalence of parkinsonism of 1 in 500. This study which is the largest to date suggests the prevalence of parkinsonism in people exposed to VPA is not as high as previously thought. However it must be borne in mind that the present study's methodology is different from earlier studies and we have not as yet clinically examined all the participants. Further studies are required to explore the incidence and aetiology of this phenomenon.

1.312
STEADY-STATE BIOEQUIVALENCE OF 25-, 50-, AND 100-mg ZONISAMIDE CAPSULES GIVEN AT EQUAL DOSES IN HEALTHY ADULT VOLUNTEERS

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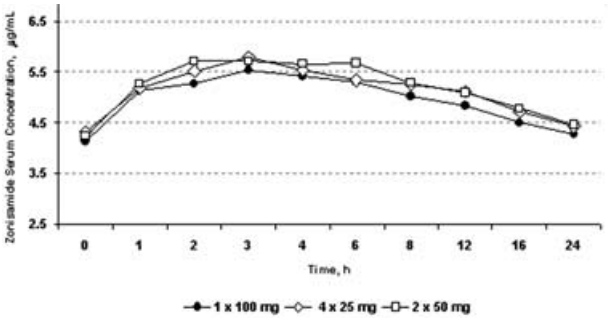
Rationale: Zonisamide was approved in the United States with a single dose strength (100-mg capsules). Subsequent clinical experience has shown that initiation of zonisamide at dosages less than 100 mg/d and maintenance dose adjustments less than 100 mg/dose are useful in optimizing therapy. In order to facilitate better therapeutic titration and improve treatment flexibility, new zonisamide dose strengths (25- and 50-mg capsules) have been developed. This study compared the bioavailability of these new formulations to that of the 100-mg capsules using equipotent dosages.

Methods: This single-center, open-label, 3-period, randomized, crossover, steady-state study was conducted to establish bioequivalence of four 25-mg or two 50-mg capsules with a single 100-mg capsule of zonisamide, each given once daily, in healthy adults. Eighteen subjects completed three 14-day periods of zonisamide treatment, 1 period for each of the 3 treatments. Attainment of steady state was assessed by comparing zonisamide predose trough concentrations on Days 12

through 14 to those on Day 15 for each treatment. Serum zonisamide concentrations were also measured over a 24-hour interval on Day 14 of each period using a high performance liquid chromatography method to determine minimum steady-state plasma concentration ($C_{min,ss}$), maximum steady-state plasma concentration ($C_{max,ss}$), time to maximum steady-state plasma concentration ($t_{max,ss}$), and area under the time-concentration curve (AUC_t).

Results: Steady state was achieved by Day 13 for each capsule strength. The pharmacokinetic parameters C_{min}, C_{max}, t_{max}, and AUC_t were similar for the 3 dosage regimens. Serum zonisamide concentrations for the 3 dosing regimens on Day 14 are shown in Fig. 1.



Bioequivalence was established for both the 25 mg × 4 and 50 mg × 2 treatments, compared with a 100-mg capsule because the geometric mean ratio estimates and associated 90% confidence intervals of log-transformed $C_{max,ss}$ and AUC_t values were within the interval of 80% to 125%.

Conclusions: Four 25- or two 50-mg zonisamide capsules once a day were found to be bioequivalent to a single 100-mg capsule, demonstrating dose-form proportionality. The lower-strength capsules will facilitate initiation of zonisamide therapy and permit small adjustments in maintenance dosages. (Supported by Eisai Inc.)

1.313
INCREASE ^{99m}Tc-SESTAMIBI (MIBI) LIVER CLEARENCE COULD IDENTIFIED EPILEPTIC PHARMACORESISTANT PATIENTS: A PRELIMINARY STUDY

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Rationale: A currently favored hypothesis in the pharmacoresistant epileptic patienst, is the overexpression of multidrug transporters, specially P-glycoprotein (Pgp-170), this is normally expressed in biliary canalicular surfaces of hepatocytes and it is responsible for the excretion of cationic metabolites from the liver. The MIBI is a substrate for Pgp-170. The aim of the present study was to determine the MIBI liver clearence characteristcs in refractory epileptic patients

Methods: We included 12 epileptic patients(EP) and 7 normal control (NC). The mean age was EP: 34,25 y (22–50) and NC :48 (44–51), 12 females. After the intravenous administration of 15 mCi of MIBI, we adquired 60/1 minute images, over the abdomen. We generated activity/times curves over the liver in order to calculated the excretion mean time(T1/2)(time to reach the 50% of maximun liver uptake). The patients and controls fasten 3 hours prior to the study. The kinetic study was analysed blinded to the clinic characteristics or pharmacological response.

Results: The NC T1/2 was 7789.7s(sd:3739). The EP T1/2 was 3200s(sd 2637.7),in four patients of this group the kinetics was identical to the NC. All of them have good pharmacological response(RP). The other eight EP, have an accelerate T1/2 (p:0.001; Table 1) and the entire group corresponding to the pharmacoresistant epileptic patients (NRP).

Conclusions: Our results, suggest that in patients with pharmacoresistant epilepsy (RE), the drug excretion mechanism could be overexpressed and actived, resulting in an accelerated drugs liver clearence. As visualized in real time by this MIBI kinetic study. We don't know if this accelerated kinetic results are secondary to the develop of refractory phenotype, or they are present as an early feature of this patients.

We conclude that the liver clearence of MIBI could be a kinetic useful and non invasive tool for better characterization of patient with pharmacoresistant epilepsy

Statistical Analysis (Analysis of variance)	
Group	AOV
EP vs NC	p:0.0099
RP vs NRP	p:0.04
NRP vs NC	p:0.001
RP vs NC	p: 0.3229 (NS)

EP: epileptic patients; RP: responsive patients; NC: normal control; NRP: non responsive patients.

Liver Clearence Mean Time (T 1/2)					
Group	n	T1/2	MINIMUN	MAXIMUN	SD
Normal Control (NC)	7	7789.7	2750	13280	3739
Epileptic Patients (EP)	12	3200.9	1690	11298	2637.7
Non Responsive Patients (NRP)	8	2168	1690	2970	459.21
Responsive Patients (RP)	4	5266	2461	11298	4060

T 1/2 expressed in seconds.

(Supported by Instituto de Investigaciones Neurologicas "Dr. Raul Carrea." Fundacion Lucha Enfermedades Neurologicas de la Infancia-FLENI Buenos Aires, Argentina.)

1.314
TALAMPANEL AND HUMAN CORTICAL EXCITABILITY: EEG AND TMS

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Rationale: Talampanel (LY 300164) is a potent and selective, orally active noncompetitive AMPA receptor antagonist with anticonvulsant and neuroprotective properties. We sought to identify human neurophysiological parameters [(EEG and TMS (transcranial magnetic stimulation)] sensitive to blockade of AMPA receptors that can be used to functionally monitor synaptic AMPA receptors during treatment trials with AMPA receptor antagonists.

Methods: Six healthy volunteers were given single oral doses of talampanel (25 or 50 mg) or placebo. An 18-lead EEG recording was acquired for 1h before treatment and for 3 h after treatment. Averaged 1 min epochs were analyzed for α, β, and γ activity by FFT. Single and paired magnetic pulses were applied over the scalp to activate the abductor pollicis brevis muscle. Resting and active motor thresholds, recruitment curves and intracortical inhibition/facilitation were determined.

Results: Talampanel treatment was associated with a dose-dependent increase in β (fast, >13 Hz) activity (peaking at 1 h) with no change in α. In the TMS studies, resting and active motor thresholds were elevated by talampanel, and the recruitment curve gradient was decreased, particularly at stimulation intensities close to the threshold value, suggesting that AMPA receptors are critical to motor unit recruitment at lower stimulation intensities. Talampanel was not associated with any consistent change in intracortical inhibition or facilitation. Placebo treatment failed to affect any of the EEG or TMS parameters.

Conclusions: Blockade of brain AMPA receptors causes an increase in EEG β activity. The resting and active thresholds for TMS-evoked

motor activity are highly sensitive to AMPA receptor blockade and there are also specific changes in the recruitment curve. These parameters can be used to monitor in real time the extent of blockade of synaptic AMPA receptors during treatment trials with AMPA receptor antagonists. (Supported by National Institute of Neurological Disorders and Stroke, NIH.)

1.315
LONG-TERM RETENTION AND EFFICACY OF LEVETIRACETAM IN A LARGE COHORT OF PATIENTS WITH CHRONIC EPILEPSY

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Rationale: To determine the long-term retention rate and outcome of treatment with levetiracetam (LEV) in patients with chronic epilepsy.

Methods: Patients with chronic epilepsy attending a tertiary referral centre for epilepsy were prospectively enrolled in this evaluation if they had LEV started within the first 24 months post-marketing of LEV in the United Kingdom. The following variables were analysed: retention rate of LEV at last follow-up; LEV dosage; percentage of patients achieving seizure freedom; percentage of patients achieving ≥50% seizure reduction; percentage of patients discontinuing LEV and reasons for discontinuation.

Results: Eight hundred and eleven patients (49% male), aged 14 to 79 years (mean 37 years), were included in the study. Longest duration of follow-up was 41 months. At last follow-up, 528 patients (65%) were continuing on LEV, of whom 426 (81%) had follow-up of 12 months or longer. LEV dosages at last follow-up ranged from 125 to 5000 mg/day (median 2000 mg/day). One hundred and forty three patients (18%) attained seizure freedom at any time during treatment, for periods ranging from 1–35 months (mean 11 months, median 10 months). At least a further 237 patients (29%) had a period of ≥50% reduction in seizure frequency. Forty-six patients achieved LEV monotherapy, and 26 of these had periods of seizure freedom ranging from 2–35 months (mean 13 months, median 11 months). Seizure freedom was attained in 120/654 (18%) patients with cryptogenic or symptomatic partial epilepsy and 15/68 (22%) patients with idiopathic generalized epilepsy. Two hundred and sixty nine patients (33%) stopped LEV; discontinuation was due to inefficacy in 110 (14%), adverse events in 81 (10%), both inefficacy and adverse events in 75 (9%) and pregnancy in 3 (0.4%).

Conclusions: Nearly two thirds of patients with chronic epilepsy were continuing on LEV therapy at last follow-up. Almost half of patients achieved a period of reduction in seizure frequency of ≥50%, with nearly one in five achieving a period of seizure freedom. This study, evaluating the largest single-centre cohort of patients taking LEV, confirms the efficacy and tolerability of LEV demonstrated in controlled trials. (Supported by The National Society for Epilepsy, United Kingdom.)

1.316
THE PHARMACOKINETICS OF LEVETIRACETAM IN HUMAN CEREBROSPINAL FLUID AND SERUM: A CONTROLLED, DOSE-RANGING STUDY IN MALIGNANT BRAIN TUMOR PATIENTS

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Rationale: Patients with malignant brain tumors frequently suffer from epileptic seizures as a complication, or often, the presenting sypmtom of the neoplasm. Levetiracetam (LEV) has been shown to have unique efficacy in the treatment of refractory seizures in brain cancer patients. LEV also does not have any clinically significant drug-drug intereaction with chemotherapy agents that may be used as a part of the patient cancer treatment program in either primary or secondary neoplasms. Data from rodents and limited human data have shown rapid central nervous system (CNS) peretration and a prolonged elimination half-time ($T_{1/2}$) as measured in the cerebrospinal fluid (CSF). We determined the temporal pharmacokincetic serum-CSF relationship in 9 patients with brain neoplasms requiring anti-epileptic treatment.

Methods: The time to maximum concentration (T_{max}) and the half-life ($T_{1/2}$) of LEV was measured concurrently in the serum and CSF in 9 patients after a single oral loading dose of LEV at 500, 750, 1000, 1500 and 2000 mg. CSF levels of LEV were obtained through an Ommaya reservoir which had been previously inserted in each patient to appropriately treat brain cancer. Serum and CSF LEV levels variously were obtained just before oral loading of LEV and after 1/2, 1, 2, 3, 5, 8, 12, 15, 24 and up to 48 hours after oral loading. All samples were stored at −75 ° C.

Results: The mean T_{max} of LEV in serum was 5.2 hours (range 1–7). The mean T_{max} of LEV in CSF was 7.3 hours (range 3–15). The mean $T_{1/2}$ of LEV in serum was 13.3 hours (range 4–20). The mean $T_{1/2}$ of LEV in CSF was 24 hours (range 13–40). Four of the 9 patients received a single dose of 2000 mg of LEV. The mean serum T_{max} for these 4 patients was 7.5 hours (range 7–11) with a mean CSF T_{max} of 9.4 hours (range 5–15) with peak LEV levels of 34.4 and 29.8 ug/ml respectively. The mean $T_{1/2}$ of these 4 patients in serum was 17.6 hours (range 10.5–20) with a mean CSF $T_{1/2}$ of 29.5 hours (range 18–40). There were no side effects at any dose except for transient somnolence in one patient after a 2000 mg loading dose.

Conclusions: Peak levels of LEV are achieved rapidly in both the serum and CSF after a single oral loading dose. LEV CSF $T_{1/2}$ is twice as long as that of LEV $T_{1/2}$ in serum. Significant CSF levels may be reached in fewer than 10 hours after a single 2000 mg oral dose. LEV may be orally loaded to obtain rapid serum and CSF levels with good tolerance for patients who may need AED therapy with LEV. The sustained half-life of LEV in the CSF indicates a long central duration of action. (Supported by UCB.)

1.317
THE DECISION POINT DOSE: RAISE THE DOSE OR ABANDON THE DRUG?

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Rationale: Traditional dogma is to increase drug dose to either complete seizure control or to clinical toxicity. Problems with this approach include difficulty in recognizing the onset of clinical toxicity and the inordinate time required to follow this procedure with multiple drug choices. A meta-analysis of published dose-response data suggests a decision on efficacy can often be made short of the point of clinical toxicity. For a particular drug, this possibility depends upon the shape of the dose-response curve. The dose above which a predefined incremental chance of clinically useful seizure reduction is unlikely may be defined as the "decision point dose." At this point, it may be more rational to switch drugs rather than persist to higher doses. This point is best definable for drugs which display a ceiling effect, for which the dose-response curve flattens out. If the percentage of patients expected to respond to a clinically-useful degree to any dose higher than this is lower than the expected response rate to a differerent drug, weighing patient-specific factors, then the better choice may be switching drugs.

Methods: The "decision point dose" was defined operationally as the dose beyond which an incremental increase in the responder rate, RR (patients with 50% improvement in seizure frequency from baseline) of more than 10% did not occur with cumulative higher doses, on average, in published dose-ranging trials, both controlled and open-label. Data for three representative drugs used as adjunctive treatment for partial-onset seizures were analyzed.

Results: Topiramate doses of 400 mg/day produce an RR of about 40%; higher doses raise this <5%. One trial reporting an RR for 450 mg/day of 50.6% did not include a comparison to lower doses. For gabapentin, doses over 2400 mg/day netted few additional responders, although doses in many studies did not exceed 1800 mg/day. On the other hand, oxcarbazepine displayed a relatively linear dose-response relationship all the way through the top dose systematically tested, 2400 mg/day.

Conclusions: Dosing strategy should vary by drug. For oxcarbazepine, it makes sense to follow the traditional strategy of gradual dose increases to the point of clinical toxicity, since there is significant incremental benefit even at a dose, 2400 mg, resulting in 67% dropouts from

adverse events. Increases above the decision point doses for gabapentin, 2400 mg, and topiramate, 400–450 mg, for patients who have not yet responded, are unlikely to provide significant benefit for most patients, but will increase expense and delay other treatments. This concept rests on the assumption that dose-response curves for individual patients, as well as for populations, are similar in shape: if many patients display no response at low doses but suddenly respond dramatically to some dose higher than the "decision point dose," then the concept is invalid; this hypothesis is testable in future trials.

1.318
PHARMACOKINETIC INTERACTION BETWEEN SODIUM VALPROATE (VPA) AND LAMOTRIGINE (LTG): EVALUATION OF THE TIME COURSE OF REVERSAL OF VPA-MEDIATED INHIBITION

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Rationale: LTG kinetics are altered by concomitant treatment with VPA. Therapeutic concentrations of VPA reduce LTG clearance by approximately 50%. Recent studies have suggested that metabolic inhibition of LTG by VPA is rapid in onset and potent. VPA concentrations of 5.6 μg/ml are associated with 50% maximal inhibition of LTG clearance (EC50). An unresolved question involves the time-course of offset, or reversal of this interaction (de-inhibition). Our objective was to characterize changes in LTG serum concentrations immediatly following VPA discontinuation.

Methods: Following written informed consent, 10 healthy adults (7 women/3 men) participated in this open label, 30 day study. At baseline, subjects received LTG (Lamictal 10 mg po q AM) plus VPA (Depakote ER 500 mg po q AM) for 15 days. Blood was obtained on days 14 and 15 in order to determine steady-state serum concentrations of LTG and VPA. VPA was then abruptly discontinued, and serum concentrations of VPA and LTG were determined serially for an additional 15 days. Dosage of LTG was unaltered during this time. VPA and LTG serum concentrations were measured using established immunofluorometric and gas chromatographic methods, respectively. Statistical analysis included ANOVA

Results: Data was analyzed for 9 subjects, (1 subject excluded due to protocol violations). Following concurrent administration for 15 days, mean steady state serum concentrations of LTG and VPA were 457 ng/ml and 43.5 μg/ml, respectively. The first day (study day 16) following VPA discontinuation, mean VPA concentration declined to 11.2 μg/ml, while LTG remained unchanged (451.6 ng/ml). Three days following discontinuation (study day 18), VPA concentration was 0.9 μg/ml. LTG concentrations had only modestly declined to 403.2 ng/ml (p = NS) Between study days 20–24, LTG concentrations progressively declined, and appeared to reach a new plateau by study days 26–28 (226.4–228.7ng/ml, $p < 0.05$ vs baseline), representing approximately a 50% decline in LTG concentrations as compared to baseline during concurrent administration.

Conclusions: These observations demonstrate that the pharmacokinetic interaction between LTG and VPA is reversible. Within 3 days following the discontinuation of VPA, LTG concentrations begin to decline. Consistent with previous observations, VPA mediated inhibition appears, even at realtively low serum concentrations. By 7–9 days following the complete disappearance of VPA from serum, LTG concentrations appear to plateau. From a practical perspective, one would therefore expect LTG concentrations to decline by approximately 50% within 2 weeks following VPA discontinuation, unless dosage adjustments of LTG are made. These observations may be important in patients who are being converted from VPA + LTG combination therapy to LTG monotherapy. (Supported by GSK Research & Development.)

1.319
DIFFERENTIAL EFFECTS OF ANTIEPILEPTIC DRUGS ON SERUM NEUROACTIVE STEROID CONCENTRATIONS IN MEN WITH LOCALIZATION-RELATED EPILEPSY

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Rationale: Androgens play an important role in sexual function. They also have metabolites with potent neuroexcitatory (estradiol-E, dehydroepiandrosterone sulfate-DHEAS) and inhibitory (androstanediol) properties that may influence seizure management. We compared serum levels of these neuroactive steroids in men with localization related epilepsy (LRE) on various antiepileptic drugs (AEDs) and normal controls (NC).

Methods: Subjects were 87 men with LRE [unmedicated > 6 months (No Rx)-12, carbamazepine (CBZ)-25, phenytoin (DPH)-25, lamotrigine (LTG)-25] and 25 NC. Sexual function scores (S-Score), hormone levels [DHEAS, bioactive (BA) testosterone (T), estradiol (BAE) and androstanediol (BAL)] and the ratios of inhibitory to excitatory neuroactive metabolites of T, i.e. BAL/BAE, were compared among groups.

Results: S-scores, DHEAS and BAT were significantly ($p < .05$) lower and BAL and BAL/BAE were significantly higher among CBZ and DPH groups than among NC and LTG groups (Table). LTG did not differ from NC in any of these measures. BAT correlated significantly with BAL/BAE for DPH ($r = .44$, $p = .02$) and CBZ ($r = .42$, $p = .03$) but not for NC ($r = .03$, p = NS) and LTG ($r = .06$, p = NS) groups.

Conclusions: In comparison to LTG, enzyme inducing AEDs (CBZ, DPH) are associated with a theoretically more favorable neuroactive steroid balance (lower DHEAS and higher BAL/BAE) for seizure management, but at the expense of reduced serum BAT levels and sexual function which are in the normal range with LTG use. (Supported by GlaxoSmithKline.)

1.320
SELENIUM DEFICIENCY AND VALPROATE-INDUCED HYPERAMMONEMIA

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Rationale: Valproic acid is a commonly used anticonvulsant agent. Hyperammonemia with or without measurable hepatic abnormalities is a well-recognized side affect of chronic valproic acid treatment. Numerous evidences suggest that selenium may ameliorate some of the adverse metabolic consequences of valproic acid. There is no established treatment for valproic acid induced chronic hyperammonemia. For the past

	S-Score (/20)	DHEAS (ug/dl)	BAT (ng/dl)	BAL (ng/dl)	BAE (pg/ml)	BAL/BAE
Controls (N = 25)	19.0 [18.6–19.4]	281 [235–327]	274 [237–311]	13.3 [10.8–15.8]	24.4 [21.4–27.4]	.62 [.50–.74]
No AED (N = 12)	17.5 [14.9–20.0]	239† [181–297]	245 [169–321]	$20.3^{**/\#\#}$ [15.6–25.0]	26.9 [21.3–32.5]	.81† [.54–1.08]
CBZ (N = 25)	$16.5^{***/\#\#\#}$ [14.8–19.2]	$93^{***/\#\#\#}$ [55–131]	$182^{***/\#\#\#}$ [191–223]	$17.4^{*/\#}$ [14.1–20.7]	21.1 [18.6–23.6]	$.85^{*/\#}$ [.72–.98]
DPH (N = 25)	$16.6^{***/\#\#\#}$ [15.3–17.9]	$119^{***/\#\#\#}$ [91–147]	$211^{***/\#\#\#}$ [189–243]	$19.1^{*/\#}$ [14.8–23.4]	23.6 [21.3–25.9]	$.86^{*/\#}$ [.64–1.08]
LTG (N = 25)	18.6 [17.9–19.3]	265 [179–351]	247 [211–283]	13.1 [14.8–23.4]	21.3 [18.8–23.8]	.67 [.51–.83]

Values are means and 95% CI limits. Comparison to control: † = $p < .10$, $^{*} = p < .05$; $^{**} = p < .01$; $^{***} = p < .001$. Comparison to LTG: $^{\#} = p < .05$, $^{\#\#} = p < .01$, $^{\#\#\#} = p < .001$.

three years we have noted a strong co-relation between selenium deficiency and valproic acid therapy. We evaluated the long-term effect of selenium on valproate-induced hyperammonemia and seizure control.

Methods: The medical records of twelve developmentally delayed adults, all with refractory epilepsy were reviewed retrospectively. Their average age was 38.25 years (ranging from 50 to 22 years). Six of the patients were female, and six were male. All patients had significantly elevated ammonia level with no explanation other than the effects of VPA. All patients had selenium deficiency according to their selenium blood level. All twelve patients received selenium supplement orally. The average length of Selenium therapy was 41.33 months (ranging from 53 to 23 months). The average daily dose was 119mg (ranging from 50 to 200 mg). All patients remained on VPA during selenium therapy. The baseline and post-treatment Se and NH3 levels were measured. One patient was temporarily discontinued from our care and her selenium was stopped. Thereafter, both her seizure frequency and intensity increased. Her selenium supplement was resumed and she was not drop out of the observation.

Results: Before supplemental selenium, the mean selenium level was 88.48 mcg/L (ranged from 67 to 120.7 mcg/ml) and mean NH3 serum level was 84.6 umol/L (ranged from 57 to 102 umol/ml). After selenium treatment, serum Se level increased 31.14% (ranged from 103 to 161 mcg/ml) and NH3 level decreased 20.71% (ranged from 37 to 130 umol/ml). One patient's selenium was discontinued because she was temporarily transferred from our care. After the discontinuation, her seizure frequency increased 25% (from 1 per month to 1.25 per month); length increased 276% (from 245 sec. per month to 922 sec. per month). There was no other explanation found for those changes aside from the discontinuation of selenium supplementation; therefore, Dr. Murti resumed her selenium. The patient has not had any seizure, after the selenium supplement resumed till the time this report is written.

Conclusions: Selenium supplement may help lower ammonia level in patients with valproate-induced hyperammonemia over long-term treatment. Selenium deficiency may lead to the lost of seizure control, even when the patient is remained on the same dose of valproic acid.

1.321

A MULTICENTRE AUDIT OF THE OUTCOME OF LEVETIRACETAM IN 9 UNITED KINGDOM CENTRES

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Rationale: The collection of pragmatic data from multiple clinical settings offers an early opportunity to assess trends in the usage and acceptability of antiepileptic medication.

Methods: Combined anonymous analysis of 9 locally performed clinical audits of the use of Levetiracetam. Data from 2 centres were taken from an intellectual disability population. Two other centres had intellectual disability patients included in their audits. One centre was a paediatric neurology centre and the remainder were from general adult populations. Data were extracted locally from the notes of all identified patients to ascertain retention and seizure change.

Results: A total of 744 patients (341 males and 367 females) were prescribed Levetiracetam in 9 UK treatment centres. Of these, 558 (75%) had partial epilepsy, 156 (21%) had generalised epilepsy and 30 (4%) could not be classified. Outcome data was available for treatment retention and seizure outcome. Follow up data was available on patients for up to 20 months. On average 76% of patients were retained per centre, this reflected a range between centres of 42%-100%. Seizure outcome was analysed on an intention-to-treat basis. 75 (10%) patients achieved seizure freedom, range between centres of 0–17%. 43% of patients, range between centres of 17–71%, showed seizure improvement. Remaining patients were defined as no change or deterioration in their seizure frequency.

Conclusions: Multicentre audit offers a unique insight into clinical practice, though is hampered by variable data gathering. This study has shown that Levetiracetam is widely used on both partial and generalised seizures, is well tolerated and is associated with seizure improvement. The ranges seen between centres is likely to reflect the heterogeneous nature of the epilepsy population. (Supported by UCB Pharma-UK.)

1.322

ADJUNCTIVE THERAPY WITH LEVETIRACETAM IN LENNOX-GASTAUT SYNDROME

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Rationale: Adjuntive treatment with Levetiracetam (LEV) may be efficacious in intractable epilepsy, however, in the developmentally delayed population with Lennox Gastaut syndrome (LGS) there is concern regarding cognitive side effects as well as the effects of polypharmacy. This may lead to early termination of the drug and lack of benefit. This study aims to demonstrate the effects of LEV on patients with LGS on multiple antiepileptic drugs.

Methods: Treatment with LEV in patients with LGS was examined in a retrospective chart review from an epilepsy clinic. Sixty-nine patients with LGS had been identified and 19 were treated with Levetiracetam as an adjunct during their evaluation and treatment over the past 4 years. Diagnosis of LGS was confirmed by demonstrating multiple seizure types and documenting EEG findings of slow spike wave with mental retardation (MR). The number of AEDs used, current and past, and the use of Vagus Nerve Stimulation (VNS) was also followed. The percent reduction in seizures and duration of therapy was calculated after the introduction of LEV. The reason for termination of LEV in patients that did not benefit from adjunctive therapy was determined to be either due to continued intractability or intolerance of side effects.

Results: Moderate to severe MR occurred in 10 males and 9 females with average age of 34.5 years. An average of 2.5 other concurrent AEDs were being used prior to initiation of LEV. An average of 5 other AEDs had be tried prior to the current regimens. Six of the 19 patients were also treated with VNS and continued to have intractable epilepsy. Average duration of treatment was 21 months. Seven patients had a reduction in seizure frequency (3 with 65–75% reduction, 3 with a 50–60% reduction and 1 with a 25% reduction). Eleven had no change in seizure frequency and one had a 60% increase in seizure rate. Side effects of lethargy and irritability were noted on the multiple drug regimens, however, all discontinuations of LEV were due to continued intractability and not due to intolerance.

Conclusions: This retrospective analysis suggests treatment of intractable epilepsy in LGS with LEV is effective when used as an adjunct with other medications. Overall, 37% of patients had a response of reduced seizures. Efficacy and tolerability was maintained despite a 21 month average length of treatment. (Supported by UCB-Pharma.)

1.323

BIOEQUIVALENCE OF SHORT-TIME INFUSIONS COMPARED TO ORAL ADMINISTRATION OF SPM 927

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Rationale: SPM 927 is in clinical development as a drug for treatment of epilepsy and neuropathic pain. The need may arise for a short-term intravenous (iv) replacement of an oral therapy with SPM 927 (eg. during surgery). This continuation of treatment could ideally be performed, if the iv formulation would be bioequivalent to the tablet. This trial was designed to investigate bioequivalence between 30 and 60 minutes (min) infusions of SPM 927 and the orally administered tablet.

Methods: In a single-center, open-label, three-fold crossover trial 24 healthy male subjects (age: 31.8 ± 6.5 ys., weight: 74.7 ± 7.6 kg) received a single dose of 200 mg SPM 927 as 30-min infusion (Treatment A), as 60-min infusion (Treatment B) and orally as tablet (Treatment C). There was a wash-out phase of one week between each treatment. 18 blood samples per subject at each treatment were taken from predose until 72 hours after administration of SPM 927. SPM 927 plasma concentrations were detected with a LC-MS/MS method.

The following pharmacokinetic parameters were determined: AUC_{0-tz}, AUC_{0-inf}, C_{max}, t_{max}, $t_{\frac{1}{2}}$, CL/f. Log transformed data of AUC_{0-tz}, AUC_{0-inf}, C_{max}, and untransformed data of t_{max} were analyzed for each treatment using analysis of variance (ANOVA). Based on these analyses point estimates and 90% confidence intervals (90% CI) for the ratio"30-min infusion/oral tablet" and "60-min infusion/oral tablet" were calculated. Furthermore the differences for t_{max} between the treatments were calculated.

Results: All 24 subjects completed the 3 periods of the trial and were included in the analysis. C_{max} was 5.95 ± 1.49 μg/mL, 5.38 ± 1.10 μg/mL and 5.15 ± 1.40 μg/mL, AUC_{0-tz} was 80.25 ± 16.64 h$*\mu$g/mL, 81.18 ± 17.62 h$*\mu$g/mL and 80.94 ± 17.52 h$*\mu$g/mL, AUC_{0-inf} was 81.60 ± 18.04 h$*\mu$g/mL, 82.38 ± 19.36 h$*\mu$g/mL and 82.65 ± 18.88 h$*\mu$g/mL, t_{max} was 0.7 ± 0.4 h, 1.2 ± 0.5 h and 1.2 ± 1.1 h, $t_{1/2}$ was 11.9 ± 1.9 h, 12.0 ± 2.1 h and 12.1 ± 2.1 h and CL/f was 2.60 ± 0.78 L/h, 2.59 ± 0.81 L/h and 2.56 ± 0.72 L/h after the administration of SPM 927 as 30-minute infusion, 60-minute infusion and orally given drug, respectively.

The ratios "30-min infusion/oral tablet" (90% CI) for C_{max}, AUC_{0-tz} and AUC_{0-inf} were 116% (109–123%), 99% (97–101%), and 99% (97–101%), respectively. The difference "30-min infusion/oral tablet" for t_{max} was −0.48h. The ratios "60-min infusion/oral tablet" (90% CI) for C_{max}, AUC_{0-tz} and AUC_{0-inf} were 106% (99–113%), 100% (98–102%), and 100% (97–101%), respectively. The difference "60-min infusion/oral tablet" for t_{max} was 0h.

Conclusions: 90% confidence intervals of AUC_{0-tz}, AUC_{0-inf} and C_{max} for ratios "30-min infusion vs. oral tablet" and "60-min infusion vs. oral tablet" were within the generally accepted bioequivalence range of 80–125%. Thus, bioequivalence to tablet was shown for both short-term infusions. Therefore, a short term replacement of an oral therapy with SPM 927 by an iv route is possible.

1.324
EFFICACY AND TOLERABILITY OF LEVETIRACETAM IN PATIENTS WITH BRAIN TUMORS AND SEIZURES

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Rationale: The management of seizures in brain tumor patients may be complicated by anti-epileptic drug (AED) interactions with antineoplastic agents, anti-emetics, antibiotics, analgesics, and other medications. Management may be further complicated by adverse effects of AEDs like bone marrow suppression, hyponatremia, and rash. Recent studies suggest that LEV carries less risk of inducing such complications, and investigation of its use in this population is warranted. Our objective was to assess the efficacy and tolerability of levetiracetam (LEV) in patients with brain tumors and seizures.

Methods: This is a retrospective study of 15 patients (ages 24 to 76 years, mean age 48) evaluated between 1-1-03 and 12-1-03. All patients had either primary or metastatic intracranial tumors involving the frontal, temporal, or parietal lobes. All patients had at least one seizure of simple partial, complex partial, or generalized convulsive type. Mean duration on LEV was 7.25 months (range: 3 weeks to 26 months). Mean dose was 1016 mg/day (range: 500 to 2000 mg/day). LEV was monotherapy in 6 patients (40%). Nine patients (60%) were on 1–3 concomitant AEDs. LEV was first-line therapy in three of the fifteen patients. All patients had a minimum of three months follow-up.

Results: Of six patients on LEV monotherapy, all were seizure free. Two of nine patients on LEV adjuvant therapy had improved seizure control. Of three patients on first-line LEV therapy, two became seizure free. Seven (47%) patients, over all, had no definite change in seizure control while on LEV.

Two of the fifteen (13%) patients required discontinuation of LEV, and one required decreased dosage. These changes were the result of behavioral adverse effects rather than efficacy. Other adverse effects were dizziness and fatigue (7%), lethargy (7%), and insomnia (7%). No abnormal blood counts, infections, rashes, or metabolic abnormalities were associated with LEV. Three patients underwent adjuvant radiotherapy for their tumors, but no dermatitis was reported.

Conclusions: LEV is an attractive AED for brain tumor patients because of its favorable pharmacokinetic profile and minimal impact on cell counts and blood chemistries. In these fifteen patients, LEV appeared to have efficacy and tolerability comparable to that seen in non-tumor patients with epilepsy. LEV monotherapy may show potential in this challenging patient population.

Future work involving larger patient numbers may allow for both statistical confirmation of these findings and more detailed evaluation of efficacy and tolerability based on tumor type and location.

1.325
BONE HEALTH IN MALES WITH EPILEPSY

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Rationale: Exposure to enzyme inducing antiepileptic drugs has been recognized as having affecting bone health, specifically osteopenia and osteoporosis in patients with epilepsy. The data has investigated this affect predominately in women with epilepsy, and moreover, postmenopausal women. Little data are available bone health in men with epilepsy. The purpose of this abstract is to present data collected from male patients with long standing epilepsy and exposure to enzyme inducing antiepileptic medications.

Methods: Identifying patients with a long history of epilepsy and exposure to enzyme inducing antiepileptic medication(s) at routine visits to the seizure clinic is being undertaken at the Boston Veteran's Hospital. The patients are then referred for bone density evaluation of hip and lumbar spine by DXA scan to determine presence of osteopenia and/or osteoporosis(T scores).All scans are conducted using a single scanner.

Results: 25 subjects were evaluated. Ages ranged from 35–83 years of age. Duration of epilepsy spanned 4- 50+ years. All patients had exposure to at least one enzyme- inducing drug (17 to one, 8 with more than one) during the course of treatment. All were currently on at least one enzyme inducing medication.76% demonstrated osteopenia/porosis. 44% demonstrated involvement of both hip and lumbar spine. Eight patients demonstrated either hip or lumbar spine involvement, 5 with hip and 3 with lumbar spine only. Six patients demonstrated no abnormality of bone density, despite 6–36 yr history of epilepsy.Of these patients, 2 were currently on dual enzyme inducing drugs, with 18 and 36 year history of epilepsy; the remaining 4 were on a single enzyme inducing agent, with 6 to 14+ year history of epilepsy. Levels of 25 OH Vit D and parathyroid hormone levels were not consistently obtained. 52% of these patients are currently receiving calcium and Vitamin D supplementation.

Conclusions: Risk of enzyme inducing antiepileptic medications on bone density is not a gender specific phenomenon. The number of drug exposures does not seem to be indicative of increased risk. The duration of epilepsy also did not appear to be a predictor, as one subject had only a 4-year history of epilepsy while others with 6–36 year history showed no evidence of abnormal bone density. Given these factors, men and women with epilepsy and exposure to enzyme inducing antiepileptic drugs should be screened for abnormalities of bone density early on, perhaps as early as 2 years of exposure. Laboratory tests should also be obtained determining 25 OH Vit D levels and parathyroid hormone levels at the very least. Referral for treatment should be undertaken as soon as abnormality is detected. Information is not yet available on the newer antiepileptic medications and their effects if any on bone health. Patients exposed to these medications should be equally evaluated. Data collection continues and will be added to this database.

1.326
USE OF VERAPAMIL AS A POTENTIAL P-GLYCOPROTEIN INHIBITOR IN PATIENTS WITH REFRACTORY EPILEPSY

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Rationale: The overexpression of P-glycoprotein (P-gp) in the central nervous system may be one mechanism of pharmacoresistance in patients with epilepsy. Based on this, it would seem beneficial to block P-gp's ability to remove AEDs from the epileptic focus in pharmacoresistant patients. One known P-gp inhibitor is verapamil, a calcium-channel blocker. Verapamil may function to block P-gp modulated efflux of AEDs in the brain, thereby raising the intracellular concentration of AEDs and ultimately decreasing seizure burden. We describe 3 patients with pharmacoresistant seizures in whom we used adjunctive verapamil therapy for its P-gp inhibitory effects.

Methods: Two women and one man were identified as having pharmacoresistant seizures as evidenced by their current seizure burden while on AED polytherapy and previous inadequacy or toxicity of every possible AED, vagus nerve stimulators and epilepsy surgery. One 25 YO woman had static encephalopathy, while the other woman (24 YO) and man (35 YO) were otherwise healthy. Verapamil sustained-release (Calan SR) 180 mg PO QD was added to each of their existing AED regimens. Due to concerns with potential hypotension caused by verapamil in these normotensive patients, they were given home blood pressure monitors. They were closely monitored for efficacy and toxicity via telephone and clinic visits. If the intervention was viewed as beneficial, the verapamil dose was titrated upward.

Results: All three patients showed improvement in seizure control and subjective quality of life. The verapamil dosages ranged from 180 to 480 mg/day. The 24 YO female patient showed the most significant improvement. The average time interval between her hospitalizations for complex partial status pre-verapamil was 55.1 $\pm$ 14.9 days. This interval more than doubled to 120.5 $\pm$ 21.9 days after the addition of verapamil. No side effects from verapamil were noted in any patient, and blood pressure readings and pulse were within the expected ranges. Two patients required a change in therapy (AED and VNS) while we were prospectively evaluating the adjunctive verapamil. The 35 YO male had to have his carbamazepine (CBZ) dose decreased due to symptomatic toxicity from adding the verapamil. Though the postulated mechanism is that verapamil is inhibiting the P-gp pump, other possible mechanisms include the metabolic inhibition of CBZ metabolism, the potential inherent anti-epileptic activity of verapamil, the 'placebo response', and/or a combination of these factors.

Conclusions: We are cautiously optimistic about the option of using verapamil as adjunctive therapy in pharmacoresistant patients. We advocate for further detailed studies. We suggest that the careful use and monitoring of adjunctive verapamil may offer hope for reduced seizure burden and improved quality of life in patients with pharmacoresistant seizures.

1.327
LEVETIRACETAM MONOTHERAPY IN ELDERLY PATIENTS WITH EPILEPSY: EFFICACY AND TOLERABILITY

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Rationale: To evaluate efficacy, safety and tolerabilty of levetiracetam monotherapy in elderly patients with seizures.

Methods: Eight elderly patients with onset of epilepsy after 65 years of age were included in the study. Seven were females and 1 male; age ranged from 74 to 93 years. All patients suffered from symptomatic focal epilepsy, related to vascular encephalopathy in 6 and to degenerative dementia in 2; partial seizures were observed in all patients, with secondary generalization in 3 cases. Six patients had been previously treated with antiepileptic (AED) drugs, which were discontinued after LEV titration: in 3 of these cases, seizures were uncontrolled by the AEDs used before adding LEV, while the other 3 were seizure free but showed severe side effects related to AED treatment. The remaining 2 patients were not treated at the time of the study and LEV was given as first-choice antiepileptic drug. The follow up period was at least six months in all patients. LEV oral dosage ranged from 1g to 2g/day. Laboratory parameters of liver and hematological function were evaluated in all patients after 1 month of LEV treatment and successively every 3 months. All patients were comedicated with non- AED drugs for treatment of various pathological conditions, mostly related to cardiovascular problems.

Results: In all patients LEV showed a good tolerabilty without relevant side effects; in particular no unfavourable effects on cognitive state, sleep-wake cycle, and behavior were reported. No alterations of hepatic and hematologic parameters were observed. In the six patients in whom LEV substituted a previous AED treatment, LEV monotherapy resulted in improvement of cognitive functioning and daily performances, particularly relevant in 3 patients. In this subgroup of 6 subjects, 3 patients were already seizure free and did not show any recurrence of seizures with LEV monotherapy; another became seizure free with LEV treatment, and the remaining 2 showed a reduction of seizures $>$ 50%. The 2 patients in whom LEV was given as the first choice drug showed a 50% reduction of seizures.

Conclusions: Treatment of epilepsy in elderly patients may be particularly difficult because of increased vulnerability of this population to adverse effects and increased risks of toxicity and unfavorable drugs interactions due to comedication. In our small sample, LEV has showed an optimal profile as an AED for elderly patients, associating efficacy, safety and good tolerability, with a considerable improvement of quality of life in patients and caregivers.

1.328
LAMOTRIGINE CONCENTRATIONS ACROSS THE MENSTRUAL CYCLE IN WOMEN WITH CATAMENIAL EPILEPSY

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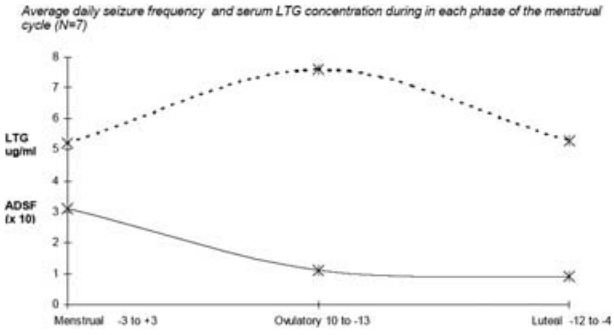
Rationale: An estimated 2/3rd of women with epilepsy have seizure exacerbations in association with the menstrual cycle, a condition known as catamenial epilepsy. Seizure exacerbations during the days prior to menstruation have been attributed to the abrupt withdrawal of progesterone metabolites that have anticonvulsant properties. The preovulatory exacerbation has been attributed to the midcycle surge of estrogen, a proconvulsant. The relationship between catamenial seizure exacerbation and antiepileptic drug (AED) serum concentrations is unknown. We report preliminary data on changes in lamotrigine (LTG) concentrations across the menstrual cycle in women with catamenial epilepsy.



Methods: Participants are part of an IRB-approved study investigating the efficacy of progesterone for the treatment of catamenial seizures. All women in this study had the perimenstrual pattern (C1) of seizure exacerbation described by Herzog et al. This was defined as a two-fold or greater increase in seizures during the perimenstrual (M phase; days -3 to $+3$) compared to the midfollicular (F phase; days $+4$ to $+$ 9) and midluteal (L phase; days -12 to -4) phases in ovulatory cycles. Ovulation was documented by urinary LH and midluteal progesterone $>$ 5 ng/ml. LTG concentrations were obtained during each phase for two consecutive cycles during which AED therapy remained constant. Average daily seizure frequency (ADSF) during each phase was calculated and correlated with LTG concentrations.

Results: Complete data were available for 7 cycles in 4 women (1 LTG monotherapy; 3 on combination therapy with phenytoin topiramate and valproic acid). ADSF was significantly greater during M phase: 0.31 (0.16–0.42) compared to F: 0.07 (0–0.33); O: 0.11(0–0.33); and L: 0.09 (0–0.44). Mean LTG for M: 5.2 ug/ml (3.1–14); O: 7.6 ug/ml (5.0–19.1); and L: 5.3 ug/ml (2.8–17). Overall, there was a 31% reduction in LTG

concentrations during M phase compared to O and 1% reduction during M phase compared to L phase (Fig. 1).

Conclusions: Alterations in AED pharmacokinetics may play a role in seizure expression surrounding menses in some women with epilepsy.

REFERENCE

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1.329
EFFECTS OF VALPROATE AND PHENYTOIN ON BONE MINERAL DENSITY AND MECHANICAL PROPERTIES IN THE RAT FEMUR

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Rationale: Previous studies have suggested anti-epileptic drugs to be risk factors for low bone mineral density and fractures in humans. In this study we have investigated the effect of the antiepileptic drugs phenytoin (PHT) and valproate (VPA)on bone mineral density at specific sites of rat femurs representing cortical and trabecular bone. Because fractures are biological endpoints of reduced bone density, we also studied the mechanical strength in these bones.

Methods: Female Wistar rats (80 days old) were fed perorally through a gastric tube with VPA (300 mg/kg), PHT (50 mg/kg), or control solution (CTR) twice daily for 90 days. After sacrification, blood was collected and whole femurs were dissected. The left femur was used for measurements of bone mineral density and content (BMD and BMC) by Dual energy X-ray absorptiometry (DXA). Regions of interest (ROI) included whole femur, collum and trochanter (mainly trabecular bone) and diaphysis (mainly cortical bone). Mechanical strength was investigated using the 3-point bending test (femoral diaphysis and collum).

Results: Mean animal weight was the same in all treatment groups (249 g, 246 g and 254 g in the VPA, PHT and CTR groups, respectively). Mean serum VPA concentration was 431 μmol/l and PHT 37 μmol/l 4 hours after last dose. VPA decreased BMD compared to CTR in all ROIs significantly in whole femur and collum, while the PHT group showed BMD lower than CTR in all ROIs except in the whole femur (significant in collum only). In both groups, BMC of collum and whole femur was significantly lower than CTR. Testing of the mechanical properties of the bones indicated that VPA reduced maximal strength and fracture energy in the femoral diaphysis. However, the fracture parameters did not show significant differences between the groups in this study.

Conclusions: Our data indicate a catabolic effect of PHT and VPA at therapeutic drug concentrations in the rat femur. Valproate also appears to reduce the mechanical strength in the femoral diaphysis. Further studies are under way to clarify the effects of these agents on bone strength, as well as the responsible mechanisms involved.

1.330
THE LIVERPOOL ADVERSE EVENTS PROFILE (LAEP) REFLECTS ANXIETY AND DEPRESSION RATHER THAN ANTIEPILEPTIC DRUG SIDE EFFECTS IN INDIVIDUAL PATIENTS

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Rationale: The Liverpool Adverse Events Profile (LAEP) was designed to quantify subjective patient reports of side-effects to antiepileptic drug (AED) treatment. More recently LAEP has been proposed as a tool to assist clinicians in the recognition and management of these side effects. This prospective study investigated LAEP with First Seizure Clinic patients.

Methods: Patients presenting to two First Seizure Clinics for investigation following a possible seizure were enrolled in a prospective longitudinal study of psychosocial and clinical outcomes. A self-administered questionnaire, including the LAEP and the Hospital Anxiety and Depression Scale (HADS), was completed at baseline and at 3 months, regardless of diagnosis.

Results: Of 201 patients who completed the baseline questionnaire, 142 were diagnosed as having had one or more seizures. Of those seizure patients 31 were already prescribed AEDs when they completed the questionnaire. There were no significant differences in the mean LAEP scores at baseline between seizure patients taking AEDs ($n = 31$, mean $= 38.91$), seizure patients not taking AEDs ($n = 111$, mean $= 37.61$) and non-seizure patients ($n = 59$, mean $= 37.91$) ($p>0.05$).

Of the 111 patients who completed the 3-month questionnaire, 77 were seizure patients and 42 of these were prescribed AEDs (26 had been started after the baseline questionnaire). Again, there were no significant differences in the LAEP scores between the three groupings (seizure + AEDs, $n = 42$, mean $= 38.94$), (seizure + no AEDs, $n = 35$,mean $=$ 36.33), (non-seizure, $n = 34$, mean $= 36.31$), ($p>0.05$).

There were no statistically significant changes in the LAEP scores from baseline to 3 months in any of the groupings ($p>0.05$).

LAEP scores for all patients correlated strongly with HADS anxiety and depression scores at baseline (anxiety: $r = 0.72$, $p < 0.001$; depression: $r = 0.61$, $p < 0.001$) and 3 months (anxiety: $r = 0.83$, $p < 0.001$; depression: $r = 0.70$, $p < 0.001$).

Conclusions: The data indicates that LAEP scores reflect levels of anxiety and/or depression in patients rather than the side-effects of AEDs. We would question the use of summed LAEP scores as a tool to quantify and manage AED side-effects in individual patients in clinical practice. (Supported by Australian Research Council; Epilepsy Foundation of Victoria.)

1.331
BETTER SEIZURE CONTROL IS ASSOCIATED WITH HIGHER CORTICAL PYRROLIDINONE LEVELS IN PATIENTS TREATED WITH GABAPENTIN

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Rationale: Gabapentin rapidly increases intracellular GABA concentrations in drug-free volunteers and patients with localization-related epilepsies. Daily gabapentin increases GABA, homocarnosine and pyrrolidinone concentrations. Homocarnosine is an inhibitory neuromodulator synthesized from GABA and histidine in a sub-class of GABAergic neurons. Low cortical homocarnosine and GABA levels are associated with poor seizure control with carbamazepine, lamotrigine, phenytoin or valproate. Patients with JME and good seizure control have high homocarnosine, but below normal GABA content. Pyrrolidinone, the internal lactam of GABA, is synthesized by the brain and comprises almost 50% of total GABA in human CSF. Pyrrolidinone and its derivatives (levetiracetam) have anticonvulsant properties. Our objective is to assess the relationship between seizure control and GABA, homocarnosine, and pyrrolidinone content in a group of patients starting gabapentin.

Methods: Serial measurements of pyrrolidinone, homocarnosine and GABA were made of a 14-cm3 volume centered in the occipital cortex using proton spectroscopy (MRS) with a 2.1-Tesla spectrometer. Ten patients (seven women) with complex partial seizures were invited to participate in this project approved by the Yale University Human Investigations Committee. Serial MRS measurements were obtained before and after starting gabapentin. Information concerning medication use and time since last aura, seizure of any type, major seizure or convulsion were obtained with each set of MRS measurements.

Results: A major seizure or convulsion in the three months before a set of MRS measurements is defined as poor seizure control. Median time since the last major seizure or convulsion was considerably longer (7.5 months, 95%CI 4.8–42) during periods of better than poor control (1.4 months, 95%CI 0.4–2.5). Mean GABA content was the same during

periods of poor seizure control (1.1 mM, 95%CI 0.8–1.3, n 11) and better control (1.1 mM, 95%CI 0.9–1.3, n 16). Homocarnosine content showed a trend ($p < 0.1$) toward higher levels with better control (0.6 mM, 95%CI 0.5–0.7) compared with poor control (0.5 mM, 95%CI 0.4 to 0.6). Higher pyrrolidinone content was associated ($p < 0.05$) with fewer major seizures (0.40 mM, 95%CI 0.36–0.43) than during poor control (0.34 mM, 95%CI 0.28–0.39). Regression analysis, using the logarithm of the time since the last major seizure or convulsion, showed significant positive associations with pyrrolidinone ($p < 0.02$) and homocarnosine ($p < 0.01$), but none with cortical GABA content.

Conclusions: Low homocarnosine levels are associated with poor seizure control on gabapentin by allowing seizures to spread from the epileptogenic zone. Higher pyrrolidinone and homocarnosine levels are associated with better seizure control, which suggests pyrrolidinone decreases cortical excitability, thereby inhibiting the spread of seizures. (Supported by NIH-NINDS NS6208 and NS32518.)

1.332

A DOUBLE-BLIND STUDY OF TOPIRAMATE (TPM) MONOTHERAPY IN OLDER PATIENTS WITH PARTIAL-ONSET SEIZURES

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Rationale: Because aging alters pharmacokinetics, antiepileptic drug (AED) profiles, particularly tolerability, may be very different in older adults. We evaluated 50 vs. 200 mg/day TPM as monotherapy in patients ≥60 yrs old with partial-onset seizures.

Methods: Patients who were drug-naïve or receiving a stable regimen of 1 AED were eligible for double-blind 24-wk study if they had ≥1 seizure in previous 6 months. TPM was titrated by 25 mg/day per week to target or maximum tolerated dose as the concomitant AED, if any, was withdrawn.

Results: 39 patients were randomized to TPM 200 (mean age, 69 yrs); 38 to TPM 50 (68 yrs). Median baseline seizure frequency was 0.3/month in both groups. Median treatment duration was 23 (TPM 200) and 18 wks (TPM 50). With TPM 200, 18 (46%) were maintained ≥12 wks on monotherapy vs. 13 (34%) with TPM 50; 56% (N = 20) and 40% (N = 14), respectively, had no seizures during double-blind treatment. Median time to 1st seizure: TPM 200, >168 days; TPM 50, 100 days. Patients reporting ≥1 AE: TPM 200, N = 24 (62%); TPM 50, N = 25 (66%). Most common AEs (≥10%) for TPM 200: depression, ataxia, injury (N = 4 each, 10%); for TPM 50: headache (N = 6, 16%), somnolence (N = 6, 16%), dizziness (N = 5, 13%), fatigue and nervousness (4, 11% each). Memory difficulty and language difficulty were reported by 3 patients each (TPM 200, N = 1; TPM 50, N = 2); 2 reported nonspecific cognitive problems (1/group) and confusion (1/group); 1 (TPM 50) reported psychomotor slowing. 7 (18%) patients discontinued due to AEs, most commonly with headache (N = 4), ataxia (3), somnolence (3), paresthesia (2), dry mouth (2), decreased appetite (2).

Conclusions: 200 mg/day was associated with a somewhat longer duration of double-blind treatment, more patients maintained on monotherapy, longer time to 1st seizure and a higher seizure-free rate compared with 50 mg/day, although the difference was not statistically significant. With 50 mg/day TPM, 40% were seizure-free. Few patients reported adverse cognitive effects, despite doses up to 200 mg/day. Overall, 200 mg/day was as well tolerated as 50 mg/day. Results of this pilot study with TPM compare favorably with other double-blind trials of newer AEDs in elderly patients. (Supported by Ortho-McNeil Pharmaceutical.)

1.333

DEVELOPMENT AND SAFETY OF $[^{13}C]_4$-VALPROIC ACID FOR PHARMACOKINETIC STUDIES IN EPILEPSY PATIENTS

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Rationale: Valproic Acid (VPA) is a widely prescribed antiepileptic medication (AED) exhibiting complex pharmacokinetics (PK). We have developed an investigational, intravenous, stable-labeled $[^{13}C]_4$-VPA formulation in order to rigorously characterize steady-state VPA PK in adult and elderly patients. Administration of stable-labeled VPA allows for measurement of half-life and absolute bioavailability in patients without interrupting AED therapy. This will be particularly important in the elderly, a group who is receiving VPA therapy for several indications and who are an understudied population. The purpose of the present study is to present preliminary safety information in patients while on steady-state VPA therapy.

Methods: Adults 18 years or older on maintenance VPA therapy were eligible to participate in the study. Exclusion criteria included the use of potentially interacting co-medications. On the day of the study, patients were given a single 250 mg intravenous (IV) infusion of a $[^{13}C]_4$-VPA formulation (equivalent to IV Depacon®, IND #67163) as part of their morning dose. The remainder of the dose was given orally. Blood samples were collected just prior to and up to 96 hours after $[^{13}C]_4$-VPA administration. Both VPA and $[^{13}C]_4$-VPA were measured in plasma by GC-MS. Non-compartmental PK analysis was done with WinNonLin® (Pharsight Corporation, version 4.0). Blood pressure (BP), respiration rate (RR), and heart rate (HR) data were collected prior to infusion, every 2 minutes during infusion, and every 15 minutes for the first hour following the completion of the infusion. Each subject was monitored by ECG before and during the infusion. The study nurse monitored the infusion site for inflammation during the infusion and at the time that the indwelling catheter was removed. Patients were asked to report any discomfort at the infusion site.

Results: Three patients (age range 20–39: 1 female and 2 male) have competed the study. VPA daily doses ranged from 1000–2250 mg/day. No changes in HR, RR, or ECG were noted. In one patient, a modest drop in diastolic BP ((5 mm Hg) was noted during infusion.

Conclusions: Our preliminary data indicate that $[^{13}C]_4$-VPA can be safely administered to healthy patients. The use of a parenteral $[^{13}C]_4$-VPA formulation permits comprehensive characterization of half-life and bioavailability of VPA in patients without interrupting therapy. After the safety phase of this project, determination of PK and bioavailability in elderly patients will be done. Preliminary PK data will be presented in the poster. (Supported by NIH NINDS P50-NS16308 and M01-RR0040, and Abbott Laboratories.)

1.334

LONG-TERM VALPROATE TREATMENT REDUCES FREE CARNITIN VERSUS TOTAL CARNITIN RATIO IN MEN: OF IMPORTANCE FOR SEMEN QUALITY?

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Rationale: A recent study of semen quality in men with epilepsy on long-term VPA or CBZ treatment, showed that both treatment groups differed from the controls regarding sperm motility, and sperm neck and head abnormalities. Men on VPA also had significantly more sperm tail abnormalities than the controls. Carnitin levels have been found to be lower in patients taking valproate. Both human and animal studies have pointed out carnitin as a marker of epididymal function, and the Sertoli cells has been considered a possible target for a widespread metabolic action of carnitin. We wanted to investigate whether carnitin deficiency is measurable in these otherwise healthy men on long-term VPA or CBZ

treatment, and to compare the results with the previous semen findings in the same patients.

Methods: Men with epilepsy, 20–40 years old, having used either VPA (n = 16) or CBZ (n = 19) for > 2 years were included and compared with 38 closely age-matched controls. Total and free carnitin were analyzed by an enzymatic method. In principle, carnitin and tritiated acetyl-CoA are converted CoASH and [^{3}H] acetylcarnitin which is separated and measured in a scintillation counter.

Results: The ratio of free carnitin/total carnitin was significantly lower in the men on long-term VPA treatment compared to controls (ratio: 0.8 vs. 0.9; $p < 0.001$), as opposed to the CBZ treated (ratio 0.9). A comparison of the two treatment groups also showed significantly lower levels of free carnitin/total carnitin ratio in the VPA treated patients than in the CBZ treated (ratio: 0.8 vs. 0.9; $p < 0.001$).

Conclusions: Reduced ratio of free carnitin/total carnitin were found in the VPA treated men. CBZ treated men, however, did not differ from healthy controls. As carnitin has been found to be of importance for sperm motility, the reduced ratio may be related to our findings in VPA treated men. These findings may have implications for fertility in men.

1.335
LEVETIRACETAM IN POSTSTROKE SEIZURES IN A COMMUNITY HOSPITAL

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Rationale: In population studies, stroke is the most commonly identified cause of epilepsy in adult populations older than 35 years.The incidence of post stroke seizure is 5.7% (3.5–7.9) at 1 year and 11.5% (4.8–18.2) at 5 years.

Treatment of epilepsy with available AEDs is often a compromise between efficacy, safety and tolerability, and ease of use. Levetiracetam (LEV) represents an advance in the treatment of seizures. LEV has unique and favorable pharmacokinetic profile that includes rapid and complete oral absorption, minimal protein binding, no hepatic metabolism, renal clearance and a half-life of 6–8 hours. These properties made us use LEV in post stroke seizure patients. We report our experience on the safety and efficacy of LEV in post stroke seizure patients.

Methods: We retrospectively studied the post stroke seizure patients that received LEV from 2001 to 2003.

We were able to retrieve 45 post stroke seizure patients on LEV for 2 years. We reviewed the demographic data, number of seizures, primary diagnosis, date of hospitalization, reason for admission, starting and final dose of LEV.

The diagnostic studies CT/MRI, laboratory values of renal, hepatic, hemotological dysfunctions were charted. Any side effects, other AEDs and other medications were recorded. Particular attention was paid to any drug interactions and any side effects that lowered or increased dose of LEV. Starting dose was 500 mg bid (range 250 to 2000 mg). Oral loading of 1500 to 3000 mg was done in 3 patients with recurrent seizures, 2 with status epilepticus (as add-on to iv fosphenytoin). The patients were followed up for 2 years.

Results: Age range of patients on LEV was 41 to 90 years, these were 19 men, 26 women. 24 had ischemic stroke and 21 had hemorrhagic stroke (ICH 11, Subdural hematoma 3, SAH 3, hemorrhagic conversion 4). 24 patients came to the hospital due to first seizure.

LEV was used as monotherapy in 24 patients and as add-on therapy in 21 patients.

20/24 (83%) patients on monotherapy and 18/21 (86%) on add-on therapy were completely seizure free. 2 patients experienced recurrent seizures on LEV. Their dosage was increased from 250 mg to 750 mg and from 500 mg to 1500 mg. 1 other patient had LEV withdrawal seizures.

Sedation was reported by 6 (13%) patients, dizziness by 2 (4.5%), psychiatric changes by 2 (4.5%). Only 2 (4.5%) discontinued due to side effects. Among the other AEDs phenytoin was given to 10 patients, iv fosphenytoin 8, sodium valproate 2, phenobarbital 1 and trileptal 2.

No interactions of LEV with other medications ie warfarin, aspirin, plavix, tPA, digoxin, antihypertensives, statins were noted. In particular no change in INR or Prothrombin time was noticed.

Conclusions: Levetiracetam is an effective AED in post stroke seizures as mono and add-on therapy. Its low adverse-effect profile, lack of protein binding and no hepatic clearance makes it a drug of choice. In patients with stroke/multiple medical problems on multiple medications, it should be considered as first-line AED.

1.336
TOPIRAMATE MONOTHERAPY: RESULTS OF A PROSPECTIVE MULTICENTER FLEXIBLE-DOSE STUDY

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Rationale: The objective of this study was to evaluate flexible doses of topiramate (TPM) in the monotherapy of epilepsy independent of seizure type or epilepsy syndrome.

Methods: Prospective open-label multicenter phase IV study. Adult patients with recently diagnosed epilepsy (<3 years), previously untreated or unsuccessfully treated with one antiepileptic drug, were evaluated at baseline and after 6, 16 and 30 weeks. In previously treated patients, transition to TPM monotherapy had to be established within 6 weeks after enrollment.

Results: 213 patients (56% male, mean age 40 ± 16 years, range 18–88 years) were enrolled. 50.5% of the patients had partial epilepsy, 40.5% had generalized epilepsy, 6.3% had a specific epilepsy syndrome, and 2.6% remained unclassified. At endpoint, the mean topiramate dose was 117 mg/day. 78.4% of the patients received 100 mg/TPM per day or less. Mean seizure frequency decreased from 5.4 in the 12 weeks prior to enrollment to 2.5 at endpoint ($p < 0.0001$). 57.9% of the patients remained seizure free during the 7-months study, and 76.8% were responders with a = 50% reduction in seizure frequency. Adverse events reported in = 5% were paraesthesia (15.3%), somnolence (8.3%) and dizziness (5.8%). 4.2% of the patients dropped out due to side effects. 77.5% continued TPM treatment beyond the study.

Conclusions: Topiramate monotherapy in patients with recently diagnosed epilepsy was associated with a significant reduction in seizure frequency, independent of seizure type or epilepsy syndrome. Doses of (100 mg/TPM day in this study were well tolerated. (Supported by Janssen-Cilag Germany.)

1.337
DOSE-RESPONSE POPULATION ANALYSIS OF Keppra(tm) ADD-ON TREATMENT IN EPILEPSY PATIENTS WITH PARTIAL ONSET SEIZURES

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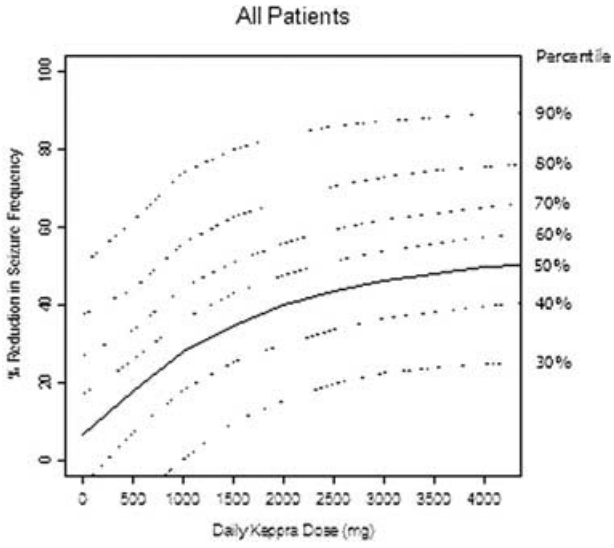
Rationale: The aim of this population analysis was to describe the individual change in seizure frequency from baseline after treatment with Keppra (levetiracetam) or placebo and to model the dose-response relationship and assess the impact of potential covariates.



Methods: Efficacy data from four double-blind, placebo-controlled parallel-group phase-III clinical trials were used. The final dataset used for the modeling of the dose-response relationship contained 4218 data rows for 958 individual epileptic patients with partial onset seizures. In the final model, the change in weekly seizure frequency for the improving patients was described by the following equation: in which the drug effect was assumed to be an additional effect on top of a placebo effect $\Delta_{Placebo}$. The changes in seizure frequency in patients improving or deteriorating on placebo and in patients deteriorating on Keppra, were described by dose-independent models. The number of seizures in an individual patient was modeled as a Poisson process and the seizure frequency between patients was assumed to be log-normally distributed. Modeling was performed using NONMEM version V.

Results: The final model successfully converged to an E_{max} dose-response relationship (Fig. 1). A typical improving patient treated with placebo is predicted to have an 11% decrease in the seizure frequency from baseline, compared to 45% increase for a typical deteriorating patient. The typical value of the maximal reduction in seizure frequency from baseline in improving patients after treatment with Keppra was estimated to be 72%. The typical value of ED_{50} (dose producing half of the maximum effect) was estimated to be 1408 mg/day. Neither gender nor race, body weight, age, or number of concomitant AEDs appeared to have an effect on the improvement or deterioration of patients.

$$\lambda = Baseline \cdot (1 - \Delta_{Placebo}) \cdot \left(1 - \frac{E_{max} \cdot Dose}{ED_{50} + Dose}\right) \cdot e^{x}$$

Conclusions: Add-on treatment of Keppra demonstrates a dose-response relationship in approximately 75% of the patients with refractory partial seizures. The current maximum recommended daily dose corresponds to twice the ED_{50} predicted by the model. (Supported by UCB Pharma SA.)

1.338
TOLERABILITY OF TOPIRAMATE IN THE ELDERLY

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Rationale: Because elderly patients are generally more susceptible to drug side effects when compared with younger adults, adverse event (AE) data in adults ≥65 yrs of age treated with topiramate (TPM) monotherapy studies were analyzed.

Methods: AE data were from 5 double-blind trials: 4 dose-controlled trials in patients with newly diagnosed epilepsy (N = 1208); 1 placebo-controlled trial in patients with essential tremor (N = 221). In epilepsy studies, target dosages were 50–500 mg/day TPM monotherapy. 3 of 4 studies allowed dose flexibility; patients had to be maintained on assigned dose (100 or 200 mg/day) in 1 study. Target dose for essential tremor patients, 400 mg/day, with dose flexibility. In 50% of tremor patients, TPM added to 1 anti-tremor agent. Median double-blind treatment duration: epilepsy patients, 8 mos; tremor patients, 6 mos. Adverse event data available for 170 epilepsy patients and 121 tremor patients ≥65 yrs of age. Epilepsy patient data pooled (TPM 50, N = 69; TPM 100, N = 15; TPM 200, N = 62; TPM 400, N = 10; TPM 500, N = 14) and compared with TPM (N = 57) and placebo-treated (N = 65) tremor patients. Data also pooled for TPM-treated epilepsy and tremor patients and compared with AE data for younger TPM-treated adults (16–64 yrs, N = 793) with epilepsy.

Results: 86% of epilepsy patients were treated with ≤200 mg/day TPM; median dose in tremor patients, 375 mg/day. Table 1 shows most common AEs (≥10% incidence) and neurobehavioral AEs occurring more frequently for TPM vs. placebo.

Conclusions: Higher incidence of paresthesia, weight decrease, appetite decrease, taste perversion, memory difficulty, nausea, concentration/attention difficulty and language problems in tremor vs. epilepsy patients may reflect higher TPM doses in tremor study. AEs occurring more often in epilepsy vs. tremor may reflect influence of epileptogenic substrate. Expectations that TPM would be more poorly tolerated in elderly patients than in younger adults, particularly in terms of neurobehavioral AEs, are not supported by these data. TPM monotherapy appears to be well-tolerated by the elderly. (Supported by Johnson & Johnson Pharmaceutical Research & Development; Ortho-McNeil Pharmaceutical.)

1.339
LONG-TERM LEVETIRACETAM TREATMENT AFFECTS OVARY SIZE AND MORPHOLOGY IN FEMALE WISTAR RATS

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	Patients,%				
	Elderly		Younger adults 16–64 yrs		
	TPM-epilepsy Monotherapy (N = 170)	TPM-tremor (N = 57)	All TPM (N = 227)	Placebo-tremor (N = 64)	TPM-epilepsy Monotherapy (N = 793)
Most common AEs (≥10% incidence)					
Fatigue	15%	18%	16%	2%	18%
Headache	15%	5%	12%	6%	20%
Paresthesia	12%	21%	16%	5%	32%
Somnolence	12%	16%	14%	5%	13%
Weight decrease	9%	26%	14%	2%	12%
Appetite decrease	9%	18%	11%	3%	10%
Taste perversion	5%	19%	8%	0	7%
Memory difficulty	4%	12%	6%	2%	8%
Nausea	7%	11%	8%	3%	12%
Specific neurobehavioral AEs					
Depression	9%	2%	5%	0	7%
Confusion	6%	4%	5%	0	4%
Insomnia	6%	5%	6%	3%	9%
Psychomotor slowing	5%	5%	5%	0	4%
Concentration/attention difficulty	2%	4%	3%	0	7%
Language problems	2%	4%	3%	0	5%
Cognitive problems, NOS	2%	0	1%	2%	3%
Speech problems	1%	1%	1%	0	3%

Rationale: Women with epilepsy have an increased risk for reproductive health disorders. This is, at least in part, due to the use of antiepileptic drugs. Valproate has been shown to induce hyperandrogenism and polycystic ovaries, while enzyme inducing drugs reduce free fractions of sex steroid hormones. Levetiracetam (LEV) is a new antiepileptic drug with rapidly increasing use. Endocrine effects of the drug have so far not been reported and LEV may therefore represent an alternative drug for women of fertile age. The aim of the study was to investigate the effect of long-term LEV treatment on ovary weight and ovarian morphology in rats.

Methods: Sixty-two female Wistar rats were fed perorally through a gastric tube with LEV 50 mg/kg (n = 15), 150 mg/kg (n = 21) or control (n = 26) solution twice daily for 90–95 days. They were killed in diesterous/early proestrous phase. The ovaries were weighed and stained by hematoxylin-eosin before light microscopical evaluation. A blinded visual evaluation was performed using a mid-ovarian section of one ovary from each animal, and the numbers of cysts, follicles and corpora lutea were counted.

Results: All animals accepted the gastric tube feeding without signs of discomfort or reduced motor activity. However, four animals died because of oesophageal rupture induced by the gastric tube. Mean LEV concentration 4 h after sacrification was 122 and 277 umol/l in low- and high dose treated animals, respectively. Mean ovary weight showed a dose-dependent and significant increase after LEV treatment (93.5 mg, 97.3 mg and 110.5 mg in controls, low- and high-dose treated animals. Controls vs high-dose: p = 0.02). Mean body weight was the same in all three groups. Mean number of cysts were 0.40 cysts/section in all LEV treated animals (low dose: 0.0 cysts/section; high-dose 0.67 cysts/section) compared to 0.83 cysts/section in control animals (not statistically different). The number of corpora lutea was significantly higher in the treated animals (mean 11.8/section) compared to controls (mean = 9.8/section)(p = 0.045). The number of secondary follicles is also significantly higher in the treated animals (mean = 8.6/section) compared to controls (mean = 6.8/section) (p = 0.034).

Conclusions: The study is the first to indicate a probable effect of LEV on reproductive function in females. Ovary weight is significantly higher in high dose LEV treated animals compared to untreated controls. The number of corpora lutea and secondary follicles are also significantly higher in the treated animals, together with a trend towards reduced number of ovarian cysts. This may indicate a higher number of ovulatory cycles. The clinical relevance of these findings is uncertain, but our observations should encourage further studies on the possible reproductive endocrine effects of LEV.

1.340
RAPID PARENTERAL VALPROATE LOADING: EFFICACY, TOLERABILITY, AND PHARMACOKINETICS

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Rationale: Usually, valproate (VPA) therapy is started orally with an increase of 300 mg every 2–3 days and a target dose of 1200–1800 mg daily, which is established after 8–18 days. Meanwhile, no sufficient anticonvulsive effect is ensured. In patients with high seizure frequency, rapid achievement of therapeutic serum levels is essential. We evaluated the efficacy, tolerability, safety and pharmacokinetics of a 4-day i.v./oral VPA loading scheme.

Methods: 49 patients with epilepsy or a first seizure under conditions that required anticonvulsive treatment, received 20 mg/kg sodium valproate i.v within 10 minutes every 12h for 2 days (n = 42). In patients with additional administration of enzyme inductors the dose was increased to 25mg/kg (n = 7). Starting from day 3 the patients received 10 mg/kg p.o. of slow-release VPA every 12h (12,5mg/kg in case of inductors). Serum levels of valproate were repetitively analyzed on day 1 and 4 at short intervals. Clinical data concerning efficacy and safety was collected on standardized case report forms. Follow-up visits took place 14 and 90 days after beginning of treatment.

Results: 6 patients were excluded, mainly due to incompliance or drug abuse. Highest VPA serum concentrations (cmax) typically were reached directly after i.v. administration (cmax/i.v. 93.8 to 213.8 mg/L, mean 140 mg/L). Lowest levels (cmin) were reached 12 h after i.v. administration (cmin/i.v. 20.3 to 57.2 mg/L, mean 39.0 mg/L). Cmax/p.o. after oral VPA administration was 52.3 to 142.5 mg/L, mean 90.6 mg/L. Cmin/p.o. was measured at day 4 prior to the morning dose (41.6 to 128.4 mg/L, mean 75.9 mg/L). The desired VPA level of 50–120 mg/L was reached in 37 of 43 patients. Subgroup analysis showed that despite of a higher dosing scheme patients additionally taking enzyme inductors reached lower concentrations, which accounts for 3 patients with serum levels below 50 mg/L. Adverse effects (day 1–4) were fatigue (n = 9, 20.9%), injection site discomfort (n = 6, 13.9%), dizziness (n = 6, 13.9%), drowsiness (n = 5, 11.6%), oral paresthesias and taste disturbances (n = 4, 9.3%), headache (n = 3, 6.9%), nausea (n = 2, 4.7%), stomach pain (n = 2, 4.7%), limb paresthesias (n = 2, 4.7%), reversible toxic CNS reaction (n = 2, 4.7%), vomiting (n = 1, 2.3%), blurred or double vision (n = 1, 2.3%), tinnitus (n = 1, 2.3%). At follow-up visits, the quantity of adverse effects was not different from those reported in the literature. All patients except one experienced complete seizure control or reduction of seizure frequency.

Conclusions: Intravenous VPA loading is an effective, rapid, well tolerated, and practicable way of VPA administration in patients at high risk of recurrent seizures. Adverse effects during i.v. VPA loading are comparable to those known from oral administration, except the occurrence of pain at the injection site and oral paresthesias with taste disturbances. (Supported by a grant from Sanofi-Synthelabo GmbH, Germany.)

Antiepileptic Drugs—All Ages 1

1.341
THE EFFECT OF POOR COMPLIANCE ON STEADY-STATE VALPROIC ACID LEVELS FOLLOWING ADMINISTRATION OF DIVALPROEX EXTENDED RELEASE ONCE DAILY AND DELAYED RELEASE TWICE DAILY: COMPUTER SIMULATIONS RESULTS

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Rationale: Divalproex extended-release (ER) is a once daily (QD) preparation for valproic acid (VPA) that was developed to improve compliance over the twice-daily (BID) divalproex delayed-release (DR). There is a concern that a missed or delayed dose from ER QD has higher potential for sub therapeutic levels than DR BID. Further, VPA exhibits non-linear binding to plasma proteins; the effect of missed and/or delayed doses is under-estimated when *total* VPA levels are used for monitoring. There is a need to characterize the effect of different patterns of poor compliance on ER (QD) and DR (BID).

Methods: Poor compliance scenarios for ER QD (1000 mg or 2500 mg) included 1) One dose taken 6 h, 12 h, 18 h, 24 h (missed dose, no make-up dose), 24 h (two doses, dose double-up) late from schedule; and 2) Two doses taken 6 h, 12 h, 18 h and 24 h after 2nd missed dose. For DR BID (500 or 1000 mg), poor compliance scenarios included: 1) One dose taken 3 h, 6 h, 9 h, 12 h (missed dose, no make-up dose), 12 h (two doses, dose double-up) late from schedule; and 2) Two doses taken 3 h, 6 h, 9 h, 12 h after 2nd missed dose. A 1-compartement model; assuming mono-therapy (adults), was used.

Results: The% of subjects on ER 1000 QD that had sub therapeutic concentrations (C_u <5 mg/l, C_{tot} < 50 mg/l) varied from (43–100%, C_u) and from (28–100%, C_{tot}). None of the subjects on ER 2500 QD had sub therapeutic concentrations when one dose is taken 12 h late but (50% of the population had sub therapeutic levels if one dose is missed; while all subjects were sub therapeutic if two doses are missed. Potential toxicity (C_{tot} >150 mg/l) may occur in 52% of the population if two doses are taken 18 h after the 2nd missed dose. While on DR 500 BID, (3–88%, C_u) and (3–77%, C_{tot}) of the population had sub therapeutic levels. For DR 1000 BID, none of the subjects experienced sub therapeutic concentrations if one dose is missed. However, if two doses (DR 1000) are delayed from schedule, 1–24% (C_u, C_{tot}) of the population might have sub therapeutic concentrations. While on DR, Replacement doses didn't result in C_{tot} >150 mg/l.

Conclusions: Since C_{tot}^{VPA} show higher inter-individual variability and can under-estimate the effect of poor compliance, The use of C_u^{VPA} for monitoring may be more useful. Patients on ER 1000 QD and DR 500 BID should replace missed doses as soon as remembered. Patients on DR 1000 BID may not need to replace one missed dose but should replace two missed doses as soon as possible, with no risk of toxicity. Patients on ER 2500 should replace missed doses up to 12 h late. Doubling the dose is not advised. Replacing two ER 2500 doses might result in toxicity. (Supported by Abbott Labs.)

1.342

COGNITIVE FUNCTION IN CHILDREN AND ADOLESCENTS WITH PARTIAL SEIZURES: AN OPEN-LABEL, RANDOMIZED, ACTIVE-CONTROL, MULTICENTER TRIAL OF OXCARBAZEPINE

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Rationale: The antiepileptic drug (AED) oxcarbazepine (OXC) is approved as monotherapy or adjunctive therapy for the treatment of partial seizures in adults and children. While some AEDs may impair cognitive function, OXC has not been found to affect cognitive function in adults with epilepsy. This study was designed to assess the effect of OXC on cognitive function in children and adolescents with partial seizures.

Methods: This multicenter, open-label, randomized, active-control study included previously untreated patients 6 to <17 years old with a history of ≥2 unprovoked partial seizures. Patients were randomized to receive OXC, carbamazepine (CBZ), or valproate (VPA) in a 2:1:1 ratio for 6 months. Patients were stratified by age group (6 to <12 years and 12 to <17 years). The primary endpoint was the Computerized Visual Searching Task (CVST) assessing mental information processing speed and attention. Secondary endpoints included psychomotor speed and alertness (assessed by finger-tapping and visual reaction-time tasks), memory and learning (assessed by recognition of words and figures and the Rey Auditory Verbal Learning Test), mental information processing speed and attention (assessed by binary choice reaction time), and an intelligence test (Raven's Standard Progressive Matrices). Comparisons were made between patients receiving OXC and the combined group of patients receiving CBZ or VPA after 6 months' treatment (ANCOVA).

Results: Overall, 112 patients (mean age: 10 years) were randomized to treatment with OXC (n = 55), CBZ (n = 28), or VPA (n = 29). In total, 99 patients (88.4%) completed the study, and 97 were eligible for assessment of the primary endpoint. Median daily doses were OXC 770 mg, CBZ 600 mg, and VPA 600 mg. The primary endpoint comparison of mean change in CVST measurements at 6-months from baseline was −3.902 s (OXC) and −0.999 s (CBZ/VPA) indicating an improvement for both treatment groups (p = 0.195). The analyses of secondary neuropsychological variables did not show any significant differences between treatment groups. Adverse events (>10%) included fatigue and headache in the OXC group, fatigue and rash in the CBZ group, and headache, increased appetite, and alopecia in the VPA group.

Conclusions: The results indicate that there is no difference between OXC and other standard first-line AED therapies in their effects on cognitive function in children and adolescents aged 6 to <17 years with newly diagnosed partial seizures. From the baseline data over the time course of 6 months, there is no evidence derived from this study that OXC adversely affects cognitive function in children and adolescents with partial seizures. All AEDs were well tolerated and the safety profile of OXC was in line with previous findings. (Supported by Novartis Pharmaceuticals.)

1.343

DOSE-DEPENDENT SAFETY AND EFFICACY OF ZONISAMIDE IN REFRACTORY, LOCALIZATION-RELATED EPILEPSY: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Rationale: To investigate the safety and efficacy of zonisamide (ZNS), a broad-spectrum antiepilepsy drug licensed in the United States and Japan and under development in Europe, as adjunctive treatment for refractory localization-related epilepsy.

Methods: A total of 351 patients with inadequately controlled partial seizures with or without secondary generalization were randomized to placebo, ZNS 100, 300, or 500 mg/d (2:1:1:2) in a double-blind trial. An upward dose-titration period (≥6 weeks) was followed by an 18-week fixed-dose assessment phase. Primary efficacy outcomes were the differences between ZNS 500 mg/d and placebo in the change in frequency of complex partial seizures (CPS) from baseline and in the proportion of CPS responders (ie, patients with a ≥50% seizure frequency decrease from baseline). Tolerability was also assessed during the study.

Results: ZNS 500 mg/d significantly reduced CPS frequency compared with placebo (by –51.2% vs –16.3%, respectively; P < .0001) and resulted in a significantly higher proportion of CPS responders (52.3% vs 21.3%, respectively; P < .001). Both ZNS 500 mg/d (P < .0001) and 300 mg/d (P = .0005) were statistically superior to placebo in reducing the frequency of all seizures. Responder rates for all seizures showed a significant (P < .0001) linear dose-response relationship, with 52.5%, 42.2%, 29.6%, and 17.9% of patients responding to ZNS 500 mg/d, 300 mg/d, 100 mg/d, and placebo, respectively. ZNS was well tolerated overall, with serious treatment-emergent adverse events occurring in a similar proportion of patients receiving ZNS 500 mg/d (7.6%), 300 mg/d (9.1%), and placebo (8.3%).

Conclusions: ZNS is a dose-dependent, effective, and well-tolerated adjunctive therapy for patients with refractory localization-related epilepsy. (Supported by Eisai Inc.)

1.344

SWITCHING FROM IMMEDIATE-RELEASE TO EXTENDED-RELEASE CARBAMAZEPINE CAPSULES: QUALITY OF LIFE IN PATIENTS WITH EPILEPSY

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Rationale: The assessment and monitoring of quality-of-life (QOL) has become increasingly important in clinical study populations. Traditional clinical trials often do not include adequate assessments of factors that play a role in determining patients' QOL. In this open-label, multicenter study, quality of life instruments were used to derive data from subjects switched from immediate-release carbamazepine (IR-CBZ) to an equal total daily dose of Carbatrol® extended-release capsules (CBZ-ERC) at a minimum of 400 mg/d.

Methods: At baseline, eligible and enrolled subjects were switched from their current IR-CBZ product to an equal total daily dose of CBZ-ERC. Grounds for exclusion from this study included: known history of generalized tonic-clonic status epilepticus or epilepsy syndromes that may potentially worsen with carbamazepine treatment, progressive neurological disorder, receiving more than 1 additional antiepileptic drug or any type of neuroleptic drug, or CBZ-ERC treatment within 90 days of study screening. Data from 453 patients with epilepsy were collected. QOLIE-31 (quality of life in epilepsy-31), and QOLIE-AD-48 (quality of life in epilepsy-adolescent-48) assessments were performed at baseline (month 0) and month 3. These assessments are validated, epilepsy-specific tools for use in adult and adolescent patients, respectively. They measure several areas of quality of life, including: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall QOL.

Results: Results of quality of life instruments from patients switched to CBZ-ERC showed significant improvement in total, as well as all subcategories of QOL assessed, for both adults ($P = .01$), and adolescents ($P = .05$).

Conclusions: Patient-rated QOL scores indicated that switching from IR-CBZ to CBZ-ERC resulted in greater improvements in QOL. These scores take into account seizure worry, medication effects, emotional well-being, social functioning, energy/fatigue, cognitive functioning, and overall QOL. The data establish that patients switched to CBZ-ERC from IR-CBZ demonstrate better quality of life related to improvement

in a wide range of variables. (Supported by Shire Carbatrol is registered in the United States Patent and Trademark Office.)

1.345
LIVER FUNCTIONS IN CHILDREN AND ADOLESCENTS WITH SUICIDAL VALPROATE OVERDOSAGE

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Rationale: Epileptic patients are at great risk of self poisoning. Safety in overdose is important when choosing and antiepileptic drug. Several conditions are known to be associated with an increased risk for valproate (VPA)-induced liver toxicity. Rare cases of fatal liver injury due to overdose with VPA were reported.

Methods: A group of 12 patients, children and adolescents, aged 12–18 years (mean 16.4) was treated for VPA-overdose with suicidal intent. Sustained-release VPA formulation was orally administered in 9 patients with idiopathic epilepsy and normal intelligence. Prescribed doses ranged between 24–38 mg/kg/daily for 8 to 52 months of continuous antiepileptic treatment. Serum concentrations were in therapeutic range (64–112 ug/ml). Regular monitoring of liver tests showed no significant abnormalities. Transient increase in serum-transaminase activity was seen in 4 patients during the first year of treatment. In remaining three non-epileptic patients, no previous VPA use was noted. The VPA overdoses ranged from 12.5 to 34 g (mean 18.2 g). No concomitant administration of cytochrome P-450-inducing drugs was noted.

Results: Acute intervention (gastric lavage) was taken in 7 of 12 patients. When admitted, their VPA serum levels ranged from 108 to 174 ug/ml. Remaining five patients were managed 2–5.5 hours after VPA overdosage. Their VPA serum levels ranged from 246 to 682 ug/ml. CNS toxicity presenting with lethargy, malaise, nausea, vomiting and seizure aggravation was observed in 7 patients. Cerebellar dysfunction including nystagmus, incoordination, dysarthria and ataxia was initial feature in half of patients. Impaired respiration and coma developed in three of them. L-carnitine was started. Serum aminotransferase, alkaline phosphatase and gama-glutamyl-transferase activity were moderately increased in 6/12 patients. The protrombin time was prolonged in one patient with no bleeding tendency. Serum ammonia levels were elevated in 8/12. Transient hypoglycemia occurred in two children. Mild jaundice developed in one girl taking 14 g of VPA with alcohol. Her liver biopsy showed drug-induced hepatitis. Serial electrocardiograms showed no abnormality through their hospital stay. Complete clinical recovery was achieved in all patients for two to five days after the ingestion of VPA overdose. Specific psychiatric intervention in epileptics with suicidal behavior was strongly recommended.

Conclusions: No significant liver lesions occurred in patients with suicidal ingestion of VPA overdoses. Excessive VPA amount ingested, without other risk-factors for liver toxicity, seemed to be associated rather with CNS toxicity than with liver injury.

1.346
A NATIONWIDE SURVEY ON TREATMENT PRACTICES AND TREATMENT GAP IN EPILEPTIC PATIENTS FROM HONDURAS

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Rationale: An important treatment gap for epilepsy in developing countries has been reported in association with economic and sociocultural factors. The objectives of our nationwide survey in Honduras, a developing Latin American country, were to assess the treatment gap, treatment compliance and treatment practices for epilepsy.

Methods: After completing an IRB approved pilot study at the University Hospital at Tegucigalpa, Honduras, a 28-question questionnaire was used countrywide. Practitioners selected to participate had been previously trained in administering epilepsy surveys at the University Hospital and they were doing follow-up of epilepsy patients in 3 private and 10 public clinics in urban and rural areas of the country between March 2002 and July 2003.

Results: We interviewed 217 patients (83 male, 134 female) averaging 31.1 years of age (range 3 to 79 years). They came from 13 of 18 Honduran counties; 102 lived in urban areas and 115 in rural regions. Average age at seizure onset was 16.9 years (range birth to 71 years). Average duration of seizure history was 12.6 years (range 0.1 to 61 years). In 89% of cases ($n = 193$) seizures were partial with or without secondary generalization and 11% ($n = 24$) were clinically suspected to be primary generalized seizures. Thirty percent of patients knew about the etiology of their seizures (mainly cysticercosis and head trauma). The majority of patients (92%) reportedly were currently taking drugs for their seizures when they were seen, but 43% reported stopping treatment in the past, most commonly because it was unavailable in the public clinics or because they could not afford treatment. However, the state paid for some or all treatment in 86% of the patients. Fifty-two percent of patients had used alternative treatments and 32% were using them at the time they were interviewed. The most popular alternative treatments were praying ($n = 70$) and taking herbs or potions ($n = 61$).

Conclusions: Our nationwide survey indicates that no matter the age of onset, type, or etiology, there is widespread treatment noncompliance throughout the country. The use of alternative therapies is common even when taking standard AEDs. Novel initiatives to address the economic and sociocultural causes of non-compliance should help close the epilepsy treatment gap that exists in the Honduran population. (Supported by Neurology Training Program, National Autonomous University of Honduras and Honduran Neurological Association.)

1.347
LONG-TERM SAFETY AND TOLERABILITY OF BROMIDES FOR INTRACTABLE SEIZURES

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Rationale: Bromides were a mainstay of seizure therapy from their discovery in 1857 until manufacture stopped in 1992, but long-term studies of its use are lacking. We examined the long-term tolerability and safety of bromides for patients prospectively enrolled in a long-term study.

Methods: Subjects were patients with seizures that did not respond to available therapy or who were taking bromides in 1992 when its commercial manufacture was stopped. Triple salts of bromides (906 mg/5 ml) were administered in a slowly escalating dose and patients were evaluated every 4–6 months, including bromide levels. Adverse events (AEs) and seizure frequency were collected as spontaneously reported. Seizure type and frequency were collected posthoc.

Results: Seventeen patients were enrolled. Mean age was 26 years (range 10–52), 12 were men, and 12 were cognitively impaired. Generalized seizures were present in 10 (7 with multiple generalized types). Etiology was cryptogenic in 14. Mean bromide dose was 10 cc/day (range 2.5–25). Mean serum level was143 mg/dl at steady state, 167 at the maximum dose and 74 at the minimum dose. Mean duration of therapy was 3.2 years (range 0.08–9.75), for a total of 51 patient-years. 152 adverse events occurred in 16 subjects, but only 44 were considered drug related. Five subjects took bromides 2 months or less. All drug-related AEs were mild or moderate. The most common AEs were acne (14), lethargy (12), ataxia (4), difficulty concentrating or confusion (3), and behavioral changes (2). Six subjects reported lack of improvement but all who received it for >2 months had reduction of seizure frequency. Median seizure frequency was reduced from 40 to 6 seizures/month ($p = 0.04$) with median reduction of 75%. Most subjects were withdrawn because seizures did not improve sufficiently, side effects were intolerable, or it was ineffective.

Conclusions: Bromides are commonly associated with acne, lethargy and ataxia. Refractory patients who can tolerate the side effects at initiation of therapy gain long-term effectiveness and may find the side effects acceptable later in therapy. Bromides remain a useful antiepileptic drug.

1.348

A LONG-TERM FOLLOW UP OF ZONISAMIDE MONOTHERAPY

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Rationale: Zonisamide (ZNS) has predominantly been used in adult patients with partial seizures as an adjunctive anti-epileptic drug (AED). However, current knowledge is limited on the long-term efficacy of ZNS monotherapy. A survey of our database was conducted to investigate the profile of patients, who were successfully treated by ZNS monotherapy.

Methods: From a cohort of 793 epileptic patients that had been treated with zonisamide in the past with or without other AEDs, 51 patients were selected for this study. The inclusion criteria of the 51 patients were 1) 29 pediatric patients under 16 years of age and 22 adult patients, having either partial or generalized seizures; 2) the seizure frequency before introduction of ZNS was reduced by 50% or more for longer than 4 months as a result of ZNS monotherapy; 3) patient data from May 1985 to December 2001. The age of the 51 patients, 24 males and 27 females, when ZNS monotherapy was started ranged from 6 months to 45 years and the duration from 9 to 180 months. Fifteen patients were treated with ZNS as their initial AED, 8 patients started ZNS monotherapy after skin rash developed with previous AEDs, 29 patients gradually started ZNS monotherapy due to insufficient efficacy of their previous mono- or bi-therapy of VPA, PHT, CBZ, PB, or DZP.

Results: ZNS monotherapy showed efficacy in controlling simple and complex partial seizures and secondarily generalized tonic-clonic seizures of temporal lobe epilepsy in 11 patients, frontal lobe epilepsy in 7 patients, occipital lobe epilepsy in 8 patients, and other symptomatic localization-related epilepsies in 6 patients. ZNS monotherapy was effective in controlling generalized tonic seizures including drop attack or violent head-nodding, generalized tonic-clonic seizures combined with atypical absences, myoclonic seizures and multiple seizures of symptomatic generalized epilepsy in 9 patients, including 1 patient with Lennox-Gastaut syndrome. ZNS monotherapy effectively controlled West syndrome in 2 patients, undetermined epilepsy in 2 patients, familial essential myoclonus and epilepsy in 2 patients and myoclonic epilepsy with ragged red fibers in 1 patient. ZNS monotherapy also controlled the seizures in idiopathic epilepsy in 3 patients, generalized tonic-clonic seizures on awakening in 2 patients, Sylvian seizures of benign partial epilepsy of childhood in 1 patient. ZNS monotherapy was continued in 38 patients, in that 32 patients showed remarkable improvement of their QOL. ZNS monotherapy had to be discontinued in 13 patients, due to lack of efficacy in 10 patients, overt restlessness and insomnia in 2 patients, and failure to take ZNS that resulted in a relapse of seizures in 1 patient.

Conclusions: ZNS was found to be effective both in pediatric and adult patients in controlling partial seizures with or without secondarily generalized seizures, and also convulsive and non-convulsive generalized seizures. (Supported by a grant from Elan Pharmaceuticals, Inc.)

1.349

OXCARBAZEPINE IS EFFICACIOUS IN PATIENTS WITH PARTIAL SEIZURES WHEN SWITCHING FROM CARBAMAZEPINE, PHENYTOIN, OR VALPROATE

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Rationale: The first-line antiepileptic drug (AED) oxcarbazepine (OXC) is widely used as monotherapy in the treatment of epilepsy. Although OXC as well as carbamazepine (CBZ) and phenytoin (PHT) are all sodium channel blockers (SCB), different mechanisms on the sodium channel may result in improved seizure control when a patient who fails to experience seizure control with one SCB is switched to another SCB. Other patients may respond to another AED with a different mode of action. The efficacy of OXC monotherapy in patients with partial seizures switched from other SCBs (CBZ and PHT) or valproate (VPA) was evaluated in a prospective, open-label, multicenter study.

Methods: Patients aged ≥12 years experiencing 2–40 partial seizures per month while receiving treatment with an AED in the 2 months prior to entry were included in the study. Following a 2-week screening phase, patients entered a 16-week treatment phase in which oxcarbazepine was initiated at daily doses of 8–10 mg/kg (patients ≤60 kg) or 600 mg (patients ≥60 kg). OXC was titrated up over 4 weeks while existing AED monotherapy was concurrently tapered off. The primary efficacy variable was the change in seizure frequency during the treatment phase compared with the 3-month retrospective baseline phase during which the patients were receiving treatment with another AED. This analysis was performed with data from patients receiving the most common AEDs at study entry: CBZ, PHT, and VPA. Data from patients with seizures at baseline, who received at least one dose of OXC, and for whom at least one post-enrollment assessment was available were included in the analysis.

Results: A total of 245 patients were enrolled in this study, 176 of which had seizure data available at baseline and post-enrollment. A >50% reduction in seizure frequency was observed in 48.0% to 64.9% of patients switched from CBZ, PHT, or VPA, and a 100% reduction was observed in 12.0% to 27.5% of patients. Mean seizure reductions from baseline for each AED are presented in the table below. The most common adverse events involved the CNS or gastrointestinal systems and occurred at similar frequency regardless of the AED switch.

Mean seizure reduction from baseline

Switched from:	>50%			>75%		100%	
	N	n	Patients (%)	n	Patients (%)	n	Patients (%)
CBZ	100	48	48.0	29	29.0	12	12.0
PHT	51	30	58.8	23	45.1	14	27.5
VPA	37	24	64.9	12	32.4	6	16.2

Conclusions: OXC monotherapy was efficacious in reducing seizure frequency in patients with partial seizures whether switching from previous treatment with the SCBs CBZ or PHT, or from VPA. The improved seizure control observed when switching patients with uncontrolled partial seizures while receiving treatment with another SCB to OXC monotherapy suggests that its mode of action may involve distinct mechanisms on the sodium channels. (Supported by Novartis Pharmaceuticals.)

1.350

SUCCESSFUL COMMUNITY-BASED USE OF BUCCAL AND/OR NASAL MIDAZOLAM TO ABORT PROLONGED SEIZURES AND SEIZURE CLUSTERING

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Rationale: Although rectal diazepam is becoming an acceptable alternative to intravenous use in emergency situations as rescue medication for prolonged or clustering seizures, there are practical problems with administration related to the dignity and social acceptability of the procedure. The long half-life is also associated with significant hangover effect. We report the successful use of midazolam being given buccally or nasally by carers in community settings as an alternative to rectal diazepam to abort prolonged seizures or clusters of seizures in adults and children with epilepsy. Our service covers a remote rural area in south west England where there is a need to explore alternatives to emergency hospital admission.

Methods: Midazolam is available in the UK in a format that renders such administration convenient, and is preferred to the formulation used

for anesthetic induction, which has unacceptably low pH and is supplied in glass containers that are inconvenient outside the clinical setting. Individual guidelines for administration were prepared for each patient and all users were trained in its use. Midazolam was prescribed as Epistatus (Special Products Ltd, UK), sugar-free buccal liquid 10 mg in 1.0 ml, in bottles each containing 4 applications of 10 mg each (standard adult dose) with plastic applicators. No glass needed to be broken for administration. Lower doses were used in children according to body weight.

Results: Of 69 patients treated, there were 26 in whom carers had previous experience of using rectal diazepam with the same patient. A customer satisfaction survey showed a strong preference for the use of midazolam by carers with experience of both midazolam and rectal diazepam because of social acceptability ($p = <0.0001$), ease of administration ($p = <0.0001$), rapid action ($p = 0.0033$) and minimal hangover effect consequent on short half-life ($p = 0.0009$). Despite its short half life there have been no problems with seizure recurrence after use compared with rectal diazepam, and no problems reported with respiratory depression after hundreds of uses in our service.

Conclusions: Midazolam given buccally or nasally by carers is an effective rescue medication for prolonged or clustering seizures. A preparation with appropriate pH and with suitable applicators is recommended, along with protocols for individual seizure management, carer training and guidelines for use. (Supported by Cornwall Partnership NHS Trust, as part of clinical practice in the National Health Service.)

1.351
CHARACTERISTICS OF SKIN RASH INDUCED BY LAMOTRIGINE

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Rationale: The adverse effects of lamotrigine is usually tolerable aside from skin rash. With the accumulation of clinical information, skin rash induced by lamotrigine is no longer regarded as drastic adverse effect as before. We tried to evaluate the characteristics of skin rash induced by lamotrigine wheter the rash is more common in specific patient group and whether the rash causes serious outcome.

Methods: We reviewed the adverse events induced by lamotrigine in 435 patients who took lamotrigine from Jul., 1997 to Dec., 2003. Age, sex, rate of titration, co-medications, and characteristics of rashes were reviewed.

Results: 23 patients(5.3%) developed skin rash 1 to 89 days after the initiation of lamotrigine(20.2 ± 20.09 days). Most of the rashes were relieved at the stage of macuopapular rash and only one patient developed into Steven-Johnson syndrome and finally relieved. Most prominet factor affecting the occurrence of skin rash was age. Only 3 out of 126 patients under fifteen years of age developed skin rash, whereas 20 out of 309 patients in adults. Monotherapy(9 out of 129) and polytherapy(14 out of 306) did not cause any difference. Seven patients developed skin rash out of 131 patients who took lamotrigine while on valproic acid. Irrelevantly rapid titration was done in 78 patients and rash occurred in 6 patients.

Conclusions: Skin rash induced by lamotrigine usually occurs in the adult. But co-medication of valproic acid and improper titration did not cause significantly higher rate of skin rash. Also, skin rash induced by lamotrigine rarely caused life-threatening event.

1.352
RHUMATISME GARDENALIQUE: REVISITED

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Rationale: Arthralgias as a consequence of anticonvulsant medications was described initially in 1934 with barbiturates and termed *rhumatisme gardenalique*. Subsequently, drug-induced lupus-like syndromes, fibromyalgia, and shoulder-hand syndrome have been described with anticonvulsants. We describe two patients with epilepsy treated with anticonvulsants with arthralgias primarily in the hands who improved with discontinuation of phenytoin.

Methods: Two case reports are described.

Results: A 22 year old woman with tonic seizures treated with phenytoin and oxcarbazepine for one year complained of episodically cold hands and occasional aches. Antinuclear antibodies (ANA) were elevated at 1:2560 and antihistone antibodies were 49 (greater than 2.5 is strongly positive). Discontinuation of phenytoin resulted in symptom improvement.

A 56 year old woman treated with phenytoin and valproic acid for 10 years complained of aching joints that became worse over the past year. She had a normal ANA and antihistone antibodies were 1.0 (weakly positive). Phenytoin taper resulted in increased range of motion of her fingers and less aching.

Conclusions: Review of the literature identified only 6 reports discussing anticonvulsants as a cause of arthralgias. The presence of arthralgias in the setting of anticonvulsant treatment should raise the possibility of this largely forgotten syndrome, *rhumatisme gardenalique*. The role of antihistone and antinuclear antibodies in the syndrome is unclear. Recognition of this syndrome is important because withdrawal of the offending anticonvulsant can lead to improvement of symptoms.

1.353
ZONISAMIDE: SAFETY IN PEDIATRIC AND YOUNG ADULT PATIENTS

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Rationale: Zonisamide, one of the newer antiepilepsy drugs, is approved in the United States for the adjunctive treatment of partial seizures in adults with epilepsy. The drug has been available in Japan since 1989, where it has been used to treat a wide spectrum of seizure types in adults and children. This chart review was conducted to expand the current knowledge base regarding the safety of zonisamide in treating pediatric and young adult patients with a variety of seizure types.

Methods: Charts of zonisamide-treated patients from a pediatric neurology clinic were reviewed. Data regarding the safety, efficacy, and tolerability of zonisamide were summarized for patients in each of the following age groups: <7 years, 7 to <10 years, 10 to <12 years, 12 to 18 years, and >18 years.

Results: A total of 171 zonisamide-treated patients (92 female, 79 male) were identified. Overall, the mean zonisamide dosage was highest in the 12-to 18-year age group (337.2 mg/d) and lowest in the <7-year age group (218.8 mg/d). However, on a mg/kg per day basis, the mean zonisamide dosage was highest in the <7-year age group (16.2 mg/kg per day) and lowest in the 12- to 18-year age group (6.8 mg/kg per day). The proportion of patients using zonisamide as monotherapy and the mean duration of zonisamide therapy were similar across age groups. Twelve patients (7.0%) discontinued zonisamide, 6 for adverse events. The >18-year age group had the highest discontinuation rate (22.2%). A total of 48 patients (28.1%) reported adverse events. The only adverse events that were reported in >10% of patients in any single age group were decreased/poor appetite (15.8% in the 10- to <12-year age group), sedation/sleepiness (10.5% in the 10- to <12-year age group), and weight loss (22.2% in the >18-year age group). Seizure response data (based on subjective reports) were available for 116 patients; of these, 101 patients (87.1%) had at least a moderate response to zonisamide, including at least 80% of patients in each age group.

Conclusions: This chart review expands the existing body of knowledge, which suggests that zonisamide is safe, effective, and well tolerated in pediatric and young adult patients across a variety of age groups. (Supported by Eisai Inc.)

1.354
INITIAL MONOTHERAPY WITH LEVETIRACETAM (LEV)

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Rationale: Levetiracetam (LEV) is an effective antiepileptic drug in add on therapy of pharmakoresistent focal epilepsies. In Europe it is not licensed for monotherapy and generalised idiopathic epilepsies. Nevertheless we have good experience in responder cases when we switched from add on to LEV monotherapy. In this study we want to present datas from initial LEV-monotherapy.

Methods: This is a retrospective observational study in drug resistant cases with focal and generalised epilepsies. In our outpatient department we analysed retrospectively the patient charts and the patients diary in respect to seizure frequency (SZF) and tolerability.

Results: From 733 patients under LEV add-on-therapy we had 48% responder with 25% seizure free patients, 104 patients were switched to monotherapy, 14 patients had an initial monotherapy (7 male, 7 female). The average duration of epilepsy was 6,7 years (1–23,83). The average follow up was 51,3 (7–154,6) months. From 14 cases, 11 (78%) were seizure free. From 6 focal epilepsies 4 and from 8 generalised epilepsies 7.

Conclusions: LEV promises to be a good antiepileptic drug even in initial monotherapy. The number of cases is too small to give a statement about a preference of efficacy either in focal or in generalised epilepsies.

1.355

AN ASSESSMENT SAFETY, PREFERENCE, EFFECTIVENESS, QUALITY OF LIFE AND TOLERABILITY (SPEQT) IN EPILEPSY PATIENTS SWITCHED FROM IMMEDIATE-RELEASE TO EXTENDED-RELEASE CARBAMAZEPINE CAPSULES

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Rationale: Ideally, the choice of treatment regimen for epilepsy patients should take into account more than simply seizure control. Increasingly, the assessment of adverse events (AEs) and of quality-of-life (QOL) have become aspects of epilepsy patient care. Traditional clinical trials have not included adequate assessment of these factors. In this study we sought to measure efficacy, safety, and medication preference data from subjects switched from immediate-release carbamazepine (IR-CBZ) to an equal total daily dose of carbamazepine extended-release capsules (CBZ-ERC).

Methods: We conducted a multi-center, open label, phase IV trial to assess the tolerability, safety, and effectiveness of switching from immediate-release carbamazepine(IR-CBZ) formulations to carbamazepine extended release capsules (CBZ-ERC) in adult and adolescent epilepsy patients. All subjects were switched from their current IR-CBZ product to an equal total daily dose of CBZ-ERC. Inclusion criteria included patients with partial epilepsy on stable IR-CBZ doses of at least 400 mg/day. Patients could be on one additional antiepileptic drug (AED). Exclusion criteria included a history of status epilepticus, epilepsy syndromes in which carbamazepine is contraindicated, progressive neurological disorders, neuroleptic drugs, and CBZ-ERC treatment within 90 days of study screening. Data from 453 patients with epilepsy were collected. Assessments included a seizure diary, adverse event profile (AEP) for adults, Hague Seizure Severity and Side Effects scales (HASS and HASES respectively) for adolescents, and QOL (quality of life) instruments. In addition, subjects, parents (of adolescent subject) and physicians completed satisfaction and medication preference instruments to evaluate potential benefits of the medication switch.

Results: Mean monthly seizure count was significantly decreased both at month 3 and at termination when compared to baseline ($P = .05$). Correspondingly, AEP scores showed significant improvement in CBZ-associated AEs in adults during treatment with CBZ-ERC ($P = .0001$). HASS and HASES ($P = .01$) showed reductions in seizure severity and medication-related side effects in adolescents. Results of quality of life instruments from patients switched to CBZ-ERC showed significant improvement across all subcategories of QOL assessed. Overall, medication satisfaction and preference instruments indicated that more subjects were satisfied with their medication at month 3 when compared to baseline.

Conclusions: Switching from IR-CBZ to CBZ-ERC in this population of patients resulted in significant improvements in seizure counts, AEP scores in adults and better HASS and HASES scores in adolescents.

This study demonstrated improvement in multiple measures of patient QOL with a change from IR-CBZ to CBZ-IR. (Supported by Shire Pharmaceutical.)

1.356

SEIZURE OCCURRENCE DURING ANTIEPILEPTIC DRUG TITRATION IN NEWLY DIAGNOSED EPILEPSY

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Rationale: Little is known about seizure recurrence in newly emergent epilepsy if an antiepileptic drug (AED) is loaded vs. being titrated. Although many double-blind randomized studies have evaluated AEDs titrated to a target dose, titration-period seizure occurrence has not been reported. We report seizure occurrence during titration in a double-blind trial comparing topiramate (TPM 100 and 200 mg/day) with carbamazepine (CBZ, 600 mg/day) or valproate (VPA, 1250 mg/day) in newly diagnosed epilepsy.

Methods: Patients ≥6 yrs were eligible if epilepsy had been diagnosed <3 mos before screening; no seizures or syndromes were excluded. Patients were untreated or treated ≤6 wks. Patients were randomized to TPM 100 or 200 mg/day or the investigator's choice of CBZ or VPA. Titration achieved target doses in 4 or 5 wks (see table). Dose reductions were not allowed. Time to 1st seizure provided means for post-hoc analysis of seizure occurrence during titration.

Results: The intent-to-treat population was 613 patients. Median time since epilepsy diagnosis, 1 mo; median time since first lifetime seizure, 5 mo. Study groups: CBZ, N = 126 patients; VPA, N = 78; TPM, 409. 68% of those randomized to TPM and CBZ and 59% randomized to VPA had 1–3 seizures in the 3-mo baseline. Table 1 shows proportion of patients having their first seizure during titration (Kaplan-Meier analysis of time to 1st seizure).

	% Patients with 1st Seizure			Dose (Cumulative % of target)			
Day	TPM	CBZ	VPA	TPM 100	TPM 200	CBZ	VPA
7	17.6	11.9	19.2	25 (20%)	25 (12.5%)	200 (33%)	250 (20%)
14	21.6	19.1	23.1	50 (50%)	50 (25%)	200 (33%)	500 (40%)
21	26.5	23.2	27.0	75 (75%)	100 (50%)	400 (67%)	750 (60%)
28	28.3	29.2	29.6	100 (100%)	150 (75%)	400 (67%)	1000 (80%)
35	30.5	30.1	29.6	100 (100%)	200 (100%)	600 (100%)	1250 (100%)

Conclusions: Although the CBZ data seem to show an advantage of more aggressive AED initiation with substantially fewer patients having ≥1 seizure within Week 1 (CBZ dose, 33% of target; VPA, 20%; TPM 100, 25%; TPM 200, 12.5%), any such advantage was short-lived; seizure recurrence was not significantly different among TPM, CBZ, or VPA-treated patients as dosages approached 100% of target and were maintained. This study, in which no seizure type or syndrome was excluded, shows that 70% of patients with newly diagnosed epilepsy can expect to have no seizures during titration. These data raise interesting questions about the risk-benefit of aggressively initiating AED therapy and provide information useful for counseling patients starting AED therapy. (Supported by Johnson & Johnson Pharmaceutical Research & Development.)

1.357

METABOLISM OF FLUOROFELBAMATE DIFFERS FROM THAT OF FELBAMATE

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Rationale: Fluorofelbamate (FFBM) is an analog of felbamate (FBM) that was designed to have similar clinical efficacy of felbamate without its serious adverse effects of aplastic anemia and liver failure. Fluorofelbamate differs from felbamate by substituting fluorine for hydrogen in the 2-position of the propane side chain of felbamate. This specific substitution is thought to prevent the production of a proposed reactive aldehyde metabolite, atropaldehyde (ATPAL), which is produced via beta-elimination from 3-carbamoyl-2-phenylprionaldeyde (CBMA)

and is thought to be responsible for the severe idiosyncratic reactions. It has been reported by Thompson et al. (Chem Res Toxicol, 1996) that CBMA is in dynamic equilibrium with 4-hydroxy-5-phenyl-tetrahydro-1,3-oxazin-2-one (CCMF) and that CBMA incubated in the presence of glutathione (GSH) was completely converted to the GSH adduct of ATPAL over 15 hours. Recent work expanded this observation to CCMF and analogous studies were initiated using the fluorinated analog, F-CCMF. Fluorofelbamate is currently in preclinical development and results of pharmacodynamic, pharmacologic, toxicologic and metabolic studies will be presented.

Methods: The pharmacodynamic and mechanistic profile of FFBM was established using standardized in-vivo anticonvulsant tests. Nonclinical studies in support of an IND submission were conducted at a qualified GLP laboratory. Recently studies in vitro were conducted to compare the metabolism of MCF, FMCF, CCMF, and FCCMF in the presence of glutathione to trap reactive metabolites formed by pooled human liver S9 fractions. Analyses of samples from these studies were performed using HPLC and HPLC/APCI/MS.

Results: FFBM demonstrated efficacy in a broad range of animal seizure models. Drug metabolism studies showed that both CCMF and FCCMF were oxidized by human liver S9 fractions to produce 3-carbamoyl-2-phenylpropionic acid (CPPA) and FCPPA. In contrast, in the presence of glutathione, adducts with ATPAL or 2-phenylpropionic acid (ATPALA), respectively, were identified following incubation with CCMF but not FCCMF. We also demonstrated that MCF is metabolized to CCMF and CPPA by human liver S9 fraction. However, FMCF did not produce FCCMF, FCPPA, CCMF or CPPA providing important additional evidence that FFBM does not produce the putative toxic metabolite ATPAL.

Conclusions: The results of these studies support the concept that FFBM's anticonvulsant profile is similar to that for FBM. The nonclinical pharmacology-toxicology work has not identified any major issues and the adduct work demonstrates that reactive intermediates are not formed from FCCMF under the conditions tested. Lastly, results from the human liver S9 metabolic studies in vitro provide evidence that fluorofelbamate will not enter the pathway that generates the putative toxic metabolite, ATPAL, that is generated from felbamate.

1.358

UNCONTROLLED EPILEPSY EMERGING AFTER AED DISCONTINUATION IN SEIZURE-FREE PATIENTS

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Rationale: Although the rate of seizure recurrence following planned discontinuation of antiepileptic drugs (AEDs) in seizure-free patients is well known, less information is available if reinstitution of treatment invariably results in prompt and complete seizure control.

Methods: A literature review was performed yielding 12 retrospective observational studies of AED discontinuation with data on seizure outcome after resumed therapy.

Results: Reinstitution of AEDs after recurrence did not result in complete seizure control during the last year of follow-up in 21% of patients (mean of 12 studies, 95%CI:15–26) after an average of 3 years of resumed treatment. In 7–9% of cases, chronic drug-resistent epilepsy was noted with many seizures over as many as 5 years. Although seizure control was regained in approximately 50% of those becoming seizure-free within one year, it took as many as 5–12 years for some patients to regain seizure-freedom after a recurrence. Factors associated with poor treatment response after recurrence were symptomatic etiology, partial epilepsy and cognitive deficits.

Conclusions: Although it is reassuring that AED reinstitution after a seizure recurrence following planned discontinuation in seizure-free patients is successful in approximately 90% of patients, complete response may be delayed as late as 12 years after restarting treatment in some cases. Unexpectedly, epilepsy may prove to be severe and uncontrollable in 7–9%. These risks must be mentioned when discussing AED discontinuation with seizure-free patients.

1.359

MULTICENTER OBSERVATIONAL STUDY OF LEVETIRACETAM IN SPAIN

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Rationale: To analyze the efficacy and safety of levetiracetam by means of an open-label, observational, transectional study.

Methods: Patients with any type of seizure and epilepsy in whom treatment with levetiracetam was started in 8 centers were included in this study. The following data were analyzed at baseline: age, age at seizure onset, seizure types, type of epilepsy, monthly seizure frequency and number of antiepileptic drugs (AEDs) tried. After a minimum of 6 months of starting levetiracetam seizure frequency, side effects (type and duration), dose of levetiracetam, reasons for discontinuation of levetiracetam and concomitant AED use were analyzed.

Results: A total of 425 patients were included in the study. Mean seizure frequency at baseline was 17.6 seizures/month and mean number of AEDs tried was 5.8. The majority of patients (90.3%) presented partial seizures with or without secondary generalization. Mean duration of treatment with levetiracetam was 7.9 months and mean dose was 1,802 mg/day. At evaluation, 64.2% of patients had experienced a >50% reduction in seizure frequency (including 25.4% of seizure free patients), 26.8% presented no changes in seizure frequency and 8.2% had an increase in seizure frequency. Side effects were reported by 111 patients (26,1%) and required withdrawing levetiracetam in 31. The most common side effects were somnolence ($n = 73$), irritability ($n = 19$), and depression ($n = 15$). At the end of the study 35 patients (8.2%) were on monotherapy with levetiracetam. When only children or elderly patients were analyzed, similar results were obtained, although less children and more elderly patients achieved a >50% reduction in seizure frequency and more elderly patients and less children presented side effects.

Conclusions: In this observational study in close-to-clinical-practice conditions, levetiracetam proved to be an effective drug in 64% of patients. Side effects were usually mild, transitory and rarely severe enough to discontinue medication. Levetiracetam also proved to be effective and safe in children and elderly patients.

1.360

EXPERIENCE OF USING LEVETIRACETAM TO TREAT REFRACTORY EPILEPSY IN ADULTS AND CHILDREN WITH INTELLECTUAL DISABILITIES

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Rationale: Levetiracetam (LVT) is currently licensed for adjunctive treatment of partial seizures in adults. Literature suggests both pediatric potential and possible efficacy in a wider range of seizures. Anecdotal evidence suggests it is well tolerated. People with intellectual disabilities (ID) are at special risk of developing refractory epilepsy (RE) often of symptomatic/cryptogenic generalized type, with difficult to treat myoclonic, atonic, tonic and atypical absence seizures. We report our experience using LVT in a specialist epilepsy service for people with ID.

Methods: LVT was added to the treatment of 64 people with ID and RE, aged 9–54 years, with follow-up 0.5–4 years. 64% were male. >70% had cryptogenic/symptomatic generalized epilepsies. Co-medications were mainly valproate, lamotrigine and topiramate, less frequently gabapentin, carbamazepine or phenytoin. Dose titration was monitored by community-based epilepsy specialist nurses. Adverse events were regularly monitored using a standardized checklist. Seizure frequency was monitored by carers and patients using standardized recording formats individually designed for each patient's seizure type. A favorable response led to attempt at reduction of concomitant medication. Where there was no response, or if carers or patients were concerned about adverse effects, LVT was withdrawn.

Results: Complete seizure control was obtained in 11% of this very refractory group. Most achieved reduction in seizure frequency between 40–80%. There was frequently a change to milder, shorter seizures. Improvement was seen in some patients with tonic seizures (often notoriously difficult to treat). Further analysis of seizure frequency was limited because in this naturalistic study there were occasionally other factors such as concomitant withdrawal of carbamazepine in patients with myoclonus. A dose-related mood change responded to slower dose escalation in one case. LVT was withdrawn in 4 cases where it was ineffective and in 2 because of behavioral change. In both latter cases it was successfully re-introduced with good results using slower dose escalation. The original problem was attributed to paradoxical normalization.

Conclusions: LVT seems generally well tolerated in people with ID, including children. As reported elsewhere it shows efficacy in generalized as well as partial seizure types. In this population it is recommended that slow dose escalation is used. It is important to consider other causes for the emergence of behavioral changes than purely drug-induced effects, such as paradoxical normalization. In such cases re-challenge with more appropriate dose escalation may be successful. Our practice supports the value of community-based specialist nurse monitoring of dose regimes and adverse events.

1.361
SYDENHAM'S-LIKE PICTURE AND TOURETTISM AS RELATED TO LAMOTRIGINE TOXICITY

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Rationale: Lamotrigine has been associated with the development of tics. The occurrence of other types of movement disorders has not been well described.

Purpose: This purpose of the poster presentation is to describe the case of a child with a clinical picture strongly suggestive of Sydenham's chorea and four patients with Tourette's like syndrome, all of whom had remission of symptoms after lowering the dosage of Lamotrigine (LTG).

Methods: This is a retrospective study aimed at identifying all patients who developed a movement disorder related to LTG. The patients had to have presented with the movement disorder after being started on LTG, and the symptoms had to have remitted after lowering or discontinuation of the LTG dosage.

Results: One girl, aged 54 months old, presented with continuous choreoathetotic movements only seen during wakefulness, and involving her head, face, all four extremities, and abdominal musculature. She has an underlying severe developmental delay and intractable secondary generalized epilepsy with multiple seizure types which appeared after an apparent encephalitic illness at 18 months old with the occurrence of dramatic developmental regression after an apparently normal early childhood. Six weeks prior to presentation, she had occurrence of positive Strep culture, ASO titers, and streptozyme, and received appropriate penecillin therapy. LTG levels had suddenly increased from 9 to 22, in the setting of slow taper and discontinuation from intercurrent ACTH, and continuing therapy with chlorazepate, while on LTG dose 25 mg/kg/d. CTV-EEG monitoring established the character of movements as non epileptic; movements dramatically regressed over a several day course of withholding LTG, then decreasing dosing to 13 mg/kg/d. Four patients, three children with focal onset epilepsy, and one adult with JME, developed multifocal tics and vocalizations at doses of 12–28 mg/kg/d with levels of 12 to 31, respectively. Symptoms remitted after the dose was lowered in all patients. None needed to have LTG discontinued.

Conclusions: Movement disorders related to LTG can present as Tourette's syndrome and can mimic Sydenham's chorea. Our observations in the above set of patients demonstrate that it is not necessar to discontinue effective LTG therapy to achieve movement disorder symptom remission.

1.362
TOLERABILITY OF TOPIRAMATE IN 342 PATIENTS: ANALYSIS BY DOSE AND SERUM CONCENTRATION

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Rationale: To determine clinical correlations of dosage and serum concentrations of topiramate (TPM) during clinical practice at a comprehensive epilepsy center.

Methods: We reviewed 1237 drug regimens and 469 serum levels from 342 patients who received topiramate. Data collected included concomitant antiepileptic drugs (AEDs), doses, clinical toxicity and specific side effects. 'Toxic' was defined as causing side effects that led to a dosage change or discontinuation of TPM. Rates of toxicity and specific side effects were calculated and analyzed for correlation with dosage and serum concentration. Correlation was tested using binary logistic regression, with significance set at $p < 0.05$.

Results: Overall, 163/1237 (13.2%) regimens included side effects requiring TPM dosage or medication change and 73/1237 (5.9%) regimens included side effects requiring TPM discontinuation. 129/342 (37.7%) patients had at least one toxic regimen and 70/342 (20.5%) patients had side effects that led to TPM discontinuation. Toxicity correlated with dosage ($p < 0.01$) but not serum concentrations. The mean TPM dosage was 222 mg/day and the mean serum concentration was 7.2 μg/ml. Cognitive side effects and drowsiness were the most common side effects and led to a dosage or medication change in 14.9% and 7.3% of patients, respectively. Both cognitive side effects and drowsiness correlated with dosage ($p < 0.05$). At dosages $\leq$200 mg/day, 26/222 (11.7%) patients experienced cognitive side effects that led to a dosage or medication change. At dosages $\geq$400 mg/day, 20/69 (29.0%) patients experienced cognitive side effects that led to a dosage or medication change. 3/342 (0.9%) patients experienced renal stones due to TPM. No patients experienced glaucoma.

Conclusions: TPM is well tolerated, with approximately 80% of patients never experiencing side effects leading to discontinuation. Tolerability of TPM is correlated with dosage but not serum concentration. The most common side effects are cognitive side effects and drowsiness, both of which are correlated with dosage. (Supported by Elan, Glaxo, Ortho-McNeil, Pfizer, and UCB Pharma.)

1.363
TOPIRAMATE MONOTHERAPY IN RECENTLY DIAGNOSED EPILEPSY: RESPONSE ACCORDING TO SEIZURE TYPE

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Rationale: Topiramate is recognized as a broad-spectrum antiepileptic drug (AED), based on results from double-blind randomized controlled trials. Because these trials are often conducted for registration purposes, they tend to enroll relatively homogenous and more selected patient populations vs. those encountered in clinical practice. A large, open-label study evaluated topiramate monotherapy in the clinical practice setting. We report the results stratified by seizure type (partial-onset or generalized) and by whether patients were treatment-naive or failed previous therapy.

Methods: Patients in whom epilepsy had been diagnosed $\leq$5 yrs before topiramate treatment were followed in an open-label, multicenter prospective study conducted in Europe and the Middle East. Patients were treatment-naive or had failed one antiepileptic drug (which was withdrawn when topiramate added). Doses were adjusted according to clinical response, with 3 mg/kg/day as the initial target dose for children 2–12 yrs and 100 mg/day for older children and adults (maximum, 9 mg/kg/day and 400 mg/day). Patients were followed for 7–13 mos. Responses were analyzed according to baseline seizure type, i.e., generalized and partial-onset.

Results: A total of 714 patients were enrolled; 690 had evaluable efficacy data. Data for 155 patients with generalized seizures (absence seizures excluded) and 431 with partial-onset seizures were analyzed. Mean baseline seizure frequency was 5.4 generalized seizures/mo and 7.7 partial-onset seizures/mo. Seizure were reduced $\geq$50%, $\geq$75%, and 100% in 89%, 80% and 63%, respectively, of patients with generalized seizures and 77%, 63% and 40%, respectively, in those with partial-onset seizures. Response rates were higher in therapy-naive patients. Changes from baseline were significant in all subgroups ($p < 0.001$). Topiramate

was generally well tolerated, with paresthesia and headache as the most common adverse events.

Conclusions: Generalized and partial-onset seizures responded well to topiramate monotherapy. Higher response rates in therapy-naive patients vs. those who had failed a previous AED are consistent with observations with other AEDs. (Supported by Janssen-Cilag.)

1.364
RESULTS OF SWITCHING TO GENERIC ANTIEPILEPTIC DRUGS IN THE TREATMENT OF EPILEPSY
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Rationale: To assess whether a switch from a brand name antiepileptic drug (AED) to a generic AED, or from a generic AED to another generic AED results in breakthrough seizures or adverse events. According to the FDA, generic drugs must be bioequivalent to brand name AEDs, defined as no less than 80% and no more than 125% average maximum plasma concentrations. Controversy exists whether AEDs, which have a narrow therapeutic range, are interchangeable with brand name drugs with respect to seizure control and adverse effects. The literature contains reports of breakthrough seizures and adverse events after generic substitution, but the extent of these occurrences is unknown.

Methods: We designed a 13 question survey for neurologists in order to evaluate whether breakthrough seizures and/or adverse events had occurred during the past year among epilepsy patients who were switched to a generic AED from a brand name AED, or from one generic AED to another generic AED. Other survey questions included the proportion of patients in the practice with epilepsy, geographic practice location, type of patient insurance, and consequences of breakthrough seizures or adverse events, if they occurred. The survey was mailed on 7/11/03 to 6,420 US neurologists, whose names and addresses were obtained from a list broker. The estimated time of completion of the survey was 5 minutes. No compensation or honoraria was offered for completion of the survey. The last date of acceptance of results was 8/25/03. Three hundred and one neurologists responded (4.7%).

Results: One hundred and ninety-six neurologists (68%) reported breakthrough seizures and 162 (56%) reported increased side effects attributable to a switch from a brand name to a generic AED in the past year. Ninety-four neurologists (33%) reported breakthrough seizures and 76 (27%) reported increased side effects attributable to a switch from one generic to another generic AED. Six percent of neurologists reported 1 patient, 47% reported 2–4 patients, and 28% reported 5 or more patients suffering from breakthrough seizures or increased side effects. In order to treat the consequences of generic drug substitution, 188 neurologists reported the need for phone consultations, 166 extra office visits, 128 emergency room visits, and 46 hospital admissions. Seventy-seven neurologists reported that patients missed work, 25 indicated that the doctor patient relationship was undermined, and 23 reported patient injury.

Fig. 1. Hyperintense DWI pattern after status epilepticus (right temporoparietal and pulvinar hyperintensities)

Conclusions: More than two thirds of neurologists who responded to this survey reported breakthrough seizures, and more than half observed increased side effects due to generic substitution of brand name AEDs in the past year. Consequences included additional phone consultations, office visits, emergency room visits, hospitalizations, loss of work, patient injury, and deterioration of the doctor patient relationship. Physicians should carefully weigh the cost/benefit ratio of switching to generic from brand name AEDs or generic to generic AEDs in patients with epilepsy. (Supported by Shire, US.)

Antiepileptic Drugs—All Ages 2

1.365
SUSTAINED EFFECTIVENESS OF LONG-TERM OXCARBAZEPINE MONOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED EPILEPSY
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Rationale: A longitudinal examination of up to 4 years' experience with oxcarbazepine monotherapy in adult and pediatric patients with newly diagnosed partial seizures or generalized tonic-clonic seizures.

Methods: Data collected during three multicenter, double-blind, randomized, flexible-dose, 1-year, active-controlled clinical trials of similar design were included in this analysis. The studies compared the efficacy and safety of oxcarbazepine and valproate in patients aged 15–65 years (Christe et al. Epilepsy Res 1997;26:451–460) or compared oxcarbazepine and phenytoin in either adult (16–65 years old) (Bill et al. Epilepsy Res 1997;27:195–204) or pediatric patients (5–18 years old) (Guerreiro et al. Epilepsy Res 1997;27:205–213). The trials were extended to include a 1-year open-label follow-up (OF) phase and a subsequent open-label extension (OLE) phase. Data were integrated into a combined database to include up to 4 years' experience with oxcarbazepine. Long-term outcomes were evaluated in patients exposed to oxcarbazepine from initiation of the double-blind treatment phase, through the OF phase, and continuing into the OLE phase.

Results: A total of 362 patients received oxcarbazepine for a mean duration of 622 days (range: 1–1666 days). In adults (>18–65 years; n = 217) and pediatric patients (5–18 years; n = 145), the median daily dose of oxcarbazepine was 900 mg (range: 300–2400 mg) and 17.8 mg/kg (range: 6.38–43.5 mg/kg), respectively. Estimated Kaplan-Meier retention rates were 71%, 61%, and 59% after 1, 2, and 4 years of treatment with oxcarbazepine, respectively. Patient discontinuations due to adverse events (AEs) were ≤6% for up to 4 years of oxcarbazepine treatment. Analysis of the intent-to-treat population from initiation of oxcarbazepine over the first year of therapy estimated that 51.9% of patients remained seizure free. Seizure freedom improved over the second year of oxcarbazepine therapy (73.8% of patients were seizure free for the enrollment period >1 year-≤2 years), and reached 74.5% after >2 years of oxcarbazepine therapy. Over 4 years of oxcarbazepine treatment, the probability of experiencing at least 1 year of seizure freedom was 78%. The most frequent AEs (>20%) occurring over the entire period were headache, somnolence, dizziness, and viral infection.

Conclusions: The seizure-free data reported in this combined analysis compare well with reported rates in newly diagnosed patients successfully treated with the first antiepileptic drug chosen (Kwan and Brodie. NEJM 2000;342:314–319). The clinical utility of long-term oxcarbazepine therapy was demonstrated by good tolerability combined with sustained long-term seizure control in patients with newly diagnosed epilepsy. (Supported by Novartis Pharmaceuticals.)

1.366
THE EFFECT OF NONADHERENCE ON ANTIEPILEPTIC DRUG EXPOSURE: A SIMULATION STUDY
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Rationale: Nonadherence is an important determinant of outcome with drug therapy. Drug concentrations are influenced by the extent of nonadherence; some drugs are expected to be more sensitive to missed doses than others. The primary factor affecting this sensitivity is the dosing schedule of the drug in relation to its pharmacokinetics. The objective of this simulation study was to quantitate changes in drug exposure in response to nonadherence to antiepileptic drug therapy.

Methods: Pharmacokinetic parameters and standard doses of zonisamide (ZNS), oxcarbazepine (OXC), levetiracetam (LEV), topiramate (TPM) and carbamazepine (CBZ) were obtained from the literature. Induced and uninduced clearance (CL) values were used for ZNS, OXC and TPM simulations. In addition, CL values of +/- 1 standard deviation were identified to correspond to above and below average elimination. Simulations were based on a one-compartment model with first-order absorption and elimination using the pharmacokinetic program NONMEM. Three levels of nonadherence were built into simulations following the attainment of steady state. Concentrations were simulated following the omission of 1, 2 and 3 consecutive days of dosing to mimic nonadherence over a single day, a weekend, and a long weekend, respectively. Two additional days of full adherence followed the period of nonadherence in the simulation. In silico subjects were created for each drug, induced and uninduced, at above, below and at average CL, and at each level of nonadherence. An area-under-the-curve (AUC) was computed

beginning with the first missed dose following steady state, continuing through the 1, 2 or 3 days of nonadherence, and ending after a second day of full adherence. This AUC was compared to the AUC that would have occurred if the subject were fully compliant.

Results: Reduction in AUC ranged from 15–33%, 25–50%, and 33–60% following missing 1, 2 and 3 days of dosing, respectively. CBZ, LEV, OXC and TPM were remarkably similar in their results. Because of its longer half-life, ZNS consistently produced the smallest changes. The effect of enzyme induction had a more notable adverse effect on drugs with the longer half-lives.

Conclusions: Some degree of nonadherence is certain in the clinical setting. Drugs with longer half-lives will maintain relatively greater exposures during periods of nonadherence. However, it will also take relatively longer for concentrations to increase back to steady state if the usual maintenance dose is resumed. In such cases, loading doses may permit more rapid attainment of steady state. This study demonstrates that drugs with longer half-lives will be associated with smaller reductions in drug exposure in situations of occasional nonadherence. (Supported by NIH NINDS P50-NS16308 and a grant from Elan Pharmaceuticals.)

1.367
LEVETIRACETAM MONOTHERAPY IN GENERALIZED EPILEPSY AND PHOTOSENSITIVITY IN CHILDREN AND YOUNG ADULTS

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Rationale: Levetiracetam (LEV) is a new antiepileptic drug proved to be effective as add-on therapy to other AEDs in reducing partial onset seizures. The objective of this study was to evaluate the efficacy and tolerability of levetiracetam monotherapy in generalised idiopathic epilepsies of childhood and adolescence, particularly those showing photosensitivity.

Methods: This is a single centre open-label study in 21 patients, ages 5.5–21.5 years. LEV monotherapy was commenced as the AED initial therapy in 16 patients and in 5 after valproate withdrawal mainly because of adverse events. The epilepsy diagnosis was based on sleep-wake video-EEG recordings. The children were classified according to their seizure type and photosensitivity. Seventeen (17) patients had generalised tonic clonic seizures (GTCS), absences and myoclonic jerks. One (1) GTCS and absences, one (1) absence seizures only, and two (2) absences and myoclonic seizures. LEV was commenced at a starting dose of and 5–10 mg/kg/day gradually increased to 35–45 mg/kg/day, (dependent on clinical effect or adverse events). The follow up period varied from 3 to 30 months.

Results: Seven (7) patients (39%), 5 of whom were photosensitive, had a complete clinical/EEG response. The follow up period was 5 to 28 months. Mean daily LEV dose was 24 ± 8 mg/kg/day. Four (4) photosensitive patients had complete clinical and 50–80% EEG response. In 6 patients on LEV, after a period of 3 to 6 months, valproate in 5 and lamotrigine in 1 were added, for complete or improved clinical response. In 4 patients the results varied from 30–50% at a mean daily dose of 15–25mg/kg/day. One patient with absence and myoclonic seizures deteriorated and was changed within one month to valproate with good response. Adverse events were few, transient and due to faster titration.

Conclusions: Levetiracetam monotherapy is effective, well tolerated and safe in idiopathic generalised epilepsies and photosensitivity in children and young adults. The maximum effective dose needs to be established.

1.368
LAMOTRIGINE INCREASES SERUM CREATININE

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Rationale: After we had noticed increased serum creatinine in single patients treated with lamotrigine (LTG) we decided to investigate the frequency and extent of this phenomenon in a greater number of patients.

Methods: In a retrospective analysis of the data base of our laboratory we selected those patients in whom LTG was started or stopped in the year 2002. The relationship between LTG treatment and creatinine serum levels was investigated.

Results: We identified 80 patients (mean age 35.8 y, 41 males) with at least one serum level of creatinine before or after treatment with LTG and one to fourteen creatinine values obtained during this treatment. In 76 patients LTG was started and in 4 patients it was discontinued. There was a correlation between LTG and creatinine serum concentrations ($r = 0.334$), which was statistically significant ($p < 0.001$, $n = 265$). In 48 patients with LTG > 10 μmol/l we compared the creatinine values corresponding to the maximum LTG levels with those obtained before or after treatment. This revealed an average increase of creatinine of 9.2 μmol/l due to treatment with LTG, which was statistically significant ($p < 0.001$, t-test). In detail, in 40 patients there was an increase ranging between 1.3 and 43 μmol/l, whereas in the remainder creatinine decreased by 2.6 to 30.2 μmol/l. However, pathological creatinine values (> 100 μmol/l) were found in only 4 patients, two of them had already patholgical values before LTG treatment. Even in these patients there were no signs or symptoms of any clinically relevant impairment of renal function due to LTG.

Conclusions: LTG leads to increased creatinine serum levels, what has not been reported up to now. The mechanism of this effect remains to be elucidated. A clinical relevance of this finding seems rather unlikely, but cannot be ruled out in individual patients.

1.369
TOPIRAMATE (TPM) VS. CARBAMAZEPINE (CBZ) AND VALPROATE (VPA) IN NEWLY DIAGNOSED EPILEPSY: EFFECTIVENESS ACCORDING TO SEIZURE TYPE

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Rationale: In a double-blind trial, TPM was at least as effective as 600 mg/day CBZ and 1250 mg/day VPA monotherapy in patients with newly diagnosed epilepsy. (Privitera 2003) We report post-hoc analyses of relative effectiveness in partial-onset (POS) and primary generalized (GEN) seizures.

Methods: Patients $\geq$6 yrs were eligible if epilepsy had been diagnosed $<$3 mos before screening. To individualize therapy, investigators selected CBZ or VPA as preferred agent. Patients were randomized to double-blind treatment with TPM (100 or 200 mg/day) or investigator's choice of CBZ or VPA. Dose reductions to manage adverse events (AEs) were not allowed. Patients exited if unable to achieve assigned dose or if therapy change required. Primary endpoint was time to exit; secondary efficacy endpoints were time to first seizure and patients seizure-free for last 6 months of treatment. TPM data pooled for comparison with CBZ and VPA. In post-hoc analyses, patients stratified by baseline seizure type: POS (simple partial, complex partial, secondarily generalized) or GEN (tonic-clonic, tonic, clonic).

Results: The intent-to-treat population was 613 patients (CBZ, $N = 126$ patients; VPA, $N = 78$; TPM, $N = 409$). 382 patients had POS (TPM, $N = 258$; CBZ, $N = 92$; VPA, $N = 32$); 211 had GEN (TPM, $N = 142$; CBZ, $N = 31$; VPA, $N = 38$). TPM did not differ significantly from CBZ and VPA in time to exit among patients with POS ($P = 0.803$) or GEN ($P = 0.720$). Retention rates were 1–3% higher in both POS and GEN for TPM vs. CBZ/VPA at all time points (90, 180, 270, 365 days). The 95% confidence interval around these differences showed that retention rates with TPM could be 11–14% higher vs. CBZ/VPA in patients with POS and 15–19% higher in patients with GEN. At the opposite limit of the 95% confidence interval, retention rates could favor CBZ/VPA by 8–10% in POS and 9–12% in GEN. The seizure-free rate was slightly lower (5%) for TPM vs. CBZ/VPA in POS but higher (6%) in GEN. From the 95% confidence interval, the seizure-free rate could favor CBZ/VPA by 15.5% in POS and 8.5% in GEN. When the difference favored TPM, the seizure-free rate could be 5.5% higher in POS and 20% higher in GEN. Retention times and time to first seizure were generally shorter in both POS and GEN in VPA- vs. TPM- or CBZ-treated patients. Overall,

differences between TPM and CBZ and VPA were not statistically significant. Discontinuation rates due to AEs were TPM 100, 19%; TPM 200, 28%; CBZ, 25%; VPA, 23%. AEs differed according to their known profiles.

Conclusions: Regardless of seizure type, TPM is at least as effective as CBZ and VPA in newly diagnosed epilepsy. (Supported by Johnson & Johnson Pharmaceutical Research & Development, LLC.)

1.370

WHAT WOULD HAPPEN IF DEPAKOTE® EXTENDED RELEASE WERE GIVEN TWICE DAILY? MONTE CARLO SIMULATIONS AND COMPARISON WITH DEPAKOTE® TWICE DAILY

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Rationale: Depakote® (or divalproex, dvpx) is a twice daily (BID) preparation for valproic acid (VPA). Depakote® extended-release (dvpx-ER) is a new preparation designed for once daily administration (QD). There is a trend among some clinicians to prescribe dvpx-ER BID, concurrent with other AEDs given BID. There is a question whether BID regimens of the two preparations are equivalent in terms of the effect of missed or delayed doses on VPA concentrations. This study investigates the effect of missed and replacement doses on dvpx and dvpx-ER; both given BID.

Methods: To account for the lower bioavailability of dvpx-ER (F = 0.89 vs. F = 1 for dvpx); 1250 mg (BID) of dvpx-ER was compared to 1000 mg (BID) of dvpx. 100 subjects were simulated for each poor compliance scenario with either one or two delayed or missed doses from schedule. Un-induced state (adults, $t_{1/2}$ = 14 h) was assumed. Unbound (C_u) and total (C_{tot}) VPA levels were determined to assess the% of subjects that had concentrations in the sub therapeutic range (C_u <5 mg/l and C_{tot} < 50 mg/l), time spent in the sub therapeutic range or time at risk (h); and% of subjects in the toxic range (C_{tot} > 150 mg/l).

Results: One missed or delayed dose at various times didn't result in sub therapeutic or toxic (in case of replacement doses) VPA concentrations for either preparation. Results for two delayed doses are shown in Table 1.

Conclusions: Dvpx and dvpx-ER, both given BID, are equivalent in terms of the effect of poor compliance on VPA concentrations, provided that dvpx-ER dose is 20% higher than dvpx. Since VPA has a relatively short half-life, twice-daily administration seems to offer protection from sub therapeutic levels if one dose is missed. Not more than 24% (dvpx) or 20% (divalproex-ER) of subjects will have sub therapeutic concentrations if two doses are taken 12 h after the 2nd missed dose. There is no risk of toxicity if two doses are replaced. (Supported by Abbott Labs.)

1.371

CLINICAL EXPERIENCE WITH FELBAMATE IN PATIENTS WITH MEDICALLY INTRACTABLE EPILEPSY

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Rationale: Felbamate (FBM) use has declined since 1994 following reports of FBM induced aplastic anemia and liver failure. Limited published data is available on the clinical experience of FBM use since 1994. We previously presented a preliminary report on a limited sample of adult patients treated at Minnesota Epilepsy Group. The current study significantly expands our observations on Felbamate therapy and includes results on pediatric as well as adult patients.

Methods: 305 patients ages 1 to 73 yrs. treated with FBM were identified and records reviewed. Data were tabulated and analyzed to include patient demographics, efficacy and tolerability. Paired *t* tests were calculated to compare mean seizure frequency prior to FBM use and at FBM optimization.

Results: Of patients reviewed, 147 female/158 were male. Mean age at start of FBM was 32 yrs for adults (>16 years) and 6.8 yrs for children (<16 years). The mean number failed AEDs was 5.5. Mean baseline frequency/seizure type/month: GTCs19 for children/7.9 for adults; CPSs 28.7 for children/27.3 for adults; SPS 9.5 for children/27.3 for adults; tonic seizures 28.7 for children/102.1 for adults; myoclonic 26 for children/121.2 for adults; atonic 10 for children/20.4 for adults. FBM therapy ranged from 1 to 156 months (mean: 36.3) with an average maximum dose 2,240-mg/day for children/3,769.3-mg/day for adults. The average FBM level was 73-mg/dl for adults/72.3-mg/dl for children. Responder rate (50% reduction in baseline seizure frequency) was 57% for children, 41% of those with >75% reduction. For adults, the responder rate was 66%, 49% having >75% reduction. Average reduction in baseline frequency per seizure type for adults: GTCs (n = 81), 52.3% ($p < 0.001$); CPS (n = 115), 24.1% ($p = 0.007$); SPS (n = 37), 29.4% ($p < 0.05$); myoclonic seizures (n = 18), 63.1% ($p = 0.03$); tonic seizures (n = 27), 49.2% (ns) and in atonic seizures (n = 8), 63.1% (ns). For children the average reduction in baseline rates were: GTCs (n = 34) 83%; CPS (n = 48) 77%; SPS (n = 18) 82%; tonic (n = 25) 70.3%: myoclonic (n = 11) 83%; atonic (n = 7) 71.8%. 34 adult patients (19.8%) and 22 children (16.2%) became seizure free. 59% of adults and 68% of children remain on FBM. Reasons for discontinuation included intolerable side effects, no perceived benefit in seizure reduction, anticipating pregnancy, and the announcement of the risk of aplastic anemia. Side effects documented included insomnia, behavioral changes, decreased appetite and headache. One patient developed aplastic anemia. No hepatic complications were documented.

Conclusions: In patients with intractable seizures including GTCs, CPS, tonic and myoclonic seizures, FBM is significantly effective in reducing mean baseline seizure frequency with some patients becoming seizure free. FBM remains an important treatment consideration in patients with intractable epilepsy.

1.372

A NEW MECHANISM OF MULTIPLE DRUG RESISTANCE IN EPILEPTIC BRAIN: THE NON-ABC TRANSPORTER RLIP76 AND NOT MDR1 IS THE PREDOMINANT EXTRUSION PROTEIN FOR PHENYTOIN TRANSPORT AT THE BBB

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Rationale: We and others have shown that the drug efflux protein P-glycoprotein (Pgp or MDR1) protects the brain from xenobiotics, but other transporters that may be involved in multiple drug resistance to

Scenario (two doses taken 'x' h after second missed dose)	% Sub therapeutic subjects based on C_u,% sub therapeutic subjects based on C_{tot}, Time at risk 'h' (range, mean, CV%) based on C_u, Time at risk 'h' (range, mean, CV%) based on C_{tot}	
	Dvpx 1000 mg	Dvpx- ER 1250 mg
3	1, 4, (2), (2–3, 3, 23)	0, 0
6	5, 9, (1–6, 3, 75), (1–8, 4, 77)	2, 4, (1), (1–7)
9	19, 15, (1–9, 3, 66), (1–11, 5, 66)	11, 13, (1–6, 4, 53), (1–11, 5, 61)
12	24, 22, (1–11, 6, 60), (1–13, 6, 66)	20, 18, (1–9, 5, 58), (1–12, 7, 55)

antiepileptic drugs may also play a role. Unlike other selective transporters, Pgp recognizes a wide range of substrates including AED. However, there is a significant overlap between molecules transported by MDR1 and the non-ABC transporter RalA Binding Protein 1 (RLIP76).

Methods: We used a combination of immunohistochemistry, Western blot analysis and pharmacokinetic assays to measure levels of expression of RLIP76; co-localization with MDR1; and relative contribution to AED extrusion. Data were obtained from 15 epileptics, age ranging from 3 month to 61 years.

Results: While MDR1 immunoreactivity was observed in neurons, glia and endothelial cells, RLIP76 was only found in endothelial and not in parenchymal cells. Experiments of drug extrusion using antibodies capable of selective inhibition of MDR1 or RLIP76 revealed that the latter mechanism was responsible for 72 ± 8% of 14C-phenytoin extrusion by epileptic BBB endothelial cells; MDR1 contributed to only 27 ± 8% of ATP-dependent drug extrusion. These findings are in agreement with the fact that transport of Pgp substrates in these cells is only weakly inhibited by the specific MDR1 blocker XR9576.

Conclusions: Our findings suggest that RLIP76 and not MDR1 is the main multiple drug resistance mechanism at the blood-brain barrier of drug resistant epileptic patients. (Supported by NIH-2RO1 HL51614, NIH-RO1 NS 43284 and NIH-RO1 NS38195.)

1.373
PORPHYROGENICITY AND HEPATIC CYTOCHROME INDUCTION WITH NEW AEDS: LEVETIRACETAM, OXCARBAZEPINE, AND ZONISAMIDE

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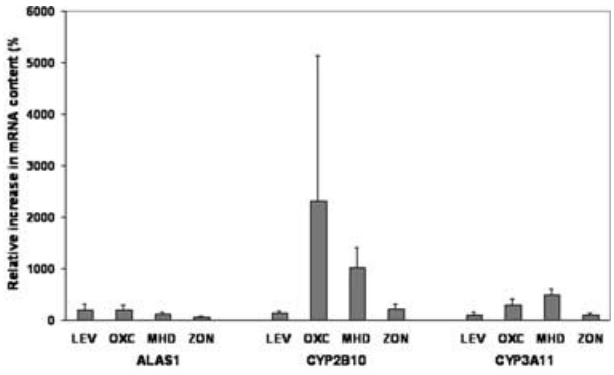
Rationale: Most of the older antiepileptic drugs (AEDs) are strong inducers of hepatic 5-aminolevulinate synthase (*Alas1*), the rate-limiting enzyme of hepatic porphyrin biosynthesis, and of hepatic cytochromes P450, which account for a significant part of total hepatic heme. Treatment of seizures in patients with acute porphyrias presents a difficult problem, since induction of these enzymes by many AEDs can lead to a porphyric attack. Induction of CYP450 and Alas1 are also important markers of AEDs' capacities to be involved in drug interactions or to induce alterations in hepatic metabolism. We investigated whether the new generation AEDs, levetiracetam (LEV), oxcarbazepine (OXC) and zonisamide (ZON) alter the expression of selected cytochrome P450 mRNAs and ALAS1 mRNA in mouse liver.

Methods: Male C57BL/6N mice were administered LEV (500 mg/kg ip.), OXC (150 mg/kg po.), MHD (150 mg/kg po.) or ZON (50 mg/kg po.) for 8 days. Expression of *Alas1*, *Cyp2b10* (phenobarbital-inducible), *Cyp2e1* (ethanol-inducible) and *Cyp3a11* (steroid hormone-inducible) was investigated using real-time PCR. Results were expressed as the relative ratio of target mRNA/β-actin mRNA and compared by Mann-Whitney U-test. Porphyrin content was determined methanol-sulphuric acid extraction and spectrofluorometric quantification.

Results: None of the AEDs tested caused an increase in fecal or urinary porphyrin excretion. In addition, none of the AEDs caused a statistically significant increase of the relative ratio of ALAS1 mRNA/β-actin mRNA (Fig. 1). LEV and ZON displayed no effect on CYP2B10, CYP2E1 or CYP3A11 mRNA. Both OXC and MHD, however, increased CYP2B10 mRNA content, and, to a lesser extent, CYP3A11 mRNA content.

Conclusions: Administration of *Alas1*-inducing drugs or cytochrome P450-inducing drugs to acute porphyria patients is strongly discouraged. Results presented in this study demonstrate that LEV, ZON and OXC do not induce ALAS1 mRNA and porphyrin synthesis. Moreover, LEV and ZON are not inducers of CYP450, which suggests that LEV and ZON may be safe for treating seizures in patients with porphyria. OXC and MHD elevated CYP2B10 and 3A11 mRNA, but they did not alter porphyrin metabolism. Since the induction of CYP2B10 mRNA suggests, at least in mice, a possible effect on hepatic heme biosynthesis, more data are needed to evaluate the safety of OXC in porphyria patients. (Supported by UCB Pharma.)



1.374
TOPIRAMATE INHIBITS THE INITIATION OF PLATEAU POTENTIALS IN CA1 NEURONS BY DEPRESSING R-TYPE CALCIUM CHANNELS

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Rationale: Cholinergic induced plateau potentials (PPs) are intrinsically generated conductances that can elicit ictal type seizure activity. The aim of this study was to investigate the actions of topiramate on the generation of PPs.

Methods: The effects of topiramate on the PP were analyzed using whole-cell patch clamp recordings from CA1 pyramidal neurons in rat hippocampal slices.

Results: In current clamp, PPs evoked following cholinergic receptor stimulation and action potential bursts were depressed by therapeutically relevant concentrations of topiramate. Conversely, in voltage clamp we discovered that I_{tail}, a cyclic nucleotide-gated current that underlies PP generation was not depressed. However, significantly longer depolarizing voltage steps were required to elicit I_{tail}. This suggested that the calcium entry trigger for evoking PPs was depressed by topiramate and not I_{tail} itself. Topiramate had no effect on calcium spikes in control conditions; however topiramate did reduce calcium spikes after cholinergic receptor stimulation. We have found that R-type calcium spikes are enhanced by cholinergic receptor stimulation. Therefore, we isolated R-type calcium spikes, which we found to be depressed by topiramate. We also tested topiramate on recombinant $Ca_V2.3$ calcium channels expressed in tsA-201 cells. Topiramate depressed $Ca_V2.3$ calcium currents by a shift in steady state inactivation.

Conclusions: Therefore, we have found that topiramate reduces seizure activity in hippocampal neurons through a novel inhibitory action of R-type calcium channels. (Supported by Canadian Institutes of Health Research, Alberta Heritage Foundation for Medical Research, Canada Research Chair in Neuroscience and R.W. Johnson Pharmaceutical for the gift of topirmate.)

1.375
UCB 34714, A NEW PYRROLIDONE DERIVATIVE, WITHOUT IMPACT ON HIGH- AND LOW-VOLTAGE ACTIVATED CALCIUM CURRENTS IN RAT ISOLATED NEURONS

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Rationale: ucb 34714 is a new pyrrolidone derivative (Kenda et al. *J Med Chem* 2004;47:530) structurally related to levetiracetam, with significant antiepileptic activity in preclinical epilepsy models *in vitro* (Margineanu et al. *Epilepsia* 2003;44(suppl. 9):261) and in vivo (Matagne et al., *Epilepsia* 2003;44(suppl 9):260). Since levetiracetam was reported to inhibit HVA calcium currents in rat hippocampal neurons (Niespodziany et al. *Neurosci Lett* 32001;306:5–8; Lukyanetz et al. *Epilepsia* 2002;43:9–18), this study explored the potential activity of ucb 34714 on neuronal high- and low-voltage activated calcium currents.

Methods: The effects of ucb 34714 on voltage activated calcium channels were studied in acutely isolated rat neurons, by whole-cell patch-clamp recordings. The high-voltage activated (HVA) Ca^{2+} currents were recorded on hippocampal CA1 neurons from 14 day-old rats; the low-voltage activated (LVA) Ca^{2+} currents were recorded on dorsal root ganglia (DRG) neurons from 1–2 month-old rats.

Results: ucb 34714, 0.1 μM–1 mM did not influence the HVA calcium current, with respect to maximal amplitude, voltage dependence, kinetics of activation and inactivation, and run-down during experimental protocols up to 20 min. Also, ucb 34714,1 μM – 2 mM did not influence the LVA calcium current with respect to maximal amplitude, voltage dependence, and kinetics of activation and inactivation.

Conclusions: This study shows that ucb 34714 is without impact on voltage activated calcium channels in acutely isolated rat neurons. (Supported by UCB Pharma, Belgium.)

1.376
THE USE OF THE ADVERSE EVENT PROFILE (AEP) FOR EVALUATING TOLERABILITY OF CARBAMAZEPINE THERAPY GIVEN AS IMMEDIATE-RELEASE AND EXTENDED-RELEASE FORMULATIONS

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Rationale: Patients with epilepsy often report that the presence or absence of AED side-effects are as important as seizure control in successful therapy. The Adverse Event Profile (AEP) has been shown to be an effective tool for detecting clinically significant anticonvulsant side-effects and for helping physicians to optimize anticonvulsant therapy. We compared patients tolerability to carbamazepine during treatment with immediate-release carbamazepine (IR-CBZ) and an equal total daily dose of Carbatrol® extended-release capsules (CBZ-ERC) in a large multi-center study using the AEP for adults ($\geq$18 years of age); and the Hague side-effects (HASES) scales for adolescents (<18 years of age).

Methods: Patients were enrolled in the multi-center study (n = 457) if they had partial-onset seizures and were currently treated with IR-CBZ. During IR-CBZ treatment, patients had baseline (month 0) evaluation with the adverse event profile (AEP; adults), the Hague seizure severity (HASS) and side-effects (HASES) scales for adolescents (<18 years of age; filled out by parent or guardian of adolescent study participant). The AEP is a 19-item questionnaire scored on a scale from 1 (never a problem) to 4 (always or often a problem), and takes into account sedation, dizziness, unsteadiness, concentration difficulty, depression, and double/blurred vision. The HASES is a 20-item questionnaire scored on a scale of 1 (not a problem) to 4 (very serious problem), and takes into account the same variables as the AEP with the exception of concentration difficulty.

Results: Adults (n = 419) converted to CBZ-ERC had significant decreases in adverse events on the AEP scale compared to AEP scores during treatment with IR-CBZ ($P = .0001$), with adults 18–59 showing the most improvement (-6.0 points on AEP total score; $P = .0001$) (Table 1).Adolescents (n = 38) also had significant decreases in side-effects in the HASES inventory ($P = .01$), with decreases in depression and sedation being most prevalent. Subscale scores of both inventories showed decreases in adverse events with conversion from IR-CBZ to CBZ-ERC. Most commonly occurring AEs were headache, dizziness, and fatigue.

Conclusions: The AEP and HASES were useful tools for documenting changes in adverse events during treatment with immediate-release and extended release formulations of carbamazepine. Patients treated with CBZ-ERC had significantly fewer CNS side-effects compared to treatment with IR-CBZ on these adverse event inventories.

Adverse Event Profile (AEP): Total Score
Adults (All Treated Subjects)

CNS AED Side Effects	Timepoint	All Adult Subjects n=419 Mean (SD)	Adults (18 - 59 years) n=348 Mean (SD)	Elderly Age (≥60 years) n=71 Mean (SD)
Total AEP	IR-CBZ	37.5 (11.6)	37.5 (11.5)	37.4 (12.0)
	ERC-CBZ (endpoint)	31.8 (10.9)	31.5 (11.0)	33.5 (10.6)
	Change at Endpoint Mean	-5.5 (10.0) **	-6.0 (10.4) **	-3.0 (7.6) **
	Percent Change at Endpoint	-11.70 (26.38)	-12.82 (27.18)	-5.63 (20.72)*

Significant at the 0.050 level; ** significant at the 0.010 level.
P-value from a one-sample t-test.

Note 1: Higher scores reflect more severe medication side effects; decreases in score indicate improvement
Note 2: Mean change and percent change from baseline values only include subjects with non-missing

(Supported by Shire Carbatrol is registered in the United States Patent and Trademark Office.)

1.377
UNVERRICHT-LUNDBORG DISEASE: CASE REPORT OF EXACERBATION OF MYOCLONUS WITH LAMOTROGINE THERAPY

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Rationale: Progressive myoclonus epilepsy of Unverricht-Lundborg type is an autosomal recessive disorder characterized by tonic-clonic seizures, myoclonus, and neurological decline. Lamotrogine (LTG) has been reported to be beneficial in the treatment of myoclonus, such as in juvenile myoclonic epilepsy (JME). We report the first known case of genetically proven Unverricht-Lundborg Disease in which progressively disabling myoclonus developed in association with LTG and subsequently improved with cessation of this therapy.

Methods: A case review of the inpatient and outpatient medical records including chart documentation, EEGs with and without prolonged video monitoring, and laboratory tests was performed in a nineteen-year-old man with genetically proven progressive myoclonic epilepsy of the Unverricht-Lundborg type. A subsequent review of medical literature of antiepileptic drug therapies for progressive myoclonic epilepsies (PME) was performed.

Results: A nineteen-year-old Caucasian man developed seizures at the age of twelve characterized by a focal visual aura lasting 15–60 seconds followed by secondarily generalized tonic clonic seizures. Valproic acid (VPA) monotherapy was initiated with control of his seizures. He subsequently developed increasingly frequent tonic-clonic seizures and myoclonus, at which time LTG was initiated as adjunctive therapy with VPA. This resulted in control of tonic-clonic seizures, but not myoclonus. Over the next seven months LTG therapy was increased to a maximum of 900 mg/day. Over that time period myoclonus intensified in frequency and duration, eventually leading to inability to ambulate and requiring hospitalization. During this period zonesamide (ZNS) and clonezepam was added with no change in frequency or intensity of myoclonus. Serial prolonged EEGs during his hospitalization exhibited increased frequency of generalized polyspike and wave discharges. LTG therapy was gradually tapered and finally discontinued, with dramatic cessation of disabling myoclonus.

Conclusions: Progressive myoclonic epilepsy of Unverricht-Lundborg type typically begins between the ages of six to fifteen. Progressive neurological decline includes clinical symptoms of seizures, dysarthria, cognitive dysfunction, and ataxia. Most patients live well into adulthood with the average onset of disability 5 years after diagnosis. Myoclonus in this disorder is often refractory to conventional therapies. Therapies for PME have included a broad spectrum of anticonvulsants, N-acetylcysteine, and baclofen. Although case reports document LTG as an effective therapy for treatment of myoclonus in JME, no medical documentation exists regarding use of LTG therapy in PME. Given the rarity of patients with PME, controlled trials to assess the impact of antiepileptic drug therapy are frequently impractical in these disorders. In our patient, increasing dosages of LTG induced disabling myoclonus which rapidly improved following cessation of therapy with LTG.

1.378
CONCENTRATED ORAL DIAZEPAM SOLUTION AS A RESCUE MEDICINE FOR PATIENTS WITH EPILEPSY

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Rationale: A widely prescribed rescue medication for patients with clustering of seizures or for prolonged attacks is rectal diazepam. For the adolescent, adult, or his caregiver, this route can be sufficiently embarrassing or unwieldy to limit its usefulness. Procedural issues have been raised in the school environment where staff may be expected to give a rectal dose to a student. Clearly other methods of delivery are needed. We have used diazepam concentrated oral solution as a rescue medicine. The oral solution contains 5 mg of diazepam for each ml of fluid and is administered with a calibrated dropper. As salivary production often increases with stimulation during seizure activity, an extra 1 to 2 ml of medication should be inconsequential for clinical aspiration.

Methods: We prospectively followed 12 patients (7 women, 5 men, ages 14–63) with intractable seizures who used concentrated oral diazepam at least twice as a rescue medicine. Patients and caregivers were instructed to instill the fluid between cheek and gum for seizure clusters or for seizures lasting longer than 5 minutes. Patients and caregivers were asked to report their experience in using the concentrate.

Results: Use of oral concentrate shortened or ended the seizure or seizure cluster in all patients and no patient had clinically evident aspiration. The patients who had difficulty with rectal diazepam were treated successfully with the oral route. Four patients self-administered the oral diazepam for clustering of partial seizures; the others had medication given by a caregiver. Ten of the twelve patients to some extent swallowed the medication rather than have it absorbed buccally. Two patients had the medicine discontinued because of overuse for partial seizures and one family was counseled about its proper use, but no patient abused it for behavioral reasons. Oral administration had a later clinical onset of action than the rectal route but was used sooner during a seizure episode often forestalling seizure generalization.

Conclusions: In this limited series of patients concentrated oral diazepam solution was used safely and effectively for adolescent and adult patients requiring rescue medication for seizures. No patient developed aspiration symptoms or required hospitalization for aspiration and in most instances seizures were satisfactorily treated. Oral concentrated diazepam solution may be a viable alternative to rectal administration. (Supported by The Bob and Vivian Smith Foundation.)

1.379

ETHINYLESTRADIOL, BUT NOT GESTAGENS, REDUCES LAMOTRIGINE SERUM CONCENTRATIONS

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Rationale: It has been shown that combined oral contraceptives reduce lamotrigine (LTG) serum concentrations by more than 50% (1). We wanted to investigate whether this finding is true only for ethinylestradiol (EE) containing preparations or also for other hormonal contraceptive methods.

Methods: We collected data from a prospective series of routine measurements of LTG serum concentration in young women. LTG concentration-to-dose ratios (CDR) of patients using any form of hormonal contraception were compared with CDR of patients not using hormonal contraception.

Results: An interim analysis of the data collected so far confirms that contraceptive drugs containing EE reduce LTG CDR by 50%. This effect was observed for the combined oral contraceptive pill as well as for the vaginal contraceptive ring. The CDR of patients using gestagen-only contraception (subdermal implant and intrauterine device) did not differ from controls. In one patient first treated with an EE-containing oral contraceptive, the CDR soon rose to values in the control range after the contraceptive was discontinued. CDR remained stable over several weeks after the introduction of a gestagen-containing implant.

Conclusions: EE, but not gestagens, decreases LTG serum concentration. This effect is independent of the administration form and is an important fact to bear in mind when counselling women with epilepsy in child-bearing age.

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1.380

ONSET LATENCY OF PSEUDOSEIZURES DURING VIDEO-EEG MONITORING

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Rationale: Pseudoseizures are sudden alterations in behaviour including motor, sensory, or consciousness unaccompanied by abnormal electrical discharges in the brain. Inpatient video EEG monitoring can be quite useful in differentiating these events from epileptic seizures. Previous studies (1,2) have demonstrated that the latency to the first pseudoseizure is typically less than 24 hours following admission. We looked at the latency to the first pseudoseizure for patients admitted to the University of Virginia during the years 2000–2004, inclusive. We were interested in determining whether our experience with the time to the first pseudoseizure is similar to that previously described and to determine if the semiology of pseudoseizures with latency longer than 24 hours is different from those with a shorter latency.

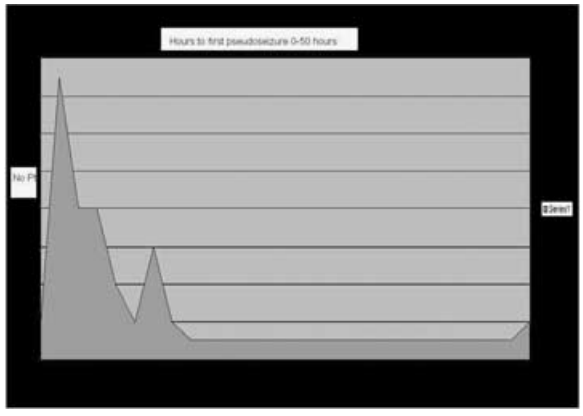
Methods: Video-EEG monitoring reports for the years 2000–2004, inclusive, were retrospectively searched for the terms 'pseudoseizure', 'nonepileptic', and 'psychogenic'. This search yielded names of 117 patients. The monitoring reports and video-EEG records of these patients were subsequently reviewed.

40 patients with physiologic nonepileptic movements, concomitant epileptic seizures, auras with preserved awareness, a diagnosed neurological abnormality, or age <12 years were excluded.

The remaining 77 patients form the basis of this study. Epidemiologic data, latency to the first pseudoseizure, number of nonepileptic events, duration of stay, and clinical semiology were analyzed.

Results: Of the 77 patient records reviewed, 80% were women and 60% were between 20–45 years of age with an average age of 36 years. Average duration of admission was 2.3 days (range 1–7 days) with 4.5 pseudoseizures recorded per admission. The average latency to first spell was 10 hrs or 0.4 days (range 1–51 hours). 53% of patients had their first pseudoseizure within 4 hours, 68% within 8 hours, 83% within 1 day and 94% within 2 days.

55/65 patients with events occurring during the first 24 hours had motor manifestations characterized by movements such as thrashing or nonrhythmic jerking of the extremities, head shaking, pelvic thrusting, or bicycling in the presence or absence of altered awareness. In contrast, 7/12 (58%) of the patients who had events after 1 day had atypical semiology which included dysesthesias, immobility, dissociation, tinnitus, jaw tightening, back arching and staring (Fig. 1).



Conclusions: 83% of our pseudoseizure patients had their first event within 1 day and 94% within 2 days. This suggests that patients with nonepileptic pseudoseizures usually have events within 2 days of video EEG monitoring. Those with event onsets greater than 1 day (58% of these patients) are more likely to have atypical semiology. Those without events in 2 days warrant reconsideration of the diagnosis.

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1.381
INTERACTION BETWEEN LAMOTRIGINE AND A PROGESTIN-ONLY CONTRACEPTIVE PILL CONTAINING DESOGESTREL 75μg (CERAZETTE®)
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Rationale: Lamotrigine (LTG) is increasingly used as AED of choice in women, because it does not impair the effectiveness of hormonal contraception and seems to have a comparatively small teratogenic risk. The clinical relevant reduction of LTG-levels by combined contraceptives (ethinylestradiol + progestin) is possibly caused by the induction of glucuronidation by ethinylestradiol. Therefore we wanted to study the effect of a progestin only oral contraceptive in a prospective evaluation.

Methods: 10 women with epilepsy on a stable LTG monotherapy received a progestin only pill containing 75 μg desogestrel daily (Cerazette®) continously for 12 weeks. Serial blood samples were drawn at baseline, week 1–2, 3–4, 7–8 and 10–12 and lamotrigine trough and peak levels determined by HPLC. In some patients a diurnal profile was performed and AUCs determined.

Results: In 7/10 patients LTG levels increased by 20–100% when treated with Cerazette® concomitantly. Surprisingly, the increase in LTG peak levels was more pronounced than the increase in trough levels in all patients. Correspondingly, some patients suffered dose-dependant adverse effects of LTG $\frac{1}{2}$-3 hours after each dose of LTG. In contrast to the rapid LTG-level reducing effect of combined oral contraceptives, the increase of LTG-level caused by desogestrel occured in most women after week two and increased steadlily up to week 8–12.

Conclusions: Previous studies that evaluated the effect of desogestrel+ethinylestradiol combined monophasic oral contraceptives on LTG showed a substantial decrease of LTG levels. Our preliminary data show the opposite effect in a clinically relevant magnitude in the majority of patients if a desogestrel only pill is used. Our data suggest that the decrease of the LTG levels seen in combined oral contraceptives is mainly an ethinylestradiol effect and not due to the progestin.

If a woman on a stable LTG regimen wants to start contraception with a desogestrel only pill, counseling on the possible occurrence of dose-dependant adverse-effects is advisable. A dose reduction of LTG might be necessary. Wether contraception with a desogestrel only pill is safe in women with epilepsy on LTG and possibly a hormonal contraception of choice remains to be determined.

1.382
LONG-TERM EFFECTIVENESS WITH OXCARBAZEPINE MONOTHERAPY IN PATIENTS WITH REFRACTORY PARTIAL SEIZURES
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Rationale: Open-label extension (OLE) studies provide effectiveness and tolerability information that are closer to experiences observed in actual clinical settings. The OLE phases of three conversion to monotherapy studies were analyzed in order to evaluate the long-term effectiveness and safety of oxcarbazepine (OXC) in patients with refractory seizures.

Methods: Pooled data from patients who participated in the OLE phase of one of three studies were analyzed. The dosage of OXC and concomitant antiepileptic drugs (AEDs) was flexible (lowest dose that achieved seizure control or maximum tolerated dose). OXC was administered on a bid schedule with a maximum allowable dose of 3000 mg/day. Three subpopulations were defined: 'true' monotherapy (oxcarbazepine monotherapy throughout), 'adjunctive' therapy (adjunctive AED during at least 1 of their last 3 visits), and 'late' monotherapy (adjunctive therapy at any visit before reverting back to monotherapy for at least their last 3 visits). Long-term patient outcomes over 4 years were analyzed, including the median number of seizures/28 days at 1-year intervals and retention rates (estimated using Kaplan-Meier analysis of time to discontinuation for any reason).

Results: A total of 266 patients provided seizure information in the combined OLEs: 53 patients in 'true' monotherapy, 167 in 'adjunctive' therapy, and 46 in 'late' monotherapy. The adjusted mean dose of oxcarbazepine ranged from 2170 mg/day to 2527 mg/day across all 4 years and treatment groups. For all three treatment groups, the 28-day seizure rate was reduced by the fourth year of the OLE compared with the first year. The overall OLE median 28-day seizure rates were 1.99 in the 'true' monotherapy group, 1.74 in the 'late' monotherapy group, and 3.70 in the 'adjunctive' therapy group. Retention rates were especially sustained over time in the 'late' monotherapy group (87% first year; 77% fourth year), and decreased from 62% to 43% in the 'true' monotherapy group and from 60% to 27% in the 'adjunctive' therapy group.

Conclusions: Based on this pooled analysis of the long-term extension phases of three pivotal studies, OXC monotherapy demonstrated sustained effectiveness for up to 4 years, with a >75% retention rate in patients reverting back to oxcarbazepine monotherapy after adjunctive therapy with another AED. These data suggest that converting patients treated with adjunctive therapy back to oxcarbazepine monotherapy may be beneficial in certain patients. (Supported by Novartis Pharmaceuticals.)

1.383
CLINICAL DRUG STUDY PARTICIPATION IMPROVES SEIZURE FREQUENCY
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Rationale: Informed consent requires that patients who are potential research subjects be informed that participation in a clinical drug study may not improve epilepsy because the drugs studied may not be efficacious. This is especially true for placebo-controlled trials in which no efficacy in the placebo arm is expected. This discourages some patients from participating because they infer that only a limited number of subjects will improve. It is our impression that participating in a clinical trial improves seizure control regardless of the specific drug's efficacy.

Methods: Demographic and seizure frequency data from patients entering antiepileptic drug studies at our institution from January 1999 to February 2004 were collected. Subjects were excluded if follow-up was less than 6 months, seizure calendars were not obtained, or they were not seen beyond the screening visit. Seizure frequency was collected from seizure calendars separately for complex partial (CPS), secondary generalized (SGTC) and all types combined. Seizure frequencies were collected from seizure calendars. Frequency at baseline was defined as that recorded during the baseline of the study or documented at study entry. "Frequency at follow-up" was defined as the frequency during the 6 months after achieving a steady dose of the drug in an open label study. If patients did not participate in an open label study, then the 6 months after exiting the study was used. Frequency at baseline was compared to seizure frequency at follow-up by Wilcoxon rank-sum tests.

Results: 42 subjects were reviewed from 8 studies; 22 starting in double-blind studies and 20 in pharmacokinetic or tolerability open-label studies. Mean age was 27 $\pm$ 13 and 25 were women. All had partial-onset seizures. CPS frequency decreased from 25 to 15 per month ($p = 0.005$). SGTC occurred in only 12 and monthly seizure frequency was unchanged (6.9 at baseline and 5.4 at follow-up, $p = 0.85$). Mean combined seizure frequency decreased from 32 to 20 per month ($p = 0.003$) with an absolute decrease in 37, unchanged in 1 and worsened in 4. Among the 7 who did not continue in an open label study, 5 improved, 1 was unchanged and 1 worsened.

Conclusions: Participating in clinical drug studies for epilepsy improves seizure frequency. Some contribution comes from efficacy of the drugs used, but patients improve even when they do not continue to receive the experimental drug, suggesting the close follow-up and education provided by study participation provides additional benefit. The findings should encourage study participation.

1.384
DIAZEPAM RECTAL GEL AS PART OF A RESCUE TREATMENT FOR BACLOFEN WITHDRAWAL
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Rationale: For patients treated with intrathecal baclofen (ITB), inability to obtain timely refills or occurrence of a pump malfunction increases

the risk for baclofen withdrawal, which can be deadly. Even minor illness may trigger increased seizures or pain in these sensitive patients. Our clinic has developed a rescue protocol, consisting of a diazepam rectal gel/oral baclofen combination, to ensure that caregivers have effective means to handle pump emergencies. This study summarizes our experience with this emergency treatment plan.

Methods: All patients with ITB received the diazepam rectal gel/oral baclofen rescue plan. Charts were reviewed to identify patients who used the plan.

Results: Eighty patients have ITB pumps; 4 patients experienced pump refill or failure emergencies. Patient 1, a 19-year-old man with cerebral palsy (CP) and spastic quadriplegia, acutely developed signs of baclofen withdrawal, including generalized rash, marked increase in tone with extreme spasticity, and respiratory distress. During a 3-hour trip to the hospital, his symptoms worsened despite treatment with 20 mg oral diazepam. Examination revealed that the baclofen level was too low in his pump. During a subsequent incident of baclofen withdrawal, treatment with 15 mg diazepam rectal gel/10 mg oral baclofen resolved the symptoms. Patient 2, a 9-year-old girl with static encephalopathy with CP and a seizure disorder, had experienced recurrent pneumonia. Her mother was concerned about potential respiratory difficulties associated with oral diazepam; diazepam rectal gel/oral baclofen were prescribed as rescue treatment. A subsequent episode of extreme spasticity and 3 consecutive seizures resolved with 10 mg diazepam rectal gel. Patient 3, a 24-year-old man with CP with spastic quadriplegia, complained of feeling tight and experiencing excruciating pain after pump replacement. Diazepam rectal gel (20 mg)/oral baclofen (10 mg QID) controlled his severe spasms while diagnostic tests were performed; results indicated that his pump was incorrectly programmed and contained insufficient medication. Patient 4, a 15-year-old boy with sacral agenesis and spastic paraplegia, was prescribed oral baclofen and oral diazepam for emergency use; however, the medication was misused by his caregiver. Diazepam rectal gel was prescribed for emergencies, and this situation was resolved.

Conclusions: The diazepam rectal gel/oral baclofen combination provides effective seizure and pain relief for patients with baclofen withdrawal. It offers distinct advantages as a rescue treatment: it is not associated with respiratory compromise; it may be administered by nonmedically trained caregivers; it is supplied in premeasured doses and is unlikely to be abused; and it is rapidly absorbed and has a more rapid onset of action than orally administered diazepam. (Supported by Xcel Pharmaceuticals.)

1.385
DETERMINATION OF ANTICONVULSANT DRUG CONCENTRATIONS IN DRIED CAPILLARY BLOOD SPOTTED ON FILTER PAPER

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Rationale: Therapeutic Drug Monitoring (TDM) of anticonvulsants is an important tool in the management of patients with epilepsy. An analytical method has been developed which enables the simultaneous quantitation of 14 different antiepileptic compounds by high performance liquid chromatography electrospray ionization tandem mass spectrometry (LC/MS/MS) from dried capillary blood spots that are collected on filter paper. This collection method allows samples to be obtained by relatively untrained caregivers or patients at critical time points, eliminating the need for phlebotomy.

Methods: Two 3/16 inch saturated filter paper circles are punched and the sample is resolubilized into a solution of acetonitrile and water. Chromatographic resolution is obtained using standard reverse phase liquid chromatography. Analytes are detected and quantified by monitoring their specific molecular fragmentation reactions on a triple quadrupole mass spectrometer. The complete panel of analytes are assayed as two separate injections of the extract, one in negative ionization mode and one in positive ionization mode. Run time for each injection is approximately 3.5 minutes.

Results: Characteristics of the method are presented in Table 1.

Performance Characteristics

Analyte	Method Linearity (μg/ml)	Precision (%CV)
Carbamazepine	0.5–25.0	5
Carbamazepine Epoxide	0.25–12.5	5
Felbamate	5.0–250.0	6
Lamotrigine	1.0–50.0	8
Oxcarbazepine mtb (MHD)	2.0–100.0	6
Gabapentin	0.5–25.0	6
Levetiracetam	2.0–100.0	5
Phenobarbital	5.0–250.0	6
Valproic Acid	5.0–250.0	7
Phenytoin	1.0–50.0	8
Primidone	1.0–50.0	6
Ethosuximide	5.0–250.0	9
Zonisamide	5.0–250.0	5
Topiramate	1.0–50.0	6

Conclusions: This analytical methodology provides a full spectrum, precise analysis of commonly prescribed anticonvulsants across typical therapeutic ranges. The collection of capillary blood spots on filter paper is minimally invasive, easy to perform, and temporally relevant. The ability of patients and caregivers to collect capillary samples in close proximity to an ictal or a toxic event without the need to find phlebotomy services not only reduces patient perceived inconvenience of performing TDM testing, but also increases the amount of useful information obtained by providing the physician with precise drug levels at time points most critical to managing an individual's epilepsy. (Supported by MEDTOX Laboratories, Inc.)

1.386
NEWER ANTIEPILEPSY DRUG OUTCOMES IN JUVENILE MYOCLONIC EPILEPSY PATIENTS

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Rationale: Valproate (VPA) is the typical treatment of juvenile myoclonic epilepsy (JME), but not all patients respond to it. VPA is also often associated with adverse effects that can cause medication discontinuation. Newer antiepilepsy drugs (AEDs) (ie, lamotrigine [LTG], topiramate [TPM], zonisamide [ZNS], and levetiracetam [LEV]) have been developed that are associated with fewer adverse effects; however no direct comparisons between these medications and VPA in JME treatment have been undertaken.

Methods: A retrospective chart review was performed at the University of Alabama, Birmingham epilepsy clinic for JME patients >15 years old who had initiation of 1 new AED at the clinic. Patients with poor documentation of seizure frequency, prior treatment with a new AED, or treatment with more than 1 new AED were excluded from the analysis. Treatment data before and after initiation of the new AED were compared. Frequency of myoclonic (MYO), absence (AB), and generalized tonic-clonic (GTC) seizures; adverse effects; VPA dosage; weight; and reasons for discontinuation of the new AED (if applicable) were evaluated.

Results: Initial data from 36 patients were evaluated (LTG, $n = 22$; TPM, $n = 6$; ZNS, $n = 4$; LEV, $n = 4$). MYO seizure frequency increased with use of LTG (by 13%) and LEV (by 20%); MYO seizure frequency decreased with use of TPM (by 34%) and ZNS (by 10%). AB seizure frequency increased with LEV treatment (by 100%), but decreased with LTG (by 24%), TPM (by 100%), and ZNS (by 80%) treatment. The frequency of GTC seizures increased with LTG (by 140%) and LEV (by 397%) treatment, but decreased by 94% and 78% in patients treated with TPM and ZNS, respectively. Dosages of VPA decreased in patients treated with ZNS (by 37%), TPM (by 53%), and LTG (by 56%), but increased by 14% with LEV treatment. VPA was discontinued in 50% of patients on TPM and ZNS, compared with 36% and 25% of patients treated with LTG and LEV, respectively. Mean patient body weight was

unchanged in LTG-treated patients, decreased by 7% in TPM-treated patients, and increased by 6% and 4% in ZNS- and LEV-treated patients, respectively. Adverse effect reports were similar before and after new AED initiation. Additional data will be presented.

Conclusions: Evaluation of patients receiving newer AEDs demonstrates that LTG and LEV may be less effective in this group of JME patients as these drugs are associated with an increase in MYO and GTC seizure frequency. On the other hand, TPM and ZNS were associated with a decrease in MYO, GTC, and AB seizure frequency, and often allowed for discontinuation of concurrent VPA use. (Supported by Eisai Inc.)

1.387
OXCARBAZEPINE ADDED TO OTHER SODIUM CHANNEL BLOCKERS OR ANTIEPILEPTIC DRUGS IMPROVES SEIZURE CONTROL IN CHILDREN WITH REFRACTORY SEIZURES

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Rationale: The sodium channel blockers carbamazepine (CBZ) and phenytoin (PHT) are established antiepileptic drugs (AEDs). Although both are sodium channel blockers (SCB), different mechanisms on the sodium channel may result in improved seizure control when combined. Oxcarbazepine (OXC) is a SCB which may also improve seizure control when added to other SCBs or other AEDs with different modes of action.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of OXC as adjunctive therapy in children aged 3 to 17 years with refractory partial seizures (with or without secondarily generalized seizures) (Glauser et al. Neurology 2000;54:2237–2244). This study consisted of a 56-day baseline phase and a 16-week double-blind treatment phase with 2 weeks' titration and 14 weeks' maintenance. Eligible patients had uncontrolled ($\geq$8 seizures/month during baseline) partial seizures while receiving treatment with 1 or 2 AEDs. OXC was initiated at a dose of 10 mg/kg/day, titrated to a target dose of 30–46 mg/kg/day or optimum daily dose, and patients were maintained on their final fixed dose. Concomitant AEDs included: CBZ, valproate (VPA), lamotrigine (LTG), and PHT. The percentage of patients who experienced seizure reductions of >50%, >75%, and 100% seizure freedom was analyzed. We performed a subanalysis by concomitant AED. Adverse events were recorded.

Results: 267 patients were randomized and treated (OXC n = 138, placebo n = 129), 236 (88.4%) completed the double-blind treatment phase, and 18 (6.7%) discontinued due to adverse events. A >50% reduction in mean seizure frequency was observed in 38.2% of OXC-treated patients who were receiving concomitant CBZ; similar results were observed for OXC-treated patients taking VPA, PHT, or LTG as part of their AED regimen. The response rates observed with each concomitant AED are shown in Table 1. The most common adverse events involved the CNS or gastrointestinal systems and occurred at similar frequency regardless of the concomitant AED.

Mean seizure reduction

		>50%		>75%		100%	
OXC + concomitant AED/placebo	N	n	Patients (%)	n	Patients (%)	n	Patients (%)
OXC + CBZ	76	29	38.2	19	25.0	3	4.0
Placebo + CBZ	54	9	16.7	1	1.9	0	0
OXC + VPA	41	17	41.5	14	34.2	3	7.3
Placebo + VPA	50	11	22.0	5	10.0	1	2.0
OXC + PHT	20	7	35.0	5	25.0	0	0
Placebo + PHT	22	7	31.8	2	9.1	0	0
OXC + LTG	24	6	25.0	1	4.2	0	0
Placebo + LTG	30	8	26.7	3	10.0	0	0

Conclusions: The efficacy of OXC as add-on therapy in children with refractory partial seizures is consistently observed whether added to CBZ, VPA, PHT, or LTG. This subanalysis demonstrates the benefit of adding OXC to the standard sodium-channel blockers CBZ or PHT in the treatment of patients with refractory seizures. (Supported by Novartis Pharmaceuticals.)

1.388
UCB 34714, A NEW PYRROLIDONE DERIVATIVE, INHIBITS Na^+ CURRENTS IN RAT CORTICAL NEURONS IN CULTURE

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Rationale: ucb 34714 is a new pyrrolidone derivative (Kenda et al. *J Med Chem* 2004;47:530) structurally related to levetiracetam, with significant antiepileptic activity in preclinical epilepsy models, both in vitro (Margineanu et al. *Epilepsia* 2003;44(suppl 9):261) and in vivo (Matagne et al. *Epilepsia* 2003;44(suppl 9):260). Aiming to further elucidate the antiepileptic mechanisms of ucb 34714, this study explored its putative activity on neuronal Na^+ currents.

Methods: The effects of ucb 34714 on the biophysical properties of the voltage-activated Na^+channel were studied on neocortical neurons of embryonic day 14 Wistar rats and grown in dissociated cell culture for 15 – 24 days. Membrane currents were recorded from neuronal soma in the whole-cell configuration of the patch-clamp method.

Results: In rat cortical neurons in culture, ucb 34714 produced a dose-dependent inhibition of voltage-dependent Na^+ currents, up to a maximum of ~65% reduction, with an IC_{50} value of 7 μM. ucb 34714, 30 μM slightly shifted the voltage-dependence of the steady-state activation of Na^+ currents toward more positive potential values (from –37 mV to –33.6 mV), and promoted their fast inactivation kinetics, upon reducing the potential constant of the decay time constants from 37.7 mV to 18 mV. These changes indicate a decrease in the inward flow of Na^+ ions in the cell.

Conclusions: This study demonstrated a noteworthy inhibition by low micromolar concentrations of ucb 34714 of neuronal voltage-dependent Na^+ channels. The extent to which this effect might contribute to its antiepileptic activity remains to be determined. (Supported by UCB Pharma, Belgium.)

1.389
EFFECTS OF GLUCOCORTICOID RECEPTOR ACTIVITY ON DIAZEPAM EFFICACY IN TERMINATING STATUS EPILEPTICUS IN ADULT RATS

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Rationale: Status epilepticus (SE) is characterized by prolonged, self-sustaining seizures lasting $\geq$30 minutes, during which patients do not gain consciousness. Clinical and animal studies suggest loss of sensitivity to diazepam (DZ) as the SE duration increases, however, the mechanism remains unclear. While studying the effect of RU486, a glucocorticoid receptor antagonist, on expression of GABA(A) receptor subunits in hippocampus after SE, we found that rats pretreated with RU486 were more sensitive to the therapeutic effects of diazepam in treating SE. In the present study, we explore the possibility of using RU486 as an adjunctive treatment for SE.

Methods: Adult male Sprague-Dawley rats were implanted with electrodes in CA1 and frontal cortex. After one week of recovery rats were put in recording cages and connected to EEG monitoring system for continuous video-EEG recording. Rats were then treated with RU486 (25 mg/kg body weight) 1 hour before the pilocarpine injection. Thirty minutes later rats were treated with scopalamine (1 mg/kg body weight) to reduce peripheral side effects of pilocarpine. Rats were injected with pilocarpine (385 mg/kg body weight) 30 minutes after scopalamine injection to induce SE. One hour after declared SE, rats were treated with DZ (6 mg/kg) to stop the seizures. Every two hours rats were monitored for signs of behavioral seizures and if required they were injected with 3 mg/kg DZ till they completely stop seizing.

Results: Rats that were pretreated with RU486 before SE induction required a significantly lower mean cumulative dose of DZ ($n = 9$; 7 ± 0.5 mg/kg body weight) to terminate seizures as compared to those without RU486 pre-treatment ($n = 18$; dose $= 9.83 \pm 0.47$ mg/kg body weight; $p = 0.001$). There was no difference in SE severity between RU486 treated and untreated rats prior to first dose of DZ, suggesting that RU486 treatment did not effect SE directly. Preliminary results from video-EEG monitoring suggest rats that received RU486 had lower frequency of spike-wave discharge and seizure recurrence over 24h hours after SE.

Conclusions: The present study suggests that pretreatment with RU486 before SE induction increases the efficacy of diazepam in stopping prolonged seizures and also improves the outcome of SE over the first 24 hours. Further studies are required to determine the possible mechanisms of this effect. (Supported by Epilepsy Foundation of America to Y.H.R. and NIH NS38595 to A.B.K.)

Non-AED/Nonsurgical Treatments—Adult

1.390
RESPONSIVE STIMULATION FOR ACUTE SUPPRESSION OF INTERICTAL EPILEPTIFORM ACTIVITY IN THE PILOCARPINE RA

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Rationale: While electrical stimulation of the brain emerges as a potential therapy for intractable epilepsy, an interest in closed-loop stimulation has developed. Currently in clinical trials, the fully implantable Responsive Neurostimulator (RNS(tm)) device (Neuropace, Inc.) is capable of customizable EEG event detection, continuous event-triggered stimulation and storage of recorded electrocorticograms (ECoGs) for analysis. We demonstrate chronic use of the RNS in a rodent model of temporal lobe epilepsy to 1) investigate acute suppression of interictal epileptiform activity in the hippocampus with closed-loop stimulation of the hippocampal circuit and 2) test the hypothesis that stimulation parameters can be manipulated to achieve optimal suppression.

Methods: Bipolar electrodes (Pt/Ir, 100μm diameter) were implanted bilaterally in the posterior dentate gyrus (DG) and perforant path (PP) of the spontaneously seizing pilocarpine rat. Electrodes were connected to an implanted RNS(tm) device, resulting in a fully subcutaneous system functional for at least 3 months. Half-wave (HW) and Area algorithms were configured to detect interictal spike and seizure events, respectively. When responsive therapy was enabled, HW event-triggered stimulations were delivered bilaterally to PP or DG at a range of parameter (pulse frequency, amplitude, pulse duration, pulse width) combinations and anode/cathode configurations. ECoGs containing baseline activity, detected seizures and responsive stimulations were stored for analysis. For quantification of suppression, the Area and Line Length (LL) of the EEG signal were calculated (MATLAB) during 2s time windows pre- and post-detection, ignoring an intervening 2s window to avoid stimulation artifact. Ratios of pre- and post-detection window values were calculated to quantify suppression.

Results: Event-triggered stimulations of PP (200Hz, 560mA, 100ms pulse duration, $n = 415$) resulted in significantly reduced LL and Area ratios in the left and right DG ($p < .01$) compared to non-stimulated event detections ($n = 110$). Event-triggered stimulations ($n = 51$) of DG (200Hz, 420mA, 100ms pulse duration) resulted in significantly reduced LL and Area ratios in the left and right DG ($p < .01$), with exception of the LL ratio in the left DG ($p <= .362$), when compared to non-stimulated event detections ($n = 36$).

Conclusions: These initial observations demonstrate that spike-triggered stimulation to PP and DG via an implantable neurostimulator can acutely suppress epileptiform EEG. Effects of parameter variations on efficacy will be discussed. (Supported by NSF IGERT Neuroengineering Training Grant DGE-9972802, Neuropace, Inc.)

1.391
IS VAGUS NERVE STIMULATION MORE EFFECTIVE IN MALFORMATIONS OF CORTICAL DEVELOPMENT?

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Rationale: In patients with drug resistant epilepsy associated with either multifocal malformations of cortical development (MCD) or a normal MRI, and not eligible for epilepsy surgery, intermittent chronic Vagus Nerve Stimulation (VNS) is a potential palliative treatment. The purpose of this study was to evaluate the efficacy of VNS therapy in these two populations.

Methods: Among 31 patients with medically intractable focal seizures, treated with VNS in our center, we identified all cases with either a MCD or a normal MRI, and evaluated the responder rates to VNS at one and two years.

Results: There were 14 patients with a normal MRI and nine with a MCD, including 4 periventricular nodular heterotopias, 2 tuberous sclerosis, 2 multifocal dysgenesis and 1 occipital polymicrogyria.

Mean age at the time of VNS implantation in the MCD and cryptogenic groups was respectively 30,1 years and 41,2 years, and mean duration of epilepsy 22,5 and 27 years. Mean follow-up of VNS was $2{,}6 \pm 2{,}5$ years in the MCD group and $2{,}5 \pm 1{,}06$ in the cryptogenic group with a minimum of one year. Mean seizure frequency per month was $29{,}5 \pm 32$ and $29{,}2 \pm 20$ in the MCD and cryptogenic group respectively.

In the group with MCD, a 50% or more reduction in seizure frequency was observed in 6 patients out of 9 (66,6%) at 1 year and in 5 patients out of 5 (100%) at 2 years, whereas in the cryptogenic group, the responder rates were 38,5% at one and two years of VNS (5 out of 13). Thus, there was a trend towards better results in the MCD group at two years of follow-up, which did not prove significant in this small sample of patients ($c^2 = 3{,}32$; $p < 0{,}1$)

Conclusions: VNS therapy represents a useful therapeutic option for individuals with refractory epilepsy, which might be more efficient in patients with MCD than in patients with cryptogenic partial seizures. A potential explanation for these results may be the implication of the serotoninergic system in both the pathophysiology of epileptogenic MCD, and the mechanisms of VNS. Further evaluation are needed to confirm these results.

1.392
QUALITY OF LIFE AND SEXUAL FUNTION IN EPILEPSY PATIENTS WITH AND WITHOUT VAGAL NERVE STIMULATORS

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Rationale: Some studies have suggested that use of vagal nerve stimulation (VNS) results in improved quality of life (QOL) in patients with medically refractory epilepsy. These study designs compared pre- and post-implantation levels of QOL, but did not compare QOL between epileptic patients with and without VNS. Because of these positive findings, we wanted to investigate further to find out whether these effects were applicable to sexual function and satisfaction in addition to general quality of life. In this preliminary study we sought to compare levels of QOL and sexual function and satisfaction between epileptic patients with and without VNS.

Methods: In a different study we sent surveys to 50 patients with nonepileptic seizures (NES) and 50 patients with epileptic seizures (ES). The survey included two standardized, previously validated psychiatric diagnostic instruments, the QOLIE-10 and the Arizona Sexual Experiences Scale (ASEX) The QOLIE includes 10 questions assessing the effects of seizures and AEDs on functioning and quality of life. The ASEX has five questions assessing sexual function and satisfaction. We extracted data for epileptic patients with and without VNS from the ES cohort of survey respondents. Data were analyzed using SPSS for Windows.

Results: There were 9 epileptic patients being managed with medication alone (ES group) and 3 epileptic patients treated with medications and vagal nerve stimulation (VNS group). All VNS patients and 8 ES

patients were female. There was no statistically significant difference in age between the groups ($p = 0.98$). On the QOLIE-10 survey, VNS patients were significantly less likely to report having memory difficulties than the ES patients ($p = 0.03$). There was a trend indicating that the VNS group had fewer work limitations ($p = 0.12$) On the ASEX, VNS patients had lower scores on all five measures (lower scores indicate greater sexual function and satisfaction). On two of the five measures there were trends toward statistical significance. VNS patients reported less troubles with physiological arousal ($p = 0.12$) and greater ease achieving orgasm ($p = 0.09$). There were no statistically significant differences in quality of life, energy, mood, social limitations, mental or physical effects of AEDs or fear of having a seizure.

Conclusions: VNS patients were significantly less likely to report memory problems than epileptic patients managed with medication alone. This is in agreement with other published studies. They reported fewer work limitations. All scores on the ASEX indicated greater sexual function and satisfaction among the patients with VNS, with a positive trend toward significance on physiological arousal and ability to achieve orgasm. These preliminary results need to be confirmed with larger numbers of patients. (Supported by Cyberonics, Inc.)

1.393

BRAIN STIMULATION FOR EPILEPSY: PILOT PATIENT RESULTS AND IMPLEMENTATION OF A CONTROLLED CLINICAL TRIAL

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Rationale: Brain stimulation is a novel therapy that may be of use for people with medically-intractable seizures. To date, no definitive controlled trial of brain stimulation for epilepsy has been performed. In 1998 a group of investigators began collaboration on the design of studies to explore stimulation of the anterior nucleus of the thalamus (AN) in patients with uncontrolled seizures. Each investigator wrote a feasibility study to be implemented through their institution. Investigators have presented their individual findings at AES meetings and 2 manuscripts have been published (Hodaie 2002; Kerrigan 2004). This abstract presents collective results from these 14 patients, including previously unpublished data.

Methods: The study designs prescribed intermittent high-frequency stimulation of the AN in patients with intractable epilepsy. Programmable neurostimulators (Medtronic ITREL II or Soletra) were implanted over the anterior chest wall, with bilateral implantation of the multi-contact electrodes into the AN. Stimulation parameters were allowed to vary. The patients (7M, 7F, ages 19–47) were from 4 clinical sites and have been followed for at least 12 months. Patients returned for visits at intervals specified by each protocol; seizure counts were monitored with a patient diary. Changes in seizure frequency were assessed relative to a pre-implantation (baseline) seizure frequency.

Results: During the first 3 months of AN stimulation, the median seizure frequency reduction, was 64% (sd 34%) in the 14 patients. Eight of these patients (57%) had a 50% or greater decrease in seizure frequency (responders). Over the 12-month period, the median reduction in total seizure frequency was 56% (sd 39%) with a responder rate of 57%. Nine of 14 patients had seizures presumed to arise from the temporal or frontal lobes. Over the first 3 months of stimulation, these 9 patients had a median 79% (sd 41%) reduction in seizure frequency and 78% of them were responders. Over the 12-month period, the median reduction in total seizure frequency was 59% (sd 47%) with a responder rate of 67%.

Conclusions: Because of clinical and pre-clinical evidence of the possible efficacy of AN stimulation, this target has been chosen for a prospective, double-blind, parallel design safety and efficacy clinical trial. The design of this study will be presented.

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1.394

A COMPARATIVE STUDY OF CHILDHOOD TRAUMA IN EPILEPSY AND NONEPILEPSY SEIZURE PATIENTS

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Rationale: Rates of childhood abuse, especially sexual, have been assumed higher in-patients with non-epileptic seizures (NES) as compared to people with epilepsy (PWE). Recently this assumption has been questioned by several studies showing no significant differences in childhood sexual abuse between patients with NES and those with epileptic seizures (ES). This study is meant to reexamine the hypothesis that childhood trauma is more prevalent in patients diagnosed with NES compared with PWE.

Methods: One-hundred sixty-one patients with intractable seizures admitted for differential diagnosis were evaluated during video EEG monitoring at Stanford University's Comprehensive Inpatient Epilepsy Unit. Childhood trauma and psychopathology were assessed using the Childhood Trauma Questionnaire-short form (CTQ). The CTQ has five sub-scales that measure physical/emotional abuse, physical/emotional neglect, and sexual abuse. Other scales used for evaluation were the Beck Depression Inventory (BDI), Dissociative Experiences Scale (DES), and Symptom Checklist-90 (SCL-90). Patients were classified according to ictal recordings as ES ($N = 42$; events captured with EEG abnormalities), NES ($N = 66$; events captured with no EEG abnormalities), BOTH ($N = 5$; events meeting definition for both NES and ES), UNCLEAR ($N = 26$; events not captured by EEG). Only those patients clearly classified as ES or NES were used in the following analyses, and the number of subjects per analyses varied due to missing data.

Results: NES patients (54 women and 12 men) had significantly higher Somatization scores on the SCL-90 than did ES patients (21 women and 21 men), $t(78) = -4.32$, $p < .001$. They also had significantly higher scores on the Anxiety and Phobic Anxiety subscales, $t(78) = -2.15$, $p = .03$; $t(78) = -3.12$, $p = .003$; respectively. Comparisons of CTQ subscale scores using the Mann-Whitney U test revealed that the two groups differed only on the CTQ sexual abuse subscale ($z = -2.03$, $p = .04$), with NES patients endorsing a greater degree of sexual abuse (mean rank = 49.6) than ES patients (mean rank = 39.6). However, a subsequent logistic regression analysis controlling for gender revealed no significant association between childhood sexual abuse and seizure type.

Conclusions: The lack of discernable differences between NES and ES groups is surprising, and may reflect the acuity of both groups of seizure patients in this study. Trauma and psychopathology may be risk factors for the development of both intractable epilepsy and non-epileptic seizures. The association between sexual abuse and NES may be also be confounded by the fact that more women than men report histories of childhood sexual abuse, and the NES group was comprised of more women than men. (Supported by Office of Technology and Licensing Research Incentive Award.)

1.395

USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE PRODUCTS BY PERSONS WITH EPILEPSY

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Rationale: Complementary and alternative medicine (CAM) products are used commonly and represent a valued aspect of self-care for many Americans. Information regarding the prevalence of CAM product use among persons with epilepsy is limited. In addition, the potential risks and benefits of many CAM products are not well defined.

Methods: A self-administered structured survey was distributed to patients attending epilepsy care clinics at two university-affiliated San Francisco medical centers. Information was gathered regarding demographics, epilepsy care and treatment response, and general health perceptions and practices.

Results: Surveys were returned by 187 adults with epilepsy or their representatives (e.g., caregivers). CAM products (including vitamin/mineral supplements, herbal, and natural products) were used by 104 respondents (56%). The most common reasons for use of CAM products were to: improve general health; to supplement diet; and, in response to a physician's recommendation. Vitamin/mineral supplements were the products most often used (83 persons). Among the 104 CAM users, 19% used a product with the potential to alter CYP450 activity (e.g., St. John's Wort, echinacea, garlic), and 14% had used a product that contained ingredients reported to potentially increase the occurrence of seizures (e.g., ephedra, ginseng, evening primrose, gingko). Only 6 persons reported using CAM products for the explicit purpose of benefiting their epilepsy condition or to alleviate antiepileptic drug (AED)-related adverse effects. CAM product use was not more common among persons with frequent seizures (as compared to infrequent seizures), nor among persons who reported adverse effects from their AED therapy. Sixty-eight percent of patients reported that they disclosed the use of CAM products to their physicians.

Conclusions: CAM products are used commonly by persons with epilepsy who attend epilepsy specialty clinics. Over one quarter of these persons used products containing ingredients with the potential to either increase the occurrence of seizures, or alter hepatic drug clearance. Additional research and education is necessary to provide evidence-based recommendations to patients and healthcare providers regarding the risks and benefits of CAM products in persons with epilepsy. (Supported by An unrestricted gift from Abbott Laboratories.)

1.396

VAGAL NERVE STIMULATION THERAPY IN PATIENTS WITH FOCAL VS. MULTIFOCAL EPILEPTOGENIC EEG PATTERNS

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Rationale: Vagal nerve stimulation (VNS) is believed to suppress seizures through alteration of polysynaptic vagal afferent function. Modulation of vagal activities occurs in the reticular activating system as well as central autonomic network and limbic system. Such stimulation consequently influences noradrenergic projections in a widespread fashion. Given the diffuse distribution of such vagal afferent network, we sought to determine if VNS use as adjunctive therapy for seizure control would have more overall impact in the care of patients with multifocal vs. unifocal epileptogenic findings on EEG.

Methods: A retrospective medical chart review was undertaken of 27 patients with pharmacoresistant epilepsy who had VNS placement and serial follow-up for at least 18 months. In all cases, EEG confirmation of an epileptogenic focus was present. Thirteen patients had seizures emanating from a single, surgically unresectable, focus. Fourteen patients had EEG's demonstrating a multifocal epileptogenic EEG pattern. Baseline weekly seizure incidence was compared to post-VNS seizure frequency at 3,6,12, and 18 month intervals.

Results: Of the patients with unifocal epileptogenic EEG patterns, there was an average reduction in seizure occurrence of twenty-seven percent in the first eighteen months of follow-up. Patients with multifocal epileptogenic EEG findings had an overall reduction in seizures of forty-three percent during this time interval.

Conclusions: By means of its diffuse effects on the noradrenergic system, in the initial eighteen months of use VNS therapy is more effective in reducing seizure incidence in persons with multifocal epilepsy than in patients with epilepsy due to a unifocal cortical epileptogenic site.

1.397

EFFICACY OF VAGAL NERVE STIMULATION IN TREATING PATIENTS WITH MEDICALLY REFRACTORY PRIMARY GENERALIZED EPILEPSY

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Rationale: The efficacy of the vagal nerve stimulator (VNS) in treating patients with refractory partial epilepsy has been well demonstrated. However, its use in patients with refractory primary generalized epilepsy has not been studied fully. This is a retrospective study to evaluate the efficacy of VNS in this patient population.

Methods: 102 patients were followed in the VNS clinic at the University of Utah Hospital in September of 2003. Of these 102 patients, 13 had refractory primary generalized epilepsy and had VNS implanted from 2000 to 2003. The diagnosis of primary generalized epilepsy was based on the clinical history, physical examination, magnetic resonance imaging (MRI) and electroencephalography (EEG) data. Patients with mental retardation were excluded from the study. The clinic notes of the 13 patients were reviewed. Clinical information including age of seizure onset, seizure frequency, number of antiepileptic drugs (AED) and VNS parameters at the time of VNS implantation, 6, 12 and 24 months afterwards, when available, was collected.

Results: Six months after implantation, 6/13 (46.15%) of patients had reduction in frequency of generalized tonic-clonic (GTC) seizures, while 3/13 (23.08%) had no change and 4/13 (30.77%) had increase in the frequency of GTC seizures. For those who had GTC seizure reduction, the average decrease in seizure frequency was 72.4%. At 12-month post-implantation, in 10 patients with available data, 6 (60%) had reduction, while 2 (20%) had no change and 2 (20%) had increase in GTC seizure frequency as compared to the pre-implantation baseline. For those who showed reduction in GTC seizure frequency, the average reduction was 81.35%. At 24-month post-implantation, in 9 patients with available data, 7/9 (77.78%) had reduction, 1/9 (11.11%) had no change and 1/9 (11.11%) had increase in GTC seizure frequency. For those who experienced seizure reduction, the average decrease in GTC seizure frequency was 84.04%. The number of AEDs at 24-month post-implantation was reduced in 4 out of 9 (44.44%) patients, unchanged in 3 patients and increased in 2 patients. However, AEDs were added in those 2 patients for headache and mood stabilization.

Conclusions: VNS is effective in reducing GTC seizure frequency in 46% to 78% patients with medically refractory primary generalized epilepsy. It also helps to reduce the number of AEDs that patients require.

1.398

SUPPRESSION OF EPILEPTIFORM ACTIVITY BY RESPONSIVE ELECTRICAL STIMULATION IN EPILEPTIC PATIENTS

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Rationale: Closed-loop responsive electrical stimulation is an emerging therapy for the treatment of intractable epilepsy. This therapy is being evaluated in clinical trials of the Responsive Neurostimulator (RNSTM) system (NeuroPace, Inc.). During these trials, the RNS device was either 1) externalized and connected to cortical strip and depth electrodes used for pre-surgical monitoring, or 2) fully implanted and connected to permanent cortical strip and depth electrodes in ambulatory patients. Data from 35 epilepsy patients were evaluated. Electrocorticograms (ECoGs) containing stimulations delivered in response to detected events as well as non-treated detected events were stored by the RNS device and uploaded to a central database for subsequent analysis. Since there may be a correlation between acute electrographic responses to responsive stimulation and clinical effects, these electrographic responses were quantified and analyzed.

Methods: Two event classes were identified for this analysis: 1) detection with stimulation ("*stim*"), and 2) detections without stimulation ("*non-stim*"). Electrographic activity was analyzed within 2-sec windows before and after each event, with an intervening 2-sec window ignored to avoid stimulation artifacts. Several features were quantified within these windows and the post-event vs. pre-event ratios and/or differences were calculated for each event (except those with stimulations occurring within either the pre-event or post-event window) and on each ECoG channel. The features analyzed include power spectral density (PSD), Line Length, and Area. Stimulated response ratios were compared between the "*stim*" and "*non-stim*" event classes.

Results: The PSD ratio responses, as well as the normalized PSD difference between pre- and post-event windows, averaged across all "*stim*" events and across patients, showed a linear energy decrease, decreasing in

magnitude with increasing frequency. In contrast, the "*non-stim*" events showed a linear energy increase, increasing in magnitude with frequency, for frequencies above 20 Hz; and between 0.5 and 20 Hz they have a small energy decrease, increasing in magnitude with frequency.

Conclusions: These observations suggest that closed-loop responsive electrical stimulation may acutely suppress epileptiform activity. The question of whether acute electrographic responses and suppression of epileptiform activity correlate with the clinical efficacy of responsive stimulation is currently under investigation. (Supported by NeuroPace, Inc.)

1.399

3/S SPIKE-WAVE COMPLEXES AND TYPICAL ABSENCES BY STIMULATION OF THE INFERIOR THALAMIC PEDUNCLE (ITP) IN PATIENTS WITH MAJOR DEPRESSION DISORDER (MDD)

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Rationale: To investigate whether or not the electrocortical and behavioural responses elicited by electrical stimulation of the centromedian thalamic nucleus in patients with Lennox-Gastaut Syndrome can be reproduced by ITP stimulation in MDD patients.

Methods: In these patients, electrodes were implanted in ITP and Nucleus Reticularis Thalami (Re) as a part of a therapeutic neuromodulation procedure. Both structures were bilaterally stimulated by 20–30 s trains, where individual pulses had 1.0 ms duration, 3 Hz frequency and increasing intensities in steps of 0.5 mAmps each. In addition, clinical symptoms were systematically recorded and changes in responsiveness were assessed by response to flash presentation of patient under a simple response task.

Results: Bilateral, intense (10.0–12.0 mAmps), 3 Hz stimulation of either ITP or Re produced generalized responses of spike-wave complexes. However, while Re responses were accompanied by only delayed reaction time, ITP responses were accompanied by all symptoms described for spontaneous typical absence attack. That is, motionless stare, fixed sight, small eye blinking and total irresponsiveness to environment stimuli and verbal command.

Conclusions: EEG and symptoms of genuine generalized seizures can be reproduced by ITP stimulation in humans with non-epileptic cortices. [Supported by Unit of Stereotactic and Functional Neurosurgery, General Hospital of México, (SSA) and Unit of Medical Research in Neurophysiology, National Institute of Social Securitiy (IMSS), México City, México]

1.400

NEUROPSYCHOLOGICAL OUTCOME OF AMYGDALOHIPPOCAMPAL STIMULATION FOR REFRACTORY TEMPORAL LOBE EPILEPSY

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Rationale: We have previously studied the efficacy of amygdalohippocampal deep brain stimulation (AH-DBS) for temporal lobe epilepsy. The present study investigated the safety of AH-DBS in terms of cognitive functioning in patients with normal MRI findings.

Methods: Eight consecutive patients (7M, 1F; 7 right-handed, 1 left-handed) with refractory CPS and normal MRI findings underwent AH-DBS on the side of temporal lobe ictal onset as defined by invasive video-EEG monitoring. Patients in whom a >50% reduction of interictal spikes and/or seizures was shown during an initial trial period with an external generator, were implanted with an abdominally located pulse generator for long-term AH-DBS. Neuropsychological testing using a comprehensive test battery was performed before and after 6 months of AH-DBS.

Results: In 7/8 patients unilateral long-term AH-DBS was performed (left-sided: 4/7; right-sided: 3/7). All 7 stimulated patients were right-handed. After a mean follow-up of 22 months (range: 6–32 months) 2/7 patients had a >90% reduction in seizure frequency; 3/7 patients had a >50% seizure reduction; 2/7 patients are non-responders. One patient did not fulfil the long-term implantation criteria and underwent a temporal lobectomy. Before chronic DBS, the average number of AEDs was 3 (range 2–4). In 6/7 patients at least one AED was tapered. None of the patients reported side effects. In one patient an asymptomatic haemorrhage occurred on the amygdalar electrode trajectory, which resolved within one week. None of the patients showed changes in bedside neuropsychological testing. Formal neuropsychological assessment in 6/7 stimulated patients was unchanged in 3 patients, mildly improved in 2 patients and globally deteriorated in one patient. Additionally, a mild decrease of verbal memory was found in 3 patients of whom one was stimulated on the language-dominant side and already showed a pre-operative verbal memory deficit.

Conclusions: This open pilot study shows a significantly decreased seizure frequency in the majority of patients treated with AH-DBS for refractory epilepsy without significant decreases in global neuropsychological functioning after 6 months of treatment. Whether AH-DBS interferes significantly with verbal memory, specifically in patients who are stimulated on the language dominant side, needs to be further investigated. [Supported by Senior Clinical Investigator Grant (P.B.), Junior Researcher ("Aspirant") Grant (K.V.) and grants 1.5236.99, B/02514 (P.C.) and 6.0324.02 from the Fund for Scientific Research (F.W.O.)-Flanders; by grant 01105399 from Ghent University Research Fund (B.O.F.) and by the Clinical Epilepsy Grant Ghent University Hospital 2000–2004.]

1.401

EARLY SAFETY EXPERIENCE WITH A FULLY IMPLANTED INTRACRANIAL RESPONSIVE NEUROSTIMULATOR FOR EPILEPSY

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Rationale: As part of a multicenter feasibility study, NeuroPace responsive neurostimulators (RNS™) have been implanted in 3 patients with refractory epilepsy. The RNS system (device and leads) is implanted in the skull to continuously monitor and record ECoG from depth or subdural strip electrodes. When electrical seizure discharges are detected, the RNS system delivers electrical stimulation to suppress ictal discharges before a clinical seizure occurs.

Methods: Subjects (age 18–65) with > = 4 disabling, partial seizures/month for 3 consecutive months were implanted with the RNS system. Responsive stimulation was enabled 1 week or later after surgery. Subjects were not blinded to stimulation. Seizure frequency, severity, and adverse events (AEs) were assessed throughout the study.

Results: Three adults were implanted with the RNS system. Two had previous invasive EEG monitoring and cortical resection. The RNS device was secured within the right (R) parietal bone in 2 subjects and the left (L) parietal bone in the other. Two 4-electrode subdural strips were connected to each RNS device (Table 1).

Automatic detection of ictal discharges was enabled immediately after surgery. It correctly detected seizures in the 2 subjects that have had seizures since implantation. In both cases seizure onsets were characterized by beta-gamma frequency activity.

Four AEs have been reported, all of which occurred in the first month postop (none during surgery) and all classified as mild. The AEs reported were edema, headache, diarrhea (Subject 1) and possible incision infection (Subject 3). The edema in Subject 1 was further classified as an adverse device effect: post-operative edema around the leads with quick recovery and no sequelae. Product relation was uncertain for one AE: Subject 3 was treated with IV antibiotic for a question of immediate postop wound infection; culture results were negative and the wound healed well. No product complaints have been reported.

Conclusions: Among the 3 subjects implanted with the RNS system as of 4/30/04, surgery has been safe. Responsive stimulation has been

	Subject 1	Subject 2	Subject 3
Surgery Duration (Hrs)	4.3	3.6	2.5
Leads	2 R Parietal	L Parietal, L Temporal	R Parietal*, Interhemispheric*, R Parietal, R Temporal
Days Implanted	85	36	30
Days Therapy Enabled	76	34	0

safe and well tolerated. The device has performed as expected. All AEs have been classified as mild. This is the first report ever of an implanted responsive neurostimulator that continuously monitors ECoG in order to automatically deliver therapy in response to ictal activity. Further implantations are scheduled prior to the Dec 2004 AES meeting. (Supported by NeuroPace.)

1.402

DOUBLE-BLIND PLACEBO-CONTROLLED PARALLEL-GROUP TRIAL OF OMEGA-3 FATTY ACID SUPPLEMENTATION IN PATIENTS WITH CHRONIC EPILEPSY

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Rationale: Nutritional studies suggest the Western diet is deficient in omega-3 fatty acids (FA). FA have important roles in determining optimal structural and functional properties of neuronal membranes. Deficiency of FA may contribute to chronic epilepsy. Studies have shown that the FA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), applied extracellularly raised stimulatory thresholds of CA1 neurones. Infusions of EPA and DHA were equipotent in raising seizure thresholds in a rat seizure model. Other studies show that pro-inflammatory mediators are elevated in models of epilepsy, whilst increasing anti-inflammatory mediators appear to have anticonvulsant effects. EPA reduces pro-inflammatory mediators by inhibiting PLA2 and COX2 enzymes and is itself metabolised to form anti-inflammatory prostaglandins. In an open study, 5 patients were given 2.3 g of DHA and 0.9 g of EPA daily. Three patients became seizure free and 2 had a greater than 50% seizure reduction at the end of the 6-month trial [Epilepsia 2002; 43(1):103–104].

Methods: Patients with chronic epilepsy and learning disability were randomised and received capsules of EPA (1g) and DHA (0.7g) daily or placebo (mixed vegetable oils) in a 12-week double blind study. All patients were then given active medication in a 12-week open maintenance phase. Seizure counts, adverse events, antiepileptic drug (AED) and red blood cell (RBC) FA concentrations were assessed during the study. UCL ethics committee gave approval for the study.

Results: Fifty-eight patients were randomised, one patient (on placebo) was withdrawn, hence 30 received active and 27 placebo (age19–65 vs 20–63; males 43% vs 82%, mean no AEDs 2.8 vs 2.4). A significantly ($p < 0.05$, CI 1.5% to 36% [17%]) greater proportion on active showed at least a 50% seizure reduction in the first 6 weeks of treatment but not in the second 6 weeks. Analysis of covariance showed a trend ($p = 0.087$) towards a greater reduction in total seizures in the active group in the first 6 weeks only. There were no relevant changes in mean AED concentrations. RBC FA concentrations showed a large increase in EPA and DHA in the active group and a much smaller increase on placebo. There were very few reports of adverse events (active 4, placebo 4). Status epilepticus occurred in one patient each on active and placebo (withdrawn from trial). One patient (also taking aspirin and naproxen) with a drop in haemoglobin concentration was withdrawn during the open phase.

Conclusions: In this study, FA supplementation appears to reduce seizures transiently in the first 6 weeks of treatment. Further studies are required to assess higher FA doses and longer treatment periods. (Supported by Seven Seas Ltd. UK provided study medication.)

1.403

SEIZURE SUPPRESSION BY FOCAL BRAIN STIMULATION MAY BE MODULATED BY GABAERGIC FAST INHIBITORY GAIN: A MODELING STUDY

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Rationale: We investigated mechanisms underlying suppression of seizures with focal brain stimulation by analyzing human trial data with a computer model of seizure generation. Data from 31 patients treated with responsive stimulation to suppress seizures during presurgical intracranial monitoring were analyzed. A computer simulation model (F. Wendling et al.) was employed to determine the hippocampal cell population most affected by responsive stimulation.

Methods: Data were grouped into two classes: Stimulated Events (Stim) and Non-Stimulated Events (NonStim). The Stim class consisted of automated detector-triggered stimulations; NonStim events were detected but not stimulated. There were a total of 3,862 Stim and 1,582 NonStim events recorded.

Simulations determined model parameter changes after reactive stimulation compared to non-stimulated events. A permutation test was conducted to determine the difference in "grand-mean" model parameters for both classes. Intracranial EEG (IEEG) was processed before and after event onsets. Each IEEG segment was matched to synthesized data generated by the model, searching all possible parameter values. Signal matching techniques were used to carry out this task, minimizing the normalized power spectrum. Differences betweem Stim and NonStim classes were tallied.

Results: There was a statistically significant change between stimulation and nonstimulation class events in the model's "G" parameter, which correlates with GABAergic fast inhibitory gain (0.1438 under Stim VS. -0.8072 under NonStim, $p = 0.02$). Changes in parameters "A" (representing excitatory gain) and "B" (slow inhibitory currents) in the model were not significant ($p = 0.23$ and 0.24 respectively).

Conclusions: Our results demonstrate that focal brain stimulation may suppress seizures through fast inihibitory GABAergic interneurons. This result may stimulate experiments to isolate function in specific populations of neurons during seizure generation and suppression. They may also help guide electrode placement and methods for tuning stimulation parameters in new implantable devices. Further research recording unit ensembles "in-vivo" in animals and humans, linked to biophysical computational neuronal modeling will provide more insight into mechanisms of seizure generation and suppression. These techiques are moving from traditional experiments in the animal laboratory to clinical practice in Neurology and Neurosurgery. [Supported by Whitaker Foundation, Dana Foundation, National Institutes of Health (grant 5R01NS041811–03), Citizens United for Research in Epilepsy (CURE), the Epilepsy Foundation, and a sponsored research agreement between the University of Pennsylvania and NeuroPace, Inc.]

1.404

CORTICAL RESPONSES FOLLOWING ELECTRICAL STIMULATION OF THE ANTERIOR THALAMUS FOR EPILEPSY

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Rationale: The response of cortex to thalamic stimulation through implanted deep brain stimulation (DBS) electrodes is largely unknown.

We studied the relation between thalamic stimulation parameters and the morphology and topographic distribution of the cortical response in patients with intractable epilepsy undergoing DBS of the anterior thalamus. The generation of such cortical responses has been suggested to predict clinical efficacy of stimulation.

Methods: Scalp-recorded cortical responses were studied in four patients who had previously undergone DBS surgery. Stimuli were delivered through contacts implanted bilaterally in the anterior thalamus (anterior and dorsal medial nuclei) using the programmable stimulation device (Medtronic ITREL II).

Results: All patients demonstrated reproducible time-locked cortical responses. The morphology of these responses, however, was quite heterogeneous, depending primarily on the site of stimulation (i.e. the contacts that were stimulated). Following bipolar 2 Hz stimulation, the typical response consisted of an ipsilateral triphasic negative-positive-negative deflection (peaking at around 25, 50 and 100 ms; maximal over the ipsilateral frontal scalp, subsequently extending to the lateral temporal scalp) followed by a broad ipsilateral biphasic positive-negative deflection (peaking at around 150 and 250 ms; maximal over the ipsilateral fronto-central scalp). The amplitude of the entire response was positively related to the strength of the stimulus (with a lower threshold for monopolar stimulation), and inversely related to the impedance of the electrode.

Conclusions: With appropriate, high-intensity stimulation parameters, robust cortical responses of considerable inter- and intra-individual variation can be recorded from the scalp following anterior thalamus stimulation. These complex cortical responses most probably reflect mixed activation of both specific and nonspecific thalamocortical pathways. The heterogeneity of the cortical response, however, suggests a certain degree of point-to-point specificity. (Supported by Swiss National Science Foundation: PA00A-101502.)

Non-AED/Nonsurgical Treatments—Pediatric

1.405
VAGUS NERVE STIMULATION IN PREADOLESCENT CHILDREN WITH PHARMACORESISTANT EPILEPSY

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Rationale: Vagus Nerve Stimulation (VNS) was approved by the FDA in 1997 as adjunctive therapy in refractory epilepsy patients with partial-onset seizures older than 12 years. Only limited published data regarding its use in younger children and other epilepsy syndromes is available.

We have reviewed our experience with VNS therapy in pre-adolescent children with medically intractable epilepsy.

Methods: We identified 22 patients under 12 years of age among the 181 consecutive patients with intractable epilepsy, who underwent VNS implantation at our institution during 1997–2003. These patients did not qualify for resective epilepsy surgery (2 had failed previous surgery).

Charts were reviewed for pre- and postoperative seizure types and frequency, epilepsy diagnosis, MRI, EEG and seizure semiology, antiepileptic drugs, magnet settings, and side effects. All patients had at least one baseline assessment within 4 to 8 weeks before surgery. Minimal follow-up was 6 months post-implantation. Nonparametric statistical analysis using the Wilcoxon signed ranks test was performed.

Results: Complete pre- and post-VNS data were available for 21/22 pre-adolescent patients. Median age at implantation was 8 years (range from 2.3 to 11 years) and median duration of epilepsy 6.1 years (1.9 to 10.6 years). Median age at onset of epilepsy was 9 months (range from birth to 8.7 years). Follow-up intervals extended to 12 months in 17/21, 24 months in 11/21, 36 months in 8/21 and 48 months in 6/21 patients.

Six children had focal epilepsy and 15 had a generalized epilepsy syndrome. Eight children had a normal brain MRI. One had hypothalamic hamartoma and 4 patients had cortical malformation (2 had tuberous sclerosis and 1 lissencephaly). MRI showed generalized volume loss in 5 and nonspecific abnormalities in three. Mild to severe developmental delay was present in all but 1 patient.

Compared to baseline, median seizure frequency reduction at 3 and 6 months was 60% and 71% respectively ($n = 20$, $p < 0.01$). In the setting of declining numbers of patients followed longer, >75% seizure reduction was maintained at 12 ($n = 17$, $p < 0.01$), 24 ($n = 11$, $p < 0.01$), 36 ($n = 8$, $p < 0.05$) and 48 months ($n = 6$, $p < 0.05$). Two patients became seizure-free 6–12 months after implantation. There was no difference in the number of AEDs used before and after VNS. VNS-related side effects were mild and transient. However, three patients developed postoperative wound infection, necessitating explantation of the device in two.

Conclusions: VNS therapy is well-tolerated and effective in pre-adolescent children < 12 years with generalized or focal pharmacoresistant epilepsy. Comparing to published series of VNS in adolescents and adults, younger children appear to respond more favorably irrespective of the epilepsy syndrome.

1.406
MEMANTINE AS ADD-ON THERAPY IN PEDIATRIC EPILEPTIC PATIENTS: EFFECTS ON COGNITIVE DEVELOPMENTAL AND SEIZURE FREQUENCY

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Rationale: Severe or chronic epileptic syndromes of childhood are known to affect cognitive or academic performances. In addition, incomplete seizure control is believed to be detrimental to development. Memantine may act as a neuroprotective, mild anticonvulsant, and cognitive enhancing drug in epileptic patients due to the pharmacological mechanism of action as an antagonist of NMDA receptor channels, and blocking the effects of glutamate on neurons. We report experience on patients with either cognitive impairment from severe epilepsy and/or continuing breakthrough seizures, using add-on therapy with Memantine.

Methods: 13 patients (6 male, 7 female, average age 6 years, 4 months) with epilepsy and cognitive delay were given Memantine as add-on therapy with no other changes made to their antiepileptic drugs (AED) or their medications for behavior. The average dosage of Memantine was 5.4 mg/day (range 2.5 to 10 mg/day). 6/13 patients were having breakthrough seizures, mainly atypical absence seizures (ave. seizure freq. was 10.9 seizures/day, range 0.1 to 50 seizures/day). 7/13 patients had controlled seizures but had cognitive or motor dysfunction or attention difficulties.

Results: In 6/13 patients with continuing epilepsy, 2 became seizure-free over 2 months. 3 had decreased frequency of seizures (ave. seizure frequency after taking Namenda 0.4 seizures/day). Cognitive or functional improvements observed in all patients included improved attention (11/13), better motor planning skills (10/13), improved language complexity (10/13), or other global improvement (11/13) as assessed by parental or clinician observation.

Conclusions: Memantine may be a therapeutic option to improve intractable seizures, and protect and enhance cognitive function in patients with epilepsy. The seizure frequency improvement after administering Namenda was most dramatic in children with atypical absence seizures. EEG correlation is still pending and further controlled studies are warranted.

1.407
EFFICACY AND SAFETY OF THE KETOGENIC DIET FOR INTRACTABLE INFANTILE SPASM

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Rationale: To evaluate efficacy and safety of the ketogenic diet (KD) in infantile spasms (IS) by reviewing our experiences.

Methods: We undertook a retrospective analysis of 34 patients with intractable IS treated with the KD from June 1995 to January 2003 at two epilepsy centers. The efficacy and safety of the classic 4:1 ketogenic diet (KD) as an add-on treatment in refractory IS were evaluated. In 9 patients, ketone milk (Ketonia, brand name) constituted mainly with medium chain triglyceride was introduced. Outcome measures included seizure frequency, EEG findings, and adverse effects during the ketogenic diet.

Results: Outcomes for a reduction of seizure frequencies are as followings; at 3 months after initiating the diet, all patients remained on the diet, 61.8% (21/34) showed a reduction of seizure frequency with over 50% including 35.3% (12/34) with seizure free; at 6 months, 67.6% (23/34) patients remained on the diet, 58.8% (20/34) with over 50% including 50% (17/34) with seizure free; at 9 months, 44.1% (15/34) patients remained on the diet, 42.2% (14/34) with over 50% including 38.2% (13/34) with seizure free; at 12 and 15 months, respectively, 35.3% (12/34) patients and 32.4% (11/34) remained on the diet with seizure free. Supplementarily introduced Ketonia was well tolerated. During the KD, 29.4% (10/34) patients should discontinue the diet due to complications in 11.8% (4/34) and/or intolerance in 17.6% (6/34). The complications included gastrointestinal troubles in 2 patients, serious infectious disease in 1 patient and lipoid aspiration pneumonia in 1 patient. By modifying the protocol to omit the initial period of fasting in 17 patients, especially in infants and early childhood period as an usual onset age of IS, we could prevent acute dehydration in most patients, with no difference in the time to ketosis or in the efficacy of the diet. EEG background rhythms with hypsarrythmia before the KD were significantly improved in 43.3% (13/30) at 3 to 6 months after starting the diet, even showing normal EEG in 1 patient.

Conclusions: Many of patients with intractable IS could be completely controlled by the KD without serious complications. The KD should be considered as a next step treatment in patients with IS refractory to other treatment modalities with expecting high efficacy and tolerability, and early trial prior to prolonged high dose anti-epileptic drugs could be considered.

1.408

LONG-TERM EFFECT ON EPILEPTIFORM ACTIVITY WITH VAGUS NERVE STIMULATION IN CHILDREN

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Rationale: We report long-term effects of Vagus Nerve Stimulation (VNS) on epileptiform activity in 15 children and how these changes are related to activity stage and to clinical effects on seizure reduction, seizure severity and quality of life (QOL).

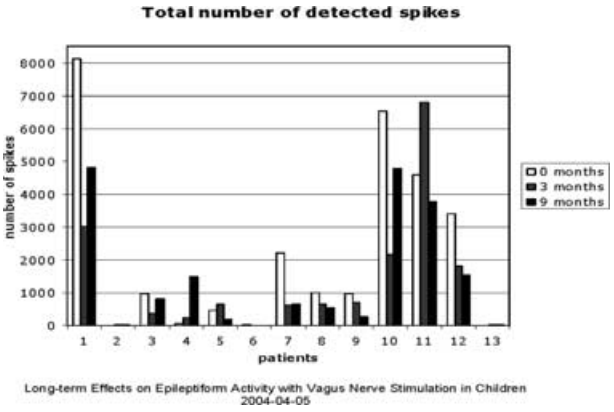
Methods: Before and after three and nine months of VNS-treatment 15 children were investigated with 24 hours ambulatory EEG monitoring for spike detection. The number of interictal epileptiform discharges (IED) and the inter spike interval's (ISI) were analysed during two hours in the awake state, and one hour of rapid eye movement (REM)-, spindle- and delta-sleep, respectively. Total number and duration of electrographic seizures were also analysed.

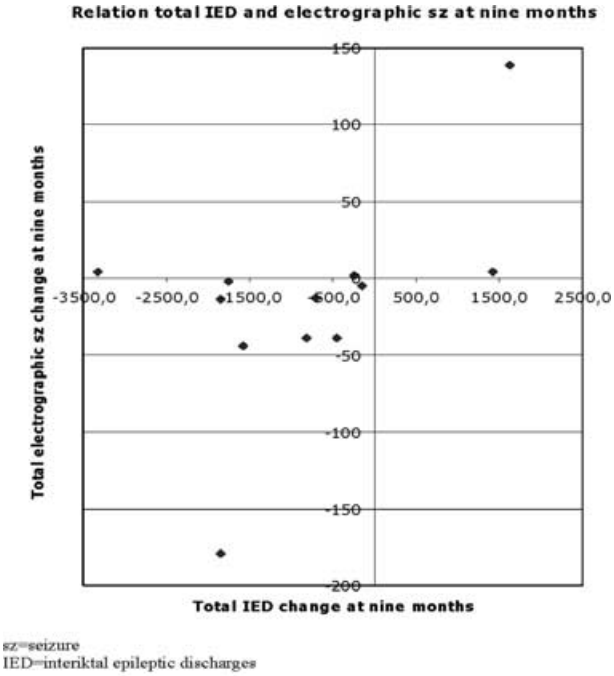
Results: At nine months the total number of IED was significantly reduced ($p = 0.03$).

There was a tendency of reduction in all activity stages and significantly so in REM ($p = 0.03$) and delta-sleep ($p = 0.02$). No significant changes of median ISI were found at three and nine months ($p = 0.27$, 0.10). Total electrographic seizure number was significantly reduced in the 24 hours EEG at three and nine months ($p = 0.03$, 0.05). There was a significant concordance in direction of changes in epileptiform activity and electrographic seizures at nine months

Fand a concordance in direction of changes in epileptiform activity and clinical effects on seizure reduction, seizure severity and QOL. However, there was no direct correlation between the extent of improvement in these clinical data and the degree of spike reduction (Figs. 1 and 2).

Conclusions: This study shows that VNS reduces IED especially in REM and delta sleep. It shows a reduction in electrographic seizure number. There is also a concordance between reduction in IED and





electrographic seizures and in IED and effects on clinical seizure reduction, seizure severity and QOL. (Supported by Orion-Pharma, Linnéa och Josef Carlssons foundation, Margaretahemmets foundation, Stiftelsen Samaritens foundation, Segerfalks foundation and SRC 084.)

1.409

VAGUS NERVE STIMULATION IN THE TREATMENT OF INTRACTABLE EPILEPSY IN PATIENTS WITH TUBEROUS SCLEROSIS

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Rationale: Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome which affects multiple organs. Neurologic manifestations are present in greater than 50% of patients and include epilepsy and mental retardation. Approximately 80% of patients with TSC and seizures are refractory to standard antiepileptic medications. Surgical treatment is beneficial if the seizure onset can localized; however, often patients are found to have a multifocal onset of seizures. In these patients were more

than one seizure focus is present, Vagus Nerve Stimulation (VNS) offers another treatment option.

Methods: Fourteen patients were identified out of the TSC clinic at Cincinnati Children's Hospital who had undergone a VNS implant. All patients had a confirmed diagnosis of TSC by either genetic analysis or meeting required major and minor diagnostic criteria. A phase one presurgical evaluation was completed on all patients. Patients had failed on average 10 medications. Seizure types included simple partial, complex partial and secondarily generalized. Seizure logs were maintained prior to and following VNS implant. VNS programming followed a protocol involving increases in output current followed by adjustments of duty cycle. Side effects and other aspects quality of life were documented at each visit as reported by the patient and family. Data was collected and analyzed at six and twelve months.

Results: Fourteen patients were identified. Age of seizure onset ranged from birth to five years. Age at time of implant ranged from 3–12 years. All patients were described as developmentally delayed. There were 12 patients with at least six month follow-up and seven patients with at least one year follow-up. Seizures were divided into simple/complex partial and secondarily generalized. The average seizure reduction for simple/complex partial seizures was 56% at 6 months and 60% at 12 months. For secondarily generalized seizures the average seizure reduction was 22% at both 6 and 12 months. A 50% reduction in simple/complex partial seizures was seen in 67% of patients at 6 months and 57% at 12 months. A 75% reduction in simple/complex partial seizures was seen in 56% of patients at six months and 43% at 12 months. All patients reported improvements in quality of life such as decreased post-ictal period and increased alertness. Side effects were mild and included coughing and voice change.

Conclusions: In our patients with TSC and intractable epilepsy who were not surgical candidates, VNS offered an alternative treatment option that was effective in decreasing both simple/complex partial seizures and secondarily generalized seizures. All patients experienced other positive effects following VNS implant. No serious side effects were seen. It is important to note that the VNS appeared to be more successful in decreasing simple/complex partial seizures than secondarily generalized seizures in our population of patients with TSC.

1.410
EARLY VERSUS LATE VAGUS NERVE STIMULATION THERAPY IN PEDIATRIC EPILEPSY

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Rationale: Adjunctive treatment with VNS has been approved for patients 12 yrs and older with refractory epilepsy since 1997. Case series have reported outcomes in mixed adult and pediatric populations, but few have concentrated on children.Our project was designed to examine outcome variables specifically in children. The objectives were to determine the difference in outcome with VNS therapy within 5 years of seizure onset versus 5 years after seizure onset. To determine the difference in antiepileptic drug usage before and after VNS therapy in both groups.

Methods: Patients who were <18 yrs of age at the time of implantation of the VNS device at VCU between November 1998 and December 2003 were included in a retrospective chart review. Data collected included sex,ethnicity,age and time interval between seizure onset and implantation,diagnoses,EEG and MRI findings,percentage seizure reduction at 3,6,9,12,18,24,36,48,72 months after implantation,type and number of AEDs used before and after.The patients were divided into two groups, Group A with implantation <5 yrs after seizure onset and Group B > 5yrs after seizure onset.

Results: 22 patients satisfied inclusion criteria,12 males,10 females; 20 Caucasians,2 African Americans. In Group A, 9 patients and in Group B, 13 patients were included. Overall seizure reduction in Group A was 52% versus 46% in Group B. Regression analysis was performed to compare seizure reduction over time and among the two groups.A statistically significant reduction over time was noted adjusting for both groups ($p < 0.003$). However, no statistically significant difference was noted when the groups were compared to each other for seizure reduction. Number of AEDs used before VNS were 3.7 in Group A and 2.5 after,and in Group B, 4.0 before and 2.7 after. An ANOVA model was used to compare the means for the two groups at each time point for AED usage.Pre and post means for both groups were statistically significant ($p < 0.004$).The interaction effect comparing both groups at each time point was not statistically significant.

Conclusions: Statistically significant seizure reduction over time was noted in both groups. Better outcome was noted in the early implantation group, however this was not statistically significant. A stastically significant decrease in AED usage was noted in both groups. Recent studies have shown only minimal benefit in seizure reduction with usage of third or subsequent AEDs in refractory epilepsy after failure of an appropriate trial of initial two AEDs. Should earlier adjunctive therapy with VNS be considered? More prospective studies are needed to answer this question.

1.411
VAGUS NERVE STIMULATORS IN VERY YOUNG CHILDREN

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Rationale: Medically refractile multifocal epilepsy in infancy can be devastating and exceptionally difficult to treat. We and others have reported favorable results from vagus nerve stimulator therapy in pediatric patients. We have utilized vagus nerve stimulator therapy in a small group of patients whose age is less than 5 years and report results here.

Methods: We reviewed the medical records and outcomes of 6 patients less than 5 years of age who underwent implantation of a vagal nerve stimulator. All patients were refractile to multiple medications and had severe multi-focal, life altering epilepsy.

Results: Six patients were identified. Average age was 23.7 months (range 9–46 months). Underlying diagnoses including mitochondrial disease, atonic seizures and idiopathic multifocal epilepsy (4 patients). Concomitant morbidity included linear nevus sebaceus syndrome (1 patient) and myelomeningocele (1 patient). Surgical procedures were uncomplicated and required an average of 74 minutes for implantation. No child lost more than 10 cc of blood. Follow up time averages 19 months (range 1–61 months). Three children have shown significant improvement in seizure control, one child has not changed and one child is worse. One child was not available for follow up.

Conclusions: Vagal Nerve Stimulator therapy is feasible and appears safe and effective in this small cohort of very young children.

1.412
THERAPEUTIC OUTCOMES OF VAGUS NERVE STIMULATION IN INTRACTABLE CHILDHOOD EPILEPSY

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Rationale: To evaluate the benefits and safety of vagus nerve stimulation (VNS) in intractable childhood epilepsy through review of our experiences.

Methods: Twelve patients who underwent VNS at two centers and could be followed up for more than 3 months were included. We retrospectively reviewed records for clinical features, therapeutic outcomes, side-effects, developmental progress and EEG changes.

Results: The mean (± SD) age at the start of VNS were 9 yrs. 9 mo. (± 60.5 mo.) (2 yrs. 9 mo. −17 yrs. 10 mo.). The mean follow-up period was 21.6 (± 23.3) mo. In five patients, follow-up period was

over 12 mo., while in seven patients, it was less than 12 mo. Nine patients were classified as Lennox-Gastaut syndrome (LGS), including one patient whose problem originated from previous encephalitis, one patient who was evolved from infantile spasms combined with tuberous sclerosis, and one patient with unknown specific underlying causes. Three patients presented with partial seizure disorder, including one with gelastic seizure caused by hypothalamic harmatoma. At 3 mo. after VNS insertion, eight patients showed more than 50% reduction in seizure frequency, and two patients with LGS became seizure-free after 3 mo. Of the five patients who could be followed up for more than 12 mo., one patient with partial seizure disorder exhibited more than 50% reduction in seizure frequency 3 mo. after VNS insertion, and over 90% reduction at 12 mo. and afterwards. One patient with LGS from previous encephalitis showed more than 50% reduction in seizure frequency after 3 mo. and over 75% after 12 mo., with maintained effect, while one patient with cryptogenic LGS showed over 50% seizure reduction after 3 mo. with maintained effect. Two patients who presented with gelastic seizure and cryptogenic LGS, however, didn't show any improvement in seizure frequency. Side effects such as hoarseness, drooling, frequent aspiration and dyspnea during sleep could be controlled by adjustment of output current. Wound infection in one patient was controlled after wound revision. In two patients who were seizure free at 3 mo. post-surgically, dramatic improvements of EEG findings were seen. Of the five patients who were followed-up for more than 12 mo., ultimate cognitive outcome was not satisfactory.

Conclusions: VNS may be an effective adjunctive therapy for intractable childhood epilepsy and transient side effects can be controlled without discontinuation of VNS therapy.

1.413
COMPLICATIONS OF THE KETOGENIC DIET

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Rationale: The Ketogenic diet(KD) has been used in the treatment of intractable epilepsy since 1920s, but the complications of KD have been rarely reported in large study group. So, we studied the tolerability and the complications of KD in large group.

Methods: This is a retrospective study in 40 children with intractable epilepsy, who were treated with the KD in the department of pediatrics, Asan medical center, from January 1996 to April 2004.

Results: The 40 children included 22 boys and 18 girls. The mean interval from diagnosis to initiation of the KD was 28 months(44 days-11.5 years), and the mean duration of the KD was 7 months(4 days-29 months). Thirty(75%) children discontinued the KD, because of refusal to eat($n = 14$, 47%), complications($n = 10$, 33%) and ineffectiveness($n = 6$, 20%). Complications were experienced in 15(38%) children; hyperlipidemia($n = 5$), elevated liver enzyme($n = 5$), gastrointestinal symptoms including vomiting and constipation($n = 6$), severe or recurrent infections($n = 4$), metabolic acidosis($n = 2$), hypoglycemia($n = 2$), hyperuricemia($n = 1$), renal stone and hematuria($n = 1$), hypoproteinemia($n = 1$). The development of metabolic acidosis was not related to the co-treatment with topiramate.

Conclusions: KD is an effective therapeutic modality in the treatment of pediatric intractable epilepsy. However, variable complications may be accompanied. Education of parents and patients and careful observation about the development of complications are recommended.

1.414
VAGUS NERVE STIMULATION FOR THE TREATMENT OF REFRACTORY EPILEPSY SECONDARY TO TUBEROUS SCLEROSIS: A PEDIATRIC PERSPECTIVE

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Rationale: Despite therapy with multiple anticonvulsants refractory epilepsy in pediatric patients with Tuberous Sclerosis is a common occurrence. Epilepsy often begins as infantile spasms and progresses over time to Lennox Gastaut Syndrome. In other patients focal seizures from a single cortical tuber or multi-focal seizures from multiple cortical tubers are observed. Vagus nerve stimulation offers an alternative therapy for refractory seizures in these patient.

Methods: A retrospective review of 425 patients followed in the Tuberous Sclerosis Clinic at the University of Chicago identified pediatric patients in which vagus nerve stimulation therapy was performed. Age, Sex, duration of vagus nerve stimulation, seizure frequency prior to stimulator implantation, and at most recent clinic visit were obtained. In addition, seizure type and anticonvulsant therapy were also recorded. Individual and mean seizure reduction were calculated. Subjective impression on quality of life after Vagus nerve stimulation was also obtained from primary caregivers.

Results: Of the 10 patients 5 were female. Mean age was 9.2 yr. Mean follow up was 26.15 ± 22.7 months. Mean stimulation current was 1.875 ± 0.57 ma. Mean seizure frequency prior to stimulator implantation was 4.3 ± 2.8 seizures per day. Mean seizure frequency after stimulation was 1.6 ± 1.5 seizures per day. ($p = 0.017$). Mean seizure reduction was 70.0 ± 18.0 percent. All patient had seizure reduction greater than 47%.

Conclusions: Vagus nerve stimulation is an effective adjunctive anticonvulsant therapy for refractory seizures in children with Tuberous Sclerosis. Mean seizure frequency was reduced from 4.3 to 1.6 seizures per day $p = 0.017$. A greater than 47% reduction of seizure frequency was observed in all 10 children in our study. In addition, over half of the children were judged subjectively by their primary care givers to be more alert and have improved performance in school. In two of the ten children rapid stimulation parameters produced an increase in seizure frequency compared to standard stimulation parameters. Early use of Vagus Nerve Stimulation in children with Tuberous Sclerosis improves seizure control and subjective quality of life for these patients.

1.415
INTERNATIONAL USE OF THE KETOGENIC DIET

Eric H. Kossoff and Jane R. McGrogan (Pediatric Epilepsy, Johns Hopkins Hospital, Baltimore, MD)

Rationale: Over the past decade, the use of the ketogenic diet internationally has increased dramatically. Our objective was to examine some of the worldwide issues in the administration of the ketogenic diet as well as gather academic center information for referrals and collaboration.

Methods: Using the Internet, email requests for information about international ketogenic diet centers were made over a three-month period. Assistance was also obtained from the Child Neurology Society and International League Against Epilepsy. Questions included patient enrollment (total and annually), year the diet was first offered, unique cultural and religious issues in their country, community opinion, and research interests.

Results: Successful communication was made with 56 academic centers in 35 countries outside the United States. Twelve (34%) countries provided information from multiple centers. Sixteen centers also provided a recipe for a ketogenic meal using native foods. The median duration offering the diet was 8 years (range 1–31). The average number of patients enrolled to date was 71.6 per country, with 5.4 started annually. Common difficulties included avoiding rice intake, tolerating high fat to protein and carbohydrate ratios (e.g. 4:1), and handling the growing interest from large population bases with limited resources. However, cultural and religious issues were generally not limiting, physician and patient acceptance is high, and most foods were similar. Centers often had great pride in their programs and international collaborative groups are forming rapidly.

Conclusions: Despite occasional difficulties, the ketogenic diet is gaining momentum abroad.

1.416
INTERMITTENT VAGUS NERVE STIMULATION IN PEDIATRIC PATIENTS WITH PHARMACORESISTANT STATUS EPILEPTICUS

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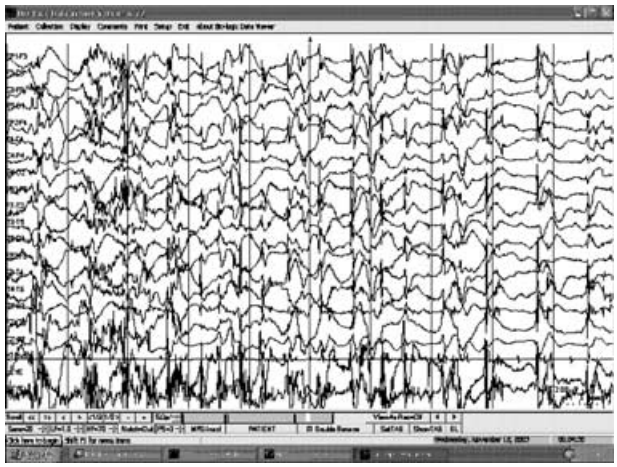
Rationale: Vagus nerve stimulator was implanted as an alternative non pharmacological intervention in three patients with pharmacoresistant status epilepticus.

Methods: Three patients were admitted to our institution whose status epilepticus failed to respond to standard pharmacotherapy. These patients were then emergently implanted with a VNS as an alternative to pharmacological therapy. On all three patients the VNS output current and duty cycle were adjusted frequently and final output current and duty cycle settings are shown in table 1.

Results: At our institution three patients were implanted with the VNS after they were diagnosed with pharmacoresistant status epilepticus. All three patients continue to have prolonged and repetitive electrographic and electroclinical seizures as documented by video EEG monitoring (Table 1; Fig. 1). There was complete resolution of status epilepticus in all three patients. Seizure frequency was reduced by >60% in the first two patients and the third patient was completely seizure free. At the eighth week follow up visit post implantation, the families of the first two patients reported significant reduction in seizure frequency whereas the third patient experienced the return of seizures at four weeks post-implantation and reported significant reduction in seizures at the visit. In our patients, all three families reported increase in alertness and improvement in quality of life.

Conclusions: Though these results are preliminary and we have discussed only three cases, they offer promising results and open a window of opportunity to perform prospective studies evaluating early use of VNS in patients whose status epilepticus has failed to respond to standard antiepileptic medication regimen. It would also be interesting to perform immediate and late cerebral blood flow studies in these patients to see if there are changes in flow volume after VNS implant.



1.417
USE OF A KETOGENIC TUBE FEEDING FOR TREATMENT OF THE PATIENT WITH ACUTE REPETITIVE SEIZURES
Kathy B. Santoro, Therese M. O'Flaherty, and Deborah L. Holder (Aerodigestive and Sleep Center; and Child Neurology Division, Cincinnati Children's Hospital Medical Center, Cincinnati, OH)

Rationale: Acute repetitive seizures are a common presenting symptom of encephalitis in children. Occasionally, the seizures are refractory to commonly used antiepileptic drugs (AED). This report reviews one patient with acute repetitive seizures successfully treated with a ketogenic formula.

Methods: A six year old male was admitted to the ICU in February 2004 with a diagnosis of encephalitis and acute repetitive seizures refractory to six antiepileptic drugs. His seizures were originating from both temporal lobes, lasting up to three minutes, and occuring every 15–30 minutes. Due to the lack of seizure control, options including barbiturate coma and the ketogenic diet were discussed. It was decided to try the diet and initially all IV fluids were changed to normal saline. Total parenteral nutrition was discontinued and an NJ was placed. The following day, a half -strength 4:1 ketogenic diet formula was initiated, and was advanced to full strength after 24 hours. The patient remained on four AEDs during the initiation of the diet including a Versed drip.

Results: The ketogenic formula was well tolerated and once the betahydroxybutyrate (BHB) reached 3.8 mmoles, the patient's seizures stopped and he was able to be extubated. A breakthrough seizure occurred the next day and the BHB was found to be 1.8 moles, due to dextrose containing fluid given with one of the patient's seizure medications. After return of BHB to previous high levels, the seizures again resolved. Three of the four AEDs were rapidly tapered. The patient was transitioned to oral feedings of a 4:1 ketogenic diet while in the rehabilitation unit. He was discharged and remained seizure free on one AED and the ketogenic diet.

Conclusions: The ketogenic diet started on a patient with acute repetitive seizures which were refractory to six AEDs was effective and well tolerated. Within forty eight hours of initiation of a ketogenic formula, the patient was seizure free. Ketosis was easily obtained with NJ feedings. It is important to assure all intravenous fluids used on the ketogenic diet are dextrose free to maintain this ketosis. The ketogenic diet should be considered as an option in patients with acute repetitive seizures.

1.418
VAGUS NERVE STIMULATION FOR REFRACTORY EPILEPSY IN PEDIATRIC PATIENTS
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Rationale: To evaluate efficacy, effects on safety, quality of life and tolerability of vagus nerve stimulation(VNS) in children with refractory epilepsy, we reviewed 7 patients who underwent VNS implantation.

Methods: We retrospectively studied medical record of 7 pediatric patients who underwent VNS implantation between December 2001 and April 2004.

Results: The age at operation ranged from 6 year 5 months to 11 year 9 months. Duration of follow-up ranged from 12 months and 44 months. In all patients, the seizure was medically intractable and one of them was medically and surgically intractable. In 4 patients the epilepsy was symptomatic. Of the 4 patients, three had a history of meningoencephalitis and one had patchygyria. Five patients(71%) had 50% or more reduction in the seizure frequency and the onset of seizure reduction ocurred within 3 months after VNS implantation. The VNS differed in efficacy according to the seizure type. A complex partial seizure was effective in 50% of the patients, but efficacy not shown with myoclonic seizure. And there was no relationship between seizure duration before VNS activation and efficacy of VNS. In four patients there were improvements in the quality of life such as alertness, mood, verbal communication and motor function. EEG was normalized in one patient. Side effects were a transient hoarseness in four patients and wound infection in one patients, but these were tolerable.

PT. Number/AGE	Duration of Epilepsy	Anti-epileptic Medications	Seizure Type	8 wk VNS setting
1 (14 mo)	5 mo	PB,TPM,LTG,PHT,LZP	Atonic,Hypomotor and Partial Seizures.	1.0/30s/1.1min
2 (3 1/2 yrs)	9 mo	CBZ,PB,VPA,ZNS,LZP,FBM	Atonic,GTC, Myoclonic Seizures	1.75/7s/0.2min
3 (10 yr)	2 mo	PB,OXC,ZNS,DPH,PTB	Multifocal Onset Seizures	2.5/7s/0.2min

s = seconds, min = minutes.

Conclusions: VNS is an effective, safe adjunctive therapy in medically or surgically refractory pediatric epilepsy and also effective in improving quality of life.

1.419
CARDIORESPIRATORY EFFECTS OF THE VAGUS NERVE STIMULATION IN EPILEPTIC CHILDREN
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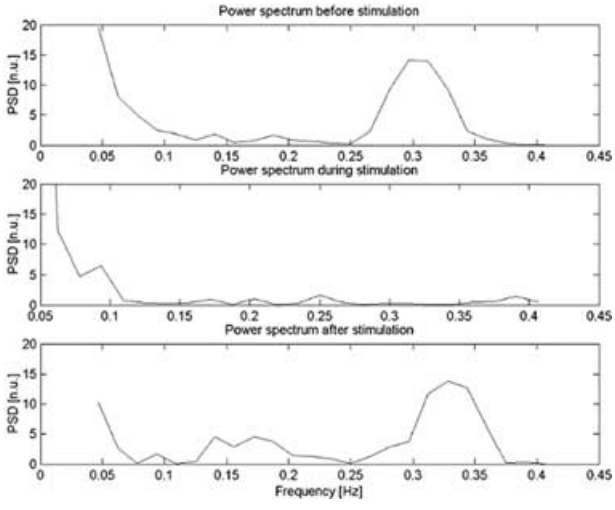
Rationale: Vagus nerve stimulation (VNS) is used as an approved treatment to reduce seizures in patients with drug resistant epilepsy. It's an empirically based method for the treatment of epilepsy by repeated stimulations of the left vagus nerve through implanted electrodes. Only few data are available in humans about the effects of VNS on respiration. VNS has also an impact on heart rate variability (HRV).

Methods: We analyzed physiological cardiorespiratory responses to VNS in 10 epileptic children during polygraphic sleep recording. In normal case, HRV presents two major components of frequency: low frequency (LF), and high frequency (HF). Modifications in the LF/HF ratio are indicative of variations in sympathovagal balance. The distribution of the power and the central frequency of LF and HF vary in relation to changes in autonomic modulations of the heart period.

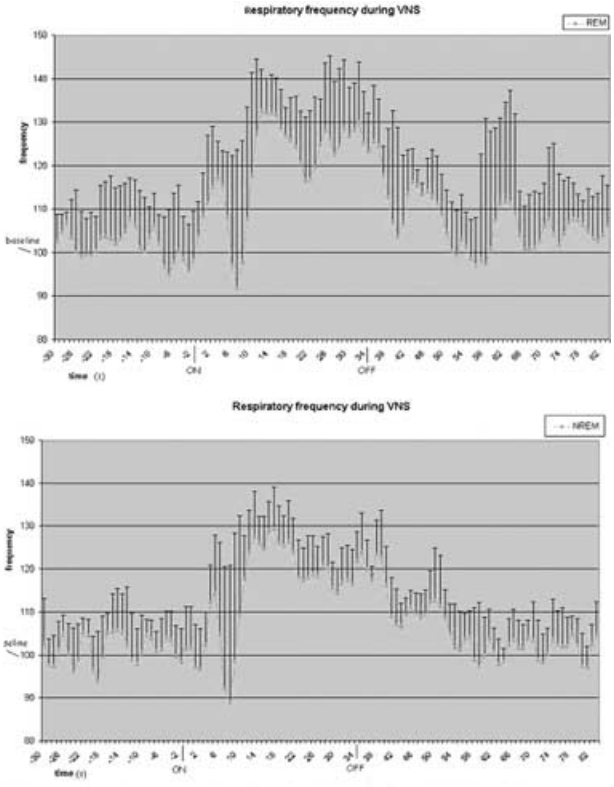
Results: We demonstrate that VNS, in children, induces repetitively a first significant increase in respiratory frequency (10% to 25%; $p < 0.05$). This first increase is followed by a decrease in respiratory frequency which reach baseline values by the end of the stimulation. In parallel, the amplitude decreases by 25% to 40% ($p < 0.05$) from baseline. For some patients these effects are more pronounced during NREM than during REM sleep. Linked to VNS, they vary during the night. This variability is also more pronounced during REM ($p = 0.0012$). These respiratory responses are proportionally related to the intensity of stimulation. In some children, these effects result in a decrease in SaO_2 (from 98% to 94%).

The tachogram analysis (Figs. 1 and 2) of the ECG of children treated by VNS, demonstrates a significant difference between the 2 components during stimulation than normal case. (2.27 ± 0.62 n.u. vs 0.55 ± 0.21 n.u.).

Conclusions: VNS induces repetitive reversible (1) respiratory restrictive syndrome (decrease of the amplitude, and increase of respiratory frequency), (2) change in sympathovagal balance and (3) decrease in SaO_2. Those VNS consequences on the vegetative system might serve to optimize the stimulation parameters when correlated to the drop in epileptic seizures.



(Supported by Alternatech, Conseil Regional de Picardie and Cyberonics.)



(Supported by Alternatech, Conseil Regional de Picardie and Cyberonics.)

Surgery—Adult

1.420
RELATIONSHIP OF SEIZURE SEMIOLOGY TO THE OUTCOME OF ANTERIOR TEMPORAL LOBECTOMY
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Rationale: Approximately 30% of patients undergoing epilepsy surgery for intractable temporal lobe epilepsy continue to have seizures despite detailed presurgical evaluation with advanced localizing techniques prior to surgery. Seizure semiology may play a part in determining outcome.

Methods: We retrospectively reviewed the seizure semiology in 30 (15 right and 15 left) patients who underwent temporal lobectomy. Seizure semiology was studied by reviewing the history and video-EEG monitoring, volumetric MRI with temporal lobe potocol and interictal PET. Eight patients underwent invasive video-EEG monitoring with subdural electrodes. Four patients had ictal and interictal SPECT, and 4 had MR spectroscopy. Surgical outcome was determined by Engel's classification, with class 1 regarded as good outcome. Presence of auras, onset and evolution of seizures, and occurence of secondary generalization were noted in all patients. Histopathologically all patients had mesial temporal sclerosis.

Results: Mean duration of follow-up of all patients was 3.5 years (range 2–7). Twenty one of the 30 patients had a good outcome (12 right, 9 left). All 30 patients has complex partial seizures. Thirteen also had secondary generalized tonic-clonic seizures(seven with good, 6 with poor outcome). Epileptic auras were present in 10 patients with class I outcome and 4 patients with class 2–4 outcome. The auras described in patients with good outcome were deja vu (1), visual hallucination(1), abdominal(5), gustatory(1) and fear(3). The 4 patients with poor outcome had nonspecific light headedness. Thirteen of 21 patients with class 1

outcome had staring spells, 10 of whom had subtle oral-facial and hand automatisms. Nine patients had poor outcome and all had staring spells with prominent motor and/or vocal automatisms, such as grabbing, wandering, yelling, and stomping of feet.

Conclusions: Specific auras like deja vu, visual hallucinations, abdominal aura, gustatory aura and fear are associated with good outcome, while nonspecific auras, such as lightheadedness, are associated with poor outcome. Presence of prominent motor and/or vocal automatisms is associated with poor outcome. Occurence of secondarily generalized seizures do not influence outcome. In addition to advanced localizing techniques, semiology may provide valuable information in predicting outcome after epilepsy surgery.

1.421
WADA'S TESTING IS NOT RELEVANT AS PART OF THE PREOPERATIVE WORKUP IN PATIENTS WITH TEMPORAL LOBE EPILEPSY ASSOCIATED WITH MESIAL TEMPORAL SCLEROSIS

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Rationale: The Wada's test (also known as the intracarotid amytal test) had been considered a key test in the preoperative work of patients with refractory epilepsy in many centers; it has been considered a good predictive factor for postoperative memory loss. More recently, after taking into consideration practical and technical aspects, many authors have discussed the actual usefulness of the test. As a result, this test is currently used only in very selected patients in many centers. This paper reports on the clinical results of patients who were submitted to cortico-amygadalo-hippocampectomy for refractory epilepsy associated to mesial temporal sclerosis without Wada's testing.

Methods: One hundred patients with refractory temporal lobe epilepsy and MR-defined mesial temporal sclerosis who were submitted to CAH were studied. They had unilateral (66%) or bilateral (34%) interictal EEG discharges. All patients were submitted to CAH at the MR's lesion side.

Results: Eighty-seven percent of the patients have been seizure-free after surgery. Forty-six percent of the patients presented improvement in memory scores postoperatively. Two patients submitted to surgery on the dominant temporal lobe presented transitory worsening of verbal memory. These two patients presented with venous infarction on the posterior border of the CAH's cortical resection which was very likely the cause of the verbal memory decline. Symptoms remitted afterwards and were not related to hippocampectomy itself.

Conclusions: Cognitive outcome, especially regarding memory, has always been a concern in temporal lobe epilepsy surgery. Patients with mesial temporal sclerosis submitted to CAH usually get improvement (and not loss) of memory function. Wada's testing has no important role in the preoperative assessment of these patients. (Supported by Sao Paulo's Secretary of Health.)

1.422
INTERICTAL SPIKE FREQUENCY PREDICTS SURGICAL OUTCOME IN MESIAL TEMPORAL LOBE EPILEPSY

Christoph Baumgartner, Krendl Reinhard, and Lurger Stefanie (Department of Clinical Epilepsy Research, Medical University of Vienna, Vienna, Austria)

Rationale: To investigate whether the absolute interictal spike frequency is of prognostic significance for postoperative outcome in patients with medically refractory mesial temporal lobe epilepsy (MTLE).

Methods: We retrospectively studied 55 patients with medically refractory MTLE. All patients were evaluated with prolonged scalp video-EEG-monitoring including true anterior temporal and sphenoidal electrodes for an average of 5 days. EEG samples of 5 minutes were automatically stored every hour during the monitoring. Patients were classified according to their absolute interictal spike frequency, either in Group I ($\geq$60 spikes/h) or in Group II ($<$60 spikes/h) and according to the relative spike distribution in a unitemporal and a bitemporal group ($\geq$90% respectively $<$90% of spikes over the affected temporal lobe). All patients underwent first time epilepsy surgery, either selective amygdalo-hippocampectomy (47 patients) or anterior medial temporal resection (6 patients). In 2 patients a more extensive anterior temporal resection was performed. Postoperative follow-up was at least 12 months.

Results: The frequent spikes group ($\geq$60 spikes/h) comprised 14 patients, the non-frequent spikes group ($<$60 spikes/h) 41 patients, the unitemporal group 35 patients and the bitemporal group 20 patients. We found that the occurrence of frequent spikes during presurgical prolonged EEG-monitoring was significantly associated with unsatisfactory surgical outcome as compared to the occurence of infrequent spikes ($p = 0.001$ for 1 year postoperative outcome; $p = 0.011$ for 2 years postoperative outcome). The outcome was non-significantly different between the unitemporal and bitemporal group ($p = 0.282$ for 1 year postoperative outcome; $p = 0.208$ for 2 years postoperative outcome

Conclusions: We conclude that the absolute interictal spike frequency is of prognostic significance for postoperative outcome in patients with medically refractory temporal lobe epilepsy.

1.423
VANDERBILT EXPERIENCE OF SELECTIVE AMYDALOHIPPOCAMPECTOMY SURGERY IN PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: More and more centers are now exploring techniques to minimize the invasiveness of the evaluation and surgical treatment of medically refractory temporal lobe epilepsy. Video-EEG monitoring, SPECT scanning, PET and MEG has greatly improved this process. At Vanderbilt University Medical Center, selective amygdalo-hippocampectomy (SAH) has been used as a less invasive alternative to a standard temporal lobectomy and involves resection of the amygdala, hippocampus and the para-hippocampal gyrus.

Although a $\geq$5 Hz ictal pattern has been associated with ipsilateral mesial temporal lobe seizure, we sought to show that a $<$ 5 Hz ictal onset pattern within 30 seconds of seizure onset in patients with non-lesional mesial temporal lobe epilepsy who undergo SAH resection also have a good outcome. We compared seizure reduction rates following SAH in patients with rhythmic theta and those with non-theta ictal onset patterns.

Methods: 28/40 patients who underwent SAH between Dec1999 and Oct 2003 at VUMC had complete medical records and were used for analysis. All patients had mesial temporal sclerosis or normal MRI. All patients had a minimum of 3 seizures recorded during EEG monitoring. We classified scalp-sphenoidal ictal EEG patterns into 2 groups: type 1 ictal patterns included a progressive buildup of a regular $\geq$5 Hz rhythm in the temporal electrodes within 30 seconds of seizure onset; type 2 ictal patterns had a frequency $<$ 5 Hz until the termination of the seizure. Patients were classified into 3 groups:

> Group 1: All seizures were associated with a regular $\geq$5 Hz lateralized rhythmic discharge on scalp EEG.
> Group 2: Some, but not all seizures were associated with a regular $\geq$5 Hz lateralized rhythmic discharge.
> Group 3: None of the seizures were associated with a regular $\geq$5 Hz lateralized rhythmic discharge.

Results: Twenty-one patients were classified into group 1, three patients in group 2 and four patients in group 3. Epilepsy surgery outcomes were classified according to Engel's Classification of Postoperative Outcome (1). Median time at followup for evaluation of seizure control post-operatively was 17.7 months (Range of 1.5–37 months).

In group 1, 17 patients had an Engel's Class I outcome, 3 patients had a Class II outcome and 1 patient had a Class III outcome.

In group 2, 2 patients had an Engel's Class I outcome and 1 patient had a Class IV outcome.

In group 3, 3 patients had an Engel's Class I outcome and 1 patient had a Class II outcome.

Conclusions: Patients with ictal pattern of ≥5Hz, regular, rhythmic lateralized discharges on scalp EEG patterns had excellent seizure control after selective amygdalo-hippocampectomy. However most patients with types II and a mixture of type I and II ictal EEG patterns whose presurgical workup was consistent with a mesial temporal focus also had good seizure control rates post-operatively.

1.424
EPILEPSY SURGERY IN ELDERLY PATIENTS

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Rationale: Elderly patients over account for about 25% of newly diagnosed epileptic seizures. Nevertheless, the proportion of older patients undergoing long term video-EEG monitoring is low and the percentage of epilepsy surgery in this particular subgroup is even lower. As a consequence, literature concerning the surgical treatment of focal epilepsies in elderly patients is sparse.

Methods: In this study the data of 37 patients (31 with mesial temporal lobe epilepsy and 6 with extra-temporal epilepsy) who underwent epilepsy surgery after the age of 50 has retrospectively been evaluated for (a) medical and social issues at the time of surgery and (b) the outcome two years after operation.

Results: At the time of presurgical evaluation, the mean age was 55 (range: 50–67), mean duration of epilepsy was 34 (range: 1–59). Seventeen patients were still in employment, 11 were retired, 1 was unemployed, 7 were housewives. Seventeen patients (46%) had vascular risk factors, e.g. arterial hypertension, intra- and/or extracranial arteriosclerosis, hypercholesterolemia, one had COPD.

Seven patients (19%) had only minor predictable surgery-related deficits (e.g. discrete upper-square scotomas or moderate contralateral sensory deficits) that did not lead to significant impairment of daily activity, and 23 patients (62%) had no deficits at all. Four patients (11%) developed perioperative cerebral infarctions and two patients (5%) suffered major psychiatric alterations after the operation (one patient committed suicide).

Two years after surgery the data of 33 patients showed that 32 of these patients had benefited from the operation (Engel class I-III) and 42% (n = 14/33) were seizure free (Engel class Ia+Ib). The number of seizure-free patients was higher after anterior temporal lobectomy (46%; n = 13/28) compared to the extra-temporal group (20%; n = 1/5).

Conclusions: In the future, the increase in life expectancy and the resulting increase in numbers of patients suffering from refractory epilepsies will become a medical and economic challenge. Our study indicates that epilepsy surgery can benefit patients older than 50. However, due to the higher surgical risk, the risk-benefit ratio should be weighed carefully.

1.425
TEMPORAL LOBE CYST AND HIGROMA AS COMPLICATIONS AFTER CORTICOAMYGDALOHIPPOCAMPECTOMY FOR TREATMENT OF REFRACTORY TEMPORAL LOBE EPILEPSY

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Rationale: Cortico-amygdalo-hippocampectomy (CAH, including all technical variants) is the most commonly performed surgical procedure for treatment of refractory epilepsy. Complications might occur in 1% of the patients and include hemathoma and ischemic or venous infarcts, leading to variable neurologic morbidity or death. This paper reports on the occurrence of higroma and temporal lobe cyst after CAH. This association has not been reported previously in the literature and occurred once in more then 400 CAHs performed in our center.

Methods: A 21-years old man with refractory temporal lobe epilepsy related to MR documented left mesial temporal sclerosis was studied. He has had febrile seizures during infancy. He had refractory epigastric simple and complex partial seizures with bimanual automatisms. There was no history of brain infection or any other specific event. He was submitted to CAH; the procedure was uneventful.

Results: The patient has been seizure's-free since surgery. Three weeks after CAH, he presented with grade-IV hemiparesis. CT showed a volumous anterior temporal lobe cyst and temporo-parietal higroma; he was submitted to higroma-peritoneal shunting, with the disappearance of hemiparesis. One month afterwards, hemiparesis reappeared. TC showed disappearance of higroma and increase in the size of the anterior temporal lobe cyst. He was submitted to surgical degloving of the cyst and ample communication with the basal cisterns was created. He has been asymptomatic since the latter.

Conclusions: Postoperative cerebrospinal fluid dynamics disturbances are rare after CAH. Treatment might include shunting (when higroma is present) or degloving (when an isolated cyst is present), or both. (Supported by Sao Paulo's Secretary of Health.)

1.426
RACE AND TEMPORAL LOBE SURGERY OUTCOME

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Rationale: The success of epilepsy surgery in mesial temporal lobe epilepsy due to hippocampal sclerosis (MTS) reaches a 60% rate of success, based on a randomized control trial. Observational studies from different epilepsy centers worldwide indicate up to a 93% rate of success. Several risk factors are attributed to the recurrence of seizures following the surgical procedure. Nonetheless whether race influences the outcome of temporal lobe surgery is unknown. The purpose of the study was to evaluate if race plays a role in outcome following surgery.

Methods: Data was obtained from the discharge database of the University of Alabama at Birmingham, video-EEG monitoring unit, between 1998 and 2003, and the clinical charts. Seizure recurrence was evaluated 1 year following surgery. The sample consisted of all patients discharged with a primary diagnosis of MTS who underwent an anterior temporal lobectomy. Multiple logistic regression analysis was used to model the presence of seizure recurrence after anterior temporal lobectomy for MTS. Two sets of logistic regression models were estimated to generate odds ratios (ORs) for seizure recurrence after an anterior temporal lobectomy for African Americans or other possible ethnic/racial group present relative to Non-hispanic Caucasians. The first model incorporated only ethnicity as the independent variable and generated unadjusted odds ratios for receiving the surgical procedure. The second set included the independent variables: duration of epilepsy, history of febrile seizures, lateralization of epileptogenic focus, handedness, and age.

Results: Of a total of 432 patients diagnosed with TLE, 130 had evidence of MTS on MRI studies. Seventy patients underwent surgical treatment and all of them had pathologic confirmation of mesial temporal sclerosis. Clinical information in five of them was incomplete. Analysis of the remaining 65 patients revealed that African-Americans were more likely than non-hispanic whites to have seizure recurrence after surgery (Odds Ratio = 2.2, 95%CI: 0.6–8.2), even though this finding was not statistically significant. After potential clinical confounders (duration of epilepsy, history of febrile seizures, lateralization of epileptogenic focus, handedness, and age) were controlled, the significance of this finding did not change (Odds Ratio = 1.3, 95%CI: 0.2–8.7).

Conclusions: Our data suggest that race does not appear to be an important factor related to seizure outcome.

1.427
INVOLVEMENT OF THE INSULAR CORTEX DURING TEMPORAL LOBE SEIZURES: INTRACRANIAL RECORDINGS IN 19 PATIENTS

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Rationale: To clarify the specific role of the insular cortex and to study ictal electroclinical patterns within temporolimbic networks during seizures involving the temporal lobe, using intracranial recordings.

Methods: We analysed stereoelectroencephalographic (SEEG) recordings of the insular cortex and of temporo-perisylvian regions in 19 patients suffering from drug-resistant partial epilepsies involving at least the temporal lobe. All SEEG investigations were individually designed according to previously acquired electroclinical and MRI data. The insular cortex was recorded because of evidence of an early perisylvian involvement or rapid extratemporal diffusion. The insular electrode was inserted with the help of a computer-driven robot using an oblique trajectory avoiding the sylvian fissure, in order to reduce the risks of bleeding and to try to improve the spatial sampling of the insular cortex along antero-posterior and dorso-ventral axis.

Results: In a first and most important group of 10 patients, we have highlighted an anteromesio-polo-insular pattern, corresponding to the spread of mesiotemporal discharges towards the insula, via the temporal pole and the amygdala. These patients were successfully treated by temporal resections sparing the insula, wether or not they had insular interictal discharges. In a second group ($n = 4$), the insula belonged to the seizures onset zone ($n = 2$) or was affected by prominent interictal discharges asynchronous from temporal interictal discharges. Among these 4 patients, 2 were operated-on with a poor post-operative outcome resulting from a temporal lobe surgery. In the 5 remaining patients, the seizures affected mainly mesial, lateral and posterior temporal regions, whereas the insular cortex was belatedly and/or slightly involved.

Conclusions: Our findings suggest that the insular cortex seems to constitute a major relay of mesiotemporal lobe discharges, presumably via the spreading through the amygdala and the temporal pole. In order to avoid failure of the surgery, intracranial recordings remain sometimes necessary to exclude insular onset during temporolimbic seizures including an early perisylvian involvement or rapid extratemporal spreading. Depth recordings of the insular cortex through an oblique trajectory seems to be safe and useful in term of spatial sampling.

1.428

RETROSPECTIVE ANALYSIS OF EPILEPSY SURGERY OUTCOME CORRELATING MRI AND HIPPOCAMPAL HISTOPATHOLOGY

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Rationale: To investigate if hippocampal histopathology can be predictive of epilepsy surgery outcome when correlated with presurgical MRI findings.

Methods: The surgical outcomes of 40 adults (ages 17–57) with refractory mesial temporal epilepsy were retrspectively analyzed and correlated with presurgical high resolution MRI of the temporal lobes and surgical histopathology specimens. All patients underwent resection of the hippocampus and amygdala between 11/96 and 1/03. Patients with lesions such as tumors, vascular malformations or dysplasias were not included. Post-surgical follow-up times ranged from 1 to 8 years (mean 4.9 years). 24 were female and 16 were male.

Results: 10/40 (75%) of patients are currently seizure free or have simple partial seizures. 34/40 (85%) had clear mesial temporal sclerosis (MTS) on high resolution MRI scan with 12/40 having right MTS and 28 having left MTS. 38/40 (95%) had gliosis and mild to severe neuronal loss in the hippocampus on histopathology. 2/40 did not have pathology results available. Of the 6 patients who had normal MRI scans, 3 continued to have refractory complex partial or convulsive seizures, 1 has rare complex partial seizures and 2 are seizure free. Of the 10 patients who continued to have seizures after surgery, 3 had normal MRI scans, and 5 had histopathology consistent with only "mild" gliosis. In the other 5 patients the histopathology results were not graded.

Conclusions: Although gliosis and neuronal loss in the hippocampus on histopathology does not guarantee seizure freedom after epilepsy surgery, the combination of hippocampal sclerosis on MRI plus hippocampal gliosis and neuronal loss on histopathology appear to be excellent predictive factors of post-surgical seizure freedom. In contrast, normal MRI findings and only minimal pathologic changes suggest a poor surgical outcome.

1.429

OBSESSIVE-COMPULSIVE DISORDER POST TEMPORAL LOBECTOMY: CASE REPORT

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Rationale: The present study aims to report and discuss development of obsessive-compulsive diorder (OCD) in a patient with temporal lopbe epilepsy and right mesial temporal sclerosis following temporal lobectomy with seizure remission.

Methods: Case Report.

Results: JAC, 47 years, caucasian, catholic, antecedant of two non-febrile seizures at age two years, onset of epilepsy at age seven years, with seizures carachterized by "icy feeling" of both leggs with upper abdominal progression, followed by leg weakness, fear, loss of contact, motor automatisms and secondary generalization. EEG, MRI and SPECT disclosed right mesial temporal sclerosis. Neuropsychological evaluation showed lower efficiency of visual functions as compared to verbal. There was no history of psychiatric disorders. In july 2003 an anterior temporal lobectomy was performed because of refractory epilepsy. The patient coursed without neurologic complications and with seizure remission. However, two weks later, she presented obsessive religious thoughts of negative content such as ofensive swearing directed to religious icons, followed by compulsive behavior carachterized by repetiteve head movements carried out to alleviate or shun these disagreable thoughts.

Conclusions: Worsening of previous psychiatric disorders as well as development od de novo diorders may occur after epilepsy surgery. Mostly, depression, psychosis and suicide attempts have been reported. OCD may occur associated with epilepsy with reports of improvement after epilepsy surgery. However, development of this disorder in patients without previous psychiatric diagnoses, following anterior temporal lobe resection is rare, and to our knowledge only two such cases had been published before.

1.430

PATIENTS' RESPONSE TO THE PROPOSAL OF EPILEPSY SURGERY

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Rationale: Physicians are usually blamed on the underutilization of epilepsy surgery. Other potential causes that could explain the low number of referrals to surgery appear to have received little attention, or to be considered less important. In a study done at seven surgical centers in the USA, only 14,3% of the eligible patients withdrew from the presurgical evaluation that had been offered to them (Epilepsia 2003; 44:1425–33). Data from hospitals lacking epilepsy surgery facilities seem to be very scarce, although this information could be very relevant.

Methods: We reviewed the records of all our patients who were proposed to undergo an evaluation for epilepsy surgery at another center. We assessed the degree of rejection to this treatment option, as well as the causes related to it. The study was done at the Neurology Department of the Hospital Xeral, a general hospital with a catchment population of 250,000 people located in Vigo (NW Spain). Only patients aged 15 or more years have access to our Department.

Results: A total of 39 patients were collected. In three cases the request for surgery came from the patients themselves and, therefore, they were excluded from this analysis. The mean age of the remaining 36 patients, at the time of the proposal, was 36,8 years (range: 15–60). There were 14 men and 22 women. Their diagnoses were: temporal lobe epilepsy in 25 (associated with hyppocampal atrophy in 13, cryptogenic or idiopathic in 8, due to benign tumors in 3, and secondary to a cavernoma in 1), non-lesional extratemporal epilepsy in 6, cortical dysplasia in 2, and cryptogenic Lennox-Gastaut syndrome with frequent drop-attacks, Rasmussen encefalitis, and parietal lobe cavernoma (1 each). Only nine (25%) out of these 36 patients accepted the proposal when first done, while another seven patients (19,4%) accepted only after repeated offers. The remaining 20 patients (55,5%) have rejected the possibility of surgical treatment, in spite of new explanations and proposals (up to seven). Most of them expressed a great concern about the potential negative consequences of brain surgery.

Conclusions: In our setting, the main reason for the underuse of epilepsy surgery was the high degree of rejection (more than 50%) showed by our patients to this type of treatment. It would be interesting to know if this attitude is also common in other general hospitals without epilepsy surgery programs. In this case, campaigns directed to patients with refractory epilepsy to make them more familial with this therapeutic option might improve their degree of acceptance to it.

1.431
LONG-TERM MEDICAL REMISSION AFTER INITIAL SURGICAL FAILURE

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Rationale: We observed a number of patients becoming seizure-free with medication changes after they appeared to have failed epilepsy surgery. It is not known if seizures become more responsive to antiepileptic drugs (AEDs) after surgical failure.

Methods: We encountered nine patients with persistent refractory seizures following epilepsy surgery, who subsequently became seizure-free with medication changes. We reviewed their medical records and recorded clinical data including seizure localization, type of epilepsy surgery, and interval between surgery and eventual remission. We also recorded the medication changes that eventually rendered patients seizure free. We noted whether the last medications added were previously failed before surgery.

Results: All nine patients had temporal lobe epilepsy. Three underwent right and six left temporal lobectomy. Seizures persisted for 2–6 years after surgery, before remission was achieved. Two patients had previously failed AEDs that later controlled the seizures- these AEDs were felbamate and levetiracetam. Among the remaining seven patients, two became seizure free after introducing lamotrogine, two after levetiracetam, two after tiagabine, and one after oxcarbazepine.

Conclusions: Surgical failure can occasionally be reversed with AED changes. In some instances AEDs previously failed become effective postoperatively, suggesting a change in seizure responsiveness in some patients who appear to have derived no benefit from surgery.

1.432
SURGICAL OUTCOME OF MRI-NEGATIVE PATIENTS IN TEMPORAL LOBE EPILEPSY EVALUATED WITH INTRACRANIAL INVASIVE MONITORING

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Rationale: The aim of the study was to assess the surgical outcome with those MRI- negative temporal lobe epilepsy patients who underwent preoperative evaluation with invasive intracranial electrodes.

Methods: Since 1988 Kuopio University Hospital has served as a national center for adult epilepsy surgery in Finland (population 5.3 million). From January 1990 to October 2003 altogether 132 patients with medically refractory epilepsy has been evaluated with intracranial EEG monitoring, and 120 of them had suspected temporal lobe epilepsy. Of the 120 patients, 60 had normal MRI findings and 39 of them were operated determined by the results of invasive monitoring. The surgical outcome in these 39 patients was assessed according to Engel's classification at one year postoperative follow-up. The reasons for not to proceed to operative treatment was analysed among those 21 patients who were considered inoperable.

Results: Twelve patients (30.8%) were seizure free at 1- year follow-up (Engel's class I) and three patients (7.7%) had rare seizures (Engel's class II). Nine patients (23.1%) had worthwhile improvement (Engel's class III) and fifteen patients (38.5%) did not benefit from the surgery (Engel's class IV). Of those 21 inoperable patients, 7 patients (33.3%) had inadequately localised extratemporal onset of the seizures and 5 patients (23.8%) had bitemporal onset of the seizures. Two patients (9.5%) had seizure onset near Wernicke's area and with two patients (9.5%) the frontotemporal differential diagnostics was not possible to demonstrate. The other five patients (23.9%) did not either get seizures during monitoring, were seizure free after registration or had generalised epilepsy.

Conclusions: It is possible to achieve satisfactory surgical outcome with this diagnostically challenging subgroup of MRI negative patients with temporal lobe epilepsy who underwent intracranial monitoring. On the other hand, with those patients who did not benefit from surgical treatment, the predicting factors for outcome need to be further analysed. [Supported by Academy of Finland, the North-Savo Regional Fund of the Finnish Cultural Foundation, the Kuopio University Hospital Research Fund (EVO Fund 577 27 19), the University of Kuopio and the Vaajasalo Foundation.]

1.433
OUTCOME OF RESECTIVE EPILEPSY SURGERY IN ADULT PATIENTS WITH LOW IQ

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Rationale: To analyze the postoperative outcome of resective epilepsy surgery among adult patients with low IQ.

Methods: In order to identify all operated adult patients with low IQ, we analyzed retrospectively all adult patients who had undergone resective epilepsy surgery at Kuopio University Hospital between 1988 and 2003. Altogether 255 resective procedures for 239 adults had been performed during the study period. For the purpose of the study low IQ was defined as preoperative full scale IQ (FSIQ) $\leq$ 70. A total of 206 patients (86%) had preoperative neuropsychological data available and 11 patients (five female, six male) with low IQ were identified (median FSIQ 67, range 43–70) among them. Additionally, one patient was included without formal preoperative neuropsychological evaluation.

Results: Mean age of the patients at the time of operation was 30$\pm$ 8 (range 16–46) years and mean duration of epilepsy was 25$\pm$ 9 (range 10–49) years. Median preoperative seizure frequency was 86 seizures (range 12–2646) per year. Probable etiologies for mental retardation were malformation of cortical development (n = 4), CNS-infection (n = 3), asphyxia (n = 1) and fragile-X (n = 1). In three patients no specific etiology was identified. Resective procedures included eight temporal resections (three selective amygdalohippocampectomies), two extratemporal resections, one multilobar resection, and one functional hemisferotomy. Three patients were reoperated. The operation was defined as curative in six patients and palliative in six patients. The mean postoperative follow up was 3.3$\pm$ 5.1 (range 1.0–6.1) years. 50% of the patients became seizure-free (Engel's class I, n = 6) and 25% had an 80% seizure reduction (Engel's class III, n = 3). 25% of the patients (n = 3) did not have significant postoperative seizure reduction. The outcome was expectedly better in curative patients and in patients with temporal lobe resections. Additionally, only one reoperation resulted in seizure reduction. Minor complications were identified in five patients.

Conclusions: Relatively few patients with low IQ were identified among the study population. However, resective surgery was found successful in most patients with low IQ, including the palliatively operated patients. [Supported by The Finnish Cultural Foundation, Finnish Medical Society Duodecim, Finnish Neurological Society, Kuopio University Hospital Research Fund (EVO grant 5178/5772719), University of Kuopio, and Vaajasalo Foundation.]

1.434
UNUSUAL FINDINGS IN BRAIN BIOPSIES OF THREE PATIENTS WITH ACUTE MRI LESIONS ASSOCIATED WITH FOCAL SEIZURES

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Rationale: Patients with focal seizures often have MRI abnormalities in the brain region of their presumed seizure focus. Neoplasms, vascular malformations, ischemic infarctions, hemorrhages, inflammatory processes, demyelinating diseases, and other specific pathologic entities have been diagnosed by biopsies of such MRI abnormalities. Three patients with this presentation had brain lesion biopsies with a leading presumptive diagnosis of glial neoplasm and were in contrast found to have indistinct histopathology.

Methods: Patient 1 was a 55yo man with new onset of right focal sensorimotor seizures corresponding with a left central region MRI lesion with high signal on T2 and mild enhancement. Patient 2 was a 38yo woman with a remote history of focal onset seizures and normal MRI, with seizure control for five years on antiepileptic medication before presenting with new onset of frequent left sensorimotor seizures. MRI showed a sharply defined increased T2 signal right parietal lesion with no definite gadolinium enhancement. Patient 3 was a 52yo right language-dominant man with new onset unprovoked seizure and an increased T2 signal throughout his right hippocampus and possible gadolinium enhancement in the anterior hippocampus. In each patient, preoperative clinical suspicion was for neoplasm or inflammatory process.

Results: Open biopsy two months after seizure onset in patient 1 revealed vascular abnormalities and other findings suggestive of subacute/chronic venous infarction. Several weeks after seizure onset, craniotomy in patient 2 and stereotactic needle biopsy in patient 3 revealed mild gliosis and perivascular hemosiderin deposition, not permitting a specific diagnosis. Postoperatively, patients 1 and 3 had normalization of their MRI and no further seizures, while Patient 2 has had some brief sensory seizures and has not yet had MRI.

Conclusions: We describe three patients who had brain biopsies of striking focal increased T2 signal MRI abnormalities associated with new onset seizures. Pathologic findings contradicted our preoperative suspicions. The findings in Patient 1 suggested venous infarction. Patients 2 and 3 had similar clinical and MRI findings. Pathologic findings were subtle but similar to patient 1 and also suggest the possibility of subacute venous infarctions. Our experience indicates that patients with new onset seizures may have an associated discrete intra-axial MRI lesion that is not a neoplasm. To our knowledge, this is the first report of focal seizure-associated MRI lesions with biopsy findings suggestive of venous infarction. Our experience does not allow us to determine if the MRI and tissue abnormalities preceded, or were caused by, the seizures.

1.435
OUTCOME OF EPILEPSY SURGERY IS NOT AFFECTED BY EPILEPSY DURATION

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Rationale: To determine the effect of epilepsy duration on seizure-freedom following resective epilepsy surgery.

Methods: A retrospective review of database information for patients treated with resective surgery between August of 1991 and 2001 in Milwaukee. General demographic information was reviewed including gender, age of seizure onset, age at time of surgery, epilepsy syndrome, and medications. Evaluative information including radiographic, neurophysiological, and neuropsychological data was included in this database. Outcome data at 6 months was compared for groups seizure-free or not with respect to the duration of their epilepsy prior their surgery. Pearson's chi- squared statistical analysis was used.

Results: We found complete data on 206 of 280 resections completed in Milwaukee from 1991 to 2001. Duration of epilepsy was 1–50 years (Mean = 20). Temporal lobe resections were most frequent (153) followed by frontal resections (27) and then miscellaneous procedures (36). Patient's were divided into two groups, seizure-free and not seizure-free at 6 months. Statistical analyses showed no relationship between duration of epilepsy and post-operative seizure status for the entire group or for the temporal lobe resection patients. Comparisons for the smaller surgical groups showed no trends but analyses were limited by small sample size. (Please see Table)

Conclusions: Seizure-freedom following epilepsy surgery is not influenced by epilepsy duration in our study. This finding supports use of epilepsy surgery independent of epilepsy duration.

1.436
PROPAGATION OF INTERICTAL DISCHARGES ON INTRAOPERATIVE ELECTROCORTICOGRAPHY DURING TEMPORAL LOBE EPILEPSY SURGERY

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Rationale: In most Epilepsy Surgery Centers that still utilizes ECoG during temporal lobe epilepsy (TLE) surgeries, the analysis are limited to incidence and amplitude of spikes. The study of propagation patterns to detect where spikes peak earlier (leading spikes) and to establish relationships between them (latencies) are rarely addressed. Detection of leading spikes (LS) can potentially better guide the resections and influence seizure outcome. This study addresses the correlations between basal and lateral spikes during ECoG of mesial TLE patients, searching for propagation patterns and LS.

Methods: We analyzed ECoG of 20 patients (8 males, 12 females, 21 to 59 years, median 39.3 years) with mesial TLE associated to unilateral hippocampal sclerosis (HS). The selection for surgery was based on multidisciplinary protocol including high-resolution MRI, Vídeo-EEG monitoring, neuropsychological, psychiatric and quality of life assessments. Pre-resection recordings were performed through subdural strips over the superior, middle and inferior temporal gyri, and strips under the temporal lobe directed towards the entorhinal córtex. Each recording lasted 10 minutes, at sampling rate of 1,000 Hz, and band-pass filtering of 0.3–300 Hz. ECoG were visually analyzed and interpeak latencies observed in 200 ms samples, exclusively between electrodes located more than 1 cm apart, in order to avoid volume conduction. LS were defined as spikes with earlier peaking, and principal leading spikes (PLE) as the ones that peaked earlier in the majority of the samples.

Results: Seven patients had right and 13 left HS. The following ECoG patterns were observed: 1) restricted basal spikes: 6/20 (30%) of patients; 2) mesial to lateral spread: 3/20 (15%) of patients; 3) restrocted neocortical spikes: 10/20 (50%) of patients; 4) lateral to mesial spread: 1/20 (5%) of patients. Multiple LSs were found in all patients. LSs were equally

Epilepsy Duration Prior to Resective Surgery Surgery Type	Seizure-free	Not Seizure-free
All Surgeries	21 years (N = 139)	22 years (N = 67)
Temporal Lobectomy	22.5 (N = 113)	19.25 (N = 40)
Left Temp Lobe	24 (N = 58)	22 (N = 18)
Right Temp Lobe	21 (N = 55)	17 (N = 22)

p> 0.747 for each comparison.

located in the basal in 10/20 (50%), and in the neocortex in 10/20 (50%) of the patients, over the superior (5/20), middle (2/20) and inferior temporal gyrus (3/20 patients).

Conclusions: Our data suggest that even homogeneous focal epilepsy syndromes can have electrophysiological heterogeneity and different patterns of spikes propagation on ECoG. There were multiples LS in half of the patients, and restricted spikes to basal temporal structures in only few patients. Despite the limitations of subdural recordings these observations suggest that even in this focal epilepsies epileptogenicity within the temporal lobe can be multifocal. (Supported by FAPESP, CNPq.)

1.437

PERISYLVIAN POLYMICROGYRIA AS A SURGICALLY REMEDIABLE EPILEPSY SYNDROME: PARTIAL LESION RESECTION CAN ACHIEVE HIGHLY FAVORABLE RESULTS

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Rationale: Polymicrogyria often affects the perisylvian regions uni or bilaterally, and may lead to refractory partial seizures. Resective surgical approaches are usually not considered due to involvement of eloquent cortex by the malformation. We report two adult patients with disbling partial epilepsy associated with unilateral perisylvian polymicrogyria, in whom partial lesion resection led to significant seizure control.

Methods: Two women, 28 and 51 years-old, respectively, with disabling, daily, complex and motor partial and secondarily generalized seizures for more than 20 years, underwent a noninvasive presurgical protocol. MRI showed extensive unilateral perisylvian polymicrogyria in the right hemisphere, involving portions of the insula, as well as of the temporal and frontal lobe. Ictal and interictal EEGs localized the abnormalities to the lesioned hemisphere. The younger patient had a mild contralateral hemiparesis. Resective surgery was guided by acute EcoG and cortical stimulation.

Results: Acute ECoG showed a massive predominance of interictal discharges in the temporal lobe in one, and in the temporal lobe and the inferior portion of the suprasylvian region in the other. A resection of the polymicrogyric cortex involving the temporal lobe, including the depths of the first temporal gyrus, was performed in both patients. The younger patient had, in addition, subpial resection of the inferior third of the pre and post-central gyrus and of the lateral opercular frontal cortex. After 18 months of follow up, the younger patient has only occasional simple partial motor seizures involving the left hand, and the older one has only auras, without disconnection from the environment.

Conclusions: Resection of the most epileptogenic portions of large perysilvian polymicrogyric lesions can lead to significant seizure control without surgical complications.

1.438

EPILEPSY SURGERY FOR REFRACTORY STATUS EPILEPTICUS IN ADULTS

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Rationale: Convulsive status epilepticus (SE) represents a major neurologic emergency, associated with high mortality and morbidity. There are patients who continue to seize despite prompt diagnosis and medical treatment, including barbiturate or general anesthesia coma. This refractory SE may resurface during weaning from this intensive treatment. In this case the physician is left with few options, including resubmit the patient to pharmacological deeper coma. An alternative is neurosurgical intervention with resection of the epileptic focus, although very few cases have been reported so far in the adult population.

Methods: We reviewed our adult epilepsy surgery database to detect all cases with refractory SE within the last 3 years. Inclusion criteria were a) partial or secondary generalized SE, b) inability of successful weaning from barbiturate coma in the intensive care unit (ICU), c) craniotomy for epileptic focus resection

Results: Out of 85 patients, who underwent epilepsy surgery, we identified 3 patients with partial SE or epilepsia partialis continua. All patients were continuously monitored with Video-EEG in the Neuro-ICU and were given appropriate doses of anti-epileptic medications for a period of 7 to 51 days, including barbiturate burst suppression of 30 to 190 seconds. All patients had history of refractory epilepsy. One patient had a history of left temporal resection for Rasmussen's encephalitis, another resection of a multicystic astrocytoma and another encephalitis of unspecified etiology. Repeat MRI studies in the first and second patient showed focal lesions and in the third generalized atrophy. Invasive monitoring with grid placement for better localization was done in the first and intraoperative mapping and corticography in the other two patients. Neurosurgical procedures included left frontal topectomies, left frontal lobectomy and right anterior temporal lobectomy. Pathology revealed findings consistent with Rasmussen' s encephalitis, recurrent glioma and gliosis, respectively. Postoperatively, all patients were successfully weaned from the barbiturate coma and extubated. The first two patients developed contralateral hemiparesis and underwent inpatient and outpatient rehabilitation. On last follow-up, the first patient continued having focal motor seizures with considerably less frequency than prior to surgery, the second patient has been seizure-free for the last 6 months with reduced anticonvulsant medications, and the third patient experienced infrequent complex partial seizures postoperatively, but became seizure-free 2 months after surgery with medication adjustment.

Conclusions: Our results suggest that resective surgery may be an effective treatment for intractable SE and should be considered in any patient with electrographic and/or neuroimaging demonstration of focal seizure onset.

1.439

ANTICONVULSIVE EFFECTS OF LEVETIRACETAM IN PHARMACORESISTANT PARTIAL SEIZURES: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TISA TRIAL

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Rationale: Since 2000, a new objective and quantitative method in clinical seizure analysis was intriduced, which is called TISA (therapeutic intensive seizure analysis) (Stefan et al 2000). In supplement to the traditional seizure frequency, it introduces a new concept on the quantitative seizure severity D/24h, which represents the total duration of seizures per 24h within continuous video-EEG monitoring for the study phases.

Methods: 24 patients with pharmacoresistant partial seizures who entered presurgical evaluation with conti nuous video-EEG monitoring in the center of epilepsy, Erlangen were enrolled in this study. The whole study phase was devided into a 48h baseline phase followed by a maximal 7-day treatment phase, which was unter continuous day-and-night video-EEG monitoring. After strict screening according to the inclusion criteria concerning age, diagnose, physical condition and complete information exchanges, eligible patients with maximal one AED stepped into the 48h basaeline phase. After at least two seizures with video-EEG evidence during the baseline phase these patients were randomized into the treatment phase receiving either verum or placebo. The daily dose of levetiracetam was 1000 mg (500 mg bid.) for the first treatment day, which was titrated to 2000 mg (100 mg bid.) from the second day on. The number and duration of seizures were exactly recorded based on the video-EEG and the duration of seizures per 24h (D/24h) were calculated. Uncover of the blindness was not done until the accomplishment of all planned patients.

Results: The blinded interim analysis showed

1) in 36% of patients complete seizure control
2) in 27% of patients more than 50% decrease of D/24h (avarage 75%),
3) increase of d/24h was observed in 24%.

The final unblinded results will be presented.

Conclusions: In this study the anticonvulsive effect of levetiracetam was evaluated as add-on therapy in pharmacoresistant focal epilepsies. The time window from the first drug dosage to the appearance of the clinical observable effects were analyzed.

1.440
TEMPORAL LOBECTOMY AFTER AGE 50
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Rationale: Temporal lobectomy is a well-established treatment for patients with intractable epilepsy. Most temporal lobectomy series comprise patients in their third and fourth decades, with very few studies focusing on patients age 50 or older. This study was undertaken to analyze the surgical outcomes and complications in this patient population.

Methods: We reviewed our surgical database and identified patients who underwent epilepsy surgery after the age of 50 at our center (University of South Florida and Tampa General Hospital) from 2000–2002. Only patients undergoing temporal lobectomy were included in the study. All patients were evaluated by an epileptologist. After a typical presurgical evaluation (EEG-video, MRI, PET or SPECT, neuropsychological testing, and Wada testing), patients underwent anterior temporal lobectomies by a single surgeon (FLV).

Results: A total of 66 temporal lobectomies were performed over the 3-year period. Of those, 20 (30%) were 50 or older, including 3 (5%) who were 60 or older.

The average age at surgery was 53.3 years, while the average duration of epilepsy was 29.5 years. 75% of the population had MRI evidence of mesial temporal sclerosis, and 15% a normal MRI. The mean follow up was 24 months. 85% achieved class I outcomes, 10% achieved class II outcomes, and 5% achieved class III. Of the patients with MRI findings of mesial temporal sclerosis, 92% had a class I outcome.

The surgical complication rate was 10%, representing two patients. One patient (with a history of diabetes and obesity) suffered a lacunar stroke in the perioperative period. The other complication was a chronic subdural hematoma at 10 weeks postoperatively in a patient with a history of alcohol abuse, which required evacuation but did not result in any neurologic sequelae.

Conclusions: Anterior temporal lobectomy is a safe and effective treatment after the age of 50. Results appear similar than in younger patients.

1.441
SAFETY AND TOLERABILITY OF DEEP BRAIN STIMULATION OF MAMMILLARY BODIES AND MAMMILLOTHALAMIC AREA IN PATIENTS WITH CHRONIC REFRACTORY EPILEPSY
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Rationale: Investigational studies established the pivotal role of mammillary bodies "MB" and mammillothalamic tracts "MTT" in mnemonic function integrity. In addition, other animal studies highlighted the noteworthy anticonvulsive effect achieved by lesioning the same structures. Here we document our preliminary experience pertaining to the safety and tolerability of bilateral deep brain stimulation of MB and MTT in patients with refractory epilepsy "RE".

Methods: Three males (41–43 years) with RE were enrolled in a prospective, randomized, double-blind study. Neither medication nor vagus nerve stimulation "VNS" were capable to achieve a satisfactory seizure control. VNS was turned off six weeks before electrodes implantation without changing the medication. At different phases of the study, EEG-video, PET-FDG scan and neuropsychological examinations (verbal and visual memory), were performed for all patients. During the pre-randomization period, after electrodes implantation and before randomization, several brief intermittent stimulation trials (maximal range 130 Hz, 200 μs, 0.3 to 3.5V) were performed for each target separately and unilaterally.

Results: Up to now, no transient or permanent related-surgery complications were recorded in any patient. No deterioration of the cardiovascular and respiratory parameters were identified. No impairment of verbal and visual mnemonic function was observed during or after the pre-randomization period. As our study still remains double-blinded, the outcomes upon seizures' frequency and severity are still pending evaluation. However, No seizures' aggravation was observed and all patients were satisfied after surgery.

Conclusions: Based on our early-stage experience, it seems that electrodes' implantation and intermittent brief electrical stimulations in MB and MTT are safe and well-tolerated in humans. These remarkable findings may encourage us to enroll more patients in this study. The potential anticonvulsive efficacy of this procedure will be analyzed at the end of the double-blind period. (Supported by Medtronic.)

1.442
FEATURES ASSOCIATED WITH THE PRESENCE OF DUAL PATHOLOGY IN PATIENTS EVALUATED FOR EPILEPSY SURGERY
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Rationale: Dual pathology is the coexistence of a potentially epileptogenic lesion and hippocampal sclerosis (HS) in a person with epilepsy. Better understanding of dual pathology may improve understanding of the pathogenesis of epilepsy and lead to better surgical treatment.

Methods: We compared features of epilepsy in all subjects with dual pathology (DP) and lesional epilepsy without HS (LES-noHS) enrolled in the Multicenter Study of Epilepsy Surgery Outcomes. Features of epilepsy and outcome following epilepsy surgery were assessed prospectively using standardized questionnaires. High quality cerebral MRI emphasizing mesial temporal structures was obtained following a uniform protocol. MRI was interpreted and coded by two blinded reviewers with good interobserver reliability. Volumetric studies not performed.

Results: 33 subjects had DP and 99 LES-noHS. DP was found in 4/29 subjects with developmental or migrational abnormalities, 4/31 with cerebral tumor, 1/21 with vascular malformation, 14/43 with focal encephalomalacia, and 11/16 with cerebral hemiatrophy (one DP and 7 LES-noHS subjects had multiple lesion types). Frequency of complex partial seizures ($p = .052$) or generalized tonic-clonic seizures ($p = .44$) in the three months prior to evaluation did not differ in DP and LES-noHS. Family history of epilepsy was uncommon in both groups. 13/33 DP and 5/98 LES-noHS subjects had experienced febrile convulsions ($p = .00000064$). Other unprovoked seizures prior to onset of epilepsy were rare in both groups. Mean age at first unprovoked seizure didn't differ in DP (13.1 yrs) and LES-noHS (16.3 yrs, $p = .25$). However, 11/33 with DP and 16/98 with LES-noHS had first unprovoked seizure prior to age 5 ($p = .038$). Mean duration of epilepsy was longer in DP (24.3 yrs) than in LES-noHS (18.1 yrs, $p = .014$). There was also a trend to longer intractable epilepsy in DP (13.7 yrs) than in LES-noHS (9.1 yrs, $p = .065$). Status epilepticus occurred in 11/31 DP and 15/98 LES-noHS subjects ($p = .013$). 24/33 DP subjects underwent epilepsy surgery. 15/24 (63%) were free of disabling seizures in the first two years following surgery.

Conclusions: Febrile convulsions, seizure onset prior to age 5, longer epilepsy duration, and status epilepticus are associated with the presence of HS in patients with potentially epileptogenic cerebral lesions. This suggests that both early cerebral insult and effects of seizures over time increase risk of HS in lesional epilepsy. [Supported by RO1 NS32375 (NIH-NINDS) and MINCEP® Epilepsy Care.]

Surgery—Pediatric

1.443
INTRACTABLE EPILEPSY IN SEVEN CHILDREN WITH EXTENDED CEREBAL VASCULAR LESIONS: EPILEPSY CHARACTERISTICS AND RESULTS OF SURGERY
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Rationale: Extensive hemispheric injury can occur as the result of vascular disease from a variety of causes. Most patients are classified as infantile hemiplegia, usually the result of a prenatal, birth or neonatal injury. Epilepsy may considerably increase disability. In hospital-based series approximately 30% appear to have recurrent seizures. The response to anticonvulsant drugs is variable; approximately 20% will prove to be drug-resistant.

Methods: We reviewed the data of 7 children with large cerebral vascular lesions, submitted to epilepsy surgery for intractable epilepsy related to a congenital vascular accident in 4; cardiac surgery in 2; viral myocarditis in one.

Results: All presented with mild to severe hemiparesis and intractable partial seizures, with secondary generalization in 2. Infantile spasms were the initial presentation in one. Epilepsy surgery consisted in simple evacuation of the porencephalic cyst or disconnection.

Three patients became seizure-free immediately after surgery and one after a second operation (left temporal lobectomy following a first operation for evacuation of the porencephalic cyst into the lateral ventricle). The sixth patient experienced 5 seizures within the year following surgery, to become seizure-free despite discontinuation of AEDs. The last patient showed considerable improvement but was not fully controlled and necessitated implantation of a VNS device. Follow-up varies from 12 months to 6 years.

Two children benefit from normal schooling, two are well integrated in professional education programs for adolescents with special needs and, one, with a previously catastrophic epilepsy shows considerable improvement n language acquisitions. Two previously retarded children showed no amelioration following surgery.

Conclusions: In children with drug resistant epilepsy, related to the presence of extended vascular lesions, surgery must be discussed, as an alternative treatment, early in the course of the disorder.

1.444
SEIZURE CONTROL AND DEVELOPMENTAL OUTCOME IN CHILDREN WITH STURGE-WEBER SYNDROME (SWS) TREATED WITH EPILEPSY SURGERY

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Rationale: To review seizure control and developmental outcome in children with SWS undergoing hemispherectomy or resective surgery for epilepsy.

Methods: Case note review of all cases with SWS undergoing hemispherectomy or resective surgery at a centre for paediatric epilepsy surgery in the UK.

Results: 10 children age 10m-17 years (median 24 months) underwent surgical treatment for epilepsy refractory to medical management. Presurgical evaluation was carried out according to protocols, including neurodevelopmental, neuropsychological and neuropsychiatric assessment, MRI, videotelemtry and in addition SPECT studies in those evaluated for resective surgery. Four infants had experienced an autistic pattern of regression in the context of severe seizure episodes prior to surgery. All children undergoing hemispherectomy had a marked hemiplegia.

Surgical treatment was functional hemispherectomy (6), lobar resection (2) and multilobar resection(2).

Median follow up was three years (7 months-10 years). Seizure frequency per month following surgery: 0 (5), <1/month (3) and >1/month (2). Number of anti-epileptic drugs (AEDs) at follow up 0 (2), 1(4), 2(4). AEDs were reducing in three cases.

Following hemispherectomy there was an increase in motor deficit (6). For the whole group, cognitive ability is within the normal range (2); Eight have developmental delay- moderate (3) severe (5). Seven have autistic features or autistic spectrum disorder. At follow up, sociability was reported as improved (5) and less good (2).

Conclusions: Surgical treatment of epilepsy in SWS can result in a marked improvement in seizure control. Early hemispherectomy may be important in reducing the likelihood of autistic regression in children. The timing of hemispherectomy may also influence the possibility of a neurological deficit emerging, especially in those without an established hemiplegia. [Supported by The Sturge-Weber Foundation (UK).]

1.445
EPILEPSY SURGERY IN CHILDREN WITH TUBEROUS SCLEROSIS COMPLEX

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Rationale: In patients with Tuberous Sclerosis Complex (TSC), 80–90% have seizures, many of which are difficult to control. For some, surgery is a treatment option. Due to multi-focality in most of these children, becoming seizure free is not an expectation for most. Children are thought to be good surgical candidates if there is an expectation of a reduction in seizure frequency and severity, and improvement in functioning. This expectation is based on the fact that their EEGs show a focal area being responsible for the majority of their seizures.

Methods: Charts were reviewed on TSC patients who had EEG/video monitoring between Jan 1995 and Jan 2004. Patients who were thought to be surgical candidates based upon results from EEG/video monitoring had been presented at the Epilepsy Surgery conference. Other factors taken into consideration included patient/parental desire for surgery, psychiatric and behavioral issues.

Results: Records of 65 patients were reviewed. After presentation at the multidisciplinary Epilepsy Surgery conference, 12 patients (18 percent) were thought to be good surgical candidates. In five of these patients, a focal resection was recommended and in the remaining seven patients, Phase II monitoring was recommended. Six of the Phase II patients had subsequent focal resections, and one did not because his seizures could not be well localized. Two of these patients had a hemispherectomy.

Follow-up ranged from six months to nine years. In the six patients with at least one year follow-up, three were seizure free (Engel Class I) and one each were in Class II, III, IV.

Conclusions: In patients with Tuberous Sclerosis Complex and intractable seizures, surgery should be considered an option in their treatment plan.

1.446
ENDOSCOPIC CORPUS CALLOSOTOMY: CADAVERIC AND PORCINE STUDIES

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Rationale: Corpus callosotomy is a highly effective surgical procedure for epilepsy but has become less utilized due to morbidity that is largely attributable to the approach. Advances in neuroendoscopy have allowed significant progress in reducing invasiveness of neurosurgical intervention while maintaining effectiveness. We have developed a new technique utilizing a brow incision with supraorbital trephination that allows introduction of an endoscope in the interhemispheric fissure and report here the effectiveness of endoscopic corpus callosotomy in a cadaveric and porcine model. This approach bypasses the conventional para sagittal approach and its attendant morbidity.

Methods: *Part 1*: 6 human cadaveric heads were secured in pins. A left midpupillary incision was made with medial retraction of the skin. A paramedian burr hole was made and a rigid endoscope inserted just lateral to the midline. The falx cerebri was followed until the genu of the corpus callosum was seen. The callosum was sectioned under endoscopic visualization. Brains were harvested and examined.

Part 2: 5 male pigs were anesthetized and placed in the supine position with the head elevated 45 degrees. After a 1 cm midline skin incision a.5cm diameter hole was made. The rigid endoscope was inserted and advanced until the corpus callosum was visualized. The callosum was sectioned, animals euthanized and brains examined.

Results: *Part 1*: All cadaveric transections of the corpus callosum were complete without injury to vascular structures. The supraorbital

approach provided an adequate corridor to manipulate the angulation of the endoscope for complete visualization of the corpus callosum.*Part 2*: The corpus callosum was readily transected in all specimens without vascular injury. All animals survived surgical intervention without new neurologic deficit.Video clips and photographs will be presented

Conclusions: Endoscopic corpus callosotomy via a supraorbital approach is technically feasible and could offer an alternative approach that substantially reduces morbidity and hospitalization associated with conventional approaches

1.447
IMPROVING OUTCOME PREDICTION IN PEDIATRIC EPILEPSY SURGERY

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Rationale: Selection of pediatric epilepsy surgical candidates requires analysis of many variables to identify patients likely to significantly benefit with minimal complication/s. This retrospective review will identify predictive trends between diagnostic variables and outcome.

Methods: We analyzed patients who underwent initial resective surgery at Minnesota Epilepsy Group from Jan 2000-Dec 2001. Seizure semiology, ictal/interictal scalp EEGs, and MRIs were analyzed. Neuropsych testing, MRS, PET with glucose, alpha-methylo-L-tryptophan, flumazenil isotopes, and SPECT studies were reviewed if obtained in the evaluation. Diagnostic abnormalities were characterized by their lateralization/location in the frontal, temporal, parietal or occipital lobe. Findings were categorized by support, neutrality or conflict with region of resection. Supporting variables were located within the region of resection. Neutral findings were ipsilateral but not in the region of resection. Any diffuse or contralateral anbormality to the region of resection was defined as a conflicing variable. Diffuse cognitive dysfunction was excluded. Patients were scored at follow-up at 6-, 12-, 24-months by Engel classification, percent seizure reduction, change in neuropsych status, and complication.

Results: 29 consecutive subjects were identified and reviewed; 13 (44.8%) underwent temporal lobe only resections; extra-temporal resections included 6 (20.7%) frontal; 1 (3.4%) parietal, 9 (31%) multi-lobe. In subjects with available follow-up data, 13/25 (52%) were seizure free at 12-months and 9/20 (45%) were seizure free at 24-months. At 12-months, 7/11 (63%) patients with temporal lobectomy were seizure free compared with 6/14 (43%) with extra-temporal resections. Age of epilepsy onset, duration, and etiology did not vary between outcome groups of Engel class I or II vs Engel class III or IV. Subjects with <2 diagnostic variables in conflict were significantly more likely to be in Engel I or II at 12- ($p < 0.001$) and 24-months ($p < 0.001$) by Fischer's Exact Test. 12/16 (75%) of subjects with <2 conflicting variables were seizure free at 12- months. Supporting and neutral variables did not differ between the outcome groups. The majority of conflicting variables were noted through scalp EEG recording, however conflicting MRI and neuropsychological variables also contributed to poor outcome.

Conclusions: Subjects with <2 diagnostic abnormalities contralateral to the targeted epileptogenic zone achieved Engel class I or II surgical outcome in 93% and 87% of cases at 12- and 24- months respectively. None of the individuals with <2 conflicting variables attained Engel I or II outcome at 24-months.

1.448
EARLY HEMISPHERECTOMY IN YOUNG CHILDREN WITH HEMIMEGALOENCEPHALY ASSOCIATED WITH CATASTROPHIC EPILEPSY

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Rationale: This paper reports on two babies younger than 6 months with hemimegaloencephaly (HME) and catastrophic epilepsy submitted to functional hemispherectomy (FH) with good clinical outcome.

Methods: Patient I: DMAS, a 2-months old baby have had seizures since the first postnatal hours. He had daily, frequent, left motor simple partial and tonic-clonic seizures. EEG showed intense right hemisphere epileptic discharges with some bilateral synchrony. MRI showed right HME. He was submitted to right FH. At the time of surgery, he had bad general physical and neurological (no neck support) conditions and prolonged status epilepticus. Patient II: VB, a 5 months old baby have had seizures since his first week of life. He had daily, frequent, left motor simple partial, complex partial and bilateral tonic seizures. EEG showed intense right hemisphere epileptic discharges and intense bilateral synchrony. MRI showed right HME. He was submitted to right FH. At the time of surgery, he had bad general physical and neurological (no neck support) conditions and status epilepticus.

Results: Patient I presented a slow but progressive motor and cognitive improvement, characterized by increased social contact, smiling, more vigorous spontaneous movement and increased tonus. He remained with daily facial motor simple partial seizures and sporadic generalized tonic-clonic convulsions. He has been followed as an out-patient and has not needed hospitalization for neurologic conditions after surgery. At the age of 11 months, the kid is starting to gain neck and trunk control. Patient II presented a significant decrease in seizure's frequency. He remained with daily facial motor simple partial seizures that eventually spread to the left arm; bilateral tonic seizures still ocurr 1–2 times per week. At the age of 8 months, the kid has been managed as an out-patient and did not need hospitalization for neurologic conditions after surgery; he started to gain neck control.

Conclusions: FH is a good option in small babies bearing HME and catastrophic epilepsy. Residual facial motor simple partial seizures appeared to be related to insular cortex left connected in place. Especial attention to the disconnection of the insula is advised during this procedure. (Supported by Sao Paulo's Secretary of Health.)

1.449
CORPUS CALLOSOTOMY AND RESECTIVE SURGERY FOR SEIZURE CONTROL

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Rationale: Corpus callosotomy (CC) is a procedure that has been shown to be effective in improving seizure control for patients who do not have a clear localized or lateralized seizure onset (i.e., not clear resective surgical candidates). A CC historically has been most helpful in tonic seizures, particularly tonic drops in children. It has been our suspicion through the years that some patients who undergo a CC (anterior 2/3 and complete CC) may ultimately be focal resective candidates in that following the CC, a lateralized and/or localized seizure onset can be identified. Therefore, we reviewed our experience at the Minnesota Epilepsy Group in patients who underwent both a CC and a resective procedure.

Methods: Since 1991, 75 anterior 2/3 and 30 complete CCs have been performed in children. Of these patients, one had resective surgery as well. The records of these patients were reviewed with particular attention to seizure type/epilepsy syndrome, time of surgical procedure, and seizure outcome.

Results: Of the thirteen patients who underwent both a CC (anterior only with or without completion), four underwent a resection with a CC (Group I). The remaining nine patients had the procedures spread over 9 months to 7 years (Group II). Seizure types and EEG correlates included tonic, atypical absence, generalized tonic-clonic and complex partial without a clearly localized EEG onset. Of the Group I patients, all had mixed seizure types (combination of generalized tonic-clonic, tonic, myoclonic, and atypical absence). The outcome of these patients was: three had Engel class I or II, one had Engel class III, and one had Engel

class IV outcomes. In Group II, six had Engel class I or II outcome, two had Engel class III, and one had Engel class IV outcome. All patients who underwent resection surgery had a frontal lobe (all or part) included in the resection. Eight had either multiple lobes (all or partial) resected as well. One had a functional hemispherectomy. Details regarding specific seizure types, etiology (if known) will be discussed as to how they relate to the timing of the procedures in these two groups as well as how the EEG findings changed.

Conclusions: Corpus callosotomy is a palliative procedure for seizure control. Some patients may be suspected of having a focal seizure disorder, but only after or in association with a CC can the EEG lateralize or localize seizure onset. In some patients with multifocal pathology (such as tuberous sclerosis), a CC may ultimately reveal a dominant focus that may respond to a successful focal resection. Indicators for the resection include a lateralized EEG and/or a focal component to the seizure semiology.

1.450
EPILEPSY SURGERY HAS NO SIGNIFICANT EFFECT ON PSYCHOMETRIC INTELLIGENCE OF CHILDREN AND ADOLESCENTS

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Rationale: To evaluate the effects of various types of epilepsy surgery on cognitive functioning as indicated by psychometric intelligence, on a two-year follow-up. Additional aims were to evaluate whether surgery type or lateralization aswell as age, gender, pre-surgical IQ or postsurgical seizure control of the patient have any effect.

Methods: Between 1991 and 2001 70 operations were performed to the patients aged between 3 and 18 years in the Epilepsy Surgery Program of Helsinki University Central Hospital. 50 of operations were either resections or hemispherotomies. Preoperative neuropsychological testing and a follow-up of two years were available for 20 patients with temporal lobe resections (TLR) and for 6 patients with extratemporal or multilobar resections (EMLR) and for 7 patients with hemispheretomy (HE-T). 18 patients had left sided and 17 patients right sided surgery. The seizure outcome of 27 patients was good (Engel 1–2). WISC-R or WPPSI-R or WAIS-R depending on the age were administered within 6 months before surgery and 6 months and two years after surgery.

Results: Verbal IQ(VIQ) varied between 41 and 133 and performance IQ between 41 and 118 before operation. IQ values remained relatively constant during the follow-up and no effect was connected to the type of surgery. All IQ values were significantly lower in the patients with left-sided surgery as well in the patients who underwent HE-T. Preoperative IQs of younger children and also for boys were already lower than those of older children and girls. The same was observed after surgery. Seizure outcome had no effect on postoperative IQ-values either. Altogether 14 patients showed more than 1 SD change of VIQ or PIQ during follow-up; 6 improved and 8 deteriorated.

Conclusions: Epilepsy surgery does not affect cognitive functioning of children or adolescents measured by psychometric IQ values. Lower IQ-values pre- and postoperatively were connected to left-sided surgery, male gender and HET as a type of surgery. (Supported by a research grant from the Hospital for Children and Adolescents, Helsinki University Hospital.)

1.451
FUNCTIONAL HEMISPHERECTOMY IN EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY AND HEMIMEGALENCEPHALY

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Rationale: Early-infantile epileptic encephalopathy (EIEE, Ohtahara Syndrome) is an early and severe age dependent encephalopathy with protean manifestations that is characterized by tonic spasms and a suppression-burst EEG pattern. The long-term prognosis is unfavorable and affected patients experience intractable seizures, near continuous epileptic EEG abnormalities, mental retardation, and poor response to medical treatment.

Methods: We report two cases of successful surgical treatment in children with malformations of cortical development who presented initially with EIEE.

Results: Magnetic resonance imaging revealed unilateral abnormalities including cortical thickening and hemimegalencephaly. At time of surgical evaluation (ages 16 months; 38 days) a focal epileptic pattern was recorded on EEG. Scalp recorded ictal video-EEG revealed seizure onset from the abnormal hemisphere and ictal SPECT demonstrated regional posterior hyperperfusion. Electrocorticography revealed near-continuous spike and slow wave discharges over the entire hemisphere. Functional hemispherectomies were performed in both cases without complication. Tissue histopathology revealed Taylor Type cortical dysplasia.

Conclusions: At postoperative follow-ups of 2 and 5.5 years, both patients are seizure-free on monotherapy and exhibit significant improvement in development. These findings emphasize the benefit of early aggressive surgical treatment for children who present with EIEE due to a unilateral malformation of cortical development.

1.452
SURGERY FOR INFANT-ONSET EPILEPTIC ENCEPHALOPATHY WITH AND WITHOUT INFANTILE SPASM

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Rationale: Childhood onset epileptic encephalopathies, including infantile spasms (IS), are disorders in which patients with frequent uncontrolled seizures are at risk for significant cognitive and neurologic disabilities. Resective neurosurgery is a treatment option for symptomatic therapy-resistant IS patients if there is a unilateral cortical abnormality. This study was designed to compare the pre- and post-surgery clinical, seizure, and developmental outcomes in infant-onset epilepsy patients with or without a history of IS.

Methods: Patients with infant-onset epilepsy were classified into those with medically refractory active IS (active IS; $n = 39$), successfully treated IS but persistent seizures (Rx'd IS; $n = 46$), or no history of IS (no H/O IS; $n = 69$). These groups were compared for pre-surgery clinical variables and EEG abnormalities, post-surgery seizure control and anti-epilepsy drug usage, and pre- and post-surgery Vineland Adaptive Behavior Scale (VABS) developmental quotients (DQ).

Results: Infant-onset seizures occurred in 55.5% of pediatric epilepsy surgery patients, and 55.6% of children with infant-onset seizures had IS. Active IS were the youngest, Rx'd IS intermediate, and no H/O IS cases the oldest at the the time of video-EEG monitoring and surgery. Similarly, active IS had the shortest, Rx'd IS intermediate, and no H/O IS patients the longest intervals from seizure onset to video-EEG monitoring and surgery. Compared with the other IS groups, active IS patients had increased interictal contralateral spikes and slowing, bilateral paroxysmal fast activity, and greater morbidity and mortality. Rx'd IS patients had numerically better seizure control 0.5 to 2 years post-surgery. Increased post-surgery VABS DQ scores were associated with greater pre-surgery DQs, Rx'd IS patient group, seizure control, and shorter seizure durations.

Conclusions: Infantile spasms were frequent in pediatric epilepsy surgery patients, and whether IS responded to medical therapy influenced pre-surgery referral, and post-surgery seizure and developmental outcomes. Furthermore, better post-surgery DQ scores were associated with shorter seizure histories, seizure freedom, and better pre-surgery DQ scores. These findings support the concept that infant-onset epilepsy surgery patients with or without IS are at risk for seizure-induced encephalopathy, and should be evaluated and treated promptly. (Supported by NIH grants RO1 NS38992 and PO5 NS02808 to G.W.M. and NS39505 to R.F.A.)

1.453

CLINICAL OUTCOME AND COMPARISON OF SURGICAL PROCEDURES IN HEMISPHEROTOMY FOR CHILDREN WITH MALFORMATION OF CORTICAL DEVELOPMENT

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Rationale: The aim of this study is to assess clinical outcome of hemispherotomy in children with malformation of cortical development (MCD) in terms of seizure outcome, follow-up MRI, and psychomotor development.

Methods: Among 48 hemispherotomy procedures, a series of 37 pediatric MCD cases followed up for >1 year postoperatively was the subject of the study. Twenty cases were hemimegalencephaly (HM) and others were hemispheric cortical dysplasia (HCD). Median age at surgery was 29 months. Clinical outcome was assessed in terms of seizure outcome, MRI, and developmental quotient (DQ) at 6, 12 months, and every one year thereafter. To evaluate MRI findings, we specifically focused on 1) the completeness of disconnection of the corpus callosum (CC) and cortical projection fibers (PF), 2) internal or external hydrocephalus, 3) morphological development of contralateral hemisphere. Clinical outcome was analyzed in terms of comparison of surgical procedures as well.

Results: CLINICAL OUTCOME. Seizure outcome at the final evaluation was 58.8/11.8/29.4/0% in HCD and 36.8/10.5/47.4/5.3% in HM (Engel Class I/II/III/IV). It was positively correlated with postoperative psychomotor development and with morphological development of the contralateral hemisphere. In Class I/II children, 45% acquired an improved DQ and 85% showed volume expansion of the contralateral hemisphere while 10% had an arrested developmental age (DA) and 5% showed no morphological development. In Class III/IV children, none acquired an improved DQ, 40% had an arrested DA, and 47% showed no morphological development. COMPARISON OF SURGICAL PROCEDURES. For disconnection of CC, interhemispheric approach (IH) and transventricular approach (TV) were compared. In 4 of 19 TV procedures, follow-up MRI revealed residual callosal fibers in the genu. IH enabled reliable disconnection of CC and was especially advantageous in anomalous and asymmetric CC frequently found in HM, while it necessitated another route for disconnection of PF. For disconnection of PF, periinsular approach (PI) and transopercular approach (TOP) were compared. PI necessitated a long corticectomy around the insula and a long disconnection down to the inferior horn behind the insular cortex, which resulted in a problematic blood loss in some cases of HM. TOP overcame the problem but resulted in a higher occurrence of impaired CSF circulation necessitating ventricular or subdural shunting (7 of 15 TOP vs. 1 of 11 PI). Reviewing these results we recently adopted Delalande's vertical hemispherotomy with our modification.

Conclusions: Hemispherotomy for pediatric MCD achieved acceptable seizure control. Favorable seizure outcome was associated with improved psychomotor development and contralateral hemispheric development. Follow-up MRI is useful in confirming the completeness of disconnection and refining this complex surgical procedure.

1.454

PERI-INSULAR HEMISPHEROTOMY FOR EPILEPSY IN CHILDHOOD

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Rationale: Over the years, the surgical approach to large hemispheric epileptic disorder has evolved toward more disconnection and less tissue removal, in an effort to limit morbidity and long-term complications. Peri-insular hemispherotomy is considered to have the maximal ratio of disconnection to excision among all procedures for hemispheric epilepsy. The goal of this study is to review the outcomes of children who have undergone this technique described in 1995.

Methods: Charts of the nine patients who underwent hemispherotomy between 1993 and 2004 were reviewed. Pre-operative evaluation included video-EEG monitoring (7), MRI (9), and functional imaging (PET or SPECT) in six patients. Seizure outcome was recorded and related to the underlying pathology.

Results: The mean age at seizure onset was 1.6 years (range: 5 days-4.8 years). Six patients had complex partial seizures and three patients had infantile spasms followed by complex and simple partial seizures. The mean age at surgery was six years (range: 8 months-16 years). The mean follow-up after hemispherotomy was four years (1 month-11 years). The etiologies of epilepsy were vascular events (5), hemimegalencephalies (2), cortical dysplasia (1) and Rasmussen's syndrome (1). At last follow-up, eight (89%) patients were seizure free and one (11%) patient with hemimegalencephaly had a more than 75% reduction of seizures. All patients had hemiparesis pre-operatively. After surgery, seven had a stable motor deficit, while one improved and one worsened. One patient had a post-operative neuropsychological evaluation and was found to have a stable global developmental delay. The surgeries were well tolerated: three patients experienced transitory fever, one patient had a hemorrhage due to blood dyscrasia and there was no fatality.

Conclusions: Peri-insular hemispherotomy is a valuable and well tolerated procedure for controlling seizures in children with intractable hemispheric epileptic disorders.

1.455

VIRTUAL INTRACRANIAL EPILEPTIFORM DISCHARGES OF MEG USING SYNTHETIC APERTURE MAGNETOMETRY COMPARISON TO INTRACRANIAL EEG RECORDING

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Rationale: Synthetic Aperture Magnetometry (SAM) is a spatial filtering technique for MEG data, using a minimum-variance beamformer. From the MEG signal, SAM estimates the time-course of source activity (dipole moment) from any specified location in the brain. This process is referred to as a virtual sensor (SAM-VS), behaving as if an intracranial electrode was recording cortical activity at the same site. The purpose of this study is to compare virtual epileptiform discharges observed by SAM-VS with actual discharges measured at the same sites by intracranial EEG.

Methods: Data for 10 children who underwent long-term intracranial EEG and surgical excision for neocortical epilepsy were selected for this study. Their preoperative MEG was analyzed retrospectively, using SAM software (CTF Systems Inc., Port Coquitlam, Canada). Virtual sensors were computed for locations corresponding to those of the intracranial subdural grid. The topographic distribution and morphological features of epileptiform discharges seen using SAM-VS and intracranial EEG were reviewed for each patient.

Results: Main morphologic features of epileptic discharges on ECoG in 10 patients consist of focal discharges in 4, focal rhythmic (sharp) train in 2, multiple independent spikes in 2, widely distributed spike discharges in 1, and focal discharges and low-amplitude fast activities in 1. Then SAM-VS demonstrated the similar results to ECoG classifications, focal discharges in 4 out of 4, focal rhythmic (sharp) train in 2 out of 2, multiple independent spikes in 2 out of 2, and widely distributed spike discharges in 1 out of 1. In 1 patient, while low-amplitude fast activities and focal discharges were defined as the main feature on ECoG, only focal discharges were observed on SAM-VS. In 5 patients, additional minor findings which were focal discharges in centro-parietal and basal frontal regions, were identified on only ECoG.

Conclusions: The spatial distribution and waveform morphology of virtual epileptiform discharges on MEG with SAM-VS analysis are comparable to actual discharges observed directly by intracranial EEG. We need further analysis of the interictal zone on MEG using SAM-VS to localize the epileptogenic zone, yet SAM-VS analysis can simulate the interictal epileptic behaviors prior to the epilepsy surgery.

1.456

EPILEPSY SURGERY IN CHILDREN WITH ULEGYRIA AND ADQUIRED CORTICAL DYSPLASIA

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Department of Neurology, Clinic Hospital, Barcelona, Barcelona, Spain, and [4]Epilepsy Surgery Program, Neurology Service, Hospital Sao Lucas PUCRS, Porto Alegre, Porto Alegre, Brazil)

Rationale: Abnormal maturation of surviving cerebral cortex following late prenatal or perinatal hypoxic – ischemic brain injuries have been related to the genesis of acquired (or destructive) cortical dysplasia, postmigrational polymicrogyria, and ulegyria. These conditions have been only sporadically noted in series of patients operated for epilepsy. Our work illustrates the spectrum of pathological findings in epileptic children with perinatal brain injuries and localized dysgiria on MRI, and evaluates the role of surgery for seizure control.

Methods: Three boys and one girl (aged 9 to 13 years, mean 10 years) are reported. All showed: 1) a previous history of perinatal complications, 2)visual and/or cognitive deficits, 3) MRI findings characterized by atrophy and dysgyria with small or mushroom-shape gyri, associated with hyperintensity in immediately subcortical areas, and 4) focal refractory epilepsy, surgically treated following complete presurgical evaluation.

Results: In three patients the lesion affected mainly the occipital lobes. Despite clear bilateral MRI involvement in 2, unilateral occipital seizure onset was documented in all, which led to unilateral cortical resection. The other patient had congenital hemiplegia and startle-induced seizures, with a lesion involving the hole hemisphere, and was treated by functional hemispherectomy. Pathological studies showed: 1) neuronal loss and gliosis at the basis of the gyri (2 cases), 2) four-layered cortex with associated laminar necrosis and subpial gliosis (1 case); 3) cytoarchitectural dysplasia (3 cases), 4) dual pathology (hippocampal sclerosis, 1 case). Seizure outcome has been good or excellent in all cases (Engel class I- 3 cases, Engel class II- 1 case).

Conclusions: Children affected by localized dysgyria related to perinatal brain injuries and refractory focal epilepsy can be good surgical candidates, including patients with bilateral occipital lesions. A continuum between ulegyria and destructive cortical dysplasia is suggested.

1.457
SURGICAL THERAPY FOR REFRACTORY EXTRATEMPORAL NONLESIONAL FOCAL EPILEPSY IN CHILDREN

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Rationale: Extra-temporal nonlesional intractable focal epilepsy in children is difficult to treat and has a poor prognosis without intervention. During the past 3 $\frac{3}{4}$ years, we have pursued an aggressive surgical approach at our institution to localize and resect the seizure focus for these children.

Methods: All patients underwent an extensive pre-surgical evaluation including video-EEG, standard or high resolution MRI, PET and/or SISCOM, and neuropsychological testing.

Results: Eighteen consecutive children with extra-temporal nonlesional seizure foci underwent surgery. The mean age at the initial surgery was 9.4 yrs (3–15 yrs). The etiology of the epilepsy was prenatal stroke (2), congenital hydrocephalus (1), encephalitis (2), childhood stroke (1), intrathecal chemotherapy and radiation (1), and unknown (11). No child had a tumor or vascular malformation.

Resections were performed in the frontal lobe in 11, parietal lobe in 4, frontal and parietal lobes in 2, and parietal and occipital lobes in one child. Three of these 18 children had repeated invasive monitoring when seizures recurred. One had 2 further resections along with VNS placement and became seizure-free after the last surgery with subsequent placement on the Adkins diet. Two patients had previously undergone a temporal lobectomy, one of whom was seizure-free for 16 months. Three children with foci in the motor strip had transient weakness after resection, and one had permanent worsening of her baseline hemiparesis secondary to cerebral edema.

Pathology showed focal cortical dysplasia in 6 and gliosis in 12. Mean follow-up was 25.6 months (2–45 months). Six children (33%) became seizure-free (Engel I), 2 had auras (Engel II), and 7 had at least an 80% reduction in seizure frequency (Engel III). Two of those with a marked reduction were in status epileptics preoperatively. Only 3 children (18%) had no significant improvement (Engel IV). Six children also had VNS placement, with only two experiencing partial improvement. The majority (14/18) experienced a marked improvement in ability to perform schoolwork associated with improved seizure control and medication reduction. Two previously nonverbal children developed over 50 word vocabularies and had communicative intent with seizure control.

Conclusions: We conclude that advanced neuroimaging techniques and an aggressive surgical approach can identify patients who were previously not considered good surgical candidates. While not without risks, this strategy provides children with nonlesional extra-temporal intractable epilepsy a hope for a much improved quality of life.

1.458
SEIZURE AND COGNITIVE-BEHAVIORAL OUTCOMES FOLLOWING HEMISPHERECTOMY FOR EPILEPSY AT CHILDREN'S HOSPITAL, BOSTON: 1990–2003

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Rationale: Hemispherectomy for intractable epilepsy associated with unihemispheric lesions has been performed since 1928. The results of surgery in relation to age at presentation, underlying pathology, seizure type and co-existing deficits are necessary for counseling parents of candidates for epilepsy surgery.

Methods: Fifty-three patients undergoing hemispherectomy between 1990 and 2003 were identified from the Children's Hospital epilepsy surgery database. Patients had received standard assessments involving clinical neurology and developmental examination, neuroradiology and neurophysiology. All patients were evaluated with MRI and video-EEG telemetry. A number of patients also underwent ictal/interictal SPECT, PET scanning and/or quantitative EEG. Twenty-one percent also had invasive EEG monitoring prior to definitive surgery.

Seizure outcome was assessed using the modified Engel scale. Pre and post-operative motor function was assessed on clinical examination. Visual field deficits were based on clinical examination and formal perimetry where possible. All children underwent formal developmental assessment by a pediatric neurologist. Behavior was assessed by neuropsychological testing or parental report.

Descriptive statistics were calculated using standard software and comparisons between groups made using non-parametric test for single and multiple group comparisons.

This study was approved by the Children's Hospital Boston Institutional Review Board.

Results: Age at surgery was 4 months to 27 years (median 2 years), with follow-up ranging from 6 months to 7 years (mean 2.5 years). Underlying pathology was acquired in 11, developmental in 22 and progressive in 20. Forty-six patients had anatomic hemispherectomy and 7 underwent functional disconnections. Twenty-three percent of patients had undergone previous surgery. At follow-up 83% were free of disabling seizures, 7% had rare disabling seizures, 2% had had worthwhile improvement and 8% had no improvement. There were 2 deaths. Seizure freedom was highest in those with developmental and progressive pathology and lowest in those with acquired pathology. Seventy-eight percent were taking 1 or less AED at follow-up. Cognitive status was improved in 66%, unchanged in 27% and worsened in 9%. Hemiplegia worsened in 70%.

Conclusions: Fifty-three children with intractable epilepsy who underwent anatomic and functional hemispherectomy showed significant improvement in seizure outcome. Our patients overall showed improvement in cognitive and behavioral status. (Supported by the Michelle and Roger Marino Fellowship.)

1.459
TEMPORAL LOBE EPILEPSY: LONG-TERM FOLLOW-UP IN PATIENTS <18 YEARS TREATED SURGICALLY

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Rationale: Temporal lobectomy is effective in children with Temporal Lobe Epilepsy (TLE), Wyllie et. al. Ann Neurol 1998. However, Jarrar et.al. Neurology 2002, reported increase seizure recurrence with longer

duration of follow-up; their patients underwent surgery before 1983. We wished to study the long term follow-up in patients treated since 1986 when advances in the presurgical evaluation became available

Methods: This is a prospective study of 28 children and adolescents with refractory TLE treated surgically between 1986–2002 by the same neurosurgeon, following a comprehensive presurgical evaluation including Video-EEG with sphenoidal electrodes. Patients were followed longitudinally at 6 wks, 3, 6, mths and yearly threreafter. Clinical manifestations, pathological diagnosis, complications, and outcome were analyzed. Engel's seizure classification was used.

Results: The age of seizure onset was 1 yr-13 yrs, age at surgery 8–17 yrs, and duration of epilepsy 3 yrs-15 yrs. 53% had history of febrile seizures, 68% had abnormal head MRIs, and 94% had ipsilateral PET hypometabolism. All had unitemporal seizures recorded on prolonged Video-EEG (11% required invasive recordings). The intracarotid amobarbital procedure showed that the contralateral hemisphere was able to support memory. All underwent temporal resections under general anesthesia; one had re-operation. There was no surgical mortality or morbidity. 54% had mesial temporal sclerosis, 21% gliosis, 7% cavernous angiomas, 14% low grade tumors, and 3.5% had no pathologic diagnosis. 78.5% became seizure free, 7% had rare seizures, and 4% had worthwhile seizure reduction, (follow-up 2 yrs to 18 yrs; mean = 9 years)

Conclusions: Our study showed that the long term outcome of children and adolescents with temporal lobe epilepsy treated since 1986 when MRI, PET and other advances in the presurgical and surgical evaluation became available remains favorable, with no surgical mortality or morbidity.

1.460

EPILEPSY SURGERY IN MULTIFOCAL (MULTILOBAR) PARTIAL EPILEPSY

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Rationale: Epilepsy surgery in patients with medically refractory multilobar epilepsy is one of the most difficult clinical situation and fraught with many difficult decisions.

Methods: We retrospectively studied patients with proven multilobar epilepsy with chronic subdural EEG recording. Seizure onset was identified by earliest sustained rhythmic change on EEG that is clearly distinguished from background EEG occurring in association with a clinical seizure. Intraoperative photographs and 3D reconstruction MRI images co-registered with subdural grids were used to identify the location of the seizure onset electrodes. The location of seizure onset zones were divided as follows: inf/medial temporal (MT), temporal neocortex (LT), lateral parietal lobe (LP), medial parietal lobe (MP), lateral frontal lobe (LF), medial frontal (MF), orbito-frontal (OF), lateral occipital lobe (LO), medial occipital (MO), inferior occipital lobe (LO). Frequency of various anatomical regions involved in seizure onset was analyzed. Outcome data was analyzed.

Results: We studied a total of 20 children (age 0.7–18 years, 14M, 6F). In patients with multilobar epilepsy, frequency of lobar involvement was as follows: temporal lobe (16/20), parietal lobe (15/20), frontal lobe (9/20) and occipital lobe (1/20). Eighteen patients had 2 lobes involved in seizure onset, while the other 2 had three lobes involvement. Most likely combination in decreasing frequency was as follows: LT-LP (6), LF-LP (4), MT-LF (3), MT-MP (2), and all other combination occurred in a single patient (LT-LF, LT-LO, MT-LP, LF-LP-MP-MT, LF-LP-MF). There are some interesting observations, seizure onset from temporal neocortex are more likely to associate with seizure onset from LP, while MT seizures more likely to combine with LF seizure onset. In most patients with seizure onset involving LF-LP, peri-rolandic region was involved.

The underlying pathology was as follows: Tuberous sclerosis 9, gliosis 6, Neuronal migrational abnormalities 4, and focal polymicrogyria with glial cytoplasmic inclusion 1. The follow-up period since surgery ranged from a month to 2.6 years (mean 1.37 years). The outcome measured per Engle classification for patients who was at least one year from surgery (13 patients): Class I :10 and Class III: 3.

Conclusions: Multilobar epilepsy usually occur in patients with widespread abnormalities of cerebral/neuronal development. Certain brain regions are more likely to be involved in tandem (LT-LP, MT-LF, LF-LP, MT-MP). This fact should be considered while planning subdural grid placement. Epilepsy surgery may provide effective treatment in selected patients with multilobar epilepsy. (Supported by NINDS grant RO1 NS045207–01.)

1.461

HEMISPHERECTOMY FOR INTRACTABLE EPILEPSY IN CHILDREN AND ADOLESCENTS

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Rationale: Hemispheric pathologies are commom etiology of intractable epilepsy in childhood. Patients may have early seizure onset and multiple seizure types. Dailly seizures or *status epilepticus* are present in the majority of cases. Interictal and ictal EEG findings are usually diffuse involving even contralateral hemisphere.

Methods: we analyse 27 patients submitted to hemispheric surgery with 18 years old or less, operated on from January 1996 to August 2003 at Ribeirao Preto Epilepsy Surgery Program (CIREP) using standardized protocols. All had medically intractable epilepsy. Presurgical evaluation included clinical history, neurologic examination, interictal and ictal video-EEG monitoring, structural and functional imaging, and neuropsychological testing. Seizure outcome was classified according to Engel schema. Fisher exact test and Mann-Whitney test were used for statistical analysis, and significance level was considered at $p < 0.05$.

Results: Patient age ranged from 11 months to 18 years old (mean: 8.85 years). Mean age at epilepsy onset was 4 years. In 22% of the patients two seizure types were present at evaluation. Seizure types included focal motor and tonic seizures (37% of patients for each), *epilepsia partialis continua* (22.2%), infantile spasms (14.8%) and complex partial seizures (11.1%). Daily seizures were present in 55.5% of the patients and 40.7% had *status epilepticus*. In 60% of the cases interictal EEG was unilateral. Ictal EEG was unilateral in 42%. Anatomical hemispherectomy were performed in five patients and hemispherotomy in 21. One patient was submitted to Delalande hemispherotomy techinic. There were no correlation between surgical techinic and demographic data. Surgical specimens revealed Rasmussen Syndrome (33.3%), porencephalic lesions (29.6%), CDA (18.6%), gliosis (7.4%), Sturge-Weber Syndrome (7.4%) and tuberous sclerosis (3.7%). Patients with Engel classification I and II corresponded to 59.3% of the cases, but 74% of patients had at least 90% seizure reduction. There were no correlation between patients with seizures in the first month post-operative ($p = 0.51$) or surgical techinic ($p = 0.42$) with outcome. Mean follow-up was 3.95 years. Two patients died in follow up.

Conclusions: Patients with hemispheric pathologies usually has abnormal neurological development and intractable epilepsy. In our series, surgical outcome was similar when considering surgical techinic, with a worst outcome in patients with Rasmussen syndrome. All patients had a subjective improvement in quality of life, with use of less antiepileptic drugs and a cognitive improvment. In conclusion, patients submitted to hemispherec surgeries had good surgical outcome and an improvement of neurological development, even in patients witch persisted with mild frequent seizures. (Supported by FAEPA and FAPESP.)

1.462

PEDIATRIC EPILEPSY SURGERY: EXPERIENCE OF CHILDREN'S HOSPITAL OF WISCONSIN, MILWAUKEE, WISCONSIN

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Rationale: Pediatric epilepsy surgery is being increasingly utilized in the treatment of intractable epilepsy in the pediatric population, but is often delayed or considered a treatment of last resort. Adult patients with epilepsy usually have a 15+ year history of uncontrolled seizures

before being referred to a tertiary epilepsy center. We have aggressively pursued epilepsy surgery in our pediatric population, with the rationale that early treatment results in improved seizure control, enhancement of development, and improved quality of life.

Methods: This was a retrospective chart review of 56 patients who underwent epilepsy surgery at Children's Hospital of Wisconsin between 2001–2003.

Results: Age range for our pediatric surgical patients was 6 months to 18 years of age, with a mean age of 9 years. Of the 56 surgeries, 28.5% were hemispherectomies; 27% frontal resections; 12.5% temporal-parietal-occipital resections; 10.5% parietal resections; 21.5% temporal lobectomies. Pathology revealed 57% cortical dysplasia; 11% encephalomalacia; 9% tuber; 9% mesial temporal sclerosis; 7% Rasmussen's encephalitis. Seizure outcomes have been Class I–68.8%; Class II–12%; Class III–9.2%.

Presurgical evaluation included CCTV EEG monitoring, MRI scan of the brain, PET and SPECT imaging. The EEG was nonlocalizing in 50% of the cases, suggestive of a generalized or multifocal epilepsy. The critical determinant for location of the epileptogenic zone was neuroimaging–primarily the MRI scan (75%) in combination with either PET or SPECT. PET scan was approximately 50% sensitive. SPECT scans were not performed on all patients, but provided congruent information in 60%.

The follow-up has ranged from one month to two and one half years. The patients in the Class III outcome were predicted to have a reduction in seizure burden, but not complete elimination of seizures. Despite this, 95% of families have reported improved development and enhancement of quality of life.

Further information about presurgical evaluation, surgical techniques, and quality of life assessment will be provided in greater detail at our presentation.

Conclusions: Early surgical intervention in appropriate pediatric candidates provides a reduction in seizure burden, improved quality of life and enhanced development.

Neuropsychology/Language/Behavior—Adult 1

1.463
MEMORY AND LANGUAGE IMPAIRMENTS AND THEIR RELATIONSHIPS TO NEURONAL DAMAGE OF MEDIAL TEMPORAL LOBE STRUCTURES IN PATIENTS WITH MEDIAL TEMPORAL LOBE EPILEPSY

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Rationale: Chronic medial temporal lobe epilepsy (MTLE) is associated with memory loss, due to damage in the hippocampal system.

Methods: We studied 39 consecutive patients with refractory MTLE and unilateral hippocampal atrophy (HA) determined by volumetric magnetic resonance imaging (MRI). MRI studies included manual morphometry of T1 MRI with 1mm isotropic voxels that underwent field non-homogeneity correction and linear stereotaxic transformation into a standard space. Structures of interest comprised hippocampus, amygdala, entorhinal, perirhinal, parahippocampal, and temporopolar cortices. Neuropsychological evaluation included Wechsler Adult Intelligence Scale – Revised, Edinburgh Handedness Inventory, Dichotic Listening Test, Verbal Fluency Test, Boston Naming Test, Strub & Black Vigilance Test, Trail Making Test, Winsconsin Card Sorting Test and Wechsler Memory Scale – Revised. The volumes of medial temporal lobe structures were compared to neuropsychological results, by means of Chi-square test and simple regression analysis.

Results: Significant positive correlations were found between volumes of left hippocampus and Verbal Memory ($p = 0.035$), Verbal Fluency ($p = 0.019$) and BNT ($p = 0.029$); left perirhinal cortex and BNT ($p = 0.038$); left entorhinal cortex and Verbal Fluency Test ($p = 0.023$); and right parahippocampal cortex and Vigilance Test ($p = 0.042$). On the other hand, the volumes of right hippocampus and right perirhinal cortex were negatively correlated to General Memory ($p = 0.042$; $p = 0.019$), Verbal Memory ($p = 0.013$; $p = 0.004$) and Verbal Fluency tests ($p = 0.008$; $p = 0.002$) and that of right entorhinal cortex, to Verbal Memory ($p = 0.028$) and Verbal Fluency tests ($p = 0.013$).

Conclusions: In patients with left MTLE, the volume of left hippocampus correlated positively to verbal memory and language functions, while the volume of left perirhinal and entorhinal cortices correlated only to language function. On the other hand, in patients with right MTLE, reduced volumes of right hipocampus, right perirhinal and entorhinal cortices correlated with better performance on general and verbal memory, and language skills. (Supported by FAPESP: grant numbers 00/07788–2 and 00/04710–2.)

1.464
GROUP TREATMENT OF MEMORY DISORDERS IN PATIENTS WITH EPILEPSY

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Rationale: Difficulties with memory are reported frequently in patients with epilepsy. There is a current lack of options for treating these symptoms. The goal of this study was to develop and study a group-based approach for treating memory difficulties specific to patients with epilepsy.

Methods: Twenty-three patients with epilepsy were enrolled in four separate groups. There were 15 female and 8 male participants. The average age was 47.5 years (range, 28–62 years). The mean level of education was 15.6 years (range, 10–20 years). Sixteen patients had received surgical intervention. The group treatment consisted of six 75-minute sessions. Each included educational presentations on epilepsy and memory. There was also instruction in the use of external devices (e.g., calendar systems and PDA's) and in the use of mnemonic techniques (e.g., imagery and association). Informational handouts were provided at each session. Participants were given homework assignments utilizing concepts presented in the group. They were also encouraged to share strategies that have been helpful for managing memory difficulties. The subjects were administered self-report questionnaires, including the Quality of Life in Epilepsy (QOLIE-10) and the Memory Complaints Inventory (MCI), at the beginning the group and 1–2 months after its conclusion. They also completed a group evaluation form.

Results: Twenty patients successfully concluded treatment. Fifteen completed self-report inventories at both timepoints. Comparisons between subjective ratings obtained before and after the group were made with pairwise t-tests. No significant changes were seen in global ratings of QOL or subjective memory, as defined by differences in total scores on the QOLIE-10 ($t = 0.40$, NS) and on the MCI. ($t = 1.46$, NS). Significant reductions were seen on the memory item (#4) from the QOLIE-10 ($t = 3.56$, $p < .01$). A significant increase in mental effects from AED's, as defined by changes in their response to item #8 ($t = 2.48$, $p < .01$) were also seen. On the MCI, they were found to have significant reductions in ratings for verbal memory impairment ($t = 2.30$, $p < .05$) and word finding difficulties ($t = 2.40$, $p < .05$). The participants gave the memory group a mean satisfaction rating of 4.20 on a scale of five. They rated "weekly handouts" ($M = 4.07$) and the "interactions with peers" ($M = 4.13$) as the most valuable components of the group.

Conclusions: Preliminary results from a trial of 15 individuals completing a six-week memory group indicate significant changes in subjective ratings following treatment. Improvement was reported in verbal memory and word finding. There was also an increase in reported side effects from medication, which is perhaps the result of increased awareness of these issues through educational presentations. These findings indicate that group intervention might provide an effective and efficient means for educating patients and addressing memory difficulties associated with epilepsy.

1.465
PREDICTORS OF PSYCHIATRIC AND BEHAVIORAL COMORBIDITY IN TEMPORAL LOBECTOMY CANDIDATES

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Rationale: Psychiatric and behavioral co-morbidity are often reported in TLE. The authors conducted a prospective study to examine factors predictive of psychiatric morbidity in patients undergoing temporal lobectomy (TL) for relief of refractory TLE.

Methods: 101 adults were evaluated for temporal lobectomy in the UMass Comprehensive Epilepsy Program from 1992–2000. 74 completed the pre-op evaluation, including neurology consultation, video-EEG telemetry monitoring, neuropsychological testing, neuropsychiatric consultation, SCL-90R and an interictal trait questionnaire. Surgical candidates underwent pre-op Wada testing and PET scanning; with repeat neuropsychological testing, neuropsychiatric consultation, and questionnaire completion 3 months post op.

Results: Of 74 patients evaluated, 35 underwent formal anterior TL with medial temporal resection (51% right/49% left), 10 lateral or extra-temporal resection, and 29 were not surgical candidates. 60% of 35 TL patients had positive psychiatric history. Average age was 37, average epilepsy duration 23.4 years, average education 12.7 years, average verbal IQ 90.5, average performance IQ 94.7. 71% had mesial temporal sclerosis (MTS). 94% had Engel class I or II outcomes.

23/35 patients (66%) had psychiatric disorders pre-op, 6 of these (26%) previously undiagnosed. 3 traits (vindictiveness, cohesiveness, and kindness) correlated inversely with education ($p < 0.001$, $p < 0.006$, $p < 0.002$ respectively). Age, epilepsy duration, gender, history of traumatic brain injury, and prior psychiatric treatment did not predict interictal traits. Temper and dysphoria correlated with use of psychiatric medication and mood disorder. Seriousness, vindictiveness, cohesiveness, religiosity, and cosmic interest correlated negatively with verbal IQ ($p < 0.001$- $p < 0.01$). Fluency and naming correlated negatively with seriousness, cosmic interest, cohesiveness, and wandering. Seriousness also correlated negatively with processing speed. Neither laterality nor presence of MTS predicted interictal traits or positive findings on the SCL-90R. 2 patients developed post-op suspiciousness without prior psychiatric problems.

17/35 patients completed post-op evaluations. 3 interictal traits decreased 40% or more with surgery (orderliness, amnesia, and misperception) ($p < 0.01$), a change not predicted by age, education, gender or laterality of focus.

Conclusions: Psychiatric co-morbidity was found in 66% of unselected patients with refractory TLE, 26% of whom were undiagnosed prior to pre-op neuropsychiatric evaluation. Education and IQ were better predictors of interictal traits than were duration of epilepsy, traumatic brain injury, or psychiatric history. Interictal traits appeared more related to cognitive status than psychiatric history.

1.466
UTILITY OF THE BOSTON NAMING TEST IN THE LATERALIZATION OF TEMPORAL LOBE EPILEPSY

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Rationale: Confrontation naming tasks have long been presumed to be sensitive to left temporal dysfunction and are frequently used in the evaluation of surgical epilepsy patients. Despite wide and frequent use, few studies have examined the validity of confrontation naming tasks in individuals with epilepsy. In 2001, Kubu and colleagues examined the diagnostic utility of the Boston Naming Test (BNT) and the Benton Naming Test using likelihood ratios in a sample of 53 individuals with temporal lobe epilepsy (TLE). They found that neither test improved significantly upon pre-test probability of identifying patients who ultimately underwent left temporal lobectomies when using standard normative data to define level of impairment. The current study sought to replicate and extend the Kubu et al. study in a larger sample of TLE patients to further examine the utility of the BNT in determining ultimate side of surgery.

Methods: The current study examined the presurgical BNT performance of 348 patients with TLE (Left = 175; Right = 173) who eventually underwent temporal lobectomies. All patients were right-handed, over the age of 17, and had full scale IQs of $\geq$ to 70. Likelihood ratios were calculated for all possible cutoff scores between 59 and 27, but were not calculated for lower scores as no right TLE patients scored below 27.

Results: The likelihood ratios for BNT cut scores from 59 to 27 ranged from 1.03 to 9.89. As in the Kubu et al. study, results indicated that, when using standard normative data to define level of impairment (scores below 10–12th percentile), BNT scores did not significantly improve upon pre-test probability of determining patients who would eventually undergo left temporal lobectomy. However, it was apparent that lower cut scores did significantly improve upon the pre-test probability of approximately.50, with post-test probabilities ranging from 50.7% to 90.8%.

Conclusions: This study supports the clinical utility of the BNT in identifying epilepsy patients who ultimately go on to have left temporal lobectomies when levels of impairment are extended beyond the standard normative cutoff. In general, patients with lower scores on the BNT are more likely to undergo left temporal lobectomies than TLE patients with higher scores, indicating that the BNT is indeed sensitive to left temporal dysfunction. The potential increase in diagnostic accuracy gained by administering the BNT routinely to pre-surgical TLE patients must be weighed against the costs associated with the test in those patients in whom the test does not significantly improve prediction beyond the known pre-test probability. We argue that the low cost, small time investment, and ease of administering this instrument support continued use of the BNT in the pre-surgical neuropsychological evaluation of TLE patients. In addition, the BNT provides a useful baseline measure against which post-operative changes in confrontation naming can be assessed.

1.467
HIPPOCAMPAL ASYMMETRY IS ASSOCIATED WITH PSYCHIATRIC DISTRESS IN TEMPORAL LOBE EPILEPSY

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Rationale: Neuroimaging studies have correlated diminished hippocampal volumes with chronic affective and psychotic disorders. Chronic temporal lobe epilepsy (TLE) is also associated with decreased hippocampal volumes, usually in the temporal lobe responsible for seizures. Given the association of decreased hippocampal volumes with both TLE and psychiatric disorders and the common observation of psychiatric distress in patients with TLE, we predicted that there would be a correlation between decreased hippocampal volumes in TLE and increased severity of psychiatric distress that these individuals exhibit.

Methods: We evaluated 39 patients with intractable, unilateral TLE. All patients completed a quantitative measure of the severity of affective, somatic, and psychotic symptoms as determined by the Symptom Checklist-90-Revised. We measured T2-weighted hippocampal volumes using our previously published protocol (Olejniczak et al 2001) and obtained the ratio of the hippocampal volume (HV) ipsilateral to the side of seizure onset divided by the contralateral HV (ie, HV epileptogenic side/HV non-epileptogenic side). We then evaluated the correlation between this ratio and the severity of psychiatric distress using a partial correlational analysis.

Results: Correlational analyses revealed that increasing severity of global psychiatric symptoms were significantly associated with decreasing volumes of the epileptogenic hippocampus as compared to the non-epileptogenic hippocampus. These results were significant after statistically removing the effects of the chronicity of seizures.

Conclusions: Our results strongly suggest that reductions in hippocampal volumes in TLE, either by themselves or through the related limbic-cortical system, may play an important role in psychiatric distress so commonly seen in TLE. Structural pathology, rather than psychosocial factors associated with epilepsy, may play the dominant role in the psychiatric symptomatology. Conversely, hippocampal-limbic structural pathology may amplify transient psychosocial factors that ordinarily may not convert into chronic psychiatric distress.

1.468
CLUSTER ANALYSIS OF NORMAL PERSONALITY TRAITS IN PATIENTS WITH PSYCHOGENIC NONEPILEPTIC SEIZURES

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Rationale: Despite ample research to differentiate patients with PNES from those with epilepsy, little information is known about prognosis and effective treatment of PNES. A recent study suggests three types of PNES patients, based on a self-report psychopathology measure[1]. To date, only that investigation offers data on different types of PNES on the basis of an objective psychological measure. **The purpose** of this investigation is to add to this preliminary area of research using the NEO-PI-R, a well developed measure of the well-validated five-factor model of personality in order to add to a foundation for future outcomes and treatment research.

Methods: All consecutive patients admitted for inpatient video-EEG monitoring completed the NEO-PI-R for the study. Patients were also routinely evaluated with a neuropsychological test battery and the MMPI-2. This investigation is based on 74 consecutive patients with PNES diagnosed with video-EEG monitoring.

Results: Three clusters were formed (1) Very high Neuroticism, Low Extraversion, Low Openness, High Agreeableness, Low Conscientiousness; (2) Average on all domains; (3) Very high Neuroticism, Average Extraversion, Low Openness, Low Agreeableness, Average Conscientiousness. No differences between clusters were seen on demographic variables, seizure variables, or psychosocial variables. Generally, clusters 1 and 3 exhibited more severe psychopathology on the MMPI-2. Cluster 2 exhibited a focused profile consistent with somatoform disorder. Clusters 1 and 3 differed significantly on neurocognitive testing, with cluster 1 significantly lower than cluster 3 in memory functioning. Cluster 2 was generally average in all neurocognitive domains and significantly higher than cluster 1.

Conclusions: None of the clusters in this sample is identical to a previous report [1], though there are similar features, such as high Neuroticism, low Extraversion, and low Agreeablenss. The prior study used a different measure of personality, which appeared more focused on abnormal variants of personality traits. The three clusters here are associated with differences in psychopathology and neurocognitive functioning as well, information that helps validate the different clusters formed by personality variables alone. *These results therefore, support the existence of clusters of types of PNES patients, and we suggest that future research should consider these clusters in order to design more successful interventions.*

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1.469
RESPECTIVE ROLES OF TYPE AND FAMILIARITY OF MATERIAL IN EPISODIC LEARNING AND MEMORY IN OPERATED-ON TEMPORAL LOBE EPILEPTIC PATIENTS

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Rationale: It is now well established that left (dominant) anterior temporal lobectomy (ATL) may cause verbal memory deficits (Jones-Gotman, 1991; Milner, 1967). However, when the right (non-dominant) temporal lobe is concerned, visuospatial memory deficits are not always clearly observed (Moore & Baker, 1996; Naugle et al., 1993). It has been argued that the absence of a clear double dissociation with regard to this material-specific hypothesis might be due to the instruments used to assess episodic memory functions (Lee et al., 2002). A second hypothesis proposed to account for this phenomenon relies on the familiarity of the material (familiar/non-familiar) to be learned, rather than on the usual verbal/visuospatial distinction. Some attempts have been made to distinguish the role of familiarity from the role of the type of material in episodic learning and memory, though the results were ambiguous (Falk et al., 2002; Redoblado et al., 2003). Thus, the goal of the present study is to test the two following hypotheses: the material-specific and the familiarity hypotheses.

Methods: 30 temporal lobe epileptic patients (13 RT; 17 LT) who underwent surgery (ATL or amygdalo-hippocampectomy) for intractable seizures, and 18 normal controls (NC), participated in the present study. In order to test the material-specific and the familiarity hypotheses in episodic learning and memory, a fully crossed design was elaborated and consisted of the four following learning and memory recognition tasks: abstract words (familiar verbal), nonsense words (non-familiar verbal), landscape photographs (familiar visuospatial), and abstract designs (non-familiar visuospatial). Free recall was also assessed for the verbal tasks.

Results: On recognition tasks, a repeated measures ANOVA 2 (familiar/non-familiar) X 2 (verbal/visuospatial) X 3 (immediate 1/immediate 2/delayed] showed the following results. Better performances were observed on non-familiar than familiar tasks, as well as on verbal than visuospatial tasks. On verbal tasks, NC and RT did not differ, and both NC and RT performed better than LT. On visuospatial tasks, NC performed better than both LT and RT, which did not differ from each other. NC performed better than both LT and RT on each recognition (1, 2 and delayed), but no difference was observed between both epileptic groups on these moment measures. Repeated measures ANOVA on free recalls of words and nonsense words showed that participants performed better on the word task than on the nonsense word test. Overall, NC performed better than LT and RT, and LT performed worse than RT.

Conclusions: Neither the material-specific hypothesis nor the familiarity hypothesis appear sufficient on their own to explain the obtained data. Indeed, both the familiarity and the type of material to be learned play a role in episodic learning and memory. (Supported by Savoy Foundation.)

1.470
^{1}H-MRS MESIAL TEMPORAL LOBE ABNORMALITIES AND NEUROPSYCHOLOGICAL FUNCTION IN EPILEPSY PATIENTS

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Rationale: Certain neuronal metabolic markers (e.g., NAA & Cr) measured by ^{1}H magnetic resonance spectroscopy (MRS) have been shown to be highly correlated with EEG abnormalities and degree of atrophy in the brain. A few studies have shown a relationship between MRS brain abnormalities and cognitive performance. This study sought to evaluate the relationship between mesial temporal functional abnormality as measured by MRS and neuropsychological test performance. We hypothesize that epilepsy patients with MRS hippocampal abnormalities will demonstrate worse neuropsychological performance than patients without MRS abnormalities. We further predict that memory function will be disproportionately involved.

Methods: The sample consisted of 41 epilepsy patients who received both magnetic resonance imaging (MRI) and MRS under an epilepsy imaging protocol. All imaging data were reviewed and interpreted by a neuroradiologist. The region of interest for MRS was the hippocampus on both sides of the brain. All patients were known to or suspected of having localization-related epilepsy of the temporal lobe. Thirty patients showed no abnormality on MRI or MRS (-MRI/-MRS) and 11 had a MRS temporal lobe abnormality (-MRI/+MRS) in the context of a normal MRI. The percentage of patients with left, right, and bilateral MRS abnormality was 36%, 46%, and 18%, respectively. The neuropsychological battery included measures of global cognitive ability, attention-concentration, learning/memory, executive function, speech/language, and information processing speed. The two groups did not differ significantly on age, education, age of seizure onset, seizure duration, or medications. There was a significant difference ($p < .05$) for gender with the -MRI/-MRS group having a greater proportion of females (73% vs. 27%).

Results: Descriptive statistics revealed a clear trend for the -MRI/+MRS group to perform worse than the -MRI/-MRS group on most measures. Univariate statistical analyses showed the -MRI/+MRS group scored significantly lower than the -MRI/-MRS group on measures of verbal memory ($p < .01$), verbal learning ($p < .01$), nonverbal memory ($p < .05$), and visuoconstruction ($p < .05$).

Conclusions: These data indicate the patients who demonstrate functional mesial temporal lobe abnormality as measured by MRS perform worse on neuropsychological testing in general, and more specifically on measures of learning/memory than patients without neuroimaging evidence for either a structural or functional lesion. The MRS offers increased sensitivity to detect mesial temporal pathology that is not obvious on structural MRI imaging. The MRS temporal lobe abnormality in isolation appears to correlate with reduced neuropsychological function, particularly learning and memory. The use of MRS in combination with MRI may be valuable in evaluating progression of mesial temporal pathology.

1.471
PHONEMIC FLUENCY AND CONFRONTATION NAMING TEST PERFORMANCE IN PATIENTS WITH LEFT FRONTAL OR RIGHT FRONTAL LOBE EPILEPSY

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Rationale: Determine the effect of left frontal (LF) versus right frontal (RF) lobe epilepsy on Boston Naming Test (BNT) and Controlled Oral Word Association Test (COWA) performance.

Methods: A retrospective database study of epilepsy patients who had undergone a pre- surgical neuropsychological evaluation between 1991 and 2004. Only those patients demonstrating localized pathology evidenced by MRI imaging and video EEG monitoring that subsequently underwent left or right frontal surgery were included for comparison. Past research on other patient populations with focal LF lesions has demonstrated relative deficits in phonemic fluency and confrontation naming compared to patients with focal RF lesions. Raw test scores of 30 patients who had left ($n = 15$) or right ($n = 15$) frontal resections in Milwaukee at the Medical College of Wisconsin or St. Luke's Medical Center from 1991 to 2004 were analyzed using independent samples *t* tests. Age of onset, gender, education level, and FSIQ did not differ between LF and RF groups, although they did differ in age at time of pre-surgical neuropsychological testing (LF = 27.1 years, RF = 35.9 years, $F = 12.76$, $p = .001$).

Results: The LF group performed significantly worse than the RF group on the BNT (LF = 44.5, RF = 52.4, $F = 10.29$, $p < .01$) (raw scores). The LF and RF groups were not significantly different in COWA performance (LF = 31.9, RF = 25.6, $F = .059$, $p = .811$)(age and education corrected raw scores).

Conclusions: LF lobe epilepsy patients demonstrated the expected deficit in confrontation naming as compared to RF lobe epilepsy patients, but did not demonstrate the expected deficit in phonemic fluency evidenced by LF lesion patients from past research. Further research is needed to explore this dissociation in patient populations.

1.472
COGNITIVE PERFORMANCE OF OLDER ADULTS WITH EPILEPSY, PATIENTS WITH MILD COGNITIVE IMPAIRMENT, AND HEALTHY OLDER CONTROLS

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Rationale: Older adults with epilepsy represent a considerable percentage of epilepsy patients. However, little is known about the cognitive effects of epilepsy in this group. We compared cognitive performance of older adults with epilepsy to older patients with mild cognitive impairment (MCI) and healthy older adults to characterize cognitive impairment in older adults with epilepsy.

Methods: 27 older adults with epilepsy (>age 60), 27 MCI patients, and 27 healthy older controls were studied. Participants with epilepsy all had clinical diagnoses of partial-onset seizures for 29 years on average. All participants completed measures of overall cognition, executive function, verbal memory, and word fluency.

Results: No significant group differences occurred for age, gender, race or education. Older controls scored significantly higher than epilepsy patients on virtually all cognitive measures. Controls also scored higher than MCI patients on all measures except initiation and word fluency. MCI patients scored significantly higher than epilepsy patients on overall cognition and initiation. Epilepsy patients did not outperform either of the other two groups (Table 1).

Conclusions: Epilepsy patients performed below MCI patients on measures of executive function and overall cognitive functioning. MCI patients presumably have temporal lobe- based memory loss while partial epilepsy commonly arises from temporal and frontal lobes, consistent with the broader array of cognitive dysfunction in the epilepsy patients compared to MCI patients. Older adults with epilepsy manifest memory impairment to the same extent as persons with a clinical memory disorder (MCI) and have more global cognitive impairments. (Supported by Centers for Disease Control and the National Institute on Aging.)

1.473
TOPOGRAPHICAL DISTRIBUTION OF AUDITORY AND VISUAL NAMING SITES IN PATIENTS WITH MEDIAL AND NON-MEDIAL TLE

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Rationale: Anterior temporal lobe resection for seizure control involving the language dominant hemisphere carries the risk of postoperative naming decline. This decline, however, is minimal in patients with the syndrome of medial TLE ("MTLE," i.e., patients with medial temporal sclerosis, "MTS") compared to that observed in patients with non-medial TLE ("nonMTLE." To explain this finding, it has been theorized that the earlier age of onset in MTLE patients elicits reorganization of cortical function. Specifically, cortical sites essential for naming might shift away from the region of seizure onset, and therefore, would less likely be included within the boundaries of an anterior temporal resection. To test this hypothesis, we compared the topographical distribution of auditory and visual naming sites identified by direct cortical stimulation in preoperative left (i.e., language dominant) MTLE and nonMTLE patients.

Methods: Subjects were 25 left TLE patients (10 MTLE, 15 nonMTLE) who underwent preoperative cortical language mapping (9 intraoperative, 16 extraoperative) utilizing visual and auditory naming tasks (mean age of on seizure onset: MTLE = 16.6, SD = 11.3, nonMTLE = 21.8, SD = 10.6). Naming was tested at 11–44 sites per patient, depending on time constraints (intraoperative) or extent of implantation (extraoperative). The anterior temporal region was defined as $\leq$ 5cm from the temporal pole, and the posterior temporal region as $>$ 5 cm from the temporal pole. The proportion of auditory and visual naming sites in the anterior and posterior temporal regions was compared in MTLE and nonMTLE patients using Fisher's exact test.

Results: In the MTLE group, 16 auditory naming and 3 visual naming sites were found in the anterior region, whereas 2 auditory naming and 8 visual naming sites were found in the posterior temporal region. In the nonMTLE group, 13 auditory naming and 5 visual naming sites were found in the anterior region, whereas 2 auditory naming and 16 visual naming sites were found in the posterior temporal region. Fisher's exact test comparing the distribution of naming sites indicated no significant differences in the distribution of auditory ($p > .05$) or visual ($p > .05$) naming sites between MTLE and nonMTLE groups. Results of independent sample T tests also showed no group differences in mean number of auditory naming sites, visual naming sites, or number of sites removed with resection (all $p > .05$).

Conclusions: These preliminary findings do not provide evidence of reorganization of naming sites within the lateral temporal region in MTLE patients. It remains possible, however, that MTLE patients develop additional naming sites in areas outside this region, such as the basal temporal area, more posterior temporoparietal cortex, or in homologous areas in the contralateral hemisphere. (Supported by NINDS grant R01NS035140 to M. J. Hamberger.)

Neuropsychological Performance of Study Groups

Neuropsychological Measure	Matched Controls	MCI Patients	Epilepsy Seniors	P Value	Post Hoc†
DRS Total Score	138.7 (3.7)	132.7 (5.5)	129.2 (8.8)	.001	C>M>E
DRS Attention	36.0 (1.1)	35.0 (1.6)	35.2 (1.5)	.024	C>ME
DRS Initiation	36.2 (1.7)	35.3 (2.5)	33.0 (3.6)	.001	CM>E
DRS Construction	5.6 (0.6)	4.9 (1.5)	5.0 (1.3)	.066	
DRS Conceptualization	36.9 (2.3)	35.2 (3.1)	33.9 (3.4)	.002	C>ME
DRS Memory	23.9 (1.1)	22.2 (2.4)	22.1 (2.3)	.002	C>ME
WMS III LM Immediate	39.7 (8.0)	29.0 (10.1)	26.4 (8.5)	.001	C>ME
WMS III LM Delay	24.4 (6.7)	16.3 (8.0)	14.7 (7.0)	.001	C>ME
CFL Fluency	35.6 (11.7)	33.0 (10.2)	26.9 (11.5)	.018	C>E

† C>M>E = control group mean is significantly greater than MCI and epilepsy group means, and MCI group mean is significantly greater than epilepsy group mean; C>ME = control group mean is significantly greater than MCI and epilepsy group means; CM>E = control and MCI group means are significantly greater than epilepsy group mean but do not differ from each other; C>E = control group mean is significantly greater than epilepsy group mean.

1.474

OXCARBAZEPINE MAY IMPROVE DEPRESSION ASSOCIATED WITH COMPLEX PARTIAL SEIZURES

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Rationale: Because depression is a common symptom among patients with uncontrolled complex partial seizures, it is important to know how antiepileptic drugs affect this co-morbid condition. In this study, we explored the effects of oxcarbazepine, a drug effective in the treatment of complex partial seizures, upon mood in patients with mild depression associated with complex partial seizures.

Methods: Twelve adults with uncontrolled complex partial seizures and mild depression who were receiving up to 2 anticonvulsant drugs, and had never been treated with oxcarbazepine, were entered into the study. The intial evaluation included a psychological evaluation which included the Montgomery-Asberg Depression Rating Scale (MADRS), the Spielberger State-Trait Anxiety Scale and the Quality of Life in Epilepsy Inventory (Qualie-89). Oxcarbazepine was initiated and titrated up to a maximum of 1200 mg per day, as tolerated,over a 4 week period. The psychological test battery was repeated at the end of 2 months of treatment. Test scores were compared using the paired t-test.

Results: Ten patients completed the study. Two patients discontinued due to side effects (rash; dizziness and nausea). There was a significant improvement in the mean Overall Score (Baseline: 18.9 {3.99 s.d.}, Treatment: 15.6 {4.33 s.d.}, $p = 0.030$}, the Apparent Sadness Scale (Baseline: 1.6 {0.52 s.d.}, Treatment 0.6 {0.70 s.d.}, $p = 0.004$), and the Pessimism Scale (Baseline 3.0 {0.00 s.d.}, Treatment 2.6 {0.516 s.d.}, $p = 0.037$) of the MADRS. There were no significant changes in the State-Trait Anxiety Scale or the Qualie-89. Oxcarbazepine levels ranged from 10 to 22 mcg/ml.

Conclusions: This study provides preliminary evidence that oxcarbazepine may improve the depression associated with uncontrolled complex partial seizures. Double-blind controlled studies are warranted. (Supported by Novartis Pharmaceuticals.)

1.475

COMPARISON OF RECEPTIVE AND EXPRESSIVE LANGUAGE FMRI ACTIVATION AND WADA LANGUAGE LATERALIZATION

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Rationale: Functional MRI has shown promise for lateralizing language in pre-surgical epilepsy patients. Previous studies found a strong correlation between Wada language scores and fMRI brain activation generated from a Semantic Decision (SD) task. Such findings indicated these techniques have similar lateralization value. A potential drawback of relying exclusively on SD as an activation paradigm for presurgical language mapping is the minimal activation of the anterior temporal lobe produced by SD. As a result, the ability of SD to predict postoperative decline may be limited in individual subjects, despite being effective in language lateralization. A paradigm that has shown promise in producing fMRI activation of the anterior temporal lobe involves having subjects generate names to aurally delivered definitions. Such Definition Naming (DN) paradigms may have potential for better prediction of postoperative language outcome than SD. To better understand the value of DN in determining language dominance and activation of language zones, DN and SD are compared to a Wada language index.

Methods: Forty-three patients with epilepsy were selected who had valid Wada testing and fMRI studies using DN and SM. Wada testing used a standardized administration and was quantitatively scored to yield an index of language dominance. Two fMRI language activation protocols were completed. In the SD protocol, patients heard the name of an animal and pressed a button if the animal was native to the United States and used by humans. In the DN protocol, patients were asked to speak the name of each of 128 aurally delivered definitions. Appropriate control tasks were contrasted with the experimental paradigms. Laterality indices for fMRI tasks were calculated by tabulating the number of task-contrast voxels of activation in left and right hemispheres and selected ROIs: $LI = (V_L - V_R)/(V_L + V_R)$.

Results: The Wada LI was found to significantly correlate with SD, $r(41) = .67$, $p < .001$, and the DN, $r(41) = .72$, $p < .001$. Despite DN requiring speech production but SD having no speech component, the LI's produced by the two tasks were significantly correlated with each other, $r(43) = .78$, $p < .001$. When voxel counts from various brain regions were examined, DN produced greater activation in dominant anterior temporal regions than the SM, $t(42) = 7.1$, $p < .001$.

Conclusions: As found in previous studies, SD and Wada language laterality index were significantly correlated. A new finding was that a DN task that requires speech generation was also significantly correlated with the Wada. In addition, DN produced greater activation of the dominant anterior temporal lobe. These findings indicate that a definition naming task may be a more useful method in predicting postoperative language functioning than a semantic decision task. (Supported by 1RO1 NS35929–04, 1RO1 NS33576, NIH M01-RR00058.)

1.476

FACTOR STRUCTURE OF THE EPILEPSY FOUNDATION OF AMERICAN CONCERNS INDEX

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Rationale: The Epilepsy Foundation of America Epilepsy Concerns Index (Gilliam et al, 1999) is a 20-question scale in which patients rate epilepsy-specific concerns on a 5-point scale. Although this scale is increasingly used to characterize both disease burden and treatment outcomes, the scores from the different questions are either studied

individually or summed into a single measure to reflect overall epilepsy concerns. We conducted Principal Components Analysis (PCA) to better understand the dimensions being assessed by this scale.

Methods: We performed PCA of the EFA Concerns Index scores of 189 patients undergoing evaluation for epilepsy surgery that were retrospectively identified. The patients averaged 34 years of age (SD = 11) with an average age of habitual seizure onset of 17 years (SD = 13). Factor scores were then compared to independent measures including the QOLIE-89, Personality Assessment Inventory (PAI), and neuropsychological measures of IQ and memory using multiple linear regression.

Results: Based upon the scree plot, the best model consisted of a 5 factor solution in which there were no varimax-rotated factors represented by fewer than 2 variables. The first factor appears to reflect affective impact on enjoyment of life and is identified by questions 16, 18, 19, 20, and to a smaller degree, questions 14 and 17. The second factor is defined by questions 1, 4, 5, 6, and 12, and appears to reflect concerns regarding general autonomy. Factor 3 is defined by 2, 7, 14, and 15 (questions 14 and 15 also load on factor 1) and reflects a fear of seizure occurrence. Factor 4 is defined by questions 9, 10, and 11, and reflects concern of being a burden to ones family. Factor 5 is defined by questions 8 and 13, and appears to reflect a perceived lack of understanding by others. Only a single question (3, having to take medication) failed to load on any of the factors. Multiple regression showed that the EFA factor scores were predicted by seven scales from the PAI, seven scales from the QOLIE-89, Performance IQ, and measures of verbal and visual memory. By contrast, only two PAI scores and four QOLIE-89 scores were associated with a single, summary EFA score.

Conclusions: This analysis confirms that the EFA Concerns Index is multidimensional, and that using a global score based upon all items may mask important specific concerns that may be relevant when applied to individual patients. Affective concerns is the strongest underlying factor, followed by autonomy, fear of seizures, family burden, and lack of understanding. These data support the validity and clinical utility of scoring the EFA Index by the 5 factors we have identified rather than relying on a single summary score.

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1.477
QUALITY OF LIFE AND SEXUAL FUNCTION IN PATIENTS WITH NES COMPARED WITH EPILEPTIC CONTROLS

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Rationale: The subjective measure of quality of life is an important variable in evaluating patients with epileptic (ES) and nonepileptic seizures (NES). Despite the different origins of the seizures, NES patients face similar struggles as patients with epilepsy, including effects of antiepileptic medications and limitations on daily activities. Use of the QOLIE, an epilepsy-specific survey on quality of life, for patients with NES has been validated. One aspect of quality of life that is frequently overlooked in clinical studies is sexual function and satisfaction. Epileptic patients have higher rates of sexual dysfunction than the general population, but physicians rarely inquire about epileptic patients' sexual activity. Less is known about sexual function in patients with NES. The objective of this study was to determine how quality of life and rates of sexual satisfaction and function compare between ES and NES patients.

Methods: We sent surveys to 50 patients with NES and 50 age- and sex-matched patients with ES; all patients' diagnoses were confirmed by vEEG monitoring. We used two standardized, previously validated psychiatric diagnostic instruments, the QOLIE-10 and the Arizona Sexual Experiences Scale (ASEX) The QOLIE includes 10 questions assessing the effects of seizures and AEDs on functioning and quality of life. The ASEX has five questions assessing sexual function and satisfaction. Data were analyzed using SPSS for Windows.

Results: 10 NES and 12 ES patients returned surveys. The NES and ES patients did not differ in age ($p = 0.37$) or gender ($p = 0.89$). NES patients were significantly less likely to report having a lot of energy ($p = 0.03$). They were significantly more likely to report being bothered by the mental effects of their antiepileptic drugs (AEDs) ($p = 0.04$), but not the physical effects ($p = 0.55$). NES patients also rated their quality of life significantly lower than ES patients ($p = 0.02$). In 3 of 5 categories rating sexual function, NES patients showed trends toward lower scores that nearly reached significance. They reported lower sex drive ($p = 0.12$), more difficulty becoming mentally aroused ($p = 0.07$), and more difficulty with physiological arousal ($p = 0.08$). They did not differ in ability to achieve or satisfaction with orgasm; these scores were extremely low in both groups.

Conclusions: NES patients reported significantly lower quality of life and level of energy than ES patients. They were significantly more bothered by mental effects of AEDs, emphasizing the importance of discontinuing AEDs in patients with exclusively nonepileptic seizures. Though ES patients have high levels of sexual dysfunction, NES patients tended to rate their sexual function and satisfaction lower than ES patients. The impact of NES on sexuality should be further clarified with larger studies.

1.478
INDIVIDUAL VARIABILITY OF HEALTHY VOLUNTEERS TO THE NEUROPSYCHOLOGICAL EFFECTS OF LAMOTRIGINE AND TOPIRAMATE

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Rationale: This study examined individual variability of the neuropsychological effects of lamotrigine (LTG) and topiramate (TPM) in healthy adults. We have previously reported that TPM produces significantly more adverse neuropsychological effects than LTG in healthy adults. Here, we examined the magnitude of effects and the variability across subjects to determine if certain individuals were more susceptible to the adverse neuropsychological effects.

Methods: This was a randomized, double-blind, two-period crossover study of 47 healthy adults (19 men and 28 women; mean age = 37 years) who completed both phases of the study. Each drug was given for 12 weeks (7 weeks dose escalation followed by 4 weeks maintenance, and then 1 week taper). Initial dose was 25mg/day, and target maintenance dose was 300mg/day for both drugs. Neuropsychological evaluations were conducted at Screening, end of First and Second Maintenance Phase, and Post-treatment Period. There were 41 variables across 17 measures: Selective Reminding Test, MCG Paragraph Memory, Boston Naming, Animal Naming, Controlled Oral Word Association, Stroop, Symbol Digit Modalities Test, Digit Cancellation, Grooved Pegboard, Choice Reaction Time, Visual Serial Addition Test, Continuous Performance Task, A-B Neurotox, SEALS, POMS, SF-12, and QOLIE-89 attention, language and memory subscales. Difference scores were calculated for each drug compared to the non-drug conditions. The number of variables with difference scores were determined for each subject across the following standard deviation (SD) ranges: ≤ -2; ≤ -1; $\geq +1$; $\geq +2$.

Results: 12 subjects on TPM had >25% of their variables reduced ≥ -2 SD compared to the non-drug condition, all 41 had >25% variables reduced ≥ -1 SD, and 12 had >50% reduced ≥ -1 SD. For LTG, 2 subjects had >25% variables reduced ≥ -2 SD, 6 had >25% variables reduced ≥ -1 SD, and none had >50% reduced ≥ -1 SD. 18 subjects on LTG had >25% of their variables increased $\geq +1$ SD, and none for TPM. No subject on either drug had >25% of their variables increased $\geq +2$ SD.

Conclusions: Lamotrigine produced fewer neuropsychological adverse effects than topiramate in monotherapy at the dosages, titrations and timeframes employed in this study. Variability of drug effects was seen across subjects. Certain individuals appear to be particularly sensitive to adverse cognitive effects. In clinical practice, recognition of

patients who are similarly hypersensitive to the adverse cognitive effects of antiepileptic drugs is important. (Supported by Glaxo SmithKline.)

1.479

NEUROMAGNETIC SUSTAINED FIELD IN RECOGNITION MEMORY TASK FOR SPOKEN JAPANESE WORDS

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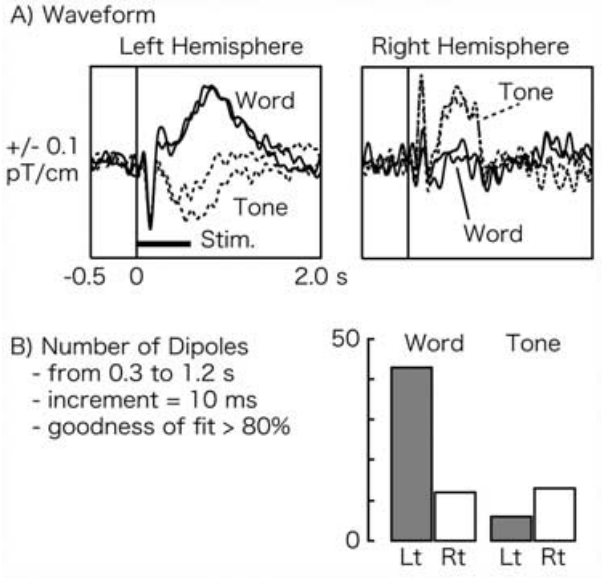
Rationale: Neuromagnetic fields evoked by a spoken-word recognition task show hemispheric asymmetry in native English and Spanish speakers but not in Mandarin-Chinese speakers (Neuropsychologia 2004; 42:967). Here, we tested whether such tasks can be used to define the language-dominant hemisphere in native Japanese speakers.

Methods: Neuromagnetic fields evoked by a spoken-word recognition task and a tone burst of 1000 Hz were measured using a helmet-shaped magnetoencephalography (MEG) system in 9 patients (7 males and 2 females, aged from 23 to 64 years old) with medically intractable epilepsy (n = 3), gliomas (n = 5), and cavernous angioma (n = 1) as a part of presurgical functional evaluation. The language-dominant hemisphere was later confirmed by correlation of the lesion and language deficit or by functional mapping with electrical cortical stimulation. All stimuli had a duration of 600 ms. One hundred responses were recorded between 500 ms prestimulus (baseline) and 2,000 ms after the stimulus onset. Digital filtering of 0.2–25 Hz was applied to all evoked data.

Results: N100m activity was found bilaterally for all stimuli followed by sustained fields from approximately 300 ms to 1200 ms (Fig. 1A). Equivalent current dipoles (ECDs) of the N100m were estimated on the posterior part of the upper surface of the bilateral temporal lobes. ECDs of the sustained fields were estimated in the bilateral temporo-parietal lobes. In 8 patients, the amplitudes and goodness-of-fit values in the ECD model for the sustained fields were dominant in the left hemisphere for the word-recognition task, but in the right hemisphere for the pure tone (Fig. 1B). The language-dominant hemisphere was later confirmed as the left in all these 8 patients. In contrast, the language-dominant hemisphere of one patient, who showed reversed laterality in presurgical MEG, was later found to be the right.



Conclusions: Combination of the spoken-word recognition task may be used to define the language-dominant hemisphere in native Japanese speakers. Cross-linguistic study may be necessary to confirm whether the sustained field can be used to determine the language-dominant hemisphere in speakers of other languages.

1.480

VOLUMETRIC MRI ABNORMALITIES AND COGNITIVE MORBIDITY IN CHRONIC TEMPORAL LOBE EPILEPSY

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Rationale: Research examining the predictors of cognitive impairment in epilepsy has traditionally focused on clinical variables associated with the cause (e.g., etiology), course (e.g., seizure frequency), or treatment (e.g., medications) of the disorder. Structural brain changes associated with chronic epilepsy, particularly temporal lobe epilepsy (TLE), have been characterized in regions both related to and distant from the primary areas of epileptogenesis, but their associations with cognitive morbidity have been examined infrequently. The purpose of this study was to determine the association between cognitve morbidity and reductions in total gray and white matter and increased CSF volumes.

Methods: Healthy controls (n = 67) and patients with TLE (n = 77), ranging in age from 14 to 60 years, underwent comprehensive neuropsychological assessment of intelligence, language, perception, verbal and nonverbal memory, psychomotor processing, and speeded fine motor dexterity. Twenty cognitive indices were derived for each subject from this test battery. Test scores were converted to adjusted (age, gender, education) z-scores and an impairment index computed for each subject, defined as the proportion of test scores exceeding z = -1.5. Test score performance was related to adjusted (ICV) quantitative volumetric measures of total cerebral gray and white matter and total CSF.

Results: Poorer cognitive function was especially associated with increased CSF volume. Specifically, increased total CSF was associated with poorer Full Scale and Performance IQ (WAIS-III), immediate and delayed visual and auditory memory (WMS-III), simple and complex psychomotor processing (Trails A and B), speeded fine motor dexterity (Grooved Pegs), and response inhibition (Stroop Test). Reductions in total cerebral white and gray matter were also significantly associated with poorer cognitive performance, but to a lesser extent. Examining the degree of cognitive morbidity exhibited by individual TLE patients (i.e., impairment index), increasing cognitive morbidity was significantly associated with increased CSF ($r = .36$, $p < 0.001$) and decreased cerebral white matter ($r = .28$, $p < 0.01$).

Conclusions: Quantitative MRI volumetric abnormalities in chronic TLE are associated with significantly increased cognitive morbidity. Increased total CSF was an especially strong correlate of neuropsychological dysfunction, with significant but somewhat weaker effects for reductions in cerebral gray and white matter. The pathways through which clinical seizure features (e.g., etiology, seizure frequency, duration, medications) result in abnormalities in brain structure remain to be clarified, but these structural changes, especially markers of atrophy such as total CSF, appear to be of clinical consequence. (Supported by NIH NS 2RO1–37738 and M01 RR03186.)

1.481

HIPPOCAMPAL VOLUMETRIC STUDY AND MAJOR DEPRESSIVE DISORDER IN PATIENTS WITH REFRACTORY TEMPORAL LOBE EPILEPSY

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Rationale: Various authors have associated structural hippocampal abnormalities and the presence of major depressive disorder (MDD) in patients with or without epilepsy. Besides these, several evidences point to a significantly greater frequency of MDD in temporal lobe epilepsy (TLE) associated with mesial temporal sclerosis (MTS). It is, therefore, believed that there is a link between MTS and MDD. The aim of this study was to evaluate the association between the degree and side of hippocampal atrophy on MRI and the presence of MDD in patients with TLE associated with MTS.

Methods: 53 patients with refractory TLE who attended at an outpatient clinic had a 1.5T MRI. The images were evaluated by only one

observer blinded to the electroclinical data which would allow for the lateralization of the epileptogenic zone. We looked for evidences of hippocampal atrophy (atrophy in T1 and/or hypersignal in FLAIR) as well as the volumetric study through the sequence FFE-T1. The atrophy was considered severe when hippocampal volume was 3 SD below the mean of a control group constituted by individuals without epilepsy (n = 13). The psychiatric evaluation consisted of an interview with the patient followed by another with the family. The diagnosis of MDD was done by the SCID-I (DSMIV). The interviewer was also blinded to the electroclinical data. Patients with concomitant personality and chronic psychotic disorders were excluded. Data was analyzed through the correlation test of Spearman.

Results: Among the MTS patients (n = 53), 56.6% were female, mean age of 34.2 yrs. and 43.4% were male, mean age 38.5 yrs. Severe hippocampal atrophy was seen in 86.8% (n = 46). This included severe bilateral atrophy in 15.2% (n = 7); unilateral on the right in 28.3% (n = 13) and unilateral on the left in 56.5% (n = 26). Depression was observed in 17/53 patients with refractory TLE (32%), this being 11/26 patients with severe atrophy of the left hippocampus (LH) (42.3%), 3/13 patients with severe atrophy of right hippocampus (23%) and 4/7 patients with bilateral severe atrophy (57%). None of the patients with slight or moderate hippocampal atrophy presented depression. Despite the greater frequency of depression associated with severe LH atrophy (3 SD below the mean), this association was not statistically significant. However, when the volumes of the LH were analyzed, we found a negative correlation between these and that of depression ($r_s = -0.308$; $p = 0.025$). Considering the adopted parameter of severe atrophy, there was a significant correlation between depression and severe bilateral atrophy ($r_s = 0.315$; $p<0.022$).

Conclusions: Our data point to the association between the presence of depressive psychopathology and refractory epilepsy related to LH atrophy and severe bilateral hippocampal atrophy. (Supported by FAPESP-Fundação de Amparo à Pesquisa do Estado de São Paulo.)

1.482

VALPROATE FOR ALTERING MOOD AFTER TRAUMATIC BRAIN INJURY

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Rationale: Mood disorders such as irritability, depression, and anxiety are commonly reported after traumatic brain injury. Valproate is frequently used as a mood stabilizing drug.

Objective: To determine whether valproate has any effect on mood in those with traumatic brain injury

Design: Randomized, double-blind, clinical trial to compare the effects of valproate and phenytoin for seizure prophylaxis. Assessments of mood were done during valproate treatment at 1 and 6 months after injury.

Setting: Level I trauma center

Patients: 189 patients on their assigned, blinded drug tested at 1 month and 145 at 6 months. Participants were at least 14 years old and had complicated mild to severe injuries.

Interventions: 1 week of phenytoin (followed by placebo) or 1 month or 6 months of valproate.

Main outcome measures: Brief Symptom Inventory (BSI)

Results: Despite depressive symptoms being quite common, there was no effect of valproate on depressive symptoms reported (37% >1sd above on BSI depression at both 1 and 6 months, p = .84 and.44 comparing groups).

BSI hostility scale reflecting irritability indicated somewhat fewer problems overall, but again no treatment effect (about 25% >1sd, p = .72 and.79).

Results on anxiety are less clear. Cross-sectionally, there was no treatment effect (p = .78 and.84), but an analysis of change from 1 to 6 months suggested a positive impact of valproate on anxiety (p = .04).

Conclusions: Despite some elevations, there is no indication valproate decreases depression or irritability. There is a suggestion of a positive effect of long-term valproate use on anxiety. (Supported by NIH/NINDS R01 NS19643. Drug and placebo provided by Abbott Labs.)

1.483

BRAIN ACTIVATIONS IN AN FMRI MEMORY PARADIGM: ARE RESULTS STABLE IN RETEST?

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Rationale: A functional magnetic resonance imaging (fMRI) memory paradigm that will reliably activate medial temporal-lobe structures has an immense potential usefulness in evaluation of patients with temporal-lobe epilepsy. It has been notoriously difficult to activate the hippocampus, but recently some successful paradigms have been devised. To be clinically useful, an fMRI memory test should activate medial structures of both hemispheres reliably in healthy individuals, so that unilateral activation would be clearly abnormal. It should also yield stable results within individuals, so that if changes are observed on retest they can be interpreted as reflecting real changes in brain function. We examined the reliability for site and extent of activations when subjects are retested, using a memory encoding paradigm that has elicited bilateral activation of medial temporal-lobe (MTL) structures in most healthy individuals tested.

Methods: Seven healthy volunteers and one patient were tested twice on a picture-encoding task during fMRI. Subjects viewed 120 pictures for later recognition, in a blocked design. The two tests used different sets of pictures equal in difficulty; order was counterbalanced. Intervals between tests varied from 2.5 to 20 months (mode = 5.5). Stability of memory test scores as well as site and degree of brain activations were analyzed.

Results: Memory scores improved in second testing ($t = 3.91$, $p < .01$) and nobody earned a lower score on retest. Three subjects activated essentially the same MTL regions in both sessions, but differences were observed in four: most were in the direction of fewer MTL activations upon retest, but changes were also seen in site and side. These changes were not related to time interval between tests. In contrast, frontal-lobe activations did not disappear on retest for 6 of 7 subjects and indeed tended to increase. The patient, whose second test followed a left anterior temporal-lobe resection and whose memory scores were excellent both times, showed bilateral MTL activations before surgery and none on the left postoperatively.

Conclusions: Results were variable among seven healthy subjects retested so far, with some showing similar activations upon retest and others not. No clear pattern emerges from this limited sample, and we are continuing to collect subjects and to investigate possible variables that may contribute to differences when they occur. If these findings remain in a bigger sample, it appears that fMRI activations are a snapshot at a moment in time and may not reflect a basic and enduring status of an individual's memory system, even for a same test paradigm. As habituation plays a role in reducing activations for repeated tests, it may be wise to test twice (using different memory tasks) in both test and retest, to obtain more representative samples. These results suggest that data from retest after surgery or other interventions should be interpreted with caution. (Supported by Canadian Institutes of Health Research.)

1.484

COMPARISON OF COGNITIVE EFFECTS OF TOPIRAMATE AND ZONISAMIDE

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Rationale: Two of the newer anticonvulsants, topiramate (TPM) and zonisamide (ZNS), have a similar chemical structure and mechanism of action. Recent reports (Lee et al, 2003; Weatherly et al, 2003) have also suggested similar cognitive side effect profiles for the two drugs. The current study aims to specifically compare the cognitive side effects of TPM and ZNS.

Methods: Thirty-eight intractable epilepsy patients were selected retrospectively who had undergone neuropsychological testing during adjunctive therapy with TPM (n = 16) and ZNS (n = 22). All patients had a baseline IQ of 70 or greater, had been taking the respective drugs for

at least three days, and did not have a progressive neurological disorder. At baseline, the TPM and ZNS groups were similar in terms of IQ and education, although the TPM group was somewhat younger (mean = 29.0 years vs. ZNS mean = 42.4 years). The mean TPM dose was 234.4 mg/day and the mean ZNS dose was 366.7 mg/day. The cognitive test battery included measures of working memory, verbal fluency, visual-motor speed, and manual dexterity. Paired t-tests were conducted within each group to compare baseline performance to mean scores while on TPM or ZNS therapy. Values of $p < .05$ were considered statistically significant.

Results: For the TPM group, significant declines from baseline were observed on measures of animal naming ($p < 0.01$), phonemic verbal fluency ($p = 0.00$), digit recall ($p = 0.00$) and mental sequencing ($p < 0.01$). For the ZNS group, significant declines were observed on measures of animal naming ($p < 0.05$), phonemic verbal fluency ($p = 0.00$), digit recall ($p = 0.00$), mental sequencing ($p < 0.01$), and visual-motor speed ($p < 0.05$). The mean percent change from baseline for each variable was similar between the two groups. However, a greater proportion of the ZNS patients declined one standard deviation or more on measures of visual motor speed and mental sequencing. A greater proportion of TPM patients declined one standard deviation or more on measures of immediate digit recall and animal naming.

Conclusions: These results suggest similar cognitive side effect profiles in patients taking TPM and ZNS, with declines noted in both groups on measures of verbal fluency and working memory. The ZNS group also experienced a decline in visual-motor speed. These findings suggest that for both drugs, performance may be more affected on tasks requiring cognitive processing as opposed to motor speed. Patients taking TPM were more likely to decline on measures of digit span and animal naming, while ZNS patients were more likely to decline on measures of mental sequencing and visual motor speed. Additional research is needed to investigate the possible effects of dose, titration, and duration of drug therapy on cognitive test performance.

1.485

DETECTING COGNITIVE DIFFERENCES BETWEEN PATIENTS WITH EPILEPSY AND PATIENTS WITH PSYCHOGENIC NONEPILEPTIC SEIZURES: EFFORT MATTERS

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Rationale: The majority of patients with PNES fail relatively easy tests of recognition memory (the Word Memory Test, or WMT) at twice the rate of patients with documented epilepsy, suggesting a greater prevalence of poor effort that invalidates neuropsychological test results (Williamson et al., 2003). Unfortunately, exploration of the effects of this "poor effort" on other neuropsychological tests has been limited. This project addresses this by assessing the effect of WMT failure across a range of neurocognitive measures. We hypothesized that:

> (a) Patients who fail the WMT will perform significantly worse on a range of neurocognitive tests than patients who pass the WMT.
> (b) If the lack of discriminability between epilepsy patients and PNES patients on neurocognitive testing is driven by effort rather than by common neuropathological substrates that affect cognition, then PNES patients who put forth valid effort should outperform epilepsy patients who put forth valid effort

Methods: 97 patients who have comprehensive diagnostic workups including video telemetry were diagnosed as having exclusively epileptic seizures ($n = 68$) or exclusively psychogenic nonepileptic seizures ($n = 29$). Level of cognitive performance was indexed by the Dodrill Discrimination Index (DDI), which depicts the percentage of 16 tests on which patients performed below normal limits. Diagnostic groups were compared overall and as stratified by WMT performance.

Results: The DDI of epilepsy patients did not differ from that of PNES patients ($p = .213$). However, the groups varied significantly when viewed in light of WMT performance ($p < .001$). The PNES patients who put forth valid effort significantly outperformed all other groups, including the patients with epilepsy who put forth valid effort ($p < .01$). The groups that put forth valid effort outperformed the groups that did not. Finally, the epilepsy and PNES patients that failed the WMT did not differ from each other ($p = .904$).

Conclusions: 1. Patients who fail the WMT perform much more poorly than those patients who pass the WMT across a range of neurocognitive measures. Some epilepsy patients who perform in this range have had seizures within the 48 hours preceding the testing, and others have documented, lifelong evidence of significant cognitive impairment. In contrast, there is no known brain-behavior relationship that could account for this level of performance in patients with PNES, most of whom live independently.

2. The common wisdom is wrong. Level of performance in neurocognitive testing **does** differentiate patients with epilepsy from patients with PNES - if one compares PNES patients who are putting forth valid effort.

Neuropsychology/Language/Behavior—All Ages

1.486

EPILEPSY DISCOVERIES AS A RESULT OF COMMUNITY MENTAL HEALTH CENTER PSYCHIATRIC REFERRALS

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Rationale: We performed a retrospective review of 83 patients referred from the Community Mental Health Center for Forsyth County, North Carolina to Epilepsy Institute of North Carolina-Department of Neuropsychology -Social Work for the years 2003 and 2004. These patients were referred for neuropsychological testing due to behavioral reasons: suspected conduct disorders, attention deficit, and learning disorders. This review determines to what extent behavioral disorders in an economically disadvantaged population coincide with Epilepsy. Outcomes could improve conduct, learning, and behavior through early Epilepsy evaluations and treatment.

Methods: Eighty three patients, ages four to seventeen, 60% female and 40% male, received a psychosocial evaluation, followed by psychological and neuropsychological testing, neurological exam, and electroencephalograms in four scheduled visits. The results are summarized in a round table discussion with the team composed of the social worker, psychologist, nurse practitioner, neurologist, and psychiatrist. Recommendations and results are presented to the patient and the patient support team with the patient present.

The following tests are performed when indicated and appropriate: 1)A psychosocial evaluation consisting of social, medical, and psychiatric histories, & caretaker self administered child behavioral evaluation through the computerized Behavioral Assessment Scale for Children.(BASC). 2) The child or adolescent concurrently was tested for general intelligence and memory, utilizing the Weschler Intelligence Scale, and memory testing with the Children Memory Scale or Weschler Memory Scale. In addition, the following instruments can be utilized: Stroop Color Word Test, Wide Range Achievement Test, Personality Assessment Inventory, and Rorschak projective testing. A subsequent session includes the Halstead-Reitan Neuropsychological Test Battery. An EEG(a,d,s,hv&p and imaging when pertinent) was adminsistered, and neurological examination.

Results: Twelve of eighty three (14.5%) patients had abnormal EEGs in the testing group. Of the twelve patients with abnormal EEGs, 90% were classified as Oppositional Defiant Disorders, 50% ADD-ADHD, and 10% others (Aspergers and Psychosis). Four of these patients reported seizures while being tested. Historically, seven patients reported staring spells or impairment of consciousness, or typical seizure manifestations. 60% of the EEGs had generalized spike and wave, 25% were localized, and 15% had 3/sec S&W.

Conclusions: The results suggest that one in seven have abnormal EEGs associated with behavioral disorders, or Epilepsy, or both. These findings suggest that all patients referred for behavioral, psycholgical, and neuropsycholgical testing by a Community Mental Health Agency should be evaluated for Epilepsy.

1.487

CEREBRAL LANGUAGE LATERALIZATION IN EPILEPTIC PATIENTS AS A FUNCTION OF HANDEDNESS AND IMAGING FINDINGS

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Rationale: The intracarotid amobarbital (Wada) test (IAT) is used to assess cerebral language lateralization in epileptic patients preceding resective surgery. Left-hemispheric language representation predominates in dextral patients. For non-dextrals, higher but widely varying incidences of atypical (right or bilateral) language were reported by previous studies. The purpose of this study was to determine the incidence of left (L), right (R), and bilateral (B) language in dextral and non-dextral subjects as a function of localization and type of lesions on MRI.

Methods: A retrospective chart review of 445 bilateral IAT (1997 to 2003) was performed. Language lateralization was assessed based on speech arrest times. Localization and type of lesion on presurgical MRI was determined. Left-hemispheric lesions were classified as "early" (congenital or perinatally acquired: malformations of cortical development, vascular malformations, perinatal encephalomalacia) and "late" (all others). Chi^2 test was used for statistical comparisons (significance: 0.05).

Results: Out of 391 dextrals, 322 (82%) were L dominant, 16 (4%) were R, 53 (14%) were B. Out of 54 non-dextrals, 26 (48%) were L, 12 (22%) were R, 16 (30%) were B. 97 patients had normal MRI (84 right-handed, 13 left-handed). Of 84 right-handed non-lesional cases, 68 (81%) were L, 3 (4%) were R, 13 (15%) were B. Out of 13 left-handed non-lesional cases, 9 (69%) were L, one (8%) was R, 3 (23%) were B. 49 patients had early left-hemispheric lesions (41 right-handed, 8 left-handed). Of 41 dextrals with early left lesions, 28 (68%) were L, 4 (10%) were R, 9 (22%) were B. Out of 8 non-dextrals with early left lesions, none (0%) was L, 4 (50%) were R, 4 (50%) were B. 65 patients had late-onset left neocortical lesions (54 right-handed, 11 left-handed). Out of 54 dextrals with late-onset left neocortical lesions, 44 (81%) were L, 3 (6%) were R, 7 (13%) were B. Out of 11 non-dextrals with late-onset left neocortical lesions, 3 (27%) were L, 3 (27%) were R, and 5 (46%) were B dominant.

Conclusions: The majority of patients without neocortical lesions are L dominant, regardless of handedness (81% of dextrals, 69% of non-dextrals), exclusive R language is rare in this group. Compared to subjects with normal MRI, right-handed subjects with left-neocortical lesions are slightly more likely R dominant ($p = 0.05$). The vast majority of left-handed patients with early left neocortical lesions are R or B dominant; none in this group was L dominant. Left-handed subjects with late-onset left neocortical lesions were most likely B dominant. Thus, most left-handed patients with left neocortical lesions display atypical language representation, with R dominance prevailing in patients with congenital or perinatally acquired lesions, and B dominance prevailing in subjects with late-onset lesions. [Supported by Innovative Medizinische Forschung (IMF), University of Munster, Germany (MO 620202).]

1.488

INCOMPLETE REORGANIZATION OF LANGUAGE TO THE RIGHT HEMISPHERE IN RESPONSE TO EARLY LEFT HEMISPHERE SEIZURE ONSET: IMPLICATIONS FOR LEFT HEMISPHERE FOCAL RESECTION

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Rationale: The intracarotid amobarbital procedure (IAP) is considered the gold standard for assessment of hemispheric dominance for language functions despite the recent development of functional imaging studies for this purpose. These methods are highly reliable when language is clearly unilateral. However, the presence of even subtle language ability in the nondominant hemisphere may place a patient at risk for postoperative aphasia. This study reports on patients who appeared primarily right hemisphere language dominant on IAP but nonetheless clearly demonstrated left hemisphere language areas during electrical stimulation studies.

Methods: Two male and two female patients, ages 11–18 years, underwent IAP and electrical stimulation studies prior to focal resection for intractable seizures involving the left frontal or temporal area. Three of four were left-handed. IQ was mildly impaired (74–81) in all patients. All four evidenced left hemisphere structural abnormalities, and three evidenced left mesial temporal sclerosis. During cortical mapping, language was tested in five modalities (rote speech, naming, repetition, comprehension and reading). These mapping data were contrasted with the IAP.

Results: All patients displayed primarily right hemispheric language dominance on IAP; however, minor language production (rote or automatic speech) was noted following right hemisphere injection in three patients, and paraphasic errors, which were sometimes subtle, were noted following left hemisphere injection in three patients. On cortical stimulation, clear frontal and temporal language areas were identified in all patients, with the exception of one patient whose subdural electrode array did not extend anterior to the motor area, precluding identification of a frontal language area.

Conclusions: Right hemisphere language dominant epilepsy surgery candidates with even subtle evidence of left hemisphere language on IAP should be considered for cortical mapping prior to resection.

1.489

RIGHT HEMISPHERE LANGUAGE MAPPING USING ELECTROCORTICAL STIMULATION IN PATIENTS WITH BILATERAL LANGUAGE

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Rationale: The configuration of language cortex in the left dominant hemisphere based on electrocortical stimulation has been described in detail in the literature. However, language representation in the right hemisphere remains unclear in patients classified with bilateral language based on the intracarotid amobarbital procedure (IAP). Herein, we report 5 patients with bilateral language who underwent placement of a right subdural electrode array (SEA) and subsequent electrocortical stimulation for language.

Methods: The right hemisphere language maps of 5 patients with bilateral language, who underwent SEA placement at Minnesota Epilepsy Group between January 1996 and February 2004, were reviewed. In each case, data were critically compared to the colored photograph of the brain and SEA implant taken intraoperatively for anatomical verification. Expressive and receptive language areas were defined based on language errors produced by electrical brain stimulation during the presentation of a formal language protocol, which included assessment of automatic speech, naming, reading, repetition and auditory comprehension.

Results: Three of the 5 patients studied demonstrated the presence of language cortex in the right frontal and/or temporal lobe analogous to the localization of classical language areas in the left hemisphere. In each of these cases, data from the IAP suggests the left hemisphere remains primary for language processing. One patient had a widespread distribution of single site language errors over the right lateral hemisphere. The language map of the remaining patient was completely silent.

Conclusions: Our results identify the presence of language cortex in the right hemisphere in 4/5 patients classified with bilateral language in IAP. These areas are presumed to be accessory language zones to the primary language processing areas of the left hemisphere. Further exploratory studies are needed to clarify these specific findings. The clinical significance of these language areas remains to be determined.

1.490

COGNITIVE FUNCTIONING IN BILATERAL PERISYLVIAN POLYMICROGYRIA

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Rationale: Bilateral perisylvian polymicrogyria (BPP) is a malformation of cortical development in which the cerebral cortex in the border and depth of the sylvian fissures is thickened and abnormally infolded on MRI. Most patients with BPP present with congenital bilateral perisylvian syndrome (CBPS), featuring pseudobulbar palsy, developmental delay, cognitive deficits, pyramidal signs and seizures. Because of severe dysarthria, many patients with CBPS are labelled as severely retarded. In this study, we investigate cognitive functioning in patients with BPP and determine whether BPP is associated with exceptionally low intellect (FS IQ < 70).

Methods: Fourteen patients (6 male, age range 23–60) were selected based on the presence of BPP on MRI and the ability to undergo neuropsychological evaluation. Medical records and EEG reports were reviewed. All MRI data were reviewed by one of the authors, blinded to the clinical features and neuropsychological findings. A ranking was made based on the anatomic extent of the perisylvian involvement according to imaging. Neuropsychological evaluation included assesment of verbal and nonverbal intelligence, verbal and visual memory, receptive and expressive language, frontal lobe function and handedness. The relationship between the extent of the cortical disorganization and the neuropsychological test scores was examined using Spearman's Rank Correlation Analysis.

Results: Seizures were present in 85%. Eleven patients had pseudobulbar features. A significant correlation was found between the extent of the cortical disorganization and the performance IQ. Criteria for mental retardation (FS IQ < 70) were met in 4 patients. Five had low IQ, 4 had low average IQ and one had normal intelligence. No selective memory impairment was associated with BPP. Frontal lobe function was well preserved.

Conclusions: This study demonstrates that cognitive function correlates with the extent of the cortical disorganization and that, despite the clinical picture of severe dysarthria, exceptionally low intellect is only present in a minority of BPP patients. Apart from the extent of BPP and age at testing, seizures can also influence the outcome of cognitive studies, since frequent seizures can aggravate speech dysfuction or cause progressive deterioration in these patients. (Supported by Savoy Foundation for Epilepsy.)

1.491
ATTENTION AND EXECUTIVE FUNCTIONING IN TEMPORAL LOBE EPILEPSY PATIENTS WITH AND WITHOUT MTS

Christina A. Palmese and Marla J. Hamberger (Neurology, Columbia University Medical Center, New York, NY)

Rationale: Results of recent studies suggest that the temporal lobe is involved in attention and executive functioning. However, few studies have assessed these functions in TLE patients, and no single study has comprehensively assessed different aspects of attention and executive functioning in this population. Within this group, we compared patients with and without MTS. Given the earlier age of onset typically associated with MTS, we hypothesized that patients with MTS would perform more poorly on these measures due to longer duration of irritative activity in the temporal region.

Methods: Eighty-nine TLE patients (51 non-MTS, onset 24 yrs; 38 MTS, onset 13 yrs, $p < .001$) underwent comprehensive neuropsychological evaluation. Measures used to assess attention and executive functions included Symbol Search, Digit Symbol Coding (psychomotor speed, selective attention), Digit Span, Arithmetic and Letter-Number Sequencing (working memory), and Similarities (abstract reasoning) subtests of the WAIS-III; Controlled Oral Word Association Test ("COWAT," verbal fluency); Trail Making A and B (tracking, selective attention, psychomotor speed, set shifting, sequencing); Wisconsin Card Sorting Test ("WCST") concept formation, mental flexibility, problem solving); and Stroop Color-Word Naming Test (mental processing speed, response inhibition). A one-way multivariate ANOVA was used to compare group means. Scores greater than one standard deviation below the normative sample mean were considered clinically meaningful. A chi square test indicated comparable numbers of left and right TLE patients in each group.

Results: Both non-MTS and MTS patients performed within normal limits on most measures, with the exception of reduced performance on Trails B (non-MTS $= 1$ SD below mean, MTS $= 1.16$ SD below mean). Performance on the COWAT approached our criterion (non-MTS $= 0.9$ SD below mean; MTS $= 0.7$ SD below mean). Patients with MTS were slower than non-MTS patients on the Stroop color naming task ($p = 0.01$). The number of WCST "loss of set" errors approached significance ($p = 0.06$), with greater loss of set in the MTS group. There were no other significant differences between groups. Additionally, there were no differences between right and left TLE patients on any measures employed.

Conclusions: These findings suggest that regardless of MTS status, attention and executive functions are compromised in TLE patients, to a limited extent. Additionally, as predicted, TLE patients with MTS exhibited slower mental processing speed and greater difficulty maintaining cognitive set than patients without MTS. Thus, longer duration of epilepsy, and/or other factors associated with MTS, appear to be detrimental to some aspects of attention and executive functioning.

1.492
BRAIN PLASTICITY AND COGNITIVE OUTCOME IN HHE SYNDROME

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Rationale: Hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome is characterized by the occurence of prolonged hemiclonic seizures followed by the development of hemiplegia, typically in the course of a febrile illness before 4 years of age. Following a variable interval (mean 1–2 years), subsequent epilepsy develops, most frequently with complex partial seizures. The motor deficit has a variable course, with some patients continuing to exhibit a definitive hemiplegia while others show complete resolution. Cognitive outcome following HHE has been poorly studied, although early descriptions reported that mental retardation was a common feature. Furthermore, little attention has been paid to the implications of side of involvement in HHE. The purpose of the current study was to evaluate speech lateralization and cognitive performance in patients with left- and right-sided HHE.

Methods: Data from eight patients were examined. Mean ages were 31.4 and 29.7 years for the right ($n = 5$) and left ($n = 3$) hemiparetic groups, respectively. All patients had their hemiconvulsive seizures before age 2 years. Age of habitual seizure onset ranged from 1.5 to 12 years. Speech lateralization was examined using intracarotid amobarbital testing (IAT) for the right hemiparetic group and dichotic words for the left group. Performance on tests of intelligence, verbal memory, and visual memory was also examined.

Results: IAT indicated atypical speech representation (right hemisphere or bilateral) in 4/5 of the right hemiparetic patients. Intellectual functioning in this subgroup was in the Borderline to Extremely Low range. These patients also obtained impaired or variably impaired scores on measures of verbal and visual memory. The one left hemisphere speech dominant patient in this group performed in the average range on tests of intellectual functioning and verbal memory, while scores on visual memory were variable. IAT was not performed with the left hemparetic patients. However, results from dichotic listening suggested left hemispheric speech representation in all three patients. Intellectual functioning was average in two patients, and in the Borderline range in one patient. Verbal and visual memory were largely intact in the left hemiparetic group, with most scores falling in the average range.

Conclusions: Atypical speech representation was common in patients with right hemiparetic HHE (involving the left hemisphere). This was associated with generally poor cognitive outcome as evidenced by intelligence and memory test scores. The one patient with left speech representation demonstrated the best cognitive performance of the group. Left hemiparetic HHE was associated with lower probability of adverse cognitive sequelae and no evidence of atypical speech representation.

The broad range of impairment in the right hemiparetic group may be related to the shift of language to the right hemisphere, although other factors (e.g., severity and age of HHE episode) may also contribute to cognitive outcome.

1.493
ROLE OF HIPPOCAMPAL FORMATION IN SENSORY-MOTOR INTEGRATION: EVIDENCE FROM A DUAL-PATHOLOGY CASE STUDY

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Rationale: Dual pathology (DP) is defined as a combination of hippocampal and extrahippocamal lesion and it is often cause of intractable focal epilepsy. Seizures may arise from both hippocampal and extrahippocampal lesion. Sensory-motor integration refers to the capacity of a specific neural circuitry to provide continually update feedback from sensory system to voluntary motor system. Posterior Parietal Cortex (PPC) and Hippocampal Formation (HF) are integral part of Sensory-Motor Integration System and are supposed to have a crucial role in voluntary movement setting.

Methods: We describe a dual pathology case with intractable seizures and a two year history of progressive left hand clumsiness.

Results: Pure sensory and motor neurological deficit were excluded by neurophysiological evaluation. Neglect, apraxia, agnosia and somatoagnosia were excluded by an extensive neuropsychological evaluation performed during EEG recording. Memory and attention impairment, congruent with a right mesial temporal sclerosis was evident. Several EEGs showed continuous and prolonged sequences of epileptiform activity over the whole right hemisphere with predominant amplitude in fronto-temporal areas. This electrical activity was recorded for several days. Functional-MRI study discovered a normal bilateral activation sensory pattern. A MRI-diffusion study showed a hyperperfusion in right mesial temporal structures but not in the right parietal cortex. An ictal SPECT showed a hyperactivation in right mesial neocortical temporal, thalamic areas and hypoactivation in right frontal area. Ictal EEG pattern disappearance was not associated with a recovery of clumsiness.

Conclusions: The overall data in our patient support the assumption of a relevant HF role in sensory-motor integration. Moreover, the persistence of clinical deficit after EEG normalization points to a neuronal loss rather than ictal pathogenensis.

1.494
LAUGHTER AND THE MESIAL AND LATERAL PREMOTOR CORTEX

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Rationale: Laughter and smiling have been reported as ictal symptoms in epileptic patients and as inappropriate signs of affect in neurological disease. Cortical electric stimulation so far has failed to demonstrate a reproducible site responsible for the generation of laughter. We report the induction of laughter and smiling by cortical electrical stimulation in the frontal lobe in two patients.

Methods: The subjects underwent presurgical epilepsy evaluation with subdural grid electrodes for identification of the epileptogenic zone and delineation of the adjacent functionally eloquent cortex. We applied biphasic, predominantly bipolar electrical stimulation at 0.3 msec, 50 Hz and 1–15 mAMP levels in patients undergoing grid subdural EEG for surgical candidacy (aged 18 months, with left frontal cortical lesion extending to the vertex and posteriorly to the motor area and 35 years, with a lesion in the right supplementary motor area, SMA; after resection, histology from both patients was classified as tuberal type cortical dysplasia).

Results: Stimulation of the prefrontal area induced reproducible laughter. The adult patient reported absence of emotional content. Slowing of speech occurred during the stimulation of electrodes in the upper and posterior vicinity. In this patient laughter was elicited under two electrodes in the cranial anterior part of the SMA. In the child, this response was induced by stimulation of the lateral prefrontal cortex near the falx cerebri. Neither of the stimulation tests that caused laughter were associated with afterdischarges.

Conclusions: The anterior portion of the SMA/lateral premotor cortex in the dominant hemisphere is involved in generating the motor pattern of laughter. Whether other cortical areas are also involved in the generation of laughter is not certain, but there is one case published in biomedical literature (1) in which laughter could be elicited by cortical electric stimulation. Laughter response was evoked in this patient by stimulation in the posterior superior frontal gyrus, representing the anterior border of the lateral premotor cortex.

REFERENCE

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1.495
CORTICAL MAPPING OF LANGUAGE WITH SUBDURAL ELECTRODES: A DIRECT COMPARISON OF ELECTROCORTICOGRAPHIC GAMMA ACTIVITY WITH ELECTRICAL CORTICAL STIMULATION MAPPING

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Rationale: Although electrical cortical stimulation (ECS) mapping remains the gold standard for predicting functional impairment after resection of human cortical tissue, this procedure may be complicated by pain, afterdischarges, or even seizures. Electrocorticographic (ECoG) recordings may be made through the same implanted subdural electrodes without the same complications, but ECoG indices of cortical activation must be tested against the gold standard of ECS before they can be used to guide surgery. Recent studies have shown that functional activation of human cerebral cortex is associated with a broadband high frequency gamma ((80–100 Hz) response in subdural ECoG. We therefore investigated the utility of this index of cortical activation for mapping language cortex.

Methods: We compared the spatial distribution of ECoG gamma during confrontation naming with the maps of naming and other language functions generated by ECS mapping in 17 subjects undergoing subdural electrode implantation for the surgical management of intractable epilepsy. Event-related ECoG gamma activity was averaged for up to 84 objects drawn from the Boston Naming Test (BNT). The sensitivity and specificity of ECoG gamma for predicting ECS impairment was calculated separately for ECS maps of (1) naming (using a subset of the same stimuli from the BNT), (2) mouth motor function (because naming involved the muscles of articulation), and (3) all language tasks–including paragraph reading, spontaneous speech, and sentence comprehension.

Results: For a maximum of 10 electrode sites per subject (the average number with significant ECoG gamma) the specificity of ECoG gamma with respect to ECS was 81% for naming, 83.7% for mouth, and 81.3% for all language tasks. The equivalent sensitivities were 28.6% for naming, 41.2% for mouth, and 26.8% for all language tasks. Improved sensitivities (with no significant effect on specificities) were obtained when they were calculated within individuals and then averaged - 32.4% for naming, 47.9% for mouth, and 27.6% for all language tasks.

Conclusions: This study indicates that event-related ECoG gamma activity during confrontation naming predicts ECS interference with naming, mouth motor function, and other language tasks with relatively high specificity but low sensitivity. If ECoG gamma is observed during naming, it is likely that ECS at the same site will interfere with the same or related function, but if ECoG gamma is not observed at a cortical site, it is an open question whether ECS would predict that resection of this site carries a risk of functional impairment. Improvements in the sensitivity of ECoG mapping will be needed before it replaces ECS mapping; however, it may already provide a useful adjunct to ECS mapping. (Supported by R01 NS40596.)

December 6, 2004
Platform Session A: Psychosocial, Neuropsychology, and Nontraditional Therapies
3:30 p.m.–5:30 p.m.

A.01
GRADUAL VERSUS FASTING INTRODUCTION OF THE KETOGENIC DIET: A PROSPECTIVE RANDOMIZED CLINCIAL TRIAL OF EFFICACY

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Rationale: The ketogenic diet (KD) is a 90% fat, 10% protein and carbohydrate diet that mimics prolonged fasting by creating a state of metabolic ketosis and is an effective treatment of intractable epilepsy in children. The implementation and management of the KD requires significant time and financial resources and has changed little since its inception in 1921. The authors hypothesized that a gradual introduction is as effective as the standard 24–48 hour fasting introduction to the KD.

Methods: Children ages one to 14 with intractable epilepsy were randomized to begin the KD using either a fasting (FAST-KD) or gradual (GRAD-KD) protocol. Both protocols were implemented during a 6-day inpatient admission. The FAST-KD protocol began with a <48 hour fast. The the 4:1 ratio (fat: carb + protein) meal was then advanced in 1/3 caloric increments over 3 days until the full meal was tolerated. The GRAD-KD protocol began without a fast, with three full calorie meals at a 1:1 ratio. The ratio of the meal was then advanced daily to a 2:1, 3:1 and finally 4:1 ratio. Seizure records were collected 28 days before the admission and for the 3-month duration of the study. Subjects were evaluated at 0.5, 1, 2 and 3 months follow up. Effectiveness was measured as% reduction in target seizure type from baseline to the 3 months evaluation.

Results: 48 subjects were randomized, 24 into each protocol. In the FAST-KD group 58% had >50% reduction in the target seizure at 3 months and 21% were seizure free. In the GRAD-KD protocol 67% had a >50% reduction in the target seizure type at 3 months and 21% were seizure free.

Based on the proportions of subjects with 50% reduction at 3 month, a one sided test of equivalence of proportions for two independent groups, with equivalence limit difference set at 20%, resulted in a p-value of 0.0325, indicating that the two protocols are equivalent.

At 3 months, the mean % reduction rate for the FAST-KD protocol was 56.3 (SD = 54.6), while for the GRAD-KD protocol, the mean % reduction rate was 56.9 (SD = 72.1). Based on logarithmic transformed percent reduction rate, a one sided test of equivalence of means for the two independent groups with an equivalence limit difference set at 20%, resulted in a p-value of 0.0002, indicating that the two protocols are equivalent.

Conclusions: These data suggest that a gradual introduction of the KD does not decrease the effectiveness of the KD in children 1-14 years of age. (Supported by RR K-23 16074, General Clinical Research Center MO1RR00240, Nutrition Center, and a private donation by Ms.Catherine Brown.)

A.02
PROGRESSION IN TEMPORAL LOBE EPILEPSY

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Rationale: Whether chronic temporal lobe epilepsy (TLE) is associated with progressive adverse changes in brain structure, cognitive function, or psychiatric status remains controversial. Much of the available evidence is cross-sectional in nature, focusing on limited areas of outcome, with few modern prospective studies. This 4-year prospective investigation assesses changes in brain structure, cognitive function, and psychiatric status in patients with chronic TLE compared to healthy controls.

Methods: An overall cohort of 160 patients with TLE and healthy controls are returning for examination four years after their baseline assessment. This report reviews the prospective outcomes for a consecutive series of 28 TLE and 21 healthy controls. All subjects underwent quantitative MRI volumetrics (total volumes of gray matter, white matter and CSF), neuropsychological status (assessment of intelligence, language, perception, memory, executive function, motor ability), and standardized psychiatric interview (SCID). Analyses included examination of group by time interactions and the proportion of TLE subjects exhibiting adverse outcomes (i.e., change exceeding 2 standard deviations of the healthy controls).

Results: *Cognition*. Significant group by time interactions ($p < 0.05$) were obtained for measures of intelligence, memory, executive function, and mental/motor speed. Post-hoc analyses indicated that these significant interaction effects were due to either lack of test-retest gain (practice effects) in TLE subjects compared to controls, frank cognitive decline in TLE subjects, or a combination of these effects. A subset of approximatly 20% of TLE subjects showed adverse cognitive outcomes. *Quantitative MRI*. There were no significant group by time interactions for the volumetric measures, but a trend of reduced overall gray matter and increased CSF was seen in the TLE subjects. *Psychiatric status*. Significant differences were evident between groups. Interval Axis I disorders were reported by 69% of TLE compared to 39% of controls ($p < .05$), with mood disorders evident in 50% of TLE and 21 % of controls ($p < .05$).

Conclusions: Adverse effects of chronic TLE were identified in this prospective investigation. Most burdensome was ongoing interictal psychiatric co-morbidity, characterized predominantly by mood disorders, and differences in cognitive trajectories over the test-retest interval. Evident trends in quantitative MR volumetrics suggested greater decreases in gray matter and increased CSF in TLE subjects compared to controls. Analyses of individual subject data suggests that a sizeable minority of subjects are at increased risk of adverse outcomes in the context of ongoing chronic TLE. (Supported by NIH NS 2RO1-37738 and M01 RR03186 (GCRC).)

A.03
EFFICACY OF THE KETOGENIC DIET: A META-ANALYSIS OF OBSERVATIONAL STUDIES

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Rationale: For approximately 20% of children with epilepsy, current available medication is either ineffective in controlling seizures or has unacceptable side effects. One alternative treatment for refractory epilepsy is the ketogenic diet, which involves a strict regimen of high fat, low carbohydrate and low protein foods. Our study sought to utilize existing observational studies to systematically investigate diet effectiveness among pediatric patients with refractory epilepsy.

Methods: A meta-analysis was performed to assess the evidence for the efficacy of the ketogenic diet in pediatric populations. A MedLine search, from 1970 to 2003 of English language studies was supplemented by articles from reference lists of all articles retrieved. Articles were included if they provided data for pediatric patients who continued or stopped the ketogenic diet at a measurable follow-up point. Using a random effects model, the authors assessed the influence of diet efficacy by comparing patients who continued treatment to those who stopped treatment. Treatment success was defined as achieving greater than 50% seizure reduction. A pooled odds ratio of treatment success was calculated.

Results: Nineteen studies involving 331 abstracts met inclusion criteria. Total sample size was 1084 patients (mean age initiation 5.78 ± 3.42 yrs (range, 0.2–29 yrs)). The pooled odds ratio of treatment success among patients staying on the diet relative to those ultimately discontinuing the diet was 2.25 (95% CI = 1.69,2.98). Among patients followed for 24 months (n = 860), 49% continued the diet (83.2% achieving success). Seizure type was statistically significant ($p < 0.005$). The highest response rates occurred with generalized seizures, infantile spasms and multiple seizure types. Reasons for diet discontinuation included: <50% seizure reduction (47.0%), diet restrictiveness (16.4%) and incurrent illness/diet side-effects (13.2%).

Conclusions: Results indicate that among patients who can tolerate the diet, the ketogenic diet is an effective therapy. The diet is effective among patients with generalized seizures and patients who responded with greater than 50% seizure reduction quickly to the diet (within three months). Current studies regarding the ketogenic diet are of low quality and focus on short-term results. Future studies should aim for improved quality, specifically randomized controlled trials, and focus on the long-term prospects of the diet. (Supported by a cooperative agreement from the Centers for Disease Control and Prevention through the Association of American Medical Colleges, grant number U36/CCU319276-02-3, AAMC ID number MM-0531-03/03. Publication and report contents are solely the responsibility of the authors and do not necessarily represent the official views of the AAMC or the CDC.)

A.04

LOW GLYCEMIC INDEX DIET AS AN ALTERNATIVE TO THE KETOGENIC DIET IN THE TREATMENT OF INTRACTABLE EPILEPSY IN CHILDHOOD

Heidi H. Pfeifer, and Elizabeth A. Thiele (Pediatric Epilepsy Program, Department of Neurology, Massachusetts General Hospital for Children, Boston, MA)

Rationale: The ketogenic diet is known to be a highly effective treatment for intractable pediatric epilepsy, but it can be difficult for children to comply with the strict diet regimen over a long period of time. We have therefore looked for alternative methods of providing seizure control through dietary changes. One metabolic consequence of the ketogenic diet is that the patients maintain low normal blood glucose levels, which remain fairly stable throughout the day. This can also be accomplished through a low glycemic index diet (LGID), which limits foods that elevate blood glucose, without limiting protein or total calories. We are investigating the possibility that a LGID can have a significant impact on seizure frequency.

Methods: Six patients were initiated on a low glycemic index diet: four after failing long term compliance with the ketogenic diet, and two prior to initiation of a ketogenic diet. A retrospective chart review was performed for demographic and clinical information, including seizure frequency by parental report.

Results: All six patients treated with a LGID experienced a significant reduction in seizure frequency. The six children ranged in age from 6 years to 15 years, and included 4 males and 2 females. Three children had absence seizures, two children had mixed seizure disorders including one with Doose's syndrome, and one child had partial complex seizures. The etiology for 5 of the six patients is unknown; one child had a frontal encephelocele. All six patients had refractory epilepsy prior to initiating dietary treatment and all had failed between 6–10 anticonvulsants prior to diet initiation.

One of the patients, a 12 year old male had up to 20 absence seizures per hour prior to initiating the classic ketogenic diet, and his seizures had not responded to 7 medications. After starting the ketogenic diet, his seizures decreased to 3–4 per day. Unfortunately he was unable to maintain compliance to the diet after one year and was transitioned to a low glycemic index diet. Subsequently, he has continued to have seizure activity with 10–20 seizures per day, and the seizure frequency fluctuates depending on his carbohydrate intake.

Another patient, a 6 year old male diagnosed with Doose's syndrome had 13–14 seizures per day prior to dietary treatment. He was started on a low glycemic index diet prior to initiating the ketogenic diet. While on the LGID, his seizure frequency dramatically decreased.

Conclusions: Although the ketogenic diet is a highly effective treatment for intractable epilepsy in childhood, it can often be difficult for children to adhere to due to its dietary retrictions. In our experience, the low glycemic index diet has proven to be well tolerated and effective for several children, and may be an alternative to the ketogenic diet in providing seizure control.

A.05

LONG TERM SOCIAL OUTCOMES OF PEDIATRIC EPILEPSY SURGERY: THE ROLE OF SEIZURE CONTROL AND MEASURES

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Rationale: One of the stated goals of pediatric epilepsy surgery is the improvement of social outcomes. Social outcomes refer to interpersonal (social relationships) and intrapersonal (affective and instrumental) aspects of functioning. This study examines social functioning in a group of young adults (18–30 years) and compares those who had epilepsy surgery and are seizure free (SF), to a group who are not seizure free after surgery (NSF), and a third comparison group with intractable epilepsy who did not undergo surgery (CTL).

Methods: The SF group ($n = 43$), NSF group ($n = 24$) and the CTL group ($n = 20$) did not differ with respect to age at the time of study, age at seizure onset, proportion of life with seizures and IQ. The two groups that underwent epilepsy surgery were also equivalent with respect to age at surgery and years since surgery. The social functioning subscale of the QOLIE-31 (Cramer et al., 1998) and the work and activity, and social and personal subscales of the Subjective Handicap of Epilepsy (SHE; O'Donoghue et al., 1998) were used to examine group differences.

Results: ANOVAs revealed group differences on all three measures of social functioning (all p's < 0.05). Post-hoc analyses (Tukey HSDs) indicated that the SF group had better QOLIE-31 social functioning subscale scores than the NSF and CTL groups ($p < 0.01$). The SF group had better scores on the work and activities subscale of the SHE ($p < 0.01$) than the other two groups. Although the SF group had better scores than the NSF group on the social and personal subscale of the SHE, the SF and IE groups did not significantly differ ($p > 0.05$).

Conclusions: This study generates evidence that those who undergo epilepsy surgery during childhood or adolescence and are seizure free in young adulthood experience better social outcomes than an intractable cohort. However, these findings may be contingent on what aspect of social functioning is assessed. We believe seizure freedom has an impact on general social functioning as measured by the QOLIE-31 social subscale and on work and activities. However, the role that seizure freedom plays in interpersonal aspects of social functioning as measured by the social and personal subscale of the SHE is less clear. (Supported by Ontario Mental Health Foundation)

A.06

SUICIDAL IDEATION IN ADULT EPILEPSY OUTPATIENTS

Hrvoje Hecimovic, Jewel Carter, Victoria Vahle, Juan Santos, and Frank G. Gilliam (Department of Neurology, Washington University School of Medicine, St. Louis, MO)

Rationale: Recent epidemiological studies indicate that suicide is a major cause of death in persons with epilepsy. Suicide risk appears to be greater in persons with epilepsy than that in general population. The increased prevalence of depression in epilepsy is presumably associated with the increased suicide risk, but this has not been systematically studied. We performed a prospective study of a large sample of epilepsy outpatients to evaluate their recent suicidal ideation.

Methods: We evaluated 193 consecutive consenting adult epilepsy patients over a two-year period in a tertiary epilepsy clinic. In addition to clinical variables, Beck Depression Inventory (BDI), Adverse Events Profile (AEP) and QOLIE-89 scores were obtained. Question 9 of the BDI was used to categorize patients into two groups based on presence or absence of suicidal ideation in the prior two weeks. Between-group differences for clinical variables and for the BDI, AEP and QOLIE-89 total scores were compared using Student's t-test. Chi-square test was used to calculate group comparisons, and a Mann-Whitney U test for independent groups comparison. A value of $p < 0.05$ was considered significant.

Results: We found that 11.9% (23 of 193) of our patients had suicidal thoughts during previous two weeks. Although the BDI, AEP and QOLIE-89 scores were significantly different between the two groups, suicidal ideation was not predicted by AEP scores, QOLIE total scores, patients' age or gender, social and vocational status, seizure frequency, localization of seizure focus, seizure type, or number of AEDs. Further, we showed that 26% (6 of 23) of epilepsy outpatients with suicidal ideation scored in the normal to minimally depressed range (total BDI score of less than 15). In our epilepsy outpatient

cohort, 38.4% of patients had at least mild depressive symptoms and a frequency of suicidal ideas increased with severity of depressive symptoms.

Conclusions: Every 8th to 9th epilepsy patient in a tertiary epilepsy clinic may have had suicidal ideation during prior two weeks. Nearly one-third of these patients will score in the euthymic to mildly depressed range on depression screening instruments. However, clinical depression remains the strongest predictor of suicidal risk when compared to quality of life or medication toxicity. (Supported by NIH grants NS01794 and NS40808 (F.G.), and the Epilepsy Foundation of America (H.H.).)

A.07

LONG-TERM FOLLOW-UP OF PATIENTS WITH THALAMIC ANTERIOR OR CENTROMEDIAN NUCLEUS STIMULATION FOR INTRACTABLE EPILEPSY

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Rationale: Based on previous animal and human observations suggesting involvement of the thalamus in the maintenance and propagation of seizures, thalamic deep brain stimulation (DBS) has been proposed as a treatment for intractable epilepsy. We present long-term follow-up results of a series of patients treated with either anterior nucleus (AN) or centromedian nucleus (CM) DBS for epilepsy.

Methods: 7 patients with intractable epilepsies of different etiologies, aged 23–51 years, were implanted with either AN or CM electrodes (or both at separate intervals in one case) and received high frequency stimulation beginning 4 weeks after implantation. These patients were followed for a period of 13–66 months (mean 4 years). No change in medication was done in the first year after implantation. Meanwhile, changes in stimulation parameters were done multiple times in all patients, including a 2-month period of single-blinded stimulation OFF.

Results: For AN patients, 66% showed >50% seizure reduction at 59, 50, 46 and 45 months. Two patients showed >75% reduction. There were no serious adverse effects. In the >50% good responders group, no change in stimulation parameters (voltages, frequency, bi- or monopolar stimulation) alone or in combination was as effective in reducing the frequency of seizures as simple implantation of the AN electrodes (ie before activation of stimulation). An excellent response to implantation only (91 and 82% reduction from baseline) was a good outcome indicator, while intermediate reductions (27 to 47%) were associated with variable outcomes after the stimulators were turned ON. There was no significant change in seizure frequency during single-blinded stimulation OFF periods in either good or poor responders. The two CM patients showed a poor response (14% or 35% increase from baseline) at 13 and 30 months, although an important reduction in generalized convulsions (from 1–3 per month to 3 in 18 months) was observed in one of the patients. Reversible stimulation dependent CM adverse effects included paresthesias, anorexia and nystagmus.

Conclusions: CM stimulation did not reduce the total number of seizures and was associated with some reversible side effects in the two patients studied. AN electrode placement and stimulation in six patients was associated with a >50% long-term seizure reduction in 66% of patients, with no adverse effects. Whether the sustained long-term beneficial response to AN DBS in this small open-label trial represents an effect of microthalamotomy caused by electrode insertion or electrical stimulation through the electrodes, or a combination of these or other factors, remains to be clarified.

A.08

EFFICACY AND SAFETY OF AMYGDALOHIPPOCAMPAL STIMULATION FOR REFRACTORY TEMPORAL LOBE EPILEPSY

[1]Paul Boon, [1]Kristl Vonck, [2]Dirk Van Roost, [1]Annelies Van Dycke, [1]Pieter Claeys, [1]Fleur Gossiaux, [3]Rik Achten, and [1]Jacques Caemaert ([1]Dept. of Neurology; [2]Dept. of Neurosurgery; and [3]Dept. of Radiology, Ghent University Hospital, Ghent, Belgium)

Rationale: Deep brain stimulation of different targets has recently been shown to be efficacious for refractory epilepsy. We have previously shown that chronic deep brain stimulation (DBS) electrodes are suitable for intracranial ictal onset localization in the medial temporal lobe. The purpose of the present study is to evaluate the efficacy and safety of long-term amygdalohippocampal (AH)-DBS in patients with normal MRI findings and temporal lobe epilepsy.

Methods: Eight consecutive patients with refractory complex partial seizures (CPS) and normal MRI findings were implanted with bilateral AH-DBS electrodes and/or subdural grids for ictal onset localization and subsequent stimulation. In patients with ictal onset in the temporal lobe, AH-DBS was initiated according to the side of ictal onset during a trial period with an external pulse generator. Patients in whom >50% reduction of interictal spikes and/or seizures was shown during the initial trial period were implanted with an abdominally located pulse generator. Prospectively, the frequency of CPS and side effects were carefully monitored, including bedside neuropsychological testing.

Results: Unilateral seizure onset in medial temporal lobe structures was found in 6/8 patients; in one patient a bilateral medial temporal lobe onset with unilateral preponderance was found; in another patient neocortical temporal lobe seizure onset was demonstrated.

In 7/8 patients unilateral long-term AH stimulation was performed. After a mean follow-up of 22 months (range: 6–32 months) 2/7 patients had >90% reduction in seizure frequency; 3/7 patients had a >50% seizure reduction; 2/7 patients are non-responders. One patient did not fulfil the long-term implantation criteria and underwent a temporal lobectomy. In 6/7 patients at least one AED could be tapered. None of the patients reported side effects. In one patient the amygdalar implantation was complicated by a minor and asymptomatic amygdalar haemorrhage, which resolved within one week. None of the patients showed changes in bedside neurological and neuropsychological testing.

Conclusions: This open study demonstrates the efficacy of DBS in medial temporal lobe structures. More than half of the patients respond well to long-term AH-DBS. Assessment of side effects including neuropsychological functioning suggests that chronic AH-DBS is a safe treatment as well. (Supported by A Senior Clinical Investigator Grant (PB), a Junior Researcher ("Aspirant") Grant (KV) and Grants 1.5236.99, B/02514 (PC) and 6.0324.02 from the Fund for Scientific Research (FWO)-Flanders; by Grant 01105399 from Ghent University Research Fund (B.O.F.) and by the Clinical Epilepsy Grant Ghent University Hospital 2000–2004.)

December 6, 2004
Platform Session B: AED
3:30 p.m.–5:30 p.m.

B.01

GETTING THE MOST OUT OF ANTIEPILEPTIC DRUG MONOTHERAPY TRIALS: A META-ANALYSIS USING DIRECT AND INDIRECT COMPARISONS

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Rationale: There are an increasing number of antiepileptic drugs (AEDS) to choose from for initial monotherapy. Reliable evidence that informs a choice among AEDS comes from randomized controlled trials (RCTS) in which AEDs are compared head to head. Trials which compare the same AEDs (i.e. make a direct comparison) can be summarised in a meta-analysis. Indirect comparisons can also be made, for example, data from trials comparing drugs A and B, and trials comparing drugs A and C can be used to estimate how drugs A and C compare. Indirect comparisons can be valuable where direct comparisons either do not exist, comprise a limited amount of data of low quality.

The aim of this project was to make the best use of existing data regarding comparative effects of AEDs in order to better inform clinical practice.

Methods: We undertook a meta-analysis using individual patient data from 18 AED monotherapy RCTs representing 4496 patients. These trials made comparisons among carbamazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital and valproate. Direct and idirect comparisons were summarised to provide a total summary of available evidence. Outcomes were time to treatment failure, time to 12 month remission from seizures and time to a first seizure. Selected results are expressed below as Hazard ratios (HR) with 95% confidence limits (95% CI).

Results: Results from direct and indirect comparisons are generally consistent. For time to first seizure, results consistently suggest valproate superior to other AEDs for generalized onset seizures (VPSCBZ 1.21 (0.97–1.50), VPS-PB 1.29 (0.92–1.80), VPS-PHT 0.97 (0.76–1.24), VPS-LTG 1.17 (0.81–1.68), VPS-OXC 1.22 (0.79–1.98) and inferior for focal onset seizures (VPS-CBZ 0.81 (0.70–0.94), VPS-PB 0.61 (0.47–0.79), VPS-PHT 0.82 (0.67–1.00), VPS-LTG 1.11 (0.83–1.49), VPS-OXC 0.72 (0.51–1.02). For lamotrigine there is no clear trend for generealised onset seizures but it is inferior for partial onset seizures. Phenobarbitone is consistently superior to other AEDs for partial onset seizures and inferior for generalized onset seizures. For phenytoin there is no clear trend for partial onset seizures but it is superior to other AEDs for generalized onset seizures. Carbamazepine was not clearly superior or inferior to other drugs for parital or generalized onset seizures.

Conclusions: This data work summarises the totality of evidence from RCTs regarding the comparative effects of AEDs when used as monotherapy. Results will inform clinical decision making as well as future RCTs. (Supported by NHS R&D UK)

B.02

RANDOMISED CONTROLLED TRIAL OF BUCCAL MIDAZOLAM VERSUS RECTAL DIAZEPAM FOR THE EMERGENCY TREATMENT OF SEIZURES IN CHILDREN

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Rationale: Rectal diazepam and, more recently, buccal midazolam have been used in the emergency or rescue treatment of acute seizures in children. There is uncertainty as to which is the most effective and safest. This purpose of this study was to compare the safety and efficacy of buccal midazolam (BM) and rectal diazepam (RD) in the emergency room treatment of acute seizures.

Methods: A multi-centre, randomised controlled trial was undertaken comparing buccal midazolam with rectal diazepam for the emergency room treatment of children aged six months and over presenting to hospital in a tonic-clonic seizure and with no intravenous access. The dose of midazolam and diazepam varied according to age from 2.5 to 10 mg. The primary end point, therapeutic success, was the cessation of seizures within 10 minutes and for at least one hour, without respiratory depression requiring medical intervention. The study received ethical approval from the Regional and Local Ethics Committees of the participating centres. Written consent was obtained. Weekly blocks of treatment to either BM or RD were randomly selected for each of the participating centres.

Results: Consent was obtained in 219 (male, 56.2%) separate episodes involving 177 (male, 55.4%) patients, median age 3 years (interquartile range, 1 to 5 years). Therapeutic success was achieved in 61 (56%) episodes treated with BM ($n = 109$) and 30 (27.3%) episodes treatd with RD ($N = 110$). Buccal midazolam was more likely to stop the seizures within 10 minutes (65% vs 41%; $p < 0.001$). The number of patients given intravenous lorazepam for continuing seizure activity after BM was 36 (33%) compared with 63 (57.3%) after RD ($p < 0.001$). Respiratory depression was recorded in 5 (4.6%) and 7 (6.4%) of the BM and RD-treated groups respectively. In logistic regression analysis where age, known diagnosis of epilepsy, use of antiepileptic drugs and duration of seizure prior to treatment were adjusted for, BM was more effective than RD ($p < 0.001$; Odds Ratio, 3.7; Confidence Intervals, 2.1–6.8).

Conclusions: Buccal midazolam was more effective than rectal diazepam for children presenting to the hospital emergency room with acute tonic-clonic seizures and was not associated with an increased incidence of respiratory depression. The nursing staff in the emergency rooms found the buccal midazolam easier and more acceptable to administer than the rectal diazepam; this view was also shared by most parents. The results of this randomised controlled trial will now be used to change the practice of the emergency or rescue treatment of acute tonic-clonic seizures in children in both hospital and out-of-hospital situations. (Supported by 'SEARCH')

B.03

MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ADJUNCTIVE LEVETIRACETAM (KEPPRA®) THERAPY (UP TO 60 MG/KG/DAY) IN PEDIATRIC PATIENTS WITH REFRACTORY PARTIAL EPILEPSY

[1]Tracy A. Glauser, [2]Laura J. Gauer, [2]Ling Chen, and LEV N159 Pediatric Study Group ([1]Division of Neurology, Cincinnati Children's Hospital, Cincinnati, OH; and [2]UCB Pharma, Inc., Smyrna, GA)

Rationale: Levetiracetam (LEV, Keppra®) is approved for the adjunctive treatment of partial onset seizures (PS) in adults (>16 years old) but its safety and efficacy in children with PS has not been systemically evaluated. Differences between pediatric and adult PS prevent simple extrapolation of adult data to children.

Methods: This study was a multicenter, double blind, randomized, placebo controlled parallel group international (U.S.A., Canada) study of adjunctive LEV therapy in children 4 to 16 years old with PS uncontrolled on one or two standard antiepileptic drugs. Eligible patients having at least 8 PS with or without secondary generalization during an 8-week baseline period were randomized to either LEV (20 mg/kg/day) or placebo. During a 6-week titration period patients received up to 60 mg/kg/day followed by an 8-week evaluation period. At the end of the evaluation phase, patients could elect to continue in an open-label, long-term, follow-up trial or enter a 6-week withdrawal period. The treatment period was defined as the titration (6 weeks) and evaluation (8 weeks) periods combined, i.e., a total of 14 weeks. Adverse events, neurological and physical status, ECG, and laboratory safety tests were assessed during the treatment period.

Results: Two hundred eighty-two (282) patients were screened, 216 were randomized, 198 patients provided evaluable data, and 193 completed the treatment period. The primary efficacy analysis was based on the intent-to-treat population of 198 patients who provided evaluable data. The percentage reduction in PS frequency over placebo during the treatment period (the primary endpoint) was 26.8% for LEV ($p = 0.0002$). The percent of patients who had at least a 50% reduction of PS frequency per week was 44.6% (45/101 patients) for patients receiving LEV and 19.6% (19/97 patients) for patients receiving placebo ($p = 0.0002$). The percent of patients who had at least a 75% reduction of PS frequency per week was 19.8% (20/101 patients) with LEV and 5.1% (5/97 patients) with placebo ($p < 0.0001$). Seven percent (7%, 7/101) LEV and one percent (1%, 1/97) placebo patients were seizure free during the treatment period. Preliminary assessments of the safety profile revealed a spectrum and frequency of treatment emergent adverse events similar to the safety profile in the current approved LEV labeling for adult use as adjunctive therapy in PS.

Conclusions: The initial analysis of this randomized, double-blind, placebo-controlled trial indicates that in children (4 to 16 years of age) with treatment resistant partial onset seizures, LEV adjunctive therapy was associated with a significant reduction in partial onset seizure frequency with a spectrum of side effects similar to that seen in adults receiving adjunctive LEV therapy. (Supported by UCB S.A., Pharma Sector)

B.04

BONE MINERAL DENSITY CHANGES AFTER ONE YEAR OF ANTIEPILEPTIC DRUG TREATMENT IN WOMEN WITH EPILEPSY

[1]Alison M. Pack, [1]Martha J. Morrell, [1]Edith Flaster, [1]Kerry L. Flynn, [1]Silvia Done, and [2]Shane Elizabeth ([1]Neurology; and [2]Medicine, Columbia University, New York, NY)

Rationale: Antiepileptic drugs (AEDs), particularly those that induce the hepatic cytochrome P450 system, have been associated with abnormal vitamin D metabolism and osteoporosis. Recent studies have reported that low bone mineral density (BMD) in adults on AEDs is common and associated with multidrug regimens, generalized seizures, longer disease duration, and increased bone turnover markers. We therefore examined the effects of individual AEDs on healthy premenopausal women with epilepsy (WWE), hypothesizing that those receiving enzyme inducing AEDs, particularly phenytoin (PHT) and carbamazepine (CBZ), would have more bone loss than those receiving valproate (VPA), an enzyme inhibitor, or lamotrigine (LTG) which has no effect on the cytochrome P450 system.

Methods: Community-dwelling WWE aged 18–40 receiving AED monotherapy for at least 6 months were recruited. BMD was measured at the lumbar spine (LS), total hip (TH) and femoral neck (FN) of the hip by dual energy X-ray densitometry at baseline and one year, if they remained on the originally prescribed AED. Serum calcium, 25-(OH) vitamin D (25-OHD), parathyroid hormone (PTH), bone specific alkaline phosphatase (BAP, marker of bone formation) and urine N-telopeptide of type I collagen (NTX, marker of bone resorption) were measured at baseline and examined with respect to percent change in BMD.

Results: Of 71 women, 11 were on PHT, 26 on CBZ, 14 on VPA and 18 on LTG. Average age was 32 +/− 5.9 years and BMI was 26.5 +/− 6.3 kg/m^2 with no significant between-groups differences. Baseline Z scores were normal at all sites and did not differ among AED groups (range: −0.42 − 0.34). BMD was stable at the LS and TH in all groups after 1 year of treatment. In women on PHT, FN BMD declined by −2.75% +/−2.76, p = 0.05, compared to the other groups (CBZ, +0.49% +/− 4.03; VPA, +1.09% +/− 3.73; LTG, −0.005% +/− 0.02). In the group overall, bone loss correlated with serum calcium levels, but not other markers of bone function.

Conclusions: In general, BMD is stable in premenopausal WWE on AED monotherapy. We observed significant bone loss at the FN in those taking PHT. The bone loss was associated with lower serum calcium levels but not with serum 25-OHD or PTH levels, nor with markers of bone turnover. Although the mechanism of the bone loss is uncertain, our results suggest that premenopausal women receiving PHT are at significant risk for considerable bone loss and warrant BMD monitoring. (Supported by Research grant from GlaxoSmithKline)

B.05

THE AED (ANTIEPILEPTIC DRUG) PREGNANCY REGISTRY: A SEVEN-YEAR EXPERIENCE

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Rationale: Pregnancy registries have been developed to provide an early signal of an increased frequency of major malformations associated with prenatal exposure to the products monitored by the registry.

Methods: The North American Antiepileptic Drug (AED) Pregnancy Registry is an ongoing surveillance system of pregnant women exposed to AEDs. By May 6, 2004, the Registry had enrolled 3,633 women from the United States and Canada since its inception seven years ago. The eligible woman must call the toll-free number. She is interviewed at enrollment, at 7 months gestation, and postpartum. Medical records were obtained about the mother's medical history and the normal or abnormal findings in the infant. The protocol and criteria for the release of findings were established prospectively by a non-industry external Scientific Advisory Committee. The inform consent to be read and signed by each woman who enrolls in the Registry was reviewed and approved by the Human Studies Committee of the Massachusetts General Hospital in Boston, where the Registry is based.

Results: The risks due to maternal exposure to two AEDs as monotherapy have recently been released: assuming a background prevalence of major nonsyndromic congenital anomalies of 1.62%, the relative risk to having an affected offspring for valproic acid-exposed women was 5.0 (95% CI: 2.9–8.6) and 3.8 (95% CI 1.7–9.0) for women exposed to phenobarbital.

Conclusions: The results from this hospital-based pregnancy registry indicate that prenatal exposure to monotherapy valproic acid or phenobarbital is associated with a significantly increased risk for fetal abnormalities. (Supported by Abbott, Elan, GlaxoSmithKline, Novartis, Ortho-McNeil and Pfizer.)

B.06

LAMOTRIGINE PLASMA LEVELS AND COMBINED MONOPHASIC ORAL CONTRACEPTIVES (COC) OR A CONTRACEPTIVE VAGINAL RING. A PROSPECTIVE EVALUATION IN 30 WOMEN

[1]Stefan R.G. Stodieck, and [2]Anneliese M. Schwenkhagen ([1]Neurology Dep.; and [2]Gynaecological Clinics, Hamburg Epilepsy Center, Hamburg, Germany)

Rationale: Enzyme inducing antiepileptic drugs affect the metabolism of combined oral contraceptives (COC) that may result in contraceptive failure. Lamotrigine (LTG) is increaslingly used as a AED of choice in woman, because it does not seem to influence the pharmacokinetics of COCs, and because it seems to be a comparatively safe drug during pregnancy. Retrospective data showed that desogestrel or levonorgestrel containing COCs may reduce LTG plasma levels (Sabers A et al. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Res 2001 47:151–4.). We wanted to further clarify time-course and magnitude of this clinically relevant interaction in a prospective evaluation.

Methods: 26 women on a stable LTG monotherapy (22) or a combination with one other AED (4) received a COC (ethinylestradiol in combination with either desogestrel or levonorgestrel or cyproterone acetate or dienogest or chlormadinon acetate) or a vaginal ring releasing ethinylestradiol and etonogestrel (Nuvaring®) for up to 3 consecutive treatment cycles (1 treatment cycle: 3 consecutive weeks on COC or Nuvaring®, 1 week off). Serial blood samples were drawn at baseline, week 1,3 and in the contraceptive free week of each cycle and analyzed for lamotrigine trough and peak levels. In some patients a diurnal profile with calculation of AUC was performed.

Results: In all patients LTG trough levels decreased between 25–70% (median >50%) during COC and 15–50% during Nuvaring treatment. Surprisingly, a marked reduction (>20%) of the LTG level was observed after only 1–3 days of COC treatment in most patients. Lowest LTG levels were observed at the end of the 3 weeks on contraceptives. In all women there was an increase of LTG levels in the contraceptive-free week up to 80–100% of baseline level. These fluctuations of LTG levels were reproducible within subsequent treatment cycles. The degree and time course of LTG level changes varied considerably between patients.

Conclusions: Our data confirm previous reports of a remarkable decrease of LTG levels when combined with hormonal contraceptives for all COCs studied. Local vaginal application (Nuvaring®) had a somewhat smaller but still relevant influence and therefore seems to be only a minor improvement. The newly demonstrated rapid fluctuation of LTG levels depending on wether the patient was in the 3 weeks on or 1 week off contraceptives was of clincal relevance in about 1/4 of our patients. Since the LTG-level changes occur so rapidly, other mechanism than the induction of uridine 5'-diphosphate-glucuronosyl transferase (UGT1A4), the enzyme primarily responsible for LTG-elimination, might also be important.

Clinicians must be aware of these interactions in order to avoid seizure recurrence on contraceptives or dose-dependant adverse effects during the contraceptive-free week.

B.07
PROGRESSION OF NEURO-RETINAL TOXICITY IN PATIENTS ON VIGABATRIN; OBJECTIVE ASSESSMENT USING THE WIDE FIELD MULTIFOCAL ELECTRORETINOGRAM
[1]Pedro A. Gonzalez, [1]Stuart Parks, [2]Kevin Kelly, and [4]Martin Brodie ([1]Ophthalmolgy, University of Glasgow; and [2]Epilepsy Unit, Western Infirmary, Glasgow, United Kingdom)

Rationale: Vigabatrin is used for treatment of partial and secondary generalized seizures and infantile spasms in Europe and Asia. A number of studies have shown that vigabatrin causes visual field defects. Many of these patients are asymptomatic. There are difficulties in assessing these patients with conventional visual fields due to poor compliance and reproducibility. The wide field multifocal electroretinogram (WF-mfERG) offers an objective test with improved spatial and temporal resolution over conventional visual fields and has been shown to be able to detect retinal pathology reliably.

Methods: A long term longitudinal study is being undertaken at the Epilepsy Unit, Western Infirmary, Glasgow to objectively assess the progression of neuro-retinal toxicity associated with vigabatrin. Ten patients with localization-related epilepsy who have been taking vigabatrin for at least 6 years have been reassessed. These patients underwent WF-mf ERG as well as logMar visual acuity, colour vision assessment, static perimetry and ERG (global retinal function) and these tests were repeated after two years. All patients underwent brain MRI, those with intracranial pathology affecting the visual pathway were excluded. Ten control patients who were matched for age, sex, duration of epilepsy and seizure control were also included. First order parameters namely the P1 and N1 amplitude and latency were measured.

Results: The WF-mf ERG showed a significant increase in P1 latency in three out of the 10 patients. There was no change in either the vigabatrin group or control group in visual fields, visual acuity or colour vision within the two year follow up period. One out of these three patients had previous normal wide field multifocal parameters.

Conclusions: The significant increase in P1 latency indicates progression of neuro-retinal toxicity. The Wide Field multifocal ERG is possibly more sensitive and specific than conventional methods of visual function testing in assessing patients on vigabatrin with progressive induced neuro-retinal toxicity. (Supported by Chief Scientist Office. Grant #CZB/4/78)

B.08
INTERACTION BETWEEN AMOBARBITOL AND CERTAIN ANTI-EPILEPTIC DRUGS DECREASE ANESTHESIA DURING THE IAP
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Rationale: Rarely, injection of amobarbital during the Intracarotid Amytal procedure (IAP or Wada test) will fail to produce sufficient anesthesia for testing. After a sudden increase in the rate of such failures, we performed a retrospective chart review study on all patients receiving IAP's at UCLA over a 2 1/2 year period. Our goal was to identify any common characteristics in the medication lot, demographics, seizure history, or medication usage than could explain these cases.

Methods: We determined all subject demographics, seizure history, perfusion patterns, current and recent medications, treating physician, and length of anesthesia during the IAP as measured by return of grip strength in successive cases. Gennder, age, seizure duration, treating physician, date of exam, perfusion patterns and medications were compared across individuals with and without reduced anesthesia.

Results: Anesthesia failures were found to be exclusively explained by concurrent or very recent use of Topiramate, Zonisamide, or antihypertensive agents, all of which have carbonic anhydrase inhibition properties. Approximately 75% of patients taking either Zonisamide or Topiramate showed reduced or absent anesthesia. No patients not taking one of these medications showed a reduced period of anesthesia during the IAP. Following withdrawal from these medications, a minimum of 8 weeks off the medications was necessary in the majority of cases before an average length of anesthesia during the IAP was found. Differences in anesthesia average times for patient taking and not taking carbonic anhydrase inhibiting drugs were very significant ($p < .0000001$).

Conclusions: We now systematically withdraw patients from these medications prior to performing the IAP. We suggest that the mechanism of action common to all medications associated with reduced anesthesia have an action of carbonic anhydrase inhibition. Both amobarbital and carbonic anhydrase inhibitors appear to act on the GABA-A receptor channel, suggesting a possible mechanism for this interaction. Such an interaction is supported by animal studies of carbonic anhydrase inhibition and barbiturates. These results have important implications for clinical care for patients undergoing IAP exams.

December 6, 2004
Platform Session C: Surgery
3:30 p.m.–5:30 p.m.

C.01
MULTIPLE SEIZURE FOCI AND MULTIPLE TUBERECTOMY FOR INTRACTABLE PARTIAL EPILEPSY IN TUBEROUS SCLEROSIS
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Rationale: Epilepsy surgery is generally accepted for tuberous sclerosis (TS) patients with stable and stereotyped partial seizures, a well-localized and single seizure focus, and a corresponding underlying tuber. TS patients with seemingly multifocal or generalized seizures are usually excluded from epilepsy surgery.

Methods: We report six children with TS, refractory partial seizures, multiple cortical tubers, global developmental delay and evidence from seizure semiology, scalp EEG monitoring and ictal SPECT of seizures arising from or involving multiple tubers. One patient had subdural EEG monitoring. All patients underwent multiple tuberectomy at age 2–17 years.

Results: Seizure onset ranged from birth to 7 years (median 4 months) and all had evidence of partial seizures. Three patients had electroclinically-discrete seizures arising independently from 3-4 regions in opposite hemispheres. Three patients had evidence for involvement of several tubers in what appeared to be a single electroclinical seizure type. The evidence implicating multiple tubers in these six patients came from seizure semiology in 5, ictal EEG onset in 3, ictal EEG propagation in 6 and ictal SPECT in 4. Bifrontotemporal subdural EEG monitoring in one patient confirmed independent focal origin of clinically-distinct seizures from separate tubers in four different regions.

Stereotactically-guided resection of 2-5 tubers was performed. Resection was staged in the three cases involving opposite hemispheres, with continued seizures between operations. Two patients with unilobar resection of 2-3 tubers are seizure free with improved alertness, behaviour and interictal EEG (follow-up 9 and 20 months). Four patients with resection of 3-5 tubers in one or more lobes have had >75% seizure reduction, including abolition of tonic and tonic-clonic seizures (follow-up 2–11 months).

Conclusions: TS patients with intractable epilepsy and partial seizures, either arising independently from different lobes or hemispheres, or seemingly involving several tubers in the one lobe, may benefit from multiple tuberectomy. (Supported by Neurological Foundation of New Zealand)

C.02

INCIDENCE AND PROGNOSTIC VALUE OF ACUTE POST-OPERATIVE SEIZURES IN CHILDREN AFTER EXTRATEMPORAL EPILEPSY SURGERY

[1]Jayanthi Mani, [1]Ajay Gupta, [1]Paul Shkurovich, [1]Deepak Lachhwani, [1]Prakash Kotagal, [2]William Bingaman, and [1]Elaine Wyllie ([1]Neurology; and [2]Neurosurgery, Cleveland Clinic Foundation, Cleveland, OH)

Rationale: Seizures in the first week following surgery for epilepsy can be alarming and raise concerns about long term seizure outcome. Data on predictive value of acute post operative seizures (APOS) is limited in children. We assessed the incidence and predictive value of APOS (within a week after surgery) on one year seizure outcome following extratemporal epilepsy surgery in children and adolescents.

Methods: 132 consecutive children (age at surgery 6 months to 18 years, mean 7.8) who underwent extratemporal surgery for epilepsy (61 hemispherectomies (HS), 71 extratemporal resections (ETR)) between 1995–2002 were studied. Odds for *good seizure outcome* (seizure free, only auras) at one year were compared in children with and without APOS (nAPOS).

Results: Of 132 patients, 107 (81%) had daily preoperative seizures and 16 were less than one year-old at surgery. 34 of 132 (25%) had APOS. Of 34 patients with APOS, 28 (82.4%) had more than one APOS, and 16 (49%) had no change in semiology from preoperative seizures. 8 of 34 (23.5%) had postoperative medical or surgical complications (complicated APOS). APOS were more frequent after ETR (26/71) than after HS (8/61) ($p < 0.01$, chi^2 test). There was no significant difference in the seizure onset age, preoperative seizure frequency, age at surgery and the incidence of medical (fever, aseptic meningitis) or surgical complications in APOS and nAPOS groups.

23 patients were excluded for the one year seizure outcome analysis due to a second surgery within a year (14, 7 each after HS and ETR) or loss of follow up (9). Of 109 patients with one year of follow up, 24 had APOS. 10 of 24 with APOS (41.6%) and 72 of 85 without APOS (84.7%) had *good outcome* at one year (**OR 7.753**, 95% CI 2.86-20.98). There was no significant difference in the incidence of *good outcome* at one year in patients whose APOS semiology was similar to their preoperative seizures (6/14) compared to those with new APOS semiology (5/10) ($p > 0.05$ Fisher's exact test). 3 of 8 children with complicated APOS had a good one year outcome compared to 6 of 16 with uncomplicated APOS (APOS without medical/surgical complications) ($p > 0.05$, Fisher's exact test).

Conclusions: Acute post-operative seizures occurred in 25% children after extratemporal epilepsy surgery. They were significantly more frequent after extratemporal resection than after hemispherectomy. Children with APOS had a significantly lower likelihood of good seizure outcome at one year compared to those without APOS. The similarity of APOS semiology to preoperative seizures, and presence of medical/surgical complications during APOS did not influence the one year outcome.

C.03

SEIZURES IN THE EARLY POST-OPERATIVE WEEKS PREDICT SUBSEQUENT SEIZURE RECURRENCE

[1,2,3]Anne M. McIntosh, [5]Renate M. Kalnins, [4,7]L. Anne Mitchell, and [1,3,6]Samuel F. Berkovic ([1]Epilepsy Research Centre; [2]School of Nursing; [3]Medicine (Neurology); [4]Radiology, University of Melbourne; [5]Anatomical pathology; [6]Neurology; and [7]Radiology, Austin Health, Melbourne, Victoria, Australia)

Rationale: Seizures in the early post-operative period after temporal lobectomy are commonly discounted when assessing seizure outcome. However, several studies have indicated these events may predict ongoing seizures. In this study, we aimed to determine the risk of epilepsy recurrence among individuals who had early post-operative seizures.

Methods: Early post-operative seizures were defined as seizures within 28 post-operative days. Epilepsy recurrence was nominated as seizures between day 29 and one post-operative year. Poisson regression analysed the recurrence risk associated with early seizures, as well as the effect of the presence of seizure precipitants (e.g. decreased medication, cerebral bleeding), and the timing, type and number of early seizures amongst those who experienced early seizures. Statistical adjustments were made for the pre-operative pathology.

Results: Of 321 cases who underwent temporal lobectomy at Austin Health in Australia, 69 (22%) experienced early post-operative seizures. Early seizures were associated with seizure recurrence (rate ratio [RR] 5.9; 95% CI 4.1 to 8.4). Amongst the patients who experienced early seizures, only the presence of precipitants to seizures was associated with (a decreased) risk of recurrence (RR 0.52, 95% CI; 0.3–1.9). The timing of the initial seizure within the first 28 post-operative days did not have a significant effect ($p = 0.26$). A further analysis was undertaken, comparing outcome for patients who did not experience early seizures against outcome for those who had early seizures with precipitants and outcome for patients who had early seizures without precipitants. Regardless of precipitant status, early seizures maintained an association with subsequent recurrence, although patients with precipitants to their seizures had a lower risk (RR 3.0; 95% CI 1.8–5.2) than those without precipitants (RR 7.6; 95% CI 5.0–11.5).

Conclusions: Patients who experienced early post-operative seizures had a higher risk of subsequent seizure recurrence compared to those who did not have early seizures. The risk was decreased but still significant if early seizures were associated with precipitating factors. Given that most post-operative seizure outcome classifications discount early seizures, these findings have implications for the measurement of outcome after temporal lobectomy. (Supported by Australian NHMRC, Austin Hospital Medical Research Foundation, Epilepsy Association Australia)

C.04

RELAPSE IN POST-SURGICAL SEIZURE-FREE PATIENTS: THE ROLE OF AED REDUCTION

[1]A. Berg, [2]B. Vickrey, [3]S. Shinnar, [4]J. Langfitt, [5]T. Walzcak, [6]S. Pacia, [7]C. Bazil, and [8]S. Spencer ([1]BIOS, NIU, DeKalb, IL; [2]Neurology, UCLA, Los Angeles, CA; [3]Neurology, Montefiore Med Ctr, Bronx; [4]Neurology, Univ Rochester School of Medicine, Rochester, NY; [5]MINCEP, Minneapolis, MN; [6]Neurology, NYU; [7]Neurology, Columbia University, New York, NY; and [8]Neurology, Yale Medical School, New Haven, CT)

Rationale: Little is known to guide the post-surgical pharmacologic management of patients who become seizure-free.

Methods: In a multicenter study of resective surgery patients who attained a $\geq$1 year remission, we quantified the relapse risk after tapering AEDs and studied potential predictors of post-tapering relapse. Tapering was at the discretion of the physician or patient. Survival methods were used for analysis. Tapering was treated as a time dependent covariate. Change in relapse rates after reduction of AEDs was estimated.

Results: Of 396 surgical patients, 299 (75.5%) had $\geq$1 year remission of whom 171 (57.2%) tapered AEDs. Of those who tapered, 49 (28.7%) were taking one, 112 (65.5%) two, and 10 (5.9%) three different AEDs. Relapses occurred in 46 patients, 32 were still tapering at the time of relapse. The relapse risk was 0.06 (95% CI 0.02, 0.10), 0.13 (0.07, 0.18), and 0.24 (0.17, 0.31) at 6m, 1y and 2y after the first reduction. On bivariate analysis, this was lower than the risk in seizure-free patients who never tapered AEDs: 0.13 (0.07, 0.19), 0.27 (0.18, 0.35), 0.34 (0.25, 0.43) at 6m, 1y, and 2y after remission ($p = 0.002$). Those who tapered, however, were more likely to have remitted immediately after surgery (no seizures since hospital discharge) than those who did not taper (78% vs 52%, $p < 0.0001$). This factor was also an important correlate of relapse. After adjustment for immediate remission, tapering AEDs (as a time-dependent covariate) was associated with a small non-significant increase in relapse rate (Rate Ratio = 1.28, $p = 0.25$). Of many factors examined, only timing of remission was associated with relapse. The risk two years after first tapering was 0.42 for delayed and 0.20 for immediate remission ($p = 0.01$). Thirty (17%) of individuals who tapered the first AED did so on their own without consulting their physician. This did not influence the risk of relapse. Currently 53 individuals are completely AED- and seizure-free. They represent 13% of the entire cohort, 18% of those seizure-free, and 33% of those who tapered AEDs.

Conclusions: Relapses occur in about a quarter of seizure-free surgical patients who taper drugs. Tapering is associated with a small

nonsignificant increased risk of relapse; however those who do and do not taper vary on prognostic factors such as timing of remission and other factors yet to be identified. Further investigation into specific clinical factors such as post-operative EEG, underlying pathology, and extent of resection is needed to inform a rational approach to post-surgical drug management of seizure-free patients. (Supported by NIH-NINDS R01-NS32375)

C.05

UNCOMMON COMPLEX MOTOR BEHAVIORS DURING TEMPORAL LOBE SEIZURES

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Rationale: Seizure semiology in temporal lobe epilepsy (TLE) has been extensively described. Most common motor behaviors are typical automatisms involving distal body segments, particularly fingers, tongue and lips. Other include unilateral arm dystonic posturing and face and arm clonic movements. Our objective was to describe less common complex motor behaviors during seizures of temporal lobe origin, both in pediatric and adult patients.

Methods: All patients admitted to the EMU between 1996 and 2003 considered to have TLE based on clinical, EEG and radiological findings were reviewed. Seizures were analyzed by 2 trained epileptologists. Patients with complex motor behaviors as the main seizure manifestation were selected. They had to be either seizure free after a temporal resection (temporal lobectomy/lesionectomy) or have a typical surface EEG temporal pattern together with a temporal lesion on MRI.

Results: Of 729 monitored patients (579 adults, 200 children), 441 (60.5%) were considered to have TLE. Of those, only 12 (8 men, 4 women) with uncommon complex behaviors were found. Mean age at evaluation was 34 years (14–58).

Movements which predominantly affected proximal segments of the limbs, producing large and occasionally violent movements (hypermotor seizures) were seen in 7 patients. Three patients had seizures consisting mainly of repetitive body rocking, one patient had pelvic thrusting and one patient had axial tonic seizures with prominent bilateral arm dystonia. Six patients had auras (3 abdominal, 1 olfactory, 2 unclassifiable) preceding the complex movements, and 7 patients had typical oral automatisms following them. EEG showed interictal epileptiform activity over the temporal lobe in all patients (unilateral in 9, bilateral in 3). Surface EEG showed unilateral regional temporal patterns in all patients. MRI showed unilateral MTS in 6 patients, cavernous angioma in the temporal neocortex in 2 patients, mesial temporal benign tumors in 2 patients, focal cortical dysplasia in the superior temporal gyrus in one patient, and focal atrophy of the temporal pole in one patient. Six patients had surgery (one lesionectomy and five temporal lobectomies). All patients are seizure free with at least one year of follow-up. Of the remaining six patients, one has become seizure free on drugs, 2 patients with mesial temporal tumors have declined temporal lobectomy and surgery was not offered to 3 patients because of failed Wada test.

Conclusions: Although uncommon, a spectrum of complex motor behaviors may be seen in temporal lobe seizures, including predominantly proximal, large and violent movements typical of frontal lobe seizures. Complex motor behaviors in TLE are often preceded by auras and followed by typical distal automatisms. These patients have an excellent prognosis after temporal lobe resections, and there is no need for invasive studies if there are congruent EEG and MRI data.

C.06

HEALTH-RELATED QUALITY OF LIFE AFTER EPILEPSY SURGERY: A FIVE-YEAR, LONGITUDINAL FOLLOW-UP AND CORRELATION WITH SEIZURE OUTCOMES

[1]Susan S. Spencer, [2]Anne T. Berg, [3]Barbara G. Vickrey, [4]John T. Langfitt, [5]Shlomo Shinnar, [6]Carl W. Bazil, [7]Michael R. Sperling, [8]Steven V. Pacia, [9]Thaddeus S. Walczak, and [10]Daniel Frobish ([1]Department of Neurology, Yale University School of Medicine, New Haven, CT; [2]BIOS, Northern Illinois University, DeKalb, IL; [3]Department of Neurology, UCLA School of Medicine, Los Angeles, CA; [4]Department of Neurology, University of Rochester School of Medicine, Rochester; [5]Departments of Neurology and Pediatrics, Montefiore Medical Center, Bronx; [6]Department of Neurology, Columbia University School of Medicine, New York, NY; [7]Department of Neurology, Thomas Jefferson University Medical School, Philadelphia, PA; [8]Department of Neurology, NYU School of Medicine, New York, NY; [9]Minnesota Comprehensive Epilepsy Program, Minneapolis, MN; and [10]Division of Statistics, Northern Illinois University, DeKalb, IL)

Rationale: Health-related quality of life (HRQOL) improves following resective surgery but most data are limited to short-term follow-up. We examined HRQOL and its relation to seizure outcome for up to five years after surgery.

Methods: In a prospective, multicenter study, 396 patients underwent resective epilepsy surgery. They completed the QOLIE-89 before, and at 3 months, and yearly after surgery. Longitudinal regression methods were used for analysis. Overall QOLIE and its domains (epilepsy-targeted, cognitive distress, physical health, mental health) were studied.

Results: In the 304 participants with baseline QOLIE and over 2 years of follow-up, overall QOLIE and domain scores rose substantially by 3-months post surgery. Further increases were largely limited to the epilepsy-targeted domain. Patients who immediately entered remission and never relapsed (Best, $N = 112$) achieved the greatest gains.The epilepsy-targeted domain continued to show small improvements over five years, from 45.3 presurgical to 55.2, 59.5, 61.1, 61.3, 61.7 and 62 at 3 months, 1, 2, 3, 4, and 5 years post-surgery ($p < 0.0001$ for trend). Participants who never became seizure-free (Worst, $N = 59$) had a smaller increase in QOLIE scores at 3 months, and dropped to presurgical levels over time (presurgical score = 42.8, and 50.2, 49.3, 48.5, 47.9, 49.3, 44.8 at 3 month, 1, 2, 3, 4, and 5 years post-surgery). Those who remitted after a few seizures were indistinguishable from the Best group. Those who remitted and later relapsed or took longer to remit had intermediate scores: when in remission, they were closer to the Best group, and scores dropped following relapse.

Conclusions: HRQOL, particularly the epilepsy-targeted domain, is sensitive to seizure remission. Most of the change is apparent soon after attaining remission. Statistically significant improvement in the epilepsy-targeted domain continues to accrue with prolonged time seizure-free. Relapse after remission results in a drop in QOLIE scores. (Supported by NIH-NINDS NS32375)

C.07

MORTALITY AFTER SURGICAL OR MEDICAL THERAPY FOR REFRACTORY EPILEPSY

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Rationale: The multicenter epilepsy surgery study has prospectively tracked patients with localization-related epilepsy treated either medically or surgically for many years. Consequently, an opportunity exists to assess mortality and influences on death rates in medically refractory patients spanning different referral populations in the U.S. We assessed risk of death in refractory epilepsy and whether mortality differs in medical and surgically treated patients.

Methods: Seven epilepsy centers enrolled patients in a study of outcome after resective epilepsy surgery. While most patients had surgery, some individuals did not and were followed on medical therapy. Patients were prospectively observed for up to 7.7 years after enrolling in the

study. Seizure outcome was assessed by office visits and telephone calls. Mortality and cause of death were determined by direct contact and searching the Social Security index. Survival analyses were performed with the product-limit method and mortality rates per 1000 person-years (p-y) were calculated along with confidence intervals (Wald method).

Results: 532 patients had adequate data for analysis. 388 had surgery and 144 had medical treatment. 282 were female, 250 were male, and mean age at enrollment was 37 yrs, (range 13.8–66.2 yrs). Mean follow-up duration was 4.5 yrs (range 0.27 to 7.7 yrs). Mortality was higher in medical than surgically treated patients ($p = .002$, Cox-Mantel). In the medical group, 11 patients (7.6%, 95% CI = 4.2–13.3%) died, a death rate of 20.3 per 1000 p-y. In the surgical group, 11 patients (2.8%, 95% CI = 1.5–5.1%) died during follow-up, a death rate of 6.0 per 1000 p-y. Most had recurrent seizures. Mortality in medical patients exceeded that of surgical patients who recurred postoperatively ($p < .01$). Of deceased medical patients with known follow-up, all had recurrent seizures. Causes of death were known in 13 patients and included probable SUDEP in 5, seizure-related in 4, suicide in 3, and cancer in 1 patient.

Conclusions: As expected, refractory epilepsy is associated with high death rates. Mortality appears to be lower in surgically treated patients than medically treated patients. This is most likely related both to elimination of seizures and inherent disease severity. Further exploration of specific risk factors is needed. (Supported by National Institutes of Health)

C.08

LONG-TERM OUTCOME OF EPILEPSY SURGERY IN 491 PATIENTS WITH PHARMACORESISTANT LOCALIZATION-RELATED EPILEPSY

Aaron A. Cohen-Gadol, Gregory D. Cascino, Fredric B. Meyer, Richard W. Marsh, and Dennis M. Cambier (Neurologic Surgery; and Neurology, Mayo Clinic, Rochester, MN)

Rationale: We reviewed the long-term outcome of focal resective surgery in a large consecutive group of patients with intractable partial epilepsy from a single institution to evaluate the durability of epilepsy surgery and preoperative factors associated with improved seizure outcomes.

Methods: This retrospective analysis included 491 consecutive patients who underwent epilepsy surgery at Mayo Clinic (Rochester, MN) between 1988 and 1998. The average age at surgery and seizure onset was 32 years (range, 3–69 years) and 13 years (range, 0–65 years), respectively. The mean duration of follow-up was 6.1 years (range, 5–14 years). Preoperative evaluation included a routine and video encephalogram (EEG) recordings, MRI head seizure protocol, neuropsychological testing, and sodium amobarbital study. Patients with undefined epiletogenic focus underwent an intracranial study. Cox regression analysis models were used to evaluate the risk factors associated with outcomes.

Results: Among these patients, 435 (89%) had temporal and 54 (11%) had extratemporal epilepsy. Histopathological examination of the resected specimen most commonly revealed gliosis in 222 (45%) patients, mesial temporal lobe sclerosis in 116 (24%), neoplasm in 36(7%), normal histopathology in 48 (10%) and other including developmental pathologies and vascular malformations in 32 (10%). Overall, 356 of 491 (73%) patients had an Engel Class I outcome (seizure-free, auras, or seizures only related to medication withdrawal). Almost all seizures occurred in the first year following surgery. Patients with medial temporal lobe sclerosis who were seizure free at one year remained seizure free at their last follow-up. Factors predictive of poor outcome from surgery were normal tissue pathology ($p = 0.028$), male gender ($p = 0.03$), previous surgery, and an extratemporal origin of seizures ($p < 0.001$). The factor associated with an improved outcome was temporal origin of seizures ($p < 0.001$). Status epilepticus was the cause of death in 13 patients during the follow-up.

Conclusions: Epilepsy surgery offers a safe and effective long-term treatment for patients with intractable localization-related epilepsy. The response to surgery during the first follow-up year is a reliable indicator of the long-term operative outcome.

December 6, 2004
Presidential Symposium—Epilepsy and Computational Neuroscience: At the Threshold of a Whole New Era
9:00 a.m.–11:30 a.m.

PS.01

EPILEPSY AND COMPUTATIONAL NEUROSCIENCE: AT THE THRESHOLD OF A WHOLE NEW ERA

Daniel H. Lowenstein, Eva Marder, Ivan Soltesz, Brian Litt (University of California, San Francisco, CA; Brandeis University; Waltham, MA; University of California, Irvine, CA; University of Pennsylvania, Philadelphia, PA)

Computational neuroscience and bioinformatics have moved onto the center-stage of modern science, linked in large part to the process of sequencing the genome of humans and other organisms, and the recognition that the astonishing complexity of biological systems can only be understood through the power of mathematical analysis and modeling. Epilepsy is clearly a manifestation of multiple pathophysiological processes impinging upon intricate networks, with the added complexity of the network dysfunction being intermittent and difficult to predict. Although computational approaches to understanding seizures and epilepsy have been around for decades, the last few years have seen major conceptual advances, and this rapidly moving field is becoming a regular part of basic epilepsy research, and it is even seeing direct, clinical application. The goal of this symposium is to provide a primer on computational neuroscience to clinicians and scientists not familiar with the field, and to then demonstrate the way the approaches and methods in this area of science are being used to understand properties of normal network function and network excitability.

December 6, 2004
Pediatric Epilepsy State-of-the-Art Symposium
7:30 p.m.–10:00 p.m.

PE.01

PEDIATRIC EPILEPSY STATE-OF-THE-ART SYMPOSIUM

Elaine Wyllie, Michael S. Duchowny, W. Donald Shields, Joseph G. Gleeson, Bernard S. Chang, Ajay Gupta, Volney Sheen, Gregory L. Holmes, and John M. Pellock (Cleveland Clinic Foundation, Cleveland, OH; Miami Children's Hospital, Miami, FL; University of California, Los Angeles, CA; Beth Israel Deaconess Medical Center, Boston, MA; Dartmouth Medical School, Lebanon, NH; Virginia Commonwealth University, Richmond, VA)

The theme of the symposium is catastrophic epilepsy in infants and children with brain malformations. Genetics, behavioral manifestations, and epilepsy will be examined in children with lissencephaly, subcortical band heterotopia, and periventricular nodular heterotopia. Clinical features, neuroimaging, and surgical issues will be explored for children with hemimegalencephaly and other predominantly unilateral brain malformations. Researchers will address cellular mechanisms of genes that cause human brain malformations, and the impact of early catastrophic epilepsy on cognitive development. Perspectives will be given on the role of new antiepileptic medications in the treatment of catastrophic epilepsy in infants and young children. Faculty will address issues from clinical and basic science perspectives, to address the mechanisms, clinical manifestations, and treatment of this important group of disorders.

December 7, 2004
Poster Session 2
8:00 a.m.–5:00 p.m.

Translational Research: Basic Mechanisms 2

2.001
GENETIC BACKGROUND INFLUENCES NEUROTROPHIN AND NEUROPILIN 2 SIGNALING DURING KAINIC ACID–INDUCED EPILEPTOGENESIS

[1]Gregory N. Barnes, [2]Andreas Walz, [2]Peter Mombaerts, [1]Kurt F. Hauser, [3]Elyse Schauwecker, and [1]George M. Smith ([1]Departments of Neurology, Anatomy/Neurobiology, and Physiology, University of Kentucky College of Medicine, Lexington, KY; [2]The Rockfeller University, New York City, NY; and [3]Department of Cell Biology/Neurobiology, USC Keck School of Medicine, Los Angeles, CA)

Rationale: Synaptic reorganization after neural injury may cause recurrent excitatory networks and the development of spontaneous recurrent seizures. Axon guidance cues including the semaphorins may participate in the synaptic reorganization and epileptogenesis. It is unknown how upstream regulatory pathways influence semaphorin signaling and its subsequent physiologic effects on epileptogenesis. Neurotrophin signaling thru BDNF and NGF plays a role in the molecular mechanisms of epileptogenesis. Through the use of genetic murine models, we have identified the semaphorins as one possible subset of neurotrophin regulated genes that participate in epileptogenesis. FVB/NJ but not C57Bl/6J mice show kainic acid status epilepticus (KA-SE), increased cell death of CA3/Hilar neurons, decreased hippocampal gene expression of Semaphorin 3F ligand and receptor (Neuropilin 2) systems, axonal sprouting of hippocampal neurons, and epilepsy.

Methods: Initial microarray experiments identified MAP kinase signaling pathways as the single regulated second messenger system which may modulate transcriptional regulatory complexes in hippocampal neurons of FVB/NJ mice 7 days after KA-SE. To evaluate the role of neurotrophin induced MAP kinase signaling on semaphorin/neuropilin gene expression, we have used adult murine hippocampal slice cultures from FVB/NJ or C57Bl/6J mice in the presence or absence of 100 ng/ml BDNF, NGF, or NT-3.

Results: NGF evokes a 5–10 fold ($p < 0.0001$) elevation of NPN2 gene expression in hippocampal cultures from FVB/NJ. Similar to kainic acid, both BDNF and NT-3 induce a 70–90% reduction ($p < 0.001$) of NPN2 gene expression in FVB/NJ cultures. None of three neurotrophins affected NPN2 gene expression in hippocampal neurons from C57Bl/6J cultures. In contrast, all three neurotrophins reduce neuropilin 1 gene expression by 80% ($p < 0.02$) irregardless of the strain origin of the hippocampal slice cultures. In vivo, disruption of NPN2 gene in FVB/NJ heterozygous NPN2 KO mice has so far prevented the development of spontaneous seizures three months post KA-SE. In contrast, their wild type FVB/NJ littermates have developed spontaneous seizures.

Conclusions: In summary, we hypothesize that BDNF signaling thru MAP kinase pathways regulate semaphorin and neuropilin gene expression to promote synaptic reorganization and development of seizures in FVB/NJ mice after KA-SE. If confirmed, this work suggests that neurotrophin signaling may contribute to the distinct responses to neural injury in mouse strains from varied genetic backgrounds. (Supported by American Epilepsy Society & Kentucky Spinal Cord/Head Injury Research Trust.)

2.002
Kv4.2 KNOCKOUT INCREASES SEIZURE SUSCEPTIBILITY

[1]L. Forbes, [1]S. Barnwell, [2]Xianghua Xu, [2]Xiaodi Lin, [2]Alicia White, [2]Victor W. Lueng, and [1,2,3]Anne E. Anderson ([1]Neurology, [2]Pediatrics, and [3]Division of Neuroscience, Baylor College of Medicine, Houston, TX)

Rationale: Kv4.2 subunits are thought to compose hippocampal A-type dendritic K^+ currents, which regulate excitability through dampening back-propagating action potentials in dendrites. In several models of limbic epilepsy, Kv4.2 channel protein is downregulated. In order to investigate whether a decrease in Kv4.2 channels contributes to altered seizure threshold, we studied seizure susceptibility of Kv4.2 null mutants.

Methods: Kainate (20 or 40 mg/kg IP) or vehicle was administered to Kv4.2 null and wildtype (WT) mice. Seizure activity was assessed and scored according to the Racine Scale by monitoring visually for behavioral seizures. An additional group of mutant and wildtype mice were monitored with video EEG after administration of kainate (40 mg/kg IP) or vehicle. Following the development of status epilepticus animals were treated with pentobarbital (15 mg/kg) and allowed to survive. Video EEG monitoring was obtained at various time points following kainate administration to assess for the development of spontaneous seizures and spike activity.

Results: Kainate 20 mg/kg induced behavioral seizures (Class 3 seizures – forelimb clonus), but not behavioral status epilepticus (recurrent Class 5 seizures – rearing and falling) in the Kv4.2 null and WT mice. The latency to onset of the first Class 3 seizures was significantly decreased ($p < 0.05$) and the frequency of Class 3 seizures was significantly increased ($p < 0.05$) in the Kv4.2 null compared to WT mice. The response to kainate 40 mg/kg was also tested and revealed a similar increase in the frequency of Class 3 seizures in the Kv4.2 null compared to WT mice ($p < 0.05$), but animals in both groups had behavioral seizures consistent with status epilepticus. In a third group of animals with cortical and hippocampal EEG electrodes implanted, we assessed the response to kainate 40 mg/kg or vehicle using video EEG monitoring. Kv4.2 null mice developed prolonged electrographic status epilepticus, requiring pentobarbital treatment. In contrast, the WT mice had a shorter period of status epilepticus, which was self-limited and did not require anticonvulsants. EEG monitoring up to two weeks following kainate administration revealed the presence of occasional electrographic seizures and frequent interictal spikes in the Kv4.2 null compared to no seizures and rare spikes in the WT mice. Monitoring with video EEG at longer time points following kainate is planned.

Conclusions: Our results demonstrate that there is increased seizure susceptibility in the Kv4.2 null compared to WT mice. These observations support the idea that the decrease in Kv4.2 channels observed in chronically epileptic animals may contribute to hyperexcitability and potentially seizure activity. (Supported by NINDS/NIH, Epilepsy Foundation, and Child Neurology Foundation.)

2.003
PAF ANTAGONISM LIMITS THE PROGRESSION OF KINDLING EPILEPTOGENESIS

Nicolas G. Bazan and Alberto E. Musto (Neuroscience, Louisiana State University, New Orleans, LA)

Rationale: Synthesis of the bioactive lipid platelet-activating factor (PAF) is enhanced during excitatory synaptic neurotransmission (*J Lipid Res* 2003;44:2221). PAF actions involve synaptic plasticity modification via multiple mechanisms that include protein kinase signaling cascades that affect permanent changes in synaptic circuits. Here we used a selective PAF-receptor antagonist (LAU-0901) to study the participation of PAF pathways in rapid kindling epileptogenesis.

Methods: Tripolar electrode units (Plastic One Inc., Roanoke, VA) were implanted in the right ventral hippocampus of male adult Wistar rats. Kindling was achieved ten days after surgery by stimulating 6 times daily for 4 consecutive days with a subconvulsive electrical stimulation (400 μA, 10 s 50 Hz, 12 sessions) at 30-min intervals. LAU-0901 (30 μg/kg) or vehicle was injected intraperitoneally at the beginning of each session. We used Racine's Scale as a semiologic score. The EEG was recorded using Enhanced Graphics Acquisition for Analysis (Version 3.63 RS Electronics Inc. Santa Barbara, CA.) and analyzed using Neuroexplorer Software (Next Technology). We characterized the epileptic events as spike, sharp waves, or abnormal amplitude and rhythms.

Results: The LAU-0901-treated group displayed a non-significant modification of the semiologic score and epileptic events between the first day and the last day of stimulation, a reduction of spike-wave amplitude, and no interictal spike; while the vehicle-treated group exhibited the opposite effects.

Conclusions: The PAF-receptor antagonist LAU-0901 when systemically injected attenuates the progression of seizures during rapid kindling epileptogenesis. We suggest that excitatory synaptic transmission up-regulation during kindling utilizes PAF as one of the mediators. The

blockade of its receptor results in lesser excitability-induced changes. We are studying signaling in epileptogenesis. (Supported by NIH NS23002.)

2.004
THE EVOLUTION OF UNTREATED SEIZURES AND THE EFFECT OF AGING IN CHRONIC EPILEPTIC RATS
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Rationale: In humans, the long term consequences of chronic epilepsy cannot be evaluated in the absence of antiepileptic drugs. To address this issue, we studied the evolution of untreated seizures and the influence of aging in chronic epileptic rats.

Methods: Male Wistar rats were submitted to the pilocarpine model of epilepsy. Surviving animals were observed 24 h/day until death or by 16 months. Aged rats were submitted to electroencephalographic recordings and echo-cardiogram evaluation. Surviving animals were perfused at the age of 16 months and the brains were processed for histological study. Deceased rats before the age of 16 months were submitted to necropsy and hystopathological examination of internal organs.

Results: In chronic epileptic rats, the seizure frequency showed a great oscillation until the 11th month. After that period, experimental rats showed 4–5 seizures per week until death. EEG recordings of aged animals showed constant epileptic activity with a higher number of spikes when compared to young experimental rats. Despite the constant epileptiform activity, the frequency of behavioral seizures in aged animals was similar to that observed in young epileptic rats. Aged control rats did not presented any EEG abnormality. Aged epileptic and control rats showed the same abnormalities in the echo-cardiogram evaluation. Aged experimental rats showed more exuberant histological alterations of the hipocampal formation, including cell loss, gliosis and axonal sprouting, when compared to young rats. Finally, the experimental group showed a higher mortality rate when compared to control group.

Conclusions: Aged epileptic rats showed a discrepancy between EEG and behavioral manifestations, in addition to a progressive neuronal damage and reorganization. Epileptic animals showed a higher mortality rate that was not related with cardiac dysfunctions. (Supported by CNPq, CAPES, FAPESP, and PRONEX.)

2.005
DENTATE GRANULE CELL FIRING INCREASES AT THE ONSET OF SPONTANEOUS SEIZURES
Mark R. Bower and Paul S. Buckmaster (Comparative Medicine, Stanford University, Stanford, CA)

Rationale: Dentate granule cells are thought to protect the hippocampus by filtering or blocking epileptiform activity from the entorhinal cortex. In previous studies, spontaneous seizures recorded in the dentate gyrus in models of temporal lobe epilepsy appear to include field excitatory post-synaptic potentials (fEPSPs), but it is not clear whether the firing rate of individual granule cells is altered. One possibility is that granule cells block epileptiform activity and maintain roughly the same firing rate for the duration of a seizure. Alternatively, the firing rate of granule cells could increase at seizure onset, and thus propagate or even amplify epileptiform input into the hippocampus. These possibilities can be distinguished by determining whether the firing rate of individual granule cells increases during seizures.

Methods: Multiple, single units were recorded from the dentate gyrus in epileptic rats at least 4 months following pilocarpine-induced status epilepticus. Broadband, tetrode recordings were made before, during and after spontaneous seizures in awake, freely-moving rats. Seizures were confirmed by behavior, and seizure onset was determined electrographically by the paroxysmal onset of rhythmic fEPSPs in the dentate gyrus. Multiple, single units were isolated offline by digital filtering, threshold detection and cluster cutting.

Results: Individual units could be placed into one of two classes based on firing properties during rest that, when compared against unit recordings from the dentate gyrus reported in the literature, corresponded to putative interneurons (mean rate > 5.0 Hz, unimodal distribution of inter-spike intervals (ISIs), symmetric spike waveform) and granule cells (mean rate < 5.0 Hz, multimodal distribution of ISIs, asymmetric spike waveform). During seizures in two rats, granule cell firing rates increased dramatically (3.4 ± 1.4 Hz to 24.2 ± 14.9 Hz, $N = 5$) and rapidly at the time of seizure onset, tens of seconds prior to the observation of population spikes in the field recordings. Following a seizure, granule cell activity was sharply attenuated for up to several minutes; i.e., during behavioral post-ictal depression. Within five minutes subsequent to the end of the seizure, granule cell activity returned to pre-seizure levels. Interestingly, in contrast to granule cells, firing rates for interneurons during seizures declined slightly, but not significantly (12.8 ± 3.3 Hz to 9.3 ± 2.1, $N = 5$).

Conclusions: These findings suggest that, in this model of temporal lobe epilepsy, dentate granule cells do not filter or block epileptiform activity from entering the hippocampus. Rather, a rapid increase in their firing suggests that granule cells might play an active role in amplifying or possibly generating seizure activity. (Supported by NIH NS07280.)

2.006
DOES A UNIQUE TYPE OF PROXIMAL CA3 PYRAMIDAL CELL IN PRIMATES BYPASS THE DENTATE GATE?
Paul S. Buckmaster (Comparative Medicine and Neurology & Neurological Sciences, Stanford University, Stanford, CA)

Rationale: The CA3 field in primates, unlike rats, includes proximal CA3 pyramidal cells with an apical dendrite that extends through the hilus and granule cell layer and into the molecular layer of the dentate gyrus. These unusual neurons are called "dentate" CA3 pyramidal cells (Buckmaster and Amaral. *J Comp Neurol* 2001;430:264). The position of their apical dendrite suggests that dentate CA3 pyramidal cells might be more responsive than other CA3 pyramidal cells to synaptic input from the entorhinal cortex to the dentate gyrus. Previous studies in rodents suggest that dentate granule cells filter or gate entorhinal input. In primates, however, dentate CA3 pyramidal cells might bypass granule cells and convey entorhinal input directly to other pyramidal cells in CA3 and CA1. To test this possibility, we stimulated the dentate gyrus molecular layer and measured the spike threshold of morphologically identified proximal CA3 pyramidal cells.

Methods: Hippocampal slices were prepared from 20 adult, male, neurologically normal monkeys (*Macaca fascicularis*) that were being euthanized for reasons unrelated to this experiment. Slices were recorded in an interface chamber at 31°. A stimulating electrode was placed in the outer molecular layer of the dentate gyrus. Stimulus intensity was standardized by the threshold for evoking a field potential population spike (T) recorded at the border of the granule cell layer and hilus, close to the site of the recorded CA3 pyramidal cell. Proximal CA3 pyramidal cells were recorded in current-clamp mode with sharp microelectrodes. The molecular layer stimulus intensity needed to evoke an action potential was measured. Cells were labeled with biocytin and processed with DAB for visualization. CA3 pyramidal cells were classified as "classical" (dendrites extended into stratum radiatum and/or stratum oriens of CA3), "nonapical" (all dendrites confined to the pyramidal cell layer), or "dentate" (apical dendrite extended through the hilus and granule cell layer and into molecular layer of dentate gyrus).

Results: In response to current injection, dentate CA3 pyramidal cells responded like other CA3 pyramidal cells. In response to stimulation of the dentate gyrus molecular layer, spike thresholds were: 1.02 ± 0.13 xT (mean $\pm$ sem) for classical CA3 pyramidal cells ($n = 12$); 0.99 ± 0.12 xT for nonapical CA3 pyramidal cells ($n = 23$); and 0.96 ± 0.09 xT for dentate CA3 pyramidal cells ($n = 7$). The differences were not significant (t test).

Conclusions: These findings suggest that dentate CA3 pyramidal cells have similar spike thresholds to stimulation of the dentate gyrus molecular layer as other types of CA3 pyramidal cells. We cannot exclude the possibility that differences might be detected with more physiological stimulation methods. The role of dentate CA3 pyramidal cells is unclear, but based on these findings, they do not appear to circumvent the dentate gate. [Supported by NIH/NINDS (NS40276).]

2.007
CHANGES IN DENTATE CIRCUIT PROPERTIES DURING THE DEVELOPMENT OF TEMPORAL LOBE EPILEPSY
Greg C. Carlson and Doug A. Coulter (Department of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA)

Rationale: The dentate gyrus of the hippocampus controls input of cortical information into the hippocampus proper. This has led to the hypothesis that in temporal lobe epilepsy (TLE) loss of this control may be associated with hippocampal involvement in seizures. Yet, there has been work suggesting that in chronic TLE, the dentate may be less likely to support throughput into the hippocampus.

Methods: To directly study dentate circuit properties, we used voltage-sensitive dye imaging to assess dentate throughput into CA3 following perforant path stimulation in two conditions: 1) in hippocampal slices from chronically epileptic rats and 2) one week following Pilocarpine-induced status epilepticus destined to produce TLE weeks later. This period following the initial insult is often referred to as the latent period: when seizures are rare but during which time the pathological processes leading to TLE develop.

Results: In chronic epilepsy, we found that dentate transfer of synaptic input into CA3 was not significantly increased despite evidence of sprouting (assessed using Timm's stain). In contrast, during the latent period excitation in the dentate was enhanced. Stimulation of the perforant path could produce increased throughput into CA3 leading to burst potentials. This suggests that during the latent period, the dentate may lose its ability to control throughput into the hippocampus proper.

Conclusions: The strong inhibitory control of the dentate can powerfully restrain reentrant excitability of the hippocampus. This transient loss of inhibitory control, concurrent with the latent period, suggests that the dentate hyperexcitability may be an important factor in post-SE epileptogenesis. (Supported by NS38572, NS32402 from NINDS, and AES.)

2.008
DNA DOUBLE-STRAND BREAK REPAIR: REGULATION FOLLOWING PROLONGED SEIZURES
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Rationale: Prolonged seizures increase oxidative stress in the brain, leading to cellular distress and DNA damage. DNA damage can reach a threshold where it initiates programmed cell death pathways in the brain, but the extent to which DNA repair mechanisms can compensate for this damage remains unknown. We hypothesized that the regulation of DNA double-strand break (DSB) repair may be a determinant of vulnerability to seizure-induced cell death. In previous studies, we found evidence for a downregulation of DSB repair mechanisms at 48 and 72 hr after seizure termination. In the present study, we examined earlier time points to see if upregulation preferentially occurs during a period preceeding cell death execution. As an indicator of DNA repair, protein levels of Ku70, a regulatory component of DSB repair machinery, were measured as a function of seizure duration.

Methods: Adult male Sprague-Dawley rats were treated with kainic acid (12.5 mg/kg, i.p.) or saline (controls without seizures) and given diazepam (30 mg/kg, i.p.) at defined durations. Nuclear and cytosolic protein levels of Ku70 were determined in specific brain regions by Western blotting at 4, 8, and 20hr after seizure termination.

Results: In rhinal cortex, a region especially vulnerable to seizure-evoked injury, seizures lasting 30 or 120 min resulted in an upregulation of Ku 70 protein that was detected at 4 and/or 8hr following seizure termination. The cellular distribution of the increase was as follows.

	4 hr After Seizure Termination	8 hr After Seizure Termination	20 hr After Seizure Termination
30 min of Seizures	Nuclear	Nuclear + Cytosolic	No increase
120 min of Seizures	Nuclear + Cytosolic	No increase	No increase

In addition, there was a trend toward a downregulation of Ku70 protein at 20 hr following both 30 and 120 min of seizures; this is consistent with our previously reported observation of downregulation at 48 and 72 hr following seizure termination. The pattern of changes in Ku70 will be compared with that for histone H2AX phosphorylation (a measure of the extent of DSB).

Conclusions: Our results indicate that the DNA repair component, Ku70, is rapidly and transiently upregulated in response to prolonged seizure activity. Furthermore, the pattern of this regulation is influenced by the duration of seizure activity. Seizures lasting 30 min were sufficient to induce what appears to be a maximal effect. This raises the possibility that the components of the DSB DNA repair mechanisms may serve as a target for neuroprotective strategies. (Supported by NIH predoctoral fellowship NS 046199, NIH grants NS 20576, MH 02040, and NS 041231.)

2.009
NICOTINIC MODULATION OF EPILEPTIFORM ACTIVITY IN THE CA3 REGION OF HIPPOCAMPAL SLICES
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Rationale: Neuronal nicotinic receptors modulate brain excitability and have recently been associated with at least one form of epilepsy. Additionally, several recent reports indicate that the genetic modification or deletion of nicotinic receptor genes in mice results in either increased or reduced thresholds for drug-induced seizures, depending upon which nicotinic receptor subtype has been modified or deleted. These results suggest that pharmacological manipulation of certain types of nicotinic receptors may be useful for treating some forms of epilepsy.

Methods: Hippocampal slices were obtained from adult (>45 days old) male mice. Spontaneous bursting of the CA3 pyramidal neurons was induced either by tetanic stimulation of the CA3 recurrent collaterals or by GABA receptor blockade and measured using extracellular and whole-cell electrophysiological recordings. Once stable rates of bursting were established, the effects of nicotinic receptor-subtype selective ligands on CA3 bursting rates were determined.

Results: Preliminary results demonstrated that bath application of selective agonists of the $\alpha 4\beta 2^*$-type nicotinic receptor reduced and in some cases stopped CA3 bursting. Conversely, bath application of the $\alpha 7^*$-type nicotinic receptor selective agonist, choline, increased bursting rates. The mechanisms (ie, receptor activation or desensitization) by which nicotinic receptors modulate hippocampal excitability will be determined using pharmacological, genetic, and electrophysiological techniques.

Conclusions: Preliminary data indicate that modulation of nicotinic receptor activity can result in dynamic modulation hippocampal excitability. Furthermore, these results suggest that nicotinic receptor systems could be exploited as novel targets for the treatment of at least some forms of epilepsy/seizure disorders. [Supported by the Epilepsy Foundation through the generous support of the American Epilepsy Society and the Milken Family Foundation (P.D.) and NS34700 (K.S.).]

2.010
NEURONAL DEGENERATION INDUCED BY STATUS EPILEPTICUS IN NEOCORTEX OF IMMATURE RATS IS AN AREA-SPECIFIC PROCESS
Rastislav Druga, Hana Kubova, and Pavel Mares (Developmental Epileptology, Institute of Physiology CAS, Prague, Czech Republic)

Rationale: To describe distribution of status epilepticus–induced neuronal degeneration in the selected neocortical and transitional cortical areas in 25–day–old rats. Time course of changes was studied to find out possible differences at various survival intervals. Specific attention was given to laminar distribution of degenerated cells.

Methods: Experiments were carried out in Wistar rat pups 25 days old. Lithium–pilocarpine model of SE was used. Lithium chloride (3 mmol/kg, i.p.) was injected 24 hours before pilocarpine (40 mg/kg, i.p.). Only animals exhibiting convulsive status epilepticus (SE) were included in this study. The rats survived for 4, 8, 12, 24, 48 hours and/or 1 week after SE. Four to five animals were processed in each survival

interval. The animals were perfused with phosphate–buffered saline (PBS) followed by 4% paraformaldehyde in PBS under an overdose of urethane anesthesia. Coronal sections (40 μm thick) were cut on a cryostat, mounted onto gelatine–coated slides, and processed with cresyl violet or with a fluorescent stain Fluoro-Jade B (FJB) used for detection of degenerated neurons in different cortical areas (motor, somatosensory, cingular, agranular insular, ectorhinal, perirhinal and retrosplenial areas). Sections were examined with an epifluorescence microscope using a filter system suitable for visualizing fluorescein or fluorescein isothiocyanate (FITC).

Results: A small to moderate number of FJB–positive neurons was found 4, 8 and 12 hours after SE in transitional cortical areas (cingular, agranular insular, perirhinal, ectorhinal area) as well as in the motor area. These neurons were distributed in supragranular as well as in infragranular layers. In contrast, degenerated neurons prevailed in infragranular layers of the retrospenial area and the somatosensory area. Majority of FJB–positive neurons were small to medium sized cells with round or spindle-shaped nonpyramidal perikarya. Basic differences between transitional cortical areas and motor cortex remained unchanged at longer survival intervals (24 and 48 hours) but the number of FJB-positive neurons significantly increased. In addition, pyramidal neurons were markedly represented among degenerated elements at these intervals. One week after SE degenerated neurons persisted in all analyzed areas but their number was reduced in comparison with preceding intervals.

Conclusions: Lithium–pilocarpine model of SE resulted in degeneration of neurons in transitional as well as in sensorimotor cortical areas in 25–day–old rats evident at all survival intervals. At shorter intervals majority of degenerated cells exhibited features of local interneurons whereas pyramidal neurons represented a substantial part of FJB-positive cells 24 hours after SE and later. Individual cortical areas exhibited characteristic laminar pattern in distribution of degenerated neurons. (Supported by grants 304/04/0464 and 309/03/0770 of the Grant Agency of the Czech Republic.)

2.011

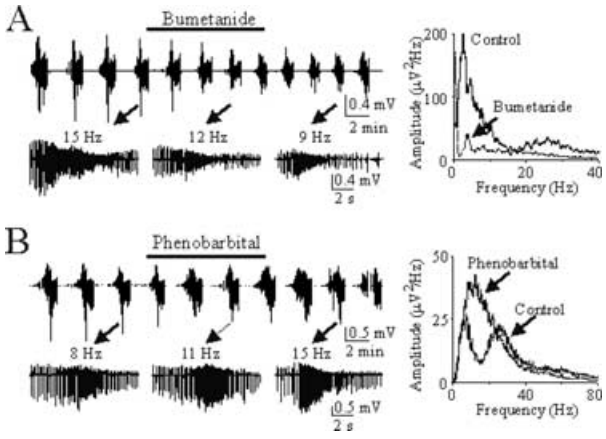
BUMETANIDE FOR NEONATAL SEIZURE THERAPY

Volodymyr I. Dzhala, Den A. Sdrulla, Audrey C. Brumback, and Kevin J. Staley (Neurology, University of Colorado Health Sciences Center, Denver, CO)

Rationale: GABA is the primary inhibitory neurotransmitter in adult mammalian brain. However, in neonates activation of Cl^--permeable GABA receptors excites many neurons and appears to depend on the expression of a Na^+-K^+-$2Cl^-$ cotransporter (NKCC1) that elevates intracellular Cl^- levels, leading to a depolarized Cl^- equilibrium potential (E_{Cl}). Excitatory actions of GABA contribute to initiation of ictal epileptiform activity in the developing hippocampus (Dzhala and Staley, 2003) and it is not surprising then that the barbiturates and benzodiazepines, drugs that increase GABA effects, fail to suppress the EEG seizures in the immature brain. A reasonable alternative would be to use drugs that work at other sites. Neonates accumulate Cl^- through the action of a NKCC1 cotransporter, which is exquisively sensisitive to the diuretic bumetanide. We propose to use bumetanide to alter the ion gradients that underlie the excitatory effects of GABA to inhibit the neonatal brain in order to improve the therapy of neonatal seizures.

Methods: Whole-cell and extracellular array recordings were used to study the efficacy of diuretic bumetanide in the treatment of high (8.5 mM) extracellular potassium induced ictal-like epileptiform activity in the immature [postnatal day (P) 7–15] hippocampal slice preparations *in vitro*. Scalp EEG recordings and video-monitoring of behavior were used to study the efficacy of diuretics in the treatment of kainate induced seizures in the neonatal rats (P8–15) *in vivo.* Recordings were subjected to power spectral analysis of frequency bands ranging from 0.1 to 200 Hz before and after drug applications.

Results: Low concentrations of bumetanide (10–20 μM) decreased frequency of ictal-like tonic discharges and depressed intensity of ictal-like epileptiform activity induced by 8.5 mM extracellular potassium in the postnatal day (P)7–15 rat hippocampal slices *in vitro* (n = 10). These effects persisted for more than one hour after wash of bumetanide. In contrast, Phenobarbital (100 μM) increased the frequency of tonic discharges and intensity of interictal epileptiform discharges in the P10–13 rat hippocampal slices *in vitro* (n = 4 from 5). Of the 9 rats injected with kainic acid (KA, 2 mg/kg), 9 developed transient seizures characterized by interictal EEG spikes and 4–12 Hz tonic-clonic discharges. Intraperitoneal (i.p.) administration of bumetanide (0.1–0.2 mg/kg) during development of seizures reduced duration of transient seizure state by 10–20% (n = 3) (Fig. 1).



Conclusions: Bumetanide strongly depresses ictal-like epileptiform activity in the hippocampal slices *in vitro*. Bumetanide attenuates transient epileptic state induced by kainate in the neonatal rats *in vivo*. These results provide evidence for a potential use of diuretic bumetanide alone and in combination with the GABA-enhancing anticonvulsants to improve the therapy of neonatal seizures. (Supported by a grant from the National Institute of Health, National Institute of Neurological Disorders and Stroke.)

2.012

DECREASED INWARDLY RECTIFYING POTASSIUM CURRENTS IN FRONTAL-PARIETAL NEOCORTICAL GLIA FOLLOWING FLUID PERCUSSION INJURY IN THE RAT

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Rationale: We have recently described the first in vivo model of post-traumatic epilepsy (PTE) in the rat where chronic recurrent seizures appear following a single episode of rostral lateral fluid percussion injury (rpFPI; D'Ambrosio et al., 2003). The frontal-parietal (FP) cortex is an early epileptic focus. To begin the identification of the epileptogenic mechanisms responsible for its onset we have examined the electrophysiological properties of FP glia before the epileptic condition arises.

Methods: Severe rpFPI was induced in 29–32 days old male Sprague Dawley rats. Coronal slices were obtained 1 day post-injury. Whole cell patch clamp recordings were performed from FP cortex (bregma 0 though–4 mm). Bath application of Ba^{2+} (40 μM) was used to block K_{IR} channels. Cells were chosen from neocortical layers IV-VI. Data are shown as mean $\pm$ S.E.M.

Results: There was a significant loss in K_{IR} currents in FP glial cells 1 day post-rpFPI. Barium–sensitive current at -140mV represented $17.2 \pm 2.9\%$ of the whole cell current in naïve glial cells (n = 9), but only $8.0 \pm 2.1\%$ in injured glial cells (n = 9; $p \leq 0.02$ with Wilcoxon test).

Conclusions: Our results demonstrated post-traumatic loss in glial K_{IR} conductance in the FP cortex 1 day post-injury. Because glial K_{IR} channels are known to be involved in proper extracellular K^+-homeostasis, and because the FP cortex later develops into an epileptic focus, the observed electrophysiological changes in FP glia are pro-epileptogenic. These results also demonstrate the utility of the rpFPI-induced PTE model in allowing putative epileptogenic mechanisms to be examined before the development of the epileptic focus.

REFERENCE

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2.013

TONIC GABA CURRENT IN SINGLE NEURON HIPPOCAMPAL MICROISLAND CULTURES

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Rationale: The tonic GABA current is a GABA receptor-mediated current that is persistently active. This is thought to be distinct from the "phasic" synaptic GABA current and mediated by extrasynaptic receptors. The tonic GABA current is regarded as an important contributor to the baseline level of neuronal excitability and a potential target for pharmacological therapy. The purpose of this study was to explore tonic GABA current in a simplified experimental model to better understand the contribution of the tonic current to normal neuronal excitability and the role of the tonic GABA current in epilepsy.

Methods: Primary hippocampal cell microcultures (100–200 μM diameter) were prepared from 1-to-3-day postnatal Sprague-Dawley rats as previously described (Mennerick et al., 1995). Cells were plated onto 35 mm plastic culture dishes pre-coated with collagen microdroplets sprayed onto a layer of agarose. Whole-cell patch-clamp recordings were performed on solitary neurons with only autaptic (recurrent) synaptic innervation 10–22 days after plating. Exogenous drugs were applied with a multi-barrel pipette coupled to miniature solenoid valves for rapid switching between solutions. Solitary excitatory neurons were identified by autaptic response polarity, kinetics and pharmacology. The tonic current was measured as the change in the holding current in the presence of 10 μM bicuculline.

Results: In an initial characterization of the tonic current, we found no relationship between time in culture and tonic current density. We then explored the source of the tonic current in this system where receptor activation by GABA from synaptic spillover is not possible as no inhibitory synapses are nearby. We tested the hypothesis that the current is mediated by non-synaptic GABA or another agonist released by cells on the microculture. First we used stop flow and rapid flow protocols to manipulate accumulation of the putative agonist and were unable to change the amplitude of the current. We then hypothesized that unliganded spontaneous openings of GABA receptor channels may underlie the tonic current. To test this idea, we used gabazine which is an ineffective antagonist of unliganded, spontaneous openings but an effective blocker of GABA-gated responses. We found that saturating gabazine concentrations had no effect on the tonic current in excitatory neurons. In contrast, in solitary inhibitory (GABAergic) neuron microcultures where synaptic overspill could possibly contribute to the tonic current, gabazine partially blocked the tonic current and completely blocked inhibitory postsynaptic currents.

Conclusions: These results suggest that the tonic GABA current in excitatory single neuron hippocampal microisland cultures is mediated by spontaneous, unliganded activation of GABA channels. This implies that spontaneous activity may contribute to the tonic GABA current *in vivo*, particularly in regions with low ambient GABA concentrations. (Supported by NIH.)

2.014

EXTERNAL STIMULATION DECREASES SEIZURE DURATION IN NEURAL NETWORK MODEL WITH ACTIVITY-DEPENDENT SYNAPTIC PLASTICITY

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Rationale: Experimental and clinical studies have demonstrated the ability to shorten or terminate epileptiform discharges by application of external electrical stimulation. However, there is no accepted explanation of the mechanism of this action. Recent experimental data illustrate the importance of the short-term frequency dependent plasticity of synapses in the epileptic brain. We used computer simulations of a large neural network model to investigate how a network with short-term synaptic plasticity responds to external stimulation with different frequency parameters.

Methods: Our model consists of an array of up to 1,000,000 synaptically connected excitatory and inhibitory neurons. Neurons are modeled using a conductance-based model producing realistic action potentials and bursts of action potentials. The synaptic connections are modeled using a double exponential conductance function producing realistic postsynaptic potentials. The strength of connections is modeled by a multiplicative synaptic weight parameter. In our previous publications we have shown that such a model can support the propagation of epileptiform activity. We have also shown that the balance between excitatory and inhibitory synaptic weights is a crucial parameter of network excitability. In this study we simulated short-term synaptic plasticity by introducing activity-dependent synaptic weights to the model. We used a model in which excitatory and inhibitory synapses have the same short-term plasticity characteristics, as well as a model in which these characteristics were different. The initial parameters of the network were set to produce the epileptiform bursting activity. External stimulation was applied to the network immediately or after a delay. The frequency and duration of the applied stimulus were varied between 0.1 Hz and 200 Hz, and between 10 ms and 200 ms, respectively.

Results: Addition of activity-dependent synaptic plasticity enhanced the observed dynamics of simulated epileptiform activity. Synchronization of this activity was dependent on the characteristics of synaptic plasticity. If there was stronger potentiation for inhibitory synapses than for excitatory synapses, the seizure terminated spontaneously. External stimulation with relatively high frequencies (>50 Hz) terminated these seizures more quickly. When synaptic weights were modeled as depressed for stimulus trains delivered at lower frequencies and potentiated for higher frequencies, a low frequency stimulation was more effective in terminating epileptiform activity.

Conclusions: Short-term activity-dependent synaptic plasticity is a plausible mechanism explaining the effects of electrical stimulation on epileptiform activity. The effectiveness of a stimulus at a particular frequency is dependent on synaptic plasticity characteristics. This suggests that different stimulus frequencies may be effective in different brain structures. (Supported by NIH grant NS38958.)

2.015

BOTH MILD AND MORE SEVERE INSULTS PRODUCE CASPASE-INDEPENDENT NECROTIC NEURONS: IN VIVO EVIDENCE FROM 60-MINUTE LITHIUM-PILOCARPINE–INDUCED SEIZURES

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Rationale: It is widely believed that mild insults produce apoptotic neurons, whereas severe insults produce necrotic neurons. We tested this hypothesis by subjecting adult rats to 60-min instead of 3-h lithium-pilocarpine-induced status epilepticus (LPCSE), and evaluated their brains 24 h afterward.

Methods: Adult male Wistar rats (220–350 g) had skull screws implanted for EEG recording, and 3–5 d later lithium chloride, 3 mEq/kg was given i.p. The next day normal saline or pilocarpine, 30 mg/kg, was given i.p., and after 60 min of continuous clonic seizures, diazepam, 20 mg/kg, and phenobarbital, 25 mg/kg, were given i.p. to stop the seizures. Twenty-four h later rats were given an overdose of pentobarbital, and either had in situ transcardiac perfusion-fixation of their brains, with subsequent removal and processing for H & E, TUNEL and active caspase-3 immunoreactivity (IR), or decapitation and rapid dissection of six brain regions (pooled from 4 rats) for DNA agarose gel electrophoresis. Thymuses of rats given normal saline or methamphetamine (MAP; 25 mg/kg i.p.) and killed 8 h later were used as controls for cellular apoptosis, active caspase-3 IR and DNA laddering. Twenty-four brain regions were assessed for the degree of neuronal death by H & E and TUNEL stain and caspase-3 activation by immunohistochemistry, using a 0–3 grading scale. Data were analyzed with a 2-factor

ANOVA and post-hoc t-tests based upon a Poisson distribution of the data.

Results: MAP-treated thymocytes showed morphological apoptosis, active caspase-3 IR and DNA laddering. Twelve of the 24 brain regions of SE rats ($n = 3$) showed significant numbers of acidophilic neurons by H & E stain, light-microscopic evidence of necrotic neurons. The mean damage score was 0.9 ± 0.1, or 10–25% damaged neurons, $p = 0.001$. Seven brain regions had TUNEL-positive necrotic neurons, but only one region showed a significant difference from controls. None of the necrotic neurons had active caspase-3 IR, and none of the six brain regions studied showed DNA laddering. Scattered morphologically apoptotic neurons were found in control and SE groups, and will be reported separately.

Conclusions: Twenty-four h after 60-min LPCSE, necrotic neurons are produced, as occurs after 3-h LPCSE. Although DNA fragmentation by TUNEL was found in 7 brain regions, there was no DNA laddering, as occurs after 3-h SE, probably because there were too few damaged neurons in the brain regions examined, and no caspase-3 activation in necrotic neurons. This suggests that in SE, a milder as well as a more severe insult produces caspase-3-independent necrotic neurons. (Supported by Department of Veterans Affairs.)

2.016
THE USE OF CHRONIC MODELS IN ANTIEPILEPTIC DRUG DISCOVERY: THE EFFECT OF RWJ-333369 ON SPONTANEOUS MOTOR SEIZURES IN RATS WITH KAINATE-INDUCED EPILEPSY

Heidi L. Grabenstatter and F. Edward Dudek (Department of Biomedical Sciences, Anatomy & Neurobiology Section, Colorado State University, Fort Collins, CO)

Rationale: Animal models with spontaneous epileptic seizures may be useful in the discovery of new antiepileptic drugs (AEDs). A recent study from our group (Grabenstatter et al., 2003, AES abstract), using a repeated-measures cross-over protocol in rats with kainate-induced epilepsy, showed that topiramate reduced seizure frequency in a dose-dependent manner. The purpose of the present study was to use this approach to evaluate the efficacy of RWJ-333369 on spontaneous motor seizures.

Methods: Kainic acid was administered in repeated, low doses (5 mg/kg) every hour until each male Sprague-Dawley rat experienced convulsive status epilepticus for >3 h. Four 1-month trials ($n = 8$–10 rats) assessed the effects of 1, 3, 10 and 30 mg/kg RWJ-333369 on spontaneous seizures. Each trial involved six AED vs. vehicle tests comprised of RWJ-333369 or 10% Solutol-HS-15 treatments administered as intraperitoneal injections on alternate days with a recovery day between each treatment day.

Results: RWJ-333369 significantly reduced relative seizure frequency at doses of 10 and 30 mg/kg ($p < 0.0001$). The effects of RWJ-333369 (1–30 mg/kg) on spontaneous motor seizures were dose dependent. Compared to our previous study using the same methods (Grabenstatter et al., 2003, AES abstract), RWJ-333369 caused a greater reduction in seizure frequency than topiramate. A dose of 30 mg/kg topiramate reduced relative seizure frequency by approximately one-half (0.51 ± 0.20), while a dose of 30 mg/kg RWJ-333369 suppressed three-fourths of the convulsive seizures (0.26 ± 0.11).

Conclusions: RWJ-333369 substantially reduced spontaneous seizures in rats with kainate-induced epilepsy. These data support the hypothesis that a repeated-measures, cross-over protocol is an effective method for testing AEDs in animal models with spontaneous seizures. Modifications of this approach to more closely mimic the treatment routines of human patients may be useful in identifying new AEDs for pharmacoresistant epilepsy, and in developing adjunct therapies. (Supported by Johnson and Johnson Pharmaceutical Research and Development, LLC.)

2.017
ALLOPREGNANOLONE EXPOSURE AND WITHDRAWAL ALTER $GABA_A$ RECEPTOR SUBUNIT EXPRESSION IN NT2-N NEURONS

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Rationale: Seizure frequency in women often correlates with changes in gonadal steroid hormone levels during the menstrual cycle, but the underlying mechanisms are uncertain. Progesterone and its metabolite, allopregnanolone (5α-pregnan-3α-ol-20-one, ALLO), have anticonvulsant properties, while β-estradiol is proconvulsant in several model systems. We hypothesized that fluctuations in steroid hormone levels could alter CNS inhibitory tone by changing the expression pattern of $GABA_A$ receptor (GABAR) subunits, affecting the likelihood of seizures. We have examined the effects of these steroid hormones on GABAR subunit expression in a simplified *in vitro* neuronal system, the NT2-N cell, derived from the human NTera2 teratocarcinoma cell line. Using RT-PCR, we have previously shown that 7 d exposure to progesterone increased $\alpha 2$ and $\gamma 3$ and decreased $\alpha 5$ subunit mRNAs, while β-estradiol exposure increased $\alpha 3$, $\beta 3$ and ε subunit mRNAs, relative to actin. ALLO does not act via the progesterone receptor, but allosterically enhances GABAR function. We thus questioned whether ALLO also affects GABAR subunit expression during treatment or after withdrawal.

Methods: NT2-N cells were maintained in culture for 5 weeks after 5 weeks retinoic acid (1 μM) treatment, then exposed to ALLO (1 μM) or vehicle (H_2O) for 2 d, and then harvested for RNA or withdrawn from ALLO for 1 d prior to RNA harvesting. After DNAse-I treatment, RNA was reacted for semiquantitative RT-PCR with 16 GABAR subunit-specific primer pairs, and analyzed by agarose gel electrophoresis with bands normalized to actin controls.

Results: ALLO treatment increased ε subunit mRNA $185 \pm 26\%$ ($n = 6$, $p < 0.05$) without significantly changing the expression of other GABAR subunits. ALLO withdrawal increased $\alpha 4$ subunit expression $380 \pm 69\%$ ($n = 6$, $p < 0.01$) and $\alpha 2$ expression $320 \pm 82\%$ ($n = 6$, $p < 0.05$). Expression of ε remained elevated during ALLO withdrawal.

Conclusions: Brief ALLO exposure and withdrawal altered the expression of specific GABAR subunits. Elevation of $\alpha 4$ subunit has been seen after ALLO withdrawal *in vivo* (Smith et al. *J Neurosci* 1998;18:5275–84) and in primary neurons in culture (Follesa et al. *Brain Res Rev* 2001;137:81–90), suggesting that similar regulatory mechanisms are involved in this simplified neuronal system. GABARs containing the $\alpha 4$ subunit are insensitive to benzodiazepines but have increased sensitivity to ALLO (Whittemore et al. *Mol Pharmacol* 1996;50:1364–75), hence changes in GABAR subunit composition may underlie increased seizure frequency and perimenstrual dysphoric states, possibly by altering interactions with endogenous GABAR modulators. These findings confirm the validity of NT2-N cells as a model of GABAR subunit regulation that may allow more detailed investigation of the mechanisms underlying neurosteroid control of GABAR composition. (Supported by The Myoclonus Research Foundation.)

2.018
LONG-TERM DEPRESSION OF AMPA RECEPTORS AND MEMBRANE TRAFFICKING OF NMDA RECEPTORS DURING SPONTANEOUS CA3 BURSTS

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Rationale: Previously we have shown that transient application of competitive NMDA antagonists induce long-term depression (LTD) at recurrent collateral synapses and thereby decrease CA3 burst probability. Molecular studies suggest that the persistence of this effect is due to metaplasticity induced by endocytosis of membrane-bound NMDA receptors. Here we further tested this hypothesis by isolating NMDA receptor activity from AMPA receptor activity.

Methods: We used the CA3 region of the hippocampus as a model of network synchronization to test the effects of NMDA and AMPA antagonists on burst propagation. Slices were superfused with a modified ACSF (in mM: 3.3 KCl, 1.3 CaCl2, 0.9 MgCl2) and extracellular recordings of spontaneous burst intervals and durations were analyzed. Long-term depression of the recurrent synapses was induced by transient blockade of the NMDA receptors through application of 2.5–10 μM D-APV, a competitive NMDA antagonist. In experiments where the spontaneous bursts were solely NMDA driven (ACSF with zero Mg^{2+}), AMPA and kainate receptors were blocked with NBQX (50 μM) or GYKI 52466 (40 μM), potassium channels were blocked with 4-AP (10 μM), and GABAA and GABAB receptors were blocked with picrotoxin (100 μM) and CGP 52432 (1 μM), respectively.

Results: In control recordings, sequentially decreasing applications of D-APV significantly increased the interburst interval by 101% after washout and decreased burst duration by 17% compared to control ($n = 15$, $P < 0.05$). However when spontaneous bursts are driven solely by NMDA receptor activation (i.e., AMPA and kainate receptors are blocked by NBQX or GYKI), interburst intervals did not increase compared to control ($n = 4$ and $n = 2$, respectively). Burst duration decreased by 21–38% in the presence of either NBQX or GYKI.

Conclusions: These electrophysiological data suggest that NMDA receptor internalization is not prominent when AMPA receptors are blocked. Further studies are ongoing to determine more precisely the conditions under which NMDA receptors undergo endocytosis. (Supported by NIH.)

2.019

INCREASED VEGF EXPRESSION FOLLOWING LIMBIC STATUS EPILEPTICUS IN THE RAT

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Rationale: Vascular endothelial growth factor (VEGF) is a potent endothelial cell mitogen that is abundantly expressed during CNS development, where it plays a fundamental role in embryonic vasculogenesis and angiogenesis. In the intact adult brain, VEGF is significantly down regulated and angiogenesis is practically nonexistent; however, VEGF becomes widely expressed in a variety of pathological conditions associated with increases in microvascular permeability, inflammation, and angiogenesis. Subtle up-regulation of VEGF gene expression has recently been reported following a single electroconvulsive seizure. Here we report the dynamics of VEGF protein expression following kainic acid-induced status epilepticus.

Methods: Several hours of limbic status epilepticus was induced in male Wistar rats by intravenous injection of kainic acid (10 mg/kg). Cohorts of rats were sacrificed at weekly intervals following status induction, along with age matched controls, and processed for paraffin embedding and VEGF immunohistochemistry. Digital images were obtained from 7μm sections at predetermined regions within the hippocampus, amygdala, and piriform cortex. The expression of VEGF within these regions was assayed by quantifying the optical density of VEGF-positive staining using NIH Image software.

Results: VEGF was minimally expressed within the regions assayed among control animals regardless of the time of sacrifice. Relative to these controls, VEGF expression was significantly up-regulated in all regions sampled among our status epilepticus animals. This elevation in VEGF expression was well established by two weeks post-status, and remained significantly elevated out to at least four weeks post-status. The expression was concentrated within the principal cell layers, and was closely associated with the neuronal cell bodies.

Conclusions: We conclude the trauma associated with status epilepticus is sufficient to induce VEGF expression in a manner analogous to that seen after other forms of neural trauma. This expression could conceivably affect vascular permeability and/or promote angiogenesis within the involved regions, which could, in turn, contribute to epileptogenesis.

2.020

"PYRAMIDAL-LIKE" PRINCIPAL NEURONS IN STRATUM RADIATUM OF HIPPOCAMPUS SHOW ALTERED SOMATODENDRITIC H-CHANNEL DISTRIBUTION

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Rationale: Pyramidal neurons in hippocampus have non-uniform distributions of ion channels. One example is the low somatic yet high dendritic density of hyperpolarization activated cation channels (h-channels; I_h). With the modulation of h-channels recently implicated in epilepsy (Poolos et al. *Nat Neurosci* 2002; 5:767), the localization of I_h within the hippocampus may be important to furthering our understanding of epileptogenesis. We investigated a distinct subset of hippocampal principal cells with pyramidal morphology located in stratum radiatum to determine if these neurons have similar non-uniform somatodendritic ion channel distributions.

Methods: Experiments were performed on hippocampal brain slices obtained from male Sprague-Dawley rats using standard techniques. We studied I_h with cell-attached voltage-clamp recordings in the soma and dendrites of neurons visualized through IR-DIC microscopy. Cells were filled with biocytin, stained with antibodies against GAD 65/67, and viewed with fluorescent confocal microscopy.

Results: The morphology, GAD immunoreactivity, and I_h kinetics for pyramidal-like principal neurons (PLPs) in stratum radiatum were compared to CA1 pyramidal neurons. Under IR-DIC, PLPs were located about 25 μm into proximal stratum radiatum of CA1. These neurons had a pyramidal soma and displayed one prominent apical dendrite extending toward stratum lacunosum moleculare that bifurcated at 110–150 μm from the soma, and had a dendritic morphology similar to CA1 pyramidal neurons. Axons emanated from the basal soma and projected toward stratum oriens/alveus, where they turned to run parallel with the alveus. PLPs were negative for GAD immunoreactivity. Cell-attached patch recordings revealed a high I_h density in the somas of PLPs. The maximal current was 33 ± 6 pA (mean $\pm$ SEM; $n = 9$), a 3–6 fold higher density than reported values for CA1 pyramidal somas (Magee JC. *J Neurosci* 1998;19:7613). The current densities of the PLP somata were comparable to pyramidal dendrites (39 ± 15 pA; $n = 7$). In the proximal PLP dendrites, current density declined (18 ± 5 pA; $n = 5$), contrary to the increase observed in pyramidal dendrites. The half-maximum activation voltage and the slow and fast activation time constants were similar between pyramidal neurons and PLPs, suggesting a similar composition of h-channels in both cells.

Conclusions: We have found that the somatodendritic distribution of h-channels can vary between two types of hippocampal principal neurons with pyramidal morphology. These findings indicate differing excitability of PLPs compared to pyramidal neurons, while their location within the hippocampus suggests they may be related to the radiatum giant cell (Gulyas et al. *Eur J Neurosci* 1998;10:3813). (Supported by NINDS and the Epilepsy Foundation.)

2.021

INVESTIGATION OF CORTICAL EPILEPTOGENESIS IN THE PERINATAL HYPOXIC-ISCHEMIC (HI) RAT MODEL WITH CHRONIC VIDEO-TELEMETRY

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Rationale: Perinatally acquired stroke syndromes which result in cortical lesions may lead to epileptogenic sequelae and intractable epilepsy. Structural and functional plasticity of the developing brain after a cerebro-vascular event in the fetal and neonatal periods is thought to play a major role in pathogenesis. We hypothesized that the P7 model for perinatal HI with modified Levine's method would induce epileptogenesis at the peri-lesional site. Spontaneous generalized tonic-clonic seizures would then occur and increase in intensity and frequency with time.

Methods: To study this phenomenon we used continous video-telemetry to monitor chronic cortical EEG's in freely behaving rats. Sprague Dawley rat pups that had undergone a permanent unilateral ligation of the right common carotid artery at P7 followed by global hypoxia (2 h of 92% nitrogen, 8% oxygen) were implanted with 3 channel (ch) telemetry units at the age of 2 months. Bipolar subdural electrodes were implanted in the following locations: ch1 over the core of the infarct, ch2 the peri-infarct somatosensory region in the ipsilateral cortex (right hemisphere) and ch3 at coordinates corresponding to ch1 in the contralateral hemisphere. Electrode placement was based on our previously described structural organization of HI-induced cortical lesion, defined by the immature nature of neonatal haemodynamics similar to the parasagittal cerebral infarcts seen in human neonates with hypoxic encephalopathy (*Soc Neurosci Abstr* 29:211.5). Telemetric data acquisition was done with the Dataquest system and was analyzed with customized software written in Visual Basic.

Results: Analysis of the EEG data detected seizures much earlier than previously determined by a 6 h per week monitoring protocol. Episodes of purely electrographic non-convulsive seizures were documented that would be difficult to identify behaviorally. The onset of seizure activity in most cases was recorded simultaneously on all three EEG channels, but when there was evidence of lateralization, the seizures predominantly started in the ipsilateral cortex with instances of a clear initiation in the peri-lesional (penumbra) zone (ch 2). Six month old rats showed a much higher frequency of seizures compared to the 2 month old rats. Seizures often appeared in clusters with robust interictal spike activity. Seizure durations ranged from 26 sec to 136 sec with an average of 86 sec. There was a correlation between severity of the motor seizures and seizure duration.

Conclusions: This study describes a rodent model to study the human condition of neonatal HI induced epilepsy which results in (1) both complex partial and generalized tonic-clonic seizures, and (2) evidence of increasing seizure frequency with time after the perinatal HI insult. (Supported by AHA 0410026Z and NS45144.)

2.022

INDUCTION OF EPILEPTIFORM ACTIVITY BY GROUP I METABOTROPIC GLUTAMATE RECEPTORS REQUIRES CALCIUM INFLUX THROUGH L-TYPE CALCIUM AND TRP CHANNELS

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Rationale: Activation of group I metabotropic glutamate receptors (mGluRs) by dihyroxyphenylglycine (DHPG) results in long-lasting changes in hippocampal physiology that includes spontaneously occurring epileptiform discharges. In this study we assess the role of calcium influx on the induction of epileptiform activity by DHPG.

Methods: Hippocampal slices were prepared from young male Sprague-Dawley rats (30–40 day old). Control slices were incubated in oxygenated artificial cerebrospinal fluid (ACSF) and racemic DHPG (100 μM) for 60–120 min before being transferred to an interface recording chamber. Slices were also incubated in the presence of DHPG and EGTA (500 μM), the L-type calcium channel blocker diltiazem (30 μM), or the transient receptor potential channel (TRPC) blocker SKF 96365 (30 μM). Once transferred, slices were bathed in control ACSF for 1 hr before extracellular recordings were made in the CA3 region to assess for spontaneously occurring epileptiform activity. Activity was characterized as interictal if less than 500 ms duration or ictal if >2 s. Control DHPG-exposed slice activity was compared to the activity in slices incubated with DHPG and a drug that interfered with calcium influx.

Results: EGTA buffering resulted in only 5% of slices displaying interictal activity ($n = 20$) compared to control DHPG-exposed slices that resulted in 32% with ictal and 32% with interictal patterns ($n = 22$). Incubation in the presence of the L-type calcium channel blocker diltiazem reduced the number of slices displaying epileptiform activity compared to DHPG-exposed slices alone (30% vs. 83% of slices, $n = 46$ and 42). The TRPC blocker SKF 96365 suppressed the induction of epileptiform activity in all 32 slices exposed to DHPG with control DHPG-exposed slices demonstrating spontaneously occurring epileptiform activity in 59% ($n = 34$). A statistically significant reduction in the induction of epileptiform activity occurred when extracellular calcium influx was inhibited compared to control DHPG-exposed slices (Chi-square, $p < 0.05$).

Conclusions: Calcium influx from the extracellular space promoted the induction of epileptiform activity by group I mGluR exposure. Influx from either the L-type calcium channel or TRP channels contributed to the induction of epileptiform activity by group I mGluRs. Recent evidence supports TRPC1 activation by group I mGluRs and our results suggest that calcium influx through a TRP channel contributes to the induction of long term changes in excitability produced by group I mGluR activation. (Supported by VA Research.)

2.023

KETONE BODIES PROTECT NEOCORTICAL NEURONS AGAINST ACUTE OXIDATIVE STRESS

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Rationale: Seizure activity is known to produce oxidative stress in neurons; conversely, recent studies have shown that exogenous oxidant administration results in neuronal hyperexcitability. Given recent data suggesting a neuroprotective role of ketone bodies, we asked whether β-hydroxybutyrate (BHB) and acetoacetate (ACA) can attenuate or prevent hydrogen peroxide-induced hyperexcitability of layer V neocortical neurons, and whether these ketones can directly reduce reactive oxygen species (ROS) production in isolated mitochondria.

Methods: Transverse 300 μm brain slices from somatosensory cortex of normal 2–3 week-old Sprague-Dawley rats were acutely prepared, and whole-cell electrophysiological recordings were made of layer V pyramidal neurons under direct visualization with infrared microscopy and Nomarski optics. Hydrogen peroxide and ketone bodies were bath applied at 31°C, and data were acquired with pCLAMP software and digitized for off-line analysis. For ROS assays, mitochondria were acutely isolated with standard subcellular fractionation techniques, and both basal and oligomycin-induced ROS production was measured using the indicator H_2DCFDA (dichlorofluorescein).

Results: Bath application of hydrogen peroxide (1.25 mM) elicited an initial hyperpolarization which was associated with a large decrease in input resistance (R_N), and upon washout, was followed by an irreversible depolarization (in 9 of 14 cells tested). When slices were pre-incubated with a cocktail of 1 mM BHB and 1 mM ACA for 30 minutes, subsequent administration of 1.25 mM hydrogen peroxide prevented the irreversible depolarization upon washout, but not the initial hyperpolarization (in 7 of 8 neurons tested). In additional control experiments, co-application of BHB and ACA (both 1 mM) to layer V pyramidal neurons decreased R_N, but did not alter resting membrane potential or spike threshold. In mitochondrial experiments, both BHB and ACA directly reduced basal and oligomycin-induced ROS production ($N = 6$/group, $P < 0.05$).

Conclusions: The major ketone bodies BHB and ACA prevent the hyperexcitability of neocortical neurons exposed to acute oxidative stress. This effect could be mediated through a direct antioxidant effect of BHB and ACA at the mitochondrial level. Thus, the antioxidant action of ketone bodies may contribute in part to the anticonvulsant effect of the ketogenic diet. [Supported by NIH K02 NS 044846 (J.M.R.) and VA Merit Review (W.J.S.).]

2.024

SEIZURE EVOLUTION CAN BE AFFECTED BY SEIZURE-INDUCED CHANGES IN SYNAPTIC EFFICACY

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Rationale: Neuronal hyperactivity and intense depolarization of neurons during seizures is accompanied by enhanced calcium influx into neurons. Increased concentration of cytosolic calcium is thought to precede changes in synaptic strength. Little is known how changes in synaptic strength influence patterns of neuronal network activity during seizures. Direct measurements of synaptic facilitation in situ are in large part limited to single synapses. We use neural network models to investigate how these synaptic changes influence network behavior during seizures.

Methods: Our network model is composed of excitatory and inhibitory neurons (Kudela et al., 2003). We adopt a phenomenological approach (Shouval et al., 2002) in which the synaptic strength change is fully determined by intracellular calcium concentration producing either synaptic potentiation or depression. Intracellular calcium is modeled in detail including calcium influx and efflux, binding, and uptake. The network is activated by random excitatory input. In order to induce the repetitive rhythmic activity, the strengths of inhibitory synaptic weights are gradually decreased. This results in recurrent synchronous bursts in all neurons in the network. The local field potential (LFP) modeled as an average membrane potential of all neurons in a network is calculated. The patterns of modeled LFPs can be compared with selected intracranial ictal EEG from humans.

Results: The addition of synaptic strength regulation in these network models affects the characteristics of simulated epileptiform activities. This is reflected in the increase of the amplitude of simulated LFPs. These increased levels of intracellular calcium in neurons produce synaptic potentiation, which amplifies LFP amplitude. After long periods (>1 min) of simulated epileptiform activities we observed changes in temporal synchronization of bursts in neurons. Strong synaptic potentiation leads to irregular bursting, a quantitative change in patterns of bursting activities and a common pattern observed late in partial seizure evolution in man.

Conclusions: Synaptic efficacy changes occurring rapidly after seizure onset and resulting from seizure activity can in turn affect dynamics of these seizures. This can result from either potentiation of existing synapses or creation of new active synaptic connections (i.e. conversion of silent synapses into active synapses). In network models, synaptic potentiation produced by raised intracellular Ca^{2+} levels in neurons is responsible for the late irregular bursting in simulated LFPs. A similar pattern is observed in human EEG prior to seizure termination. The amplitude and the time frequency characteristics of simulated LFPs are in agreement with those obtained for ictal EEG from humans. These neural network models can provide insights into potential mechanisms for seizure evolution and termination. (Supported by Epilepsy Foundation and NIH grant NS 38958.)

2.025

MECHANISMS OF PHARMACORESISTANCE: LONGITUDINAL PET STUDIES IN EXPERIMENTAL ANIMAL MODELS OF EPILEPSY

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Rationale: The $GABA_A$-receptor plays an important role in epileptogenesis. An important question is to what extent down regulation of the $GABA_A$ receptor can explain pharmacoresistance to antiepileptic drugs. Positron Emission Tomography (PET) with [^{11}C]flumazenil ([^{11}C]FMZ) is a method that can be used to quantify the $GABA_A$-receptor expression *in vivo*. We have developed a new quantitative method, which makes it possible to measure the receptor expression (B_{max}) and the affinity (K_D) simultaneously.

Methods: After injection of an excess amount of FMZ, which fully saturated the receptors, the concentration time curves of FMZ in brain (using a single LSO layer HRRT PET scanner) and arterial blood (using HPLC-UV) were measured. B_{max} and K_D were then estimated by population Pharmacokinetic/Pharmacodynamic (PK/PD) modelling, using a 4-compartment PK model, comprising a blood, tissue and 2 brain (free and specifically bound) compartments. Population PK/PD modelling allows analysis of the data of all animals simultaneously, taking inter-individual variability of parameters into account.

Results: 24 rats were used, which received either 2000 mg (n = 2), 1000 mg (n = 1), 500 mg (n = 7), 100 mg (n = 3), 50 mg (n = 3), 25 mg (n = 2), or 1 mg (n = 6). Simultaneous analysis of all data with the proposed model resulted in the precise estimation of the specific binding of FMZ in the brain, as characterised by B_{max} (32.7 ± 7.95 ng/ml) and K_D (10.1 ± 2.61 ng/ml).

Conclusions: In conclusion a novel full saturation approach is reported, which allows simultaneous estimation of both B_{max} and K_D in a single experiment. This model will be used to assess changes in $GABA_A$-receptor properties in relation to progression of epilepsy in various experimental animal models. Moreover, this approach can also be used in human studies. (Supported by National Epilepsy Fund; grant 02-06.)

2.026

GENOME-WIDE EXPRESSION PROFILING IN KINDLING EPILEPTOGENESIS

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Rationale: Gene-expression changes and genetic mechanisms underlying kindling epileptogenesis are not well understood. The use of DNA arrays and gene-expression profiling provides one strategy to enhance our understanding of global transcription patterns that accompany kindling. In this study we have analyzed RNA message abundance for 12000 gene transcripts in the mouse hippocampus using kindling as a model for epileptogenesis.

Methods: Eight-week-old, C57BL/6 mice were implanted with Tripolar electrode units (Plastic One Inc., Roanoke, VA) in the right dorsal hippocampus; a ground electrode was attached to the occipital bone. Ten days post surgery, kindling was achieved by stimulating 6 times daily for 4 days with a subconvulsive electrical stimulation (a 10-s train containing 50-Hz biphasic pulses of 300-μA amplitude) at 30-min intervals. Seizures were graded according to Racine's Scale. Total RNA was extracted and purified using phenol-guanidine isothiocyanate reagents. RNA samples were screened for spectral purity and integrity using RNA LabChips (Caliper Technologies, Mountain View, CA) and a 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA). DNA-array analysis was performed using murine U74v2 GeneChip probe arrays (Affymetrix, Santa Clara, CA). Gene-expression data were mined and analyzed for significance using GeneSpring (Silicon Genetics, Redwood City, CA) and Microarray Data Mining Tool (Affymetrix) software.

Results: Surprisingly, only a relatively small number of genes (N = 8) reached a high significance of 2-fold or greater in up- or down-regulation with ANOVA ($p < 0.05$) under the experimental conditions used. Using the following format: gene name (abbreviated form) ∗ [fold-change] ∗ (ANOVA); the most significantly up- and down-regulated genes included: glial fibrillary acidic protein (GFAP) ∗ [+2.1] ∗ (0.001); neuronal pentraxin 2 (NP2) ∗ [+2.88] ∗ (0.022); mouse-specific tolloid-like protein (MSTLP) ∗ [+2.80] ∗ (0.03); mouse-specific homer 1A (MSH1A) ∗ [+2.72] ∗ (0.167); transcription factor for growth inhibitory factor (TF-GIF) ∗ [+2.1] ∗ (0.006); neurotrophin 3 (NT3) ∗ [−2.84] ∗ (0.167); aquaporin 1 (AQ1) ∗ [−2.7] ∗ (0.167); vascular endothelial factor (VEGF) ∗ [−2.11] ∗ 0.167.

Conclusions: GFAP up-regulation suggests induction of gliosis or glial-mediated events; up-regulation of NP2 and MSTLP suggests triggering of inflammatory signaling, and up-regulation of MSH1A and TG-GIF suggests modulation of long-term potentiation and inhibition of neural growth and/or differentiation. Down-regulation of NT3, AQ1, and VEGF suggests repression of neurotrophic support, water transport at the blood-brain barrier, and angiogenesis-related signaling, respectively. These profiling data provide new insights into the cellular and molecular basis of epileptogenesis and may provide novel genetic targets for the development of anti-epileptogenic drugs. (Supported by NIH AG18031, NS22002 and COBRE NIH P29RR16816–02.)

2.027

DIFFERENT EFFECT OF NMDA AND NON-NMDA ANTAGONISTS ON THRESHOLDS FOR ELICITATION OF CORTICAL AFTERDISCHARGES IN IMMATURE RATS

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Rationale: Antagonists of ionotropic excitatory amino acid receptors were shown to exhibit anticonvulsant action in adult as well as immature laboratory rats. The aim of our study was to compare action of antagonists of two types of ionotropin glutamate receptors on phenomena elicited by stimulation of sensorimotor cortex.

Methods: Stimulation electrodes were implanted to Wistar rat pups 12, 18 and 25 days old over the right sensorimotor cortical area. Three recording electrodes were on the left hemisphere, the fourth one over the right occipital area. Rhythmic stimulation (series of biphasic pulses lasting 1 ms; frequency = 8 Hz; duration = 15 s) was repeated with an increasing current intensity in steps from 0.2 to 14 mA. EEG activity and motor phenomena were recorded. An action of a noncompetitive NMDA antagonist dizocilpine (MK-801, dissolved in saline) and a competitive AMPA antagonist NBQX (dissolved in dimethylsulfoxide) was compared. Dizocilpine was administered in doses of 0.1 or 0.5 mg/kg, NBQX in doses of 30 or 60 mg/kg, both intraperitoneally 15 min before the first stimulation series. Control siblings were injected with solvens (physiological saline or dimethylsulfoxide, respectively). Each age and dose group was formed by 8–10 rats. Threshold intensities for movements directly elicited by stimulation, spike-and-wave afterdischarges,

clonic seizures accompanying these afterdischarges and transition to another type of seizures (limbic type) were evaluated.

Results: Both antagonists exhibited only moderate effect on movements directly elicited by stimulation of sensorimotor cortex. In contrast, threshold currents for epileptic afterdischarges of the spike-and-wave type and accompanying clonic seizures were significantly increased by both drugs. The youngest age group was the most sensitive one, the threshold intensities were nearly doubled by higher doses of the two antagonists. Afterdischarges in 25-day-old rats could be suppressed only by dizocilpine. In addition to an increase of threshold intensities, dizocilpine markedly diminished amplitude of spike-and-wave complexes. Threshold for the second type of afterdischarge (limbic type) was increased by dizocilpine but not by NBQX.

Conclusions: Our data confirmed high sensitivity of immature brain to excitatory receptor antagonists. The results speak in favor of involvement of both NMDA and nonNMDA receptors in generation of spike-and-wave type of afterdischarges. Only NMDA receptors might play a role in the transition of epileptic activity into limbic structures. (Supported by Center for Neuropsychiatric Studies, project No. LNB00B122.)

2.028

GALANIN TYPE 2 RECEPTORS IN DENTATE GYRUS REGULATE SEIZURES, NEURONAL SURVIVAL, AND NEUROGENESIS

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Rationale: Neuropeptide galanin has been implicated in inhibiting seizures and protecting hippocampal neurons from excitotoxic injury. In the hippocampus galanin acts through two receptor subtypes, GalR1, expressed in CA1, and GalR2, abundant in dentate gyrus. We examined the role of hippocampal GalR2 in regulating seizures, neuronal survival and plasticity in the rat model of self-sustaining status epilepticus (SSSE), using a selective semi-chronic knockdown of GalR2 in the hippocampus.

Methods: The experiments were done in adult male Wistar rats. Local down-regulation of GalR2 was achieved by seven-day infusion of peptide nucleic acid antisense (PNA, 25 μM) targeted at GalR2. The effectiveness of GalR2 knockdown was measured using radioligand binding assay with selective GalR2 agonist galanin (2–11). SSSE was induced by 30-min electrical stimulation of perforant path (PPS) through chronically implanted electrode. Electrographic activity was recorded from ipsilateral dentate gyrus and analyzed off-line using Harmonie software (Stellate Systems). Mixed GalR1/GalR2 agonist galanin (1–29), or selective GalR2 agonist Ala^2-galanin (both 5 nmole) were injected into hippocampus ipsi-, or contralateral to PNA. Neuronal injury was assessed 3 days after PPS using FluoroJade B staining. Neural progenitor division and neuronal profile of proliferating cells in the dentate gyrus was studied using bromodeoxyuridine, neuron-specific enolase, NeuN and PROX1 immunohistochemistry.

Results: Administration of GalR2 PNA resulted in fifty-percent reduction of GalR2 binding in the hippocampus.GalR2 knockdown led to the augmentation of SSSE, evident as the increase of the cumulative seizure time and of the average duration of seizure events. PNA treatment weakened anticonvulsant effects of galanin (1–29) and abolished anticonvulsant action of Ala^2-galanin, when the peptides were injected into the site of PNA injection. PNA delivery did not affect seizure-protecting effects of peptides, when the latter were administered contralateral to PNA. GalR2 knockdown alone led to mild neuronal injury in the hilus of dentate gyrus. Furthermore, GalR2 knockdown potentiated SSSE-induced hilar injury. Down-regulation of GalR2 inhibited both SSSE-induced increase of neural progenitor proliferation in subgranular zone of dentate gyrus, and differentiation of neuronal progenitor into neurons, without affecting glial proliferation associated with SSSE.

Conclusions: GalR2 in the dentate gyrus plays important role in counteracting seizure activity, promoting neuronal survival and plasticity in response to seizures. The data are useful for understanding brain defensive mechanisms involved in seizure control and neuroprotection. (Supported by NIH grant NS 43409, and Swedish Research Council of Natural Sciences.)

2.029

A GLIOTOXIN MODEL OF FOCAL OCCIPITAL EPILEPSY IN RATS

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Rationale: Astroglial cells play a key role in energy metabolism and cycling between the inhibitory and excitatory neurotransmitters. Impaired glial metabolism due to intracortical microinjection of fluorocitrate, which reversibly inhibits glial tricarboxylic acid can induce seizures at higher doses. Further studies are required to determine the epileptogenic properties of fluorocitrate at various doses.

Methods: Male SD rats (250–400gm,n = 18) were anesthetized with pentobarbital to implant 8 EEG electrodes and a cannula. The electrodes were secured with dental cement and animals were allowed to recover for a week. Fluorocitrate solutions (1 mM, 2 mM, 3 mM, 4 mM, 6 mM, 8 mM) were prepared according to a published method. On the experiment day, 0.2 μL of saline (control) or fluorocitrate was injected in the right occipital cortex through the cannula 1.2 mm below the skull surface. EEG and behaviour were monitored for 6 hours and again one hour daily before they were sacrificed and perfused with 4% paraformaldehyde to perform immunohistochemistry with glial fibrilary acidic protein (GFAP) and neuronal counting 48 hours after the injection. Three rats were studied with each dose.

Results: All the rats injected with 4 mM and higher doses of fluorocitrate developed seizures for up to 6 hours but none experienced seizures with lower doses of fluorocitrate or saline. Four rats that received 6 mM and 8 mM of fluorocitrate developed status epilepticus and required diazepam i.p. to terminate seizures. These rats developed seizures within 1 minute of injection of fluorocitrate. Other rats showed a delayed affect with seizures 2 hours after the injection. Only one rat that received 4 mM of flourocitrate experienced one seizure 24 hours later. Other rats did not have seizures in subsequent recordings. All rats exhibited hyperactivity within the first 6 hours but abnormally low activity on subsequent days compared to control animals. There was a significant increase in GFAP staining with enlarged astrocytes that had swollen processes in doses greater and equal to 4 mM of fluorocitrate. Only minimal GFAP staining at the injection site was seen with 2 mM of fluorocitrate but none with 1 mM or saline injection. There was no neuronal loss.

Conclusions: Fluorocitrate exhibits a dose-dependent epileptogenic property in SD rats resulting in focal seizures with secondary generalization. This gliotoxin can be used as a suitable animal model to study glial involvement in the development of seizures. Lower doses of fluorocitrate that do not case seizure can be used to study early metabolic changes leading to seizures. (Supported by Canadian Institutes of Health Research.)

2.030

FUNCTIONAL GENOMICS OF A γ2 GABA$_A$ RECEPTOR SUBUNIT MUTANT MOUSE MODEL OF GENERALIZED EPILEPSY

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Rationale: Mutations in the gene for the γ2 subunit of the GABAA receptor [GABRG2(R43Q)] have been shown to underlie some forms of familial human absence epilepsy. We have previously demonstrated marked reductions in the binding potential (Bmax/KD) for the PET benzodiazepine receptor ligand [^{11}C]flumazenil in heterozygous family members. To disambiguate the effects of receptor density (Bmax) and affinity (KD), we examined the interaction between [^{3}H]flumazenil and benzodiazepine receptors in wild type and GABRG2(R43Q) 'knockin' mice.

Methods: Wild type (RR; n = 3), heterozygous (RQ; n = 3) and homozygous (QQ; n = 3) GABRG2(R43Q) 'knockin' C57 Black 6 mice were studied at P15. Following light anesthesia and decapitation, the brain minus cerebellum was removed and homogenized. Following

centrifugation and resuspension of the pellet, the protein concentration was determined using a bicinchoninic acid assay. Saturation experiments were performed using Millipore Multiscreen 96-well filter plates with 0.1 mg protein/well and varying concentrations of [^{3}H]flumazenil (0.2–30 nM, 78.6 Ci/mmol). Unlabeled flumazenil was used to determine non-specific binding. After a 30 min incubation (20 °C) the plate was aspirated on a Vacuum Manifold and washed (3 × 200 μl TRIS-HCl). Radioactivity bound to filters was counted using a Beckman LS6500 scintillation counter after equilibration with Ultima Gold scintillation cocktail. Bmax and KD were estimated using a non linear least squares fit of the observed bound and free radioligand concentrations.

Results: Mean (±standard deviation) Bmax values for RR, RQ and QQ mice were 400 ± 37, 235 ± 19 and 6 ± 2 pmol/mg protein respectively ($p < 0.001$ for Turkey's HSD for all two way comparisons following one way analysis of variance). Mean (±standard deviation) KD values for RR and RQ mice were 2.6 ± 0.4 nM and 3.3 ± 0.6 nM respectively ($p = 0.21$). Poor counting statistics resulting from almost non-existent binding precluded reliable estimates of KD for QQ animals.

Conclusions: The GABRG2(R43Q) mutation results in dramatic changes in benzodiazepine receptor density. Receptor affinity for [^{3}H]FMZ in the heterozygotes was equivalent to that in wild type mice. These findings support the hypothesis that reduced binding potential in PET studies of humans with the mutation results from a reduction in receptor density. Perturbations in γ-aminobutyric acid type A (GABAA) receptor mediated inhibitory neurotransmission may underlie epileptogenic hyperexcitability in thalamocortical circuits. The observed changes in γ2 GABAA subunit function may be a marker of these abnormalities or may have a more direct causative role if reduced binding by an endogenous receptor ligand modulates thalamocortical excitability. (Supported by National Health and Medical Research Council of Australia and Bionomics Limited.)

2.031

ETHOSUXIMIDE, BUT NOT CLONAZEPAM, BLOCKS PENTYLENETETRAZOLE-INDUCED SEIZURES IN $GABA_A$ RECEPTOR α3 SUBUNIT MUTANT MICE

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Rationale: In a previous study (Sohal et al. *J Neurosci* 2003) we demonstrated that clonazepam (CLZ) lacks efficacy in the suppression of abnormal in vitro thalamocortical rhythmicity in mice carrying a point mutation in the α3 subunit. Here we examined the effect of two anti-absence medications Ethosuximide (ES) and CLZ on EEG changes in the low dose pentylenetetrazole (PTZ) mouse model of Absence Epilepsy (AE).

Methods: P35 wild-type (WT) and α3(H126R) mutant mice (Rudolph et al. *Nature* 1999) were implanted for chronic EEG recording via three trans-calvarium screws wired to a pedestal connection. PTZ (40 mg/kg) was administered alone or with CLZ (0.03 mg/kg) or ES (150 mg/kg), all via intraperitoneally injection. In addition whole-cell voltage clamp recordings were obtained from thalamic reticular neurons (TRN) and thalamocortical relay cells (TC) in slices of P6-P17 WT and α3(H126R) mutant mice to study the effect of CLZ (100 nM) and Zolpidem (ZLP, 100 nM) on $GABA_A$ receptor-mediated spontaneous inhibitory post-synaptic currents (sIPSCs), isolated by appropriate pharmacological treatment.

Results: While EEG recordings in WT mice revealed that both ES and CLZ decreased PTZ induced spike wave discharges (ES: 93% reduction, CLZ: 55%) ES delayed seizure onset (by 17%). By contrast, in the α3(H126R) mutant, CLZ failed to block epileptic discharge while ES efficacy was unaffected. In patch-clamp recordings from WT TRN cells, CLZ and ZLP prolonged the weighted decay time constant ($\tau_{d,w}$) of sIPSCs by 40% and 30%, respectively, but not in the mutant, whereas no difference in enhancement between WT and mutant mice could be seen in TC cells, which do not express α3.

Conclusions: The inability of CLZ to control in vivo seizure activity in the α3 mutant demonstrates that the $GABA_A$ receptor α3 subunit is the site of antiepileptic action for benzodiazepines (BZ). These EEG results are consistent with the fact that neither CLZ nor ZLP could enhance $GABA_A$ receptor mediated sIPSCs in α3 mutant TRN neurons in whole cell recordings. Our findings uncover the unique role of the $GABA_A$ receptor α3 subunit, most likely within the thalamic reticular nucleus, for the efficacy of BZs and related compounds in the treatment of AE. [Supported by the NINDS and FWF (Austrian Science Fund).]

2.032

SEIZURE-INDUCED FORMATION OF ISOFURANS: A NOVEL LIPID PEROXIDATION PRODUCT FAVORED BY INCREASED OXYGEN TENSION

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Rationale: Free radicals have been implicated in the pathogenesis of many neuronal diseases with the notable exception of the epilepsies. We have shown that free radical production and resultant oxidative damage to vulnerable targets (proteins, lipids and DNA) occurs following kainate-induced status epilepticus and mitochondria play a major role in this oxidative stress. We previously reported seizure-induced lipid peroxidation in hippocampal subregions using GC/mass spectrometric analysis of isoprostanes (IsoPs), one of the most reliable approaches for assessing oxidative stress in vivo (Patel et al. *J Neurochem* 2001). Recent work (Fessel et al. *Proc Natl Acad Sci* 2002) demonstrates that higher oxygen tension limits IsoP formation but favors the formation of alternate products including isofurans (IsoFs). Additionally, since local increases of oxygen tension can result from mitochondrial dysfunction, we determined 1) the time course of seizure-induced changes in IsoFs, 2) the ratios of IsoF to IsoP and 3) the correlation between IsoF formation and other indices of mitochondrial oxidative stress.

Methods: IsoP and IsoF levels were measured in microdissected hippocampal subregions and the cerebellum by GC/mass spectrometry at various times (8, 16, 48 hours and 7 days) following kainate administration. To correlate IsoF formation and other indices of mitochondrial oxidative stress, hippocampal mitochondrial DNA oxidation and redox status was measured by analyzing the ratios of 8-hydroxy-2-deoxyguanosine/2-deoxyguanine (8OhdG/2DG) ratios and reduced/oxidized glutathione (GSH/GSSG), respectively by HPLC-EC.

Results: Kainate-induced induced status epilepticus resulted in increased formation of both IsoP and IsoFs, with overlapping but distinct time courses in hippocampal subregions but not cerebellum. The IsoF/IsoP ratio, a putative index of tissue oxygenation peaked 48 hr post kainate in hippocampal subregions. In comparison with IsoP formation, the time course of IsoF formation correlated more closely with the increase in mitochondrial 8OhdG/2DG formation and decreases in mitochondiral GSH/GSSG levels.

Conclusions: These results suggest that 1) seizure-induced increase in IsoF/IsoP ratios may reflect the increased tissue oxygen tension resulting from mitochondrial dysfunction and decreased utilization of oxygen and 2) the combined measurement of IsoPs and IsoFs allows a more reliable assessment of seizure-induced oxidative stress and changes in tissue oxygenation. (Supported by NIH NS39587.)

2.033

ELIMINATION OF EPILEPTIFORM DISCHARGES BY ELECTRICAL STIMULATION IS ACCOMPANIED BY DEPRESSION OF EXCITATORY NEUROTRANSMISSION IN BICUCULLINE-TREATED NEOCORTICAL BRAIN SLICES

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Rationale: Direct open- and closed-loop electrical stimulation of the epileptogenic zone has recently been proposed as a potential novel treatment modality for intractable epilepsy. In this study I used bicuculline treated neocortical brain slices to examine on the one hand the efficacy of different electrical stimulation paradigms in preventing and prematurely terminating inter-ictal like epileptiform discharges and seizure-like events, and on the other hand study the cellular mechanisms underlying the antiepileptic effect of cortical electrical stimulation.

Methods: The study was performed on rat neocortical brain slices treated with the GABA-A receptor blocker bicucculine (BCC, 10 μM). Intracellular voltage recordings were performed using whole-cell recordings from single pyramidal neurons. Extra-cellular recordings from a population of neurons were performed using glass pipettes placed in different regions of the slice. Electrical stimulation was performed using a computer controlled extra-cellular stimulator and either a pipette filled with ACSF or a platinum iridium metal electrode.

Results: Bicucculin treated neocortical brain slices produced both inter-ictal like discharges and seizure-like events. Continues recurrent electrical stimulation at frequencies of 0.3–2 Hz eliminated both spontaneous and evoked inter-ictal like discharges and seizure-like events. This effect was dependent on the stimulus intensity and the distance between the origin of the epileptiform discharges and the location of the stimulating electrode. In addition short trains of high frequency electrical stimulation (50–100 Hz, 0.5–2 second-long) terminated 40 $\pm$ 12% of seizures. To investigate possible mechanisms underlying the antiepileptic effect of electrical stimulation, I examined its effect on excitatory synaptic transmission and on action potential firing. Both short trains of high frequency stimulation and recurrent low frequency electrical stimulation resulted in a significant reduction of the EPSP amplitude in a frequency dependent manner. High frequency stimulation also decreased the excitability of neurons, and impaired their ability to fire high frequency action potentials.

Conclusions: Both recurrent low frequency electrical stimulation and short hig frequency electrical stimulation has an antiepileptic effect in bicuculline treated neocortical brain slices *in-vitro*. This effect is probably mediated, at least in part, by stimulus evoked depression of excitatory synaptic transmission, in the case of high frequency stimulation decreased excitability of neurons. Further studies are required to examine the antiepileptic effect of electrical stimulation in animal models and humans *in-vivo*. (Supported by The Chutick Foundation.)

2.034
OPTICAL IMAGING OF TOPOGRAPHIC RELATIONSHIP BETWEEN SPONTANEOUS INTERICTAL AND ICTAL EVENTS IN CHRONIC LESIONAL AND NONLESIONAL MODELS OF RODENT NEOCORTICAL EPILEPSY

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Rationale: The topographical relationship between interictal spikes and ictal onsets in human neocortical epilepsy is variable and involves shifting populations of highly interconnected networks. Previous investigations in acute models have not shown this variability. We investigated the shifting topography of epileptiform events in a lesional and nonlesional model of chronic rodent neocortical epilepsy with optical mapping of intrinsic signals.

Methods: We injected 200–400 mM/2.5–5 μl of $FeCl_2$ (lesional; n = 3) or 50 ng/0.5 μl of tetanus toxin (nonlesional; n = 3) into the somatosensory cortex of adult Sprague-Dawley rats. Video-EEG monitoring was performed via an implanted telemetry device (DSI). Average seizure frequency was calculated using a custom seizure detection algorithm (Matlab). After two-month of EEG monitoring, the animals were placed in a stereotactic frame and underwent a craniotomy with general anesthesia (Urethane). Field potential electrodes were inserted into the neocortex near the injection site. A CCD camera was focused 500 μm below the brain surface that was illuminated by filtering a halogen lamp at different wavelengths (546 $\pm$ 10 nm, 605 $\pm$ 10 nm, 630 $\pm$ 10 nm and 700 $\pm$ 10 nm) and images were acquired at 100–600 ms/frame. Animals were sacrificed for histology.

Results: Both models induced frequent but stable epileptiform events in all rats during the two-month monitoring period (lesional: 3.75 $\pm$ 1.66 sz/hr; nonlesional: 3.85 $\pm$ 1.2 sz/hr). Even under general anesthesia, a variety of epileptiform events persisted, including single interictal spikes (IIS), poly-spikes, and ictal events. Optical epilepsy maps, revealed that the IISs arose from a variety of locations surrounding the injection site. Likewise, ictal onsets were variable in location but always arose from adjacent regions of cortex with occasional secondary generalization and cross callosal spread. Inverted optical signals were recorded from surrounding cortex with a dynamic relationship with the epileptiform events.

Conclusions: This is the first report of optical imaging of spontaneous epileptiform events in a chronic model of rodent neocortical epilepsy. We report that, unlike in acute models, the relationship between ictal onsets and interictal spikes is dynamic and spatially variable in relation to both nonlesional and lesional cortical irritation. (Supported by NIH.)

2.035
MULTIDRUG RESISTANCE AND ANTICONVULSANTS: NEW STUDIES WITH SOME ENAMINONES

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Rationale: Multidrug resistance (MDR), often conferred by the active extrusion of drugs from the cell, is a phenomenon often seen in cancer cells that may become resistant to a wide spectrum of drugs with varying chemical structures or cellular targets. Human P-glycoprotein (P-gp) encoded by MDR1 and the multidrug resistance-associated protein (MRP1) are both members of the superfamily of ATP binding cassette (ABC) transporter proteins. This MDR1 gene product P-gp has been found in tumor cells and due to its overexpression in these cells, allows for protection against several anticancer drugs. In addition to cancer chemotherapy, the presence of MDR has been noted in drug resist to other diseases, i.e. malaria, AIDS and epilepsy. Studies in our laboratories on this occurrence has been noted in the pharmacokinetic evaluation of several anticonvulsant enaminones which have shown high efflux ratios and are recognized by P-gp and/or the MRP. This study was designed to evaluate the potential inhibition of the enaminones on paclitaxel efflux in vitro compared to cyclosporin A, a known P-gp inhibitor and the effectiveness of select enaminones on paclitaxel oral absorption in rats.

Methods: Caco-2 transport of [14C]paclitaxel was evaluated in the presence of various enaminones at 10–5 M. Concentration-effect (10–10 to 10–4 M) profiles for the enaminones, 3-(4-chlorophenyl amino)-5-methylcyclohex-2-enone (DM27) and/or methyl 4-(3-phenyl propylamino)-6-methyl-2-oxocyclohex-3-ene carboxylate (DM40), with paclitaxel and cyclosporin A were determined. Male Sprague-Dawley (250–275 g) rats were orally administered either [14C]paclitaxel (30 μCi/kg) or[14C]paclitaxel/DM (7 mg/kg) and blood samples were collected. Paclitaxel brain concentrations were measured.

Results: Papp(A-B) of [14C]paclitaxel, with DM27 and DM40 at 10–5 M, was significantly ($P < 0.05$) higher versus control. DM27 produced a 360% and 139% increase in Papp(A-B)Paclitaxel and Papp(A-B)Cyclosporin, respectively. DM40 displayed a 131% increase in Papp(A-B)Paclitaxel whereas cyclosporin A produced a 21% increase in Papp(A-B)Paclitaxel. Rats in the DM27 group displayed large Vdss/F values (23.35 liters/kg versus 14.62 liters/kg) and lower AUC (5.47 μg/mL min. versus 8.74 μg/mL min.) versus control. However, significantly higher levels (2.25-fold) of paclitaxel were observed in the brains of the DM27 group.

Conclusions: This study presents the enaminones as promising P-gp inhibitors with comparable potency to other P-gp inhibitors. Further, the enaminones may improve conventional therapy when used in combination with P-gp substrate drugs. [Supported by a grant from the National Institutes of Health (1R21 GM63494–01) (K.R.S.) and from the National Cancer Institute (CA87564–01A).]

2.036
SECRETION AND FUNCTIONAL ANALYSIS OF LGI/EPITEMPIN FAMILY MEMBERS

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Rationale: One form of autosomal dominant partial epilepsy with auditory features (ADPEAF) is caused by mutations in the LGI1 (leucine-rich gene, glioma inactivated) gene, which was first identified as a putative tumor suppressor in glioblastoma cells. Apart from its decreased expression levels in these abnormally proliferating cells, little information is available concerning the normal function of the LGI/Epitempin

protein in neurons, or how it causes an epileptic disorder affecting the temporal lobe. Furthermore, LGI1/Epitempin is only one member of a family of 4 highly related proteins. It is not known at this time whether the three other family members may also play a role in ADPEAF or, perhaps, in other forms of epilepsy. LGI1 contains a putative membrane spanning motif that may determine localization of the protein. In order to identify the functional pathway of this gene, we expressed LGI family members in various cell lines and localized the proteins by immunoblot techniques.

Methods: cDNAs were generated by PCR from adult mouse brain. Epitope tagging [Flag (M2), hemagluttinin (HA), and myc (9E10)] was performed by PCR mutagenesis. 293T cells were transfected with cDNAs for LGI1 and additional family members. Both conditioned media and cell lysates were collected and analyzed by immunoblot.

Results: We observed that LGI1 is a constitutively secreted protein and find that approximately 90–95% of LGI1 protein is secreted with only a small fraction retained in the cell lysate, possibly in the ER, golgi and secretory vesicles. We have analyzed the additional LGI family members and find differences in cellular localization of the various family members that may be relevant to vesicle compartmentalization or could be due to epitope tagging which is necessary to visualize these other family members due to inavailability of specific antisera for LGI2–4.

Conclusions: Our results strongly suggest that LGI1 is a secreted protein, thus having implications regarding CNS development. As a consequence of its secretion, LGI1 may exert its activities in a non-cell autonomous way, i.e. at some distance from the cell type in which it is initially produced. Further studies are underway to analyze the effects of LGI1 secretion on neuronal cell growth and survival in order to understand how LGI and its family members could contribute to an epilepsy phenotype. (Supported by NINDS NS29709, NINDS NRSA Training Grant NS045376–03, and Developmental Brain Disorder Training Grant NS43124.)

2.037

NEWLY GENERATED DENTATE GRANULE CELLS FROM EPILEPTIC RATS EXHIBIT ELONGATED HILAR BASAL DENDRITES

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Rationale: Previous studies have shown that neurogenesis occurs in the dentate gyrus of the adult and recent evidence suggests that these newly generated granule cells integrate into pre-existing hippocampal circuitry. Newly born neurons in the developing dentate gyrus have been shown to exhibit a transient basal dendrite. In adult pilocarpine-induced epileptic rats, basal dendrites are ectopically located in the hilus where they receive synaptic input from mossy fiber axons. For this study our goals were to confirm that basal dendrites are found on newly born neurons in the adult control rat, and, to determine whether the basal dendrites of newly born neurons from epileptic rats were longer than those in the control.

Methods: Using an immunocytochemical method for doublecortin which labels newly born neurons, we examined newly generated granule cells and their dendritic processes in light microscopic preperations. The lengths of the basal dendrites were measured using a grid reticule overlay method. Student's t-test was used to compare the data on length.

Results: Newborn granule cells in control and pilocarpine treated rats showed basal dendrites with extended growth cones at the border of the subgranular zone and granule cell layer. Doublecortin (DCX)-labeled cells were typically found in the subgranular zone, at the border between the subgranular zone and the granule cell layer, or in the granule cell layer. Morphological analysis of the DCX-labeled cells with basal dendrites revealed that they have a distinctly different appearance in the epileptic animals compared to the controls. Quantitative analysis showed that in the pilocarpine animals ($X = 16\ \mu m$), the basal dendrites from newly born granule cells are significantly longer than those found in the control rats ($X = 6\ \mu m$) ($P < .01$). We also demonstrate that the percentage of cells with a basal dendrite that enters the granule cell layer at an angle of 30 degrees or more is greater in the pilocarpine-induced epileptic rats.

Conclusions: The data show that newly born neurons from epileptic rats have elongated basal dendrites that invade the hilus. It is unclear what mechanisms cause this neuroplastic change for these dendrites. We speculate that the formation of hilar basal dendrites might relate to either the sprouting mossy fiber phenomenon, or hilar neuronal loss with associated gliosis both of which occur in pilocarpine-induced epileptic rats. (Supported by NIH grants R01-NS38331 and training grant T32-NS045540.)

2.038

CANNABINOID MODULATION OF EXCITABILITY IN THE DENTATE GYRUS OF PILOCARPINE-TREATED EPILEPTIC MICE

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Rationale: The use of cannabinoid (CB) agonists for treating seizure disorders has been proposed, but results of case study analyses have been mixed. Most known effects of CBs in the brain are mediated by CB type 1 receptors, usually located on presynaptic GABA terminals. In the pilocarpine-treated mouse, development of spontaneous seizures is associated with mossy fiber sprouting, recurrent excitatory synapse formation between granule cells of the dentate gyrus, and increased synaptic excitability. These experiments were designed to determine how cannabinoids modulate neural activity in the dentate gyrus in a murine model of temporal lobe epilepsy (TLE) in order to understand effects of the substance on a system that has undergone synaptic reorganization.

Methods: Pilocarpine-induced seizures in CD1 mice led to spontaneous seizures, mossy fiber sprouting, and recurrent excitatory circuit formation in the dentate gyrus. Extracellular field potential and whole-cell patch-clamp (voltage-clamp) recordings were made from dentate gyrus granule cells in transverse hippocampal slices from epileptic and control mice in the presence of bicuculline and low extracellular Mg^{2+}. Antidromic activity was evoked after stimulation of mossy fibers in the hilus, and spontaneous excitatory postsynaptic currents (EPSCs) were also recorded. Effects of CB receptor agonists on synaptically-driven population responses following antidromic stimulation and spontaneous EPSCs were examined. Timm staining was performed on recorded slices.

Results: Electrical stimulation of mossy fibers produced an antidromic population spike followed by prolonged bursts of activity in the dentate gyrus of epileptic mice with mossy fiber sprouting. Bursts were sensitive to glutamate receptor antagonists, indicating they were synaptic in nature. Application of the CB receptor agonists, anandamide (1–10 μM; $n = 5$) or WIN55,212–2 (10 μM; $n = 2$) reversibly inhibited the synaptic responses. Spontaneous bursts of EPSCs and synaptically-driven activity were also observed in epileptic mice, which were attenuated by anandamide ($n = 4$). Timm staining showed mossy fiber sprouting in epileptic mice but not controls. Little or no effects of the agonists were observed in slices from control mice.

Conclusions: Enhanced excitatory synaptic activity in the dentate gyrus in mice with pilocarpine-induced TLE is attributable to activation of newly-formed recurrent excitatory circuits between granule cells. In the absence of GABAA receptor-mediated inhibition, cannabinoids can inhibit synaptically-induced epileptiform activity in the dentate gyrus. Whereas CB receptor agonists often suppress GABA release in the normal hippocampus, the inhibition of epileptiform activity and glutamatergic EPSCs in the pilocarpine-treated mouse dentate gyrus suggests treatment strategies specific for TLE patients, whose brains may have undergone synaptic reorganization. (Supported by Louisiana Board of Regents and the Epilepsy Foundation of America.)

2.039

PATTERNS OF PRION PROTEIN EXPRESSION IN THE HIPPOCAMPAL FORMATION AND NEOCORTEX OF RATS SUBMITTED TO PILOCARPINE-INDUCED EPILEPSY

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Rationale: Mice lacking cellular prion protein (PrPc) are more sensible to seizures induced by four different pharmacological protocols. The hippocampal formation of these animals disclose supragranular mossy

fiber sprouting which resembles those observed in patients with mesial temporal lobe epilepsy related to hippocampal sclerosis (MTLE-HS). A variant allele at position 171, absent in controls, was found in heterozygosis (Asn171Ser) in 23% of patients ($p < 0.0001$). Patients carrying the Asn171Ser variant had a five times higher chance of continuing to have seizures after temporal lobectomy (95% CI 1.65 to 17.33, $p = 0.005$) than those carrying the normal allele. These findings suggest that the PrPc may be involved with epileptogenesis in MTLE-HS. Here we investigated the immunohistochemical localization of the PrPc in the hippocampus of animals submitted to the pilocarpine model of temporal lobe epilepsy.

Methods: Status epilepticus (SE) was induced using pilocarpine (300 mg/kg, i.p.) in five different groups of adult Wistar rats. The survival animals ($n = 3$–5 animals/group) were sacrificed one hour, 12 hours, 5 days, two months, and four months after the pilocarpine-induced SE for histopathological analysis. The qualitative results were compared among different groups and with the respective saline-injected controls. Brains were processed for Nissl staining, neo-Timm and imunohistochemistry for PrPc.

Results: Expression of PrPc differed according to the different phases of the pilocarpine model. In comparison with controls, no significant changes in prion protein expression were found 1 hour after SE. At 12 hours, we observed increased expression of PrPc in neurons of CA1, CA2, and CA3 regions. Neurons of the superficial layers of the neocortex were also intensively labeled. In chronic animals, (2 and 4 months after SE) prion protein expression was found in the fascia dentata inner molecular layer. Adjacent sections revealed a close co-localization with neo-Timm supragranular mossy fiber sprouting.

Conclusions: Prion protein is differentially expressed at different phases of the pilocarpine model of epilepsy. Transient expression of prion protein in animals few hours after SE may reflect changes which may render cells more resistant to seizure-induced damage, may be related with apoptosis or may be related with initial phases of neuroplasticity. In the chronic period prion protein is co-expressed in the same regions the mossy fiber sprouting occurs. We are tempting to think that it might be related with epileptogenic processes, neurotransmission or, alternatively, it might be implicated in cellular protection against recurrent seizures. The functional roles of abnormal PrPc expression remain to be solved. (Supported by FAPESP, CAPES, CNPq.)

2.040

DEVELOPMENT OF THE DENTATE GRANULE CELL REGION IN HIPPOCAMPAL ORGANOTYPIC CULTURES FROM p35 KNOCKOUT MICE

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Rationale: p35 is a highly expressed protein in the brain and a specific activator of cyclin-dependent kinase 5 (Cdk5). The p35/Cdk5 complex, in turn, is part of a signaling mechanism that regulates neuronal migration during development. The p35 knockout mouse exhibits hippocampal aberrations in neuronal development and migration, as well as spontaneous seizure activity. To better understand the correlation between morphological abnormalities and seizures, we have begun to study dentate development in hippocampal organotypic cultures from p35 knockout (-/-) mice. We hypothesize that granule cells (GC) in the p35 -/- dentate gyrus (DG) in vitro will show migrational and morphological abnormalities similar to those observed in vivo.

Methods: Organotypic slice cultures were prepared based on the method of Stoppini et al. (1991). Seven- to eight-day old p35 wildtype and knockout mouse pups were used to generate cultures. Under sterile conditions, 400-μm transverse sections were cut from the hippocampus (with the attached entorhinal cortex). Slice cultures were maintained for up to 21 days in vitro (DIV); they were prepared for histological analyses (fixed in 4% paraformaldehyde) at three developmental timepoints—7, 14, or 21 DIV. Cell staining (cresyl violet, biocytin) and immunocytochemistry (NeuN, GFAP, GABA, parvalbumin) were used to follow and characterize cell features.

Results: The dentate granule cells in slice cultures from wildtype mice developed organotypically, showing a normal morphological progression similar to GCs in vivo. Typical neuroanatomical features of the dentate included: a clear boundary between the GCs and the hilus and molecular layer; GC dendrites with regular apical orientation and branching, dendritic spines, GC axonal arborization within the hilus, and GABA and parvalbumin expression in DG interneurons. GC development in slice cultures from knockout mice recapitulated many of the abnormal characteristics described for this model in vivo, including: aberrant GC migration into the hilar and molecular regions; and presence of abnormal dendritic trees (e.g., basal dendrites, misoriented branches).

Conclusions: The present study demonstrates the preservation of typical GC development in organotypic hippocampal slice cultures. Moreover, dentate granule cells in cultures from p35 mutant mice exhibit abnormal migration patterns and histopathological features comparable to those observed in the in vivo p35 $-/-$ preparation. These baseline data will allow us to use in vitro methods to elucidate the regulation of granule cell migration and development as they relate to developing epileptogenicity. [Supported by U.C. Davis Health Sciences Research Award (H.J.W.).]

2.041

ACQUISITION OF A PHOTOPAROXYSMAL RESPONSE IN ADULT RATS FOLLOWING EXPOSURE TO REPETITIVE VISUAL STIMULI

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Rationale: Photosensitive epilepsy is the most common form of reflex epilepsy. Many elements of photosensitive epilepsy are studied, including characteristics of triggering stimuli and relation to epilepsy type. Less well understood is the derivation of the underlying photosensitive condition/state. Genetics or lesions do not explain fully the etiology of photosensitivity, and some clinical and basic science reports raise the question of the role of environmental experience. The goal of the present study was to test previous suggestions that photosensitivity may also arise following repeated exposure to certain visual stimuli.

Methods: Adult rats of several ordinary strains were implanted with electrodes for chronic electrocorticographic recording. Following a period of recovery and habituation to the recording chamber, the animals were exposed to short trains of intermittent strobe stimulation, usually at 8 Hz. In some studies, stimulating electrodes were placed in the thalamic lateral geniculate nucleus so we could monitor the efficacy of geniculo-cortical transmission.

Results: Visual stimulation initially elicited a weak visual response or photic driving in occipital cortex (n = 36 rats). However, repeated exposure to strobe stimulation led to the rapid, progressive development of a high amplitude photoparoxysmal response (PPR) in 34/36 rats that could persist 3–4 stimulus cycles after strobe train offset. The epileptiform characteristics of the PPR included spike-wave morphology, generalization, and sensitivity to ethosuximide. Acquisition of photosensitivity required high intensity strobe stimuli, but once acquired, low intensity strobes could trigger a PPR, suggesting that, once photosensitivity has been acquired, the mechanisms that underlie acquisition of photosensitivity differ from those for triggering the PPR. Acquisition of photosensitivity was paralleled by potentiation of the response to electrical stimulation of the LGN. Acquisition was blocked by systemic application of an NMDA antagonist, suggesting involvement of long-term potentiation mechanisms.

Conclusions: Photosensitivity in ordinary adult rats can be acquired through repeated exposure to high intensity strobe stimulation. This provides evidence that environmental factors may play some role in the evolution of photosensitivity in humans. (Supported by NIH.)

2.042

EXPRESSION OF MULTIDRUG TRANSPORTERS MRP1 AND MRP2 DURING EPILEPTOGENESIS IN A RAT MODEL FOR TEMPORAL LOBE EPILEPSY

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Rationale: Overexpression of drug transporters has been shown in epileptogenic brain material and might play a role in the development of

pharmacoresistance. However, it is not known whether overexpression is due to an initial insult, or evolves more gradually because of recurrent spontaneous seizures. In the present study, we investigated the expression of the multidrug transporters MRP1 and MRP2 during epileptogenesis in a rat model for temporal lobe epilepsy.

Methods: Using immunocytochemistry, we examined protein expression in relation to the occurrence of a status epilepticus (SE) and the progression of recurrent seizure activity later in life in rats that were continuously EEG monitored.

Results: MRP1 and MRP2 were transiently upregulated in glial cells within the hippocampus 1 day and 1 week after SE. On the contrary, MRP1 and MRP2 were persistently overexpressed in chronic epileptic rats, especially in glial cells that surrounded blood vessels in ventral parts of the brain (piriform, perirhinal and entorhinal cortex). Overexpression of these drugtransporters was related to the occurrence of SE, since rats that were stimulated but had not exhibited SE were similar to control rats. Increased expression was most evident in rats with a high seizure frequency and less prominent in rats that had occasional seizures.

Conclusions: The present results indicate that MRP proteins are not only induced by the SE itself but that they are also upregulated in the chronic epileptic phase, although at more restricted brain regions. Whether this might contribute to reduction of the extracellular drug concentration in these regions, leading to drug-refractoriness is presently under investigation. [Supported by Epilepsy Clinics Foundation Heemstede (Lopes da Silva fellowship).]

2.043

ROLE OF TESTOSTERONE AND ITS METABOLITES IN MASCULINIZATION OF THE SUBSTANTIA NIGRA PARS RETICULATA GABAERGIC SEIZURE-CONTROLLING NETWORK

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Rationale: The substantia nigra pars reticulata (SNR) controls seizures via its GABAergic system in a sex specific manner. In postnatal day (PN) 15 rats, muscimol (a GABAA receptor agonist) in the SNR has a proconvulsant effect in males ("male phenotype") but no effect in females or in males castrated at PN0 ("female phenotype"). We have previously shown that the presence of testosterone may be responsible for this sex-specific effect. Daily administration (PN0–14) of testosterone (TP) induces the "male phenotype" in females or neonatally castrated males. Both androgen and estrogen receptors are present in the SNR at PN0. In this study we determined whether the natural early perinatal surge of testosterone and which of its neuroactive metabolites (dihydrotestosterone; DHT or estrogen; DES) are responsible for determining of the "male phenotype" (masculinization).

Methods: We used following groups of rats: males castrated at PN3 (natural testosterone early perinatal surge); males castrated at PN0 and females treated with TP (0.1 mg) or DHT (0.1 mg) or DES (2 μg) at PN0–2. At PN13, rats were implanted bilaterally into the SNR. Muscimol (100 ng/0.25 μl) was infused at PN15; after 30 minutes rats were exposed to flurothyl, a volatile convulsant, and the latency to first clonic and tonic-clonic seizure was recorded. Cannula placements were confirmed histologically.

Results: Presence of testosterone or its metabolites during the early neonatal period results in masculinization of the nigral seizure controlling GABAergic network. Thus, in females or in neonatally castrated males treated with testosterone or DHT or DES, muscimol infusions had a procovnulsant effect.

Conclusions: Early perinatal testosterone surge is responsible for the development of "male phenotype" of the SNR muscimol response. Activation of both estrogen and androgen receptors is important for the masculinization of the nigral seizure controlling GABAergic network. (Supported by NIH grants NS 20253, NS 36238, CURE grant, and the Heffer Family Medical Foundation.)

2.044

REDOX STATE IN THE HIPPOCAMPUS FOLLOWING EPILEPTOGENESIS INDUCED BY FE^{3+} INJECTION INTO RAT AMYGDALA

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Rationale: Free radical compounds are difficult to measure in brain extracts since brain tissue has a synergistic effect with reductants. To counter this problem, assessment of reductants is best performed using animals that are both alive and in the freely moving state. We used electron paramagnetic resonance (EPR) spectroscopy to perform qualitative analysis of in vivo antioxidant function with animals freely moving. Our aim was to evaluate the changes in redox state associated with epileptogenesis.

Methods: Experimental and control animals were injected in the amygdala with either $FeCl_3$ (Fe group, n = 6) or saline (control, n = 6) and then 25 days later had surgical placement of a guide cannula implanted to allow introduction of an in vivo microdialysis probe into the ipsilateral hippocampus. Five days after recover from this procedure in vivo microdialysis was performed. Following 2 hr of stabilization perfusion, the BBB-permeable nitroxide radical (3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl (PCAM), 0.2 M in saline, 1.6 ml/kg) was injected with animals in the interictal state. The concentration of nitroxide radical transferred into the brain was then measured with EPR.

Results: When plotted on a semilogarithmic scale, the signal intensity decayed in a linear and highly reproducible fashion, indicating the exponential decay in nitroxide radical transfer into the brain. The half-life of decay reflected the antioxidant ability of the biologic system to eliminate free radicals. The half-life (min) of the EPR signal of PCAM in the Fe group was 24.295 +/− 4.302 (mean +/− SE) min, and that in the control group was 13.385 +/− 3.916 min. The half-life for the Fe group was significantly longer than that for the control group (Mann-Whitney U-test, $p < 0.01$), indicating a decrease in the antioxidant ability of the Fe group.

Conclusions: Hippocampal regions of rats with chronic $FeCl_3$-induced seizures showed prolonged half-life of electron paramagnetism of PCAM consistent with decrease in ability to respond to and vulnerability to oxidative stresses. We propose that chronic and repetitive seizures lead to decrease in regional antioxidant levels and thus vulnerability to lipid peroxidation and epileptogenesis.

Translational Research: Animal Models 2

2.045

EVOLUTION OF PAROXYSMAL DISCHARGES IN THE NEONATAL RAT FOLLOWING CEREBRAL HYPOXIC-ISCHEMIC INJURY

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Rationale: Electroencephalograms (EEGs) have been used to detect seizures and partially characterize the extent of encephalopathy after neonatal cerebral hypoxia-ischemia. However, in one of the most commonly used animal models of cerebral hypoxia-ischemia, there are few studies that use electrographic monitoring of the injury. Therefore, we investigated electrophysiological changes in the postnatal day (PND) 7-rat model of cerebral hypoxia-ischemia.

Methods: After unilateral carotid artery ligation under general anesthesia, fifteen PND-7 rats were exposed to hypoxia (8% oxygen) for 3 hours at 36.5 °C. At the time of the carotid artery ligation, each animal had two subdural electrodes placed over each cerebral hemisphere and a separate ground electrode placed on the skull. Each animal underwent multiple, serial five-minute segments of electrocorticographic (ECoG) recordings before, during and following exposure to hypoxia. Control animals (n = 11) were subjected to sham operation and hypoxia or ligation without hypoxia and had ECoG recordings similar to the animals subjected to hypoxia-ischemia.

Results: In the rats subjected to cerebral hypoxia-ischemia, during the period of hypoxia, paroxysmal low voltage, rhythmic 2–3/sec activity was recorded in approximately half of the animals. This rhythmic activity occurred variably over the cerebral hemisphere ipsilateral, as well

as the cerebral hemisphere contralateral to the carotid artery ligation. Immediately after the animals were removed from hypoxia, medium to high voltage paroxysmal discharges (PDs) were recorded in 3 animals on the contralateral side with lower amplitude discharges on the ipsilateral side. During the period 1 and 3 hours after hypoxia-ischemia, 3 animals displayed medium to high voltage PDs on the contralateral side. In 2 of these animals, lower amplitude PDs appeared simultaneously on the ipsilateral side. During the period 6 and 9 hours after hypoxia-ischemia, 2 animals displayed PDs on both sides of the brain. Similar to previous recording periods, the discharges on the contralateral side had a much higher voltage amplitude range than those appearing on the ipsilateral side. In the period of time 12 and 16 hours post-hypoxia-ischemia, one animal displayed medium voltage PDs, appearing exclusively on the ipsilateral side. No PDs were recorded in any of the control animals.

Conclusions: We speculate that the PDs are manifestations of spontaneous hypoxic-ischemic seizures. Importantly, these discharges occurred early and late in relationship to the injury and often without behavioral symptoms, making these manifestations strikingly comparable to those observed in the asphyxiated human neonate. (Supported by Neurophysiology Research Fund, Kennedy Krieger Institute.)

2.046

EFFECTS OF VAGUS NERVE STIMULATION ON EXTRACELLULAR SEROTONIN CONCENTRATION IN DORSAL RAPHE NUCLEUS AND HIPPOCAMPUS: A MICRODIALYSIS STUDY

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Rationale: Vagus nerve stimulation (VNS) is a treatment for patients with medically refractory epilepsy. Although its efficacy has been well established, the mechanism of action of VNS remains unknown. As an inhibitory neurotransmitter, serotonin displayed its antiepileptic effect on various animal models of epilepsy. It was thought to be involved in VNS' antiepileptic mechanism after VNS' antidepressant effect was demonstrated. From the point of view of nervous anatomy, there is a close relationship between vagus nerve, nucleus of the solitary tract (NTS) and raphe nucleus, which is the major source of serotoninergic neurons. Based on this knowledge, we hypothesized that VNS could evoke a serotonin release in the dorsal raphe nucleus and hippocampus.

Methods: Male Sprague Dawley rats were implanted with a cuff electrode on the left cervical vagus nerve. The next day, 2 microdialysis probes were implanted respectively in the dorsal raphe nucleus and hippocampus. 2 hours after the probes implantation, dialysates were sampled every 20 minutes. After the establishment of baseline, VNS was given to the rats in stimulation groups ($n = 6$) for 20 minutes while the controls ($n = 5$) received a sham stimulation. Dialysates continued to be collected after VNS for 3 hours and then analysed by HPLC (High Performance Liquid Chromatography) and electrochemical detection. Relative concentration of 5-HT was calculated as the ratio of the measured value at any time point to that of the baseline data.

Results: No change in 5-HT concentration was detected during the 20 min stimulation period. Conversely, the extracellular serotonin concentration decreased significantly during the following 2 hours in the dorsal raphe nucleus of stimulated animals ($37\% \pm 13\%$) as compared to controls ($79\% \pm 27\%$) ($p < 0{,}01$). This effect was not observed in the hippocampus.

Conclusions: The decrease of extracellular serotonin concentration in the dorsal raphe nucleus observed in this study suggests that the synthesis, release or reuptake of serotonin could be modified by an acute VNS, although our results are contrary to our primary hypothesis. (Supported by Cyberonics, Inc.)

2.047

TARGETED LOSS OF HIPPOCAMPAL INTERNEURONS LEADS TO EPILEPTOGENESIS AND PROGRESSIVE HIPPOCAMPAL SCLEROSIS, THE SSP-SAPORIN MODEL

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Rationale: The syndrome of mesial temporal lobe epilepsy is generally associated with neuronal loss in the hippocampus and reorganization of neuronal circuits leading to chronic hyperexcitability. The pattern of neuronal loss involves subpopulations of GABAergic inhibitory interneurons. It has been hypothesised that this loss of inhibitory interneurons may play a role in the process of epileptogenesis. However this remains unclear and controversial, as some changes appear to be pro and others antiepileptogenic in classical epilepsy models. In the present study, using a neurotoxin SSP-saporin conjugate, we selectively destroyed these interneurons to investigate their role in the process of epileptogenesis.

Methods: The SSP-saporin congugate was injected in adult Sprague-Dawley rats into the left ventricle ($AP = -0.8$, $L = +1.5$ and $DV = -4.5$ mm, ref. to bregma), in a concentration of 4 μg/10 μl in 0.9% sterile saline at a rate of 1 μl/min. Control rats received an equivalent volume of saline. At the same time, two EEG bipolar electrodes were implanted into the ventral hippocampus ($AP = -3.8$; $ML = +2.0$; $DV = -3.0$ mm ref. to bregma) and cortex ($AP = -1.0$; $ML = +4.0$; $DV = -1.5$ mm ref. to bregma). Video-EEG recordings were performed 30 min/day. Once the incidence and timing of the EEG and clinical epileptic events were defined, the rats were sacrificed at different time points. The nature, extent and timing of cellular loss were afterward assessed, using Cresyl violet staining and different imunohistological markers for GABAergic interneurons.

Results: The EEG recordings of the SSP-rats were characterised, 24–48 hrs after the SSP-injection, by periods (30–60 sec) of slow (2–3 Hz) rhythmic delta activity of high amplitude (>150 mv) in the hippocampus and cortex. These rhythmic discharges were not associated with apparent clinical events, but with a loss of GABAergic interneurons, without any principal cell loss. At 48–72 hrs after SSP injection, the EEG showed periods (15–60 sec) of slow spikes-and-wave discharges (3–4 Hz) of moderate amplitude (20–50 mv) originating from the hippocampus. These were correlated clinically with wet dog shakes and myoclonic jerks. Freezing was observed in half of the SSP-rats, the EEG were then characterised by periods (10–30 sec) of rapid spikes-and-wave discharges (11–13 Hz) of moderate (20–50 mv) and high amplitude (>150 mv).Six days after the SSP injection, a loss of principal cells was observed in the CA1 and CA3 regions of the hippocampus.

Conclusions: Our results confirm that an initial loss of GABAergic interneurons leads to electrical discharges followed by clinical spontaneous recurrent seizures even before the loss of principal cells. This argues for a key role of GABAergic inhibitory interneurons in the process of epileptogenesis and for therapeutic interventions targeted to prevent their selective loss following an acute insult. (Supported by Savoy Fundation.)

2.048

A ROLE OF SEROTONIN IN MODULATING RESPIRATORY ARREST IN A MODEL OF SUDDEN DEATH IN EPILEPSY (SUDEP) IN DBA/2 MICE

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Rationale: SUDEP is devastating for epileptic patients and their families but has been difficult to model in animals, which has been a barrier to developing therapeutic interventions. The basis of SUDEP in patients may involve convulsion-induced respiratory failure. We propose that SUDEP can be modeled by the DBA/2 mouse. There is a high incidence of convulsion-induced death in DBA/2 mice, which can be prevented by prompt respiratory support. Major components of the respiratory neuronal network of mammals is known to reside in the brainstem, and this network is modulated by several neurotransmitters, including serotonin (5HT). The present study examined whether agents that affect 5HT neurotransmission can affect the susceptibility of DBA/2 mice to SUDEP.

Methods: DBA/2 mice (24 day old) were initially screened for susceptibility to audiogenic seizures (AGS) and SUDEP by exposing them to an electrical bell (122 dB SPL) until the onset of tonus for a maximum duration of 60 sec. Attempts to revive animals that exhibited SUDEP involved placement of a nasal tube connected to a rodent respirator (180 strokes/min). The surviving mice were subsequently placed into two groups: the SUDEP group exhibited respiratory arrest, while the

non-SUDEP group experienced AGS but maintained respiration. The SUDEP mice were given the 5HT uptake inhibitor, fluoxetine (fluox, ip), and the non-SUDEP mice were given the 5HT antagonist, cyproheptadine (cypro, ip), 24 hr after the initial AGS.

Results: Of 145 DBA/2 mice tested, 73% exhibited SUDEP, and in our most recent study, most of these mice (94%) could be revived using respiratory support. The DBA/2 mice in the recent study exhibited SUDEP (76%, of 46 mice), while the remainder (N = 11), were in the non-SUDEP group. Fluox (10 mg/kg) in SUDEP-expressing DBA/2 mice resulted in block of SUDEP in 100% of animals (N = 9), and the mice returned to SUDEP susceptibility (89%, N = 9) 72 hr later. The incidence of tonic hind limb extension (THE) was significantly reduced by fluox concomitantly. Cypro (1 mg/kg) in non-SUDEP DBA/2 mice resulted in respiratory arrest in 83% (N = 6) of mice that exhibited THE, and it could be reversed with respiratory support. Most (90%) non-SUDEP DBA/2 mice that did not exhibit THE (N = 10) also did not exhibit respiratory arrest.

Conclusions: These data indicate that the DBA/2 mouse model of SUDEP exhibits respiratory-mediated death but can be revived by respiratory support. SUDEP in DBA/2 mice is modulated by agents that alter 5HT neurotransmission, which suggests that agents which enhance the effect of 5HT might be useful in SUDEP prevention, while agents that block 5HT action should be avoided in epileptic patients that might be subject to SUDEP. Respiratory cessation in DBA/2 mice is also closely associated with expression of THE in this SUDEP model. (Supported by CURE, Christopher Donalty Memorial Award.)

2.049
FLUROTHYL-INDUCED STATUS EPILEPTICUS EARLY IN LIFE MODIFIES SUSCEPTIBILITY TO TRANSIENT FOCAL ISCHEMIC INJURY IN ADULTHOOD

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Rationale: In humans, the highest incidence of status epilepticus (SE) is in childhood, while ischemic stroke affects mainly adulthood. In a previous study we found that, in rats, an early bout of SE with seizures of limbic origin and secondary generalization increases the susceptibility to ischemic stroke in adulthood. In the present study we evaluated the effect of SE at PN15 with flurothyl ether (FE), a model of SE with primarily generalized clonic-tonic seizures.

Methods: Male Sprague Dawley rats at PN15 were submitted to 1-hour SE by continuous exposure to FE in a sealed chamber. One month after SE the same animals were subjected to middle cerebral artery occlusion (MCAo) by the intraluminal filament technique, for one or two hours. Twenty-four hours after MCAo the infarct volume for each rat was evaluated by computer scanning of 2 mm-brain sections stained with triphenyl-tetrazolium-chloride (TTC). Before sacrifice a graded neurological exam was determined using the following scale: 0 = no deficit, 1 = forelimb flexion; 2 = decreased resistance to lateral push; 3 = the same as 2 with circling.

Results: In adulthood, after 1 hour of ischemia rats submitted to FE-induced SE at PN15 had a significantly smaller volume of infarction as compared to littermates controls (36.82 ± 9.75 mm^3, and 101.24 ± 25 mm^3, respectively; $p < 0.05$ with t-student test), while the effect of two hours of ischemia was not modified (232 ± 72 mm^3 in the FE-SE group versus 208 ± 48 mm^3 in controls). Accordingly, a larger percentage of rats previously exposed to SE had no motor impairment after 1-hour ischemia as compared to controls (FE-SE: grade 0 = 86.7%; grade >1 = 13.3%. Controls: grade 0 = 42.1%; grade >1 = 57.9%). The protective effect of FE-induced SE on stroke volume was not due to FE by itself but rather to the SE; exposure at PN15 to the same amount of FE, but at such a low rate that did not induce seizures, did not alter the effect of one-hour ischemia in adulthood (volume of infarction 99.5 ± 31.13 mm^3). A potential "hypoxia-preconditioning" effect toward ischemic damage was also ruled out, since arterial pO2 after one hour of FE-SE was not different from baseline (127.46 ± 7.2 and 138.5 ± 522.8 mmHg, respectively).

Conclusions: These results suggest that the exposure of the immature brain to FE-SE attenuates the susceptibility to ischemic injury in adulthood. However, the net effect on stroke of a previous SE might be model-dependent, since we previously showed a worsening effect of an early Kainate-induced SE on 1-hour ischemia in adulthood. [Supported by NIH grant NS20253 and Heffer Family Medical Foundation (S.L.M.), and by NIH EY11053 (D.M.R.).]

2.050
IDENTIFICATION OF SURROGATE MARKERS FOR HEAD TRAUMA–INDUCED EPILEPTOGENESIS IN RAT BY QUANTITATIVE MRI: A 6-MONTHS FOLLOW-UP STUDY

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Rationale: Penetrating head injury leads to the development of epilepsy in (50% of patients. Non-invasive detection of surrogate markers that predict development of post-traumatic epilepsy would be of value for predicting prognosis of traumatic brain injury (TBI) and for development of antiepileptogenic treatments. We applied quantitative MRI to follow progression of tissue alterations in a rat model of TBI-induced epileptogenesis. At the end of the study, MRI will be correlated with the development of epilepsy. Here we show an interim analysis of the study that will be completed in June.

Methods: TBI was induced in Spraque Dawley rats (n = 14) by fluid percussion [1]. MRI data were acquired 3 h, 3 d, 9 d, 23 d, 2 mo, 3 mo, and 6 mo after TBI at 4.7 T. Volumetric changes were detected using T_2-wt SE imaging (TE = 70 ms, TR = 3 s, 128 * 256 pts, FOV 3 * 3 cm^2, thk = 0.75 mm, 19 slices). T_2, $T_{1\rho}$, and trace of the diffusion tensor (D_{av}) were quantified from a single slice using a fast SE sequence (TR = 3.0s, 128 * 256pts, FOV 3 * 3 cm^2, thk = 1.5 mm; T_2: TE = 20–80 ms; $T_{1\rho}$: spin-lock times = 18–78 ms, B_1 = 0.8 G; D_{av}: b-val = 90–1014 s/mm^2). T_2^* was measured using a GE sequence (TE = 5–15 ms, TR 0.7 s). At 6 mo rats will undergo 2 wk of video-EEG monitoring for seizure detection followed by perfusion for histology.

Results: T_2^* images showed signal void areas due to hemorrhage in 11 animals. Three animals developed severe damage at 2 mo, characterized by a large cortical lesion (>40 mm^3) and elevated relaxation times and D_{av} in the ipsilateral cortex ($T_2 > 300$ ms, $T_{1\rho} > 400$ ms and $D_{av} > 2.0 * 10^{-3}$ mm^2/s vs. $T_2 = 56.4 \pm 0.3$ ms, $T_{1\rho} = 82.0 \pm 1.2$ ms and $D_{av} = 0.70 \pm 0.01 * 10^{-3}$ mm^2/s in controls). Four animals had no MRI changes at 2 mo, in spite of initial increases in relaxation times (by 6–10%) and decreased D_{av} (~4%). The rest of the animals (n = 7) displayed decreased D_{av} in the cortical lesion in the initial phase (typical for cytotoxic oedema) followed by an increase in D_{av} after day 9. T_2 was initially increased by ~26% ($p < 0.01$) at day 3, but this declined to an ~8% ($p < 0.01$) increase at 2mo. Interestingly, $T_{1\rho}$ showed a similar initial increase but no recovery. In the ipsilateral hippocampus, relaxation times were slightly increased (3–7%, $p < 0.01$) 3 d after induction of TBI after which they recovered. Interestingly, D_{av} showed an increase of ~5% ($p < 0.01$) at 2 mo probably due to delayed tissue damage in the hippocampus. Progression of the damage was also evident from increased ipsilateral ventricle and hippocampal atrophy.

Conclusions: Our interim analysis indicates that a subpopulation of animals develops cortical and/or hippocampal damage that continues to progress during epileptogenic phase, several weeks after TBI. Association of these alterations with epileptogenesis will indicate which of the markers best associate with tissue pathology and predict epileptogenesis.

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2.051
A FOCAL COOLING SYSTEM FOR TERMINATION OF EXPERIMENTAL NEOCORTICAL SEIZURES

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Rationale: Several studies have demonstrated a reduction of epileptiform activities in models of epilepsy after gradual cooling. More recently, there was a report of rapid termination of spontaneous epileptiform activity in humans with the application of cold saline. It may be possible to develop medical instruments for terminating seizures automatically with focal cooling after detecting epileptiform discharges on electroencephalogram (EEG). To realize such a therapy, we assembled a new cooling system with a thermoelectric (Peltier) chip and explored its performance to suppress experimental neocortical seizures.

Methods: A Peltier chip (4.0 × 4.0 mm and 2 mm thick) was used for cooling. It was covered with a heat sink made of aluminum to which 37 °C water was supplied to remove the heat absorbed by the chip. Halothane-anesthetized adult, male Sprague-Dawley rats (480–520 g, n = 12) were used in this study. Kainic acid (3 μg) was stereotaxically injected through a craniotomy (10 × 9 mm) in the right sensorimotor cortex to produce experimental neocortical seizures. The cooling device was placed over the dura-arachnoid and a constant current (1A) was applied from a power supply. We investigated the EEG and the temperature on the cortex, and analyzed changes in amplitude of epileptiform discharges before and during cooling. We also investigated the histological changes of the cortex with Klüver-Barrera's staining after cooling.

Results: The temperature of the cortex decreased from 36.0 ± 0.4 °C (mean ± SE) to 23.0 ± 1.0°C within 30 seconds after cooling. The mean amplitudes of epileptiform discharges were suppressed to 79.6 ± 6.2% (mean ± SE, $p = 0.7$) and 72.5 ± 5.8% ($p < 0.01$) in 1 and 2 minutes after cooling, respectively. A statistically significant decrease of the amplitude was observed in slower components (<8 Hz) of epileptiform discharges. Histologically, there were no obvious changes in the cortex after cooling.

Conclusions: We demonstrated the efficiency of our cooling device with Peltier chip on the suppression of experimental epileptiform activities. This device may contribute to the development of functional mapping systems or implant automatic seizure termination systems. [Supported by The Ministry of Education, Culture, Sports, Science and Technology of Japan, Grand-in-Aid for Scientific Research (C) (No.15591527).]

2.052

ANDROSTERONE, A METABOLITE OF TESTOSTERONE THAT POSITIVELY MODULATES $GABA_A$ RECEPTORS, PROTECTS AGAINST SEIZURES IN ANIMAL MODELS: IN VIVO AND IN VITRO STUDIES

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Rationale: Progesterone- and deoxycorticosterone-derived neuroactive steroids that positively modulate $GABA_A$ receptors are potent anticonvulsants in animal models. Androstanediol (5α-androstan-3α-ol-17β-diol) and androsterone (5α-androstan-3α-ol-17-one) are major metabolites of testosterone that also positively modulate $GABA_A$ receptors. Recently, we have shown that androstanediol protects against seizures with potency lower than that of other neuroactive steroids. As of now, however, the possible anticonvulsant effects of androsterone have not been well characterized. Thus, we sought to determine the activity of this neuroactive steroid in whole animal and hippocampal slice seizure models.

Methods: Male NIH Swiss mice were pretreated with androsterone and its protective effects were assessed in 6Hz and maximal electroshock (MES) models: corneal electrical stimulation (3 s, 32 mA, 6 Hz) and (0.2 s, 50 mA, 60 Hz), respectively. Additionally, pentylenetetrazol (PTZ) and pilocarpine seizure models were utilized. Androsterone-induced motor impairment was assessed in the inverted screen test. The ED_{50} (dose protecting 50% of animals), TD_{50} (dose producing motor impairment in 50% of animals) and protective index (PI) ($PI = TD_{50}/ED_{50}$) were determined.Epileptiform discharges in hippocampal slice, recorded as extracellular field potentials in CA3 region, were induced by perfusion with 4-aminopyridine (4-AP, 55 μM). The effects of androsterone on 4-AP-induced discharges were studied in 10 min epochs during 1 hr recording.

Results: Androsterone protected mice from seizures with increasing rank of potencies in MES, pilocarpine, PTZ and 6 Hz models. The respective ED_{50} values were: 223.7 (182.5–274.1), 105.4 (47.7–232.7), 43.5 (31.6–60.0) and 29.1 (16.2–52.1) mg/kg. The TD_{50} value obtained in the inverted screen test was 152.3 (133.9–173.1) mg/kg. Accordingly, the respective PIs values were calculated: 0.68, 1.44, 3.5 and 5.23. Androsterone also inhibited epileptiform activity in hippocampal slices. At 100 μM it almost completely blocked discharges induced by 4-AP.

Conclusions: We have found that androsterone is a broad-spectrum anticonvulsant. Its anticonvulsant potency is higher than that of the other testosterone metabolite, androstanediol. These data, taken together, support a role of androsterone in regulation of seizure susceptibility and might open further investigations concerning the possible utility of this neuroactive metabolite of testosterone in the treatment of human epilepsy. (Supported by NINDS/NIH.)

2.053

IN VITRO HYPEREXCITABILITY IN THE RAT FREEZE LESION MODEL OF CORTICAL DYSPLASIA DOES NOT TRANSLATE INTO CLINICAL EPILEPTOGENICITY

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Rationale: Malformations of cortical development (MCD) in humans are a frequent cause of refractory epilepsy in humans. The freeze-lesion model in rats has histopathological features similar to human polymicrogyria. Previous studies reported in-vitro hyperexcitability in this model, but in-vivo epileptogenicity has never been confirmed.

Methods: A deep-freeze metal probe was applied unilaterally to Sprague-Dawley rat pups (n = 10) on P0/P1 to induce a cortical lesion. Sham-operated animals (where the probe was kept at room temperature) were used as the control group (n = 10). On P60, animals of both groups were implanted bilaterally with epidural electrodes in the frontal and parietal cortex and subsequently underwent 4 weeks of long-term video-EEG monitoring. The threshold for pentylenetetrazol (PTZ) induced seizures was determined. Afterwards, the animals were sacrificed and coronal brain sections were cresylecht violet stained for histology. In addition, epileptiform field potentials (EFP) was studied in brain slices prepared from freeze-lesioned (FL slices) and sham-operated rats (CTRL slices) in-vitro. EFP repetition rate, maximum amplitude, duration, and burst integral were compared between both groups.

Results: No interictal spikes and no electrographic or clinical seizures were found in both groups during 4 weeks of continuous EEG monitoring. The median threshold for PTZ-induced seizures was 60 mg for the lesioned group, and 45 mg for the control group. This difference was not statistically significant. No spontaneous EFP were recorded from either FL slices or CTRL slices bathed in normal artificial cerebrospinal fluid (ACSF). Upon omission of Mg^{2+} from the bath solution, EFP were elicited that showed a significantly higher burst integral in FL slices, compared to CTRL slices.

Conclusions: Neocortical freeze lesions induced in newborn rat pups show histological characteristics reminiscent of human cortical dysplasia. Brain slices containing neocortical freeze lesions display hyperexcitability in-vitro, but the same lesion does not appear to be epileptogenic in-vivo. [Supported by Innovative Medical Resarch (IMF) grants of the University of Münster/Germany to C.K. (KE 620201) and G.M. (MO 620202), National Institutes of Health (NIH) grant K08 NS02046, and 1R21 NS42354 to I.N.]

2.054

REPEATED BRIEF SEIZURES IN NEONATAL RATS ATTENUATE PROGRAMMED CELL DEATH INDUCED BY MK-801

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Rationale: We have previously demonstrated the neuroprotective effects of repeated brief seizures evoked by low-intensity (minimal) electroconvulsive shock (ECS) in adult rats. However, we do not know if repeated brief seizures can also exert a neuroprotective action in

neonatal animals. In the present study, we evaluated the impact of repeated ECS-induced seizures on the programmed cell death (PCD) which has been demonstrated to occur in the neonatal rat brain in response to exposure to the NMDA receptor antagonist, MK-801. We also examined the interaction between ECS and exposure to valproic acid (VPA) and levetiracetam, two anticonvulsant agents.

Methods: Sprague-Dawley male and female rat pups between P5 and P8 were used in all experiments. **ECS** was applied to rat pups via corneal electrodes (200 msec, 35 mA) which induced minimal motor seizures lasting 5–10 sec. A single treatment session consisted of 3 ECS seizures, given at 0, 30 and 60 min. Control (sham-treated) rats received the same handling but no current was passed through the electrodes. Either MK-801 (0.5 mg/kg), valproic acid (400 mg/kg) or levetiracetam (1000 mg/kg) were injected intraperitoneally 24 hr prior to sacrifice. ECS treatment sessions were given at varying intervals (6–24 hr apart), before and/or during the drug exposure. TUNEL assay and Fluoro-Jade B staining were used to detect neurodegeneration in various brain regions.

Results: ECS (3 daily sessions or 3 sessions/day) consistently and significantly reduced MK-801-induced neuronal cell death in striatum (30% reduction) and thalamus (25% reduction). However, the ECS treatment did not significantly attenuate valproic acid-induced neurodegeneration in the same brain regions. Surprisingly, levetiracetam did not induce neuronal death either in the presence or absence of ECS.

Conclusions: Our data indicate that repeated brief seizures can attenuate the PCD induced by MK-801 in the neonatal brain. However, the ECS treatment did not reduce neuronal cell damage induced by valproic acid. Our results suggest that in the developing brain, 1) ECS can exert a neuroprotective action and 2) this action may depend on the mechanism by which PCD is induced. Levetiracetam is distinct from other anticonvulsant drugs in its lack of pro-apoptotic action. The functional impact of the regional changes in PCD in the developing brain will be evaluated by testing animals for cognitive function as they mature. (Supported by NIH grants NS 20576, MH 02040, NS 041231, Epilepsy Foundation predoctoral fellowship.)

2.055

β-HYDROXYBUTYRATE DECREASES FLUROTHYL-INDUCED SEIZURE SUSCEPTIBILITY IN RATS

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Rationale: The ketogenic diet (KD) remains a therapy in search of explanation although it is an established treatment for patients with intractable seizures. It was designed to mimic the biochemical changes seen upon fasting, specifically the formation of ketone bodies: acetoacetate (ACA), β-hydroxybutyrate (BHB), and to a lesser extent, acetone. Investigators have observed that ketosis is necessary but not always sufficient for seizure control with the KD. In addition, Rho et al. (*Epilepsia* 2002;43:358–61.) recently reported that ACA and acetone exhibited anticonvulsant in Frings audiogenic seizure-susceptible mice. The data suggest that the anticonvulsant efficacy of the KD may be due in part to the direct actions of ACA and acetone. The present study was designed to investigate the protective effect of BHB on flurothyl-induced seizures in rats.

Methods: Thirty-four male Sprague-Dawley rats were divided into two equal groups. Experimental rats ($n = 17$) were injected intraperitoneally with BHB (20 mmol/kg), while control animals ($n = 17$) with normal saline. Fifteen minutes later, seizures were chemically induced by flurothyl infusion (40 μl/min). Seizure susceptibility was defined as the latency from the start of flurothyl infusion to the onset of a generalized seizure (loss of posture with bilateral hindlimb tonic extension). Shorter latencies reflect greater seizure susceptibility.

Results: The mean ($\pm$SEM) latency to the onset of a generalized seizure in the experimental animals treated with BHB was 476.5 $\pm$ 13.9 seconds, which was significantly ($p < 0.05$) longer than the control (438.0 $\pm$ 10.5 seconds).

Conclusions: This study demonstrates the significant decrease in flurothyl-induced seizure susceptibility in rats treated with BHB. Our results suggest that BHB may be directly anticonvulsant. [Supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (02-PJ1-PG10-21301-0001).]

2.056

PLACE CELLS IN IMMATURE RATS

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Rationale: The hippocampal formation is important for spatial learning and memory. Many individual pyramidal cells of CA1 and CA3 in normal rats act as place cells. Each place cell discharges rapidly only when the rat's head is in a cell-specific part of the environment called the firing field. Firing fields are stable over long times (weeks or months) in a constant environment, implying that the across-cell representation is remembered and not created de novo each time the rat enters the environment. Previous studies have shown that immature rats are capable of learning visual-spatial tasks, such as the hidden platform in the water maze, as early as postnatal day (P) 20. However, the performance of young rats in the water maze is impaired compared to adult rats. Previous reports have found that reliable place cells do not occur prior to P50 raising the possibility that the poor specificity and stability of hippocampal location firing may account for the poor visual-spatial skills seen in these animals. The goal of this study was to determine whether young animals have reproducible place cells.

Methods: Rats had electrode placement at P25 ($n = 5$) or P70 ($n = 7$). A movable array of sixteen 25 micron electrodes was used. Place cells were recorded at P31-P38, P48, or P80.

Results: Well-delineated place cells were recorded as early as P31. Place cells were recorded at P31–P38 ($n = 25$ cells), P48 ($n = 9$ cells), and P80 ($n = 21$ cells). There were no differences in center rate, field rate or field area in the three groups. However, the coherences were lower in the immature rats than the adults demonstrating the precision of the firing field was higher in adults compared to the immature rats. Stability of the cells was lower in the immature rats with significant differences in angular displacement among the three groups. While similarity scores increased with age, the differences were not statistically different. When angular displacement and similarity scores were compared after 6 hour in the P31–38 and P80 recordings the angular displacement and similarity scores were significantly longer in the in younger rats (Angular displacement P31–P38: 61.57 $\pm$ 10.66, P80 8.40 $\pm$ 2.30, $p < 0.001$; Similarity score P31–P38: 0.494 $\pm$ 0.052, P80 0.620 $\pm$ 0.030, $p = 0.036$).

Conclusions: In this study we demonstrated that well-formed place cells can be recorded in very young rats. When we utilized a small chamber we found pace cells were easy to record and were quite robust in their firing patterns. However, we found place cells in young rats had reduced coherences, a measure of the local smoothness of spatial firing patterns. In addition, stability of place cells as measured by angular displacement and similarity score, was reduced in the younger animals compared to older animals. [Supported by National Institutes of Health (NINDS) (NS044296).]

2.057

DEVELOPING A KAINIC ACID–INDUCED TEMPORAL LOBE EPILEPSY MODEL IN BEHAVING SQUIRREL MONKEYS

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Rationale: To initiate the development of a temporal lobe epilepsy (TLE) model that produces chronic, non-lethal seizures in freely-behaving monkeys, so that novel drugs and neuroprosthetic devices can be tested in primates and in natural circumstances.

Methods: Two male squirrel monkeys (*Saimiri sciureus*) were used. A bipolar EEG electrode - microinjection cannula unit (Apollo Microsurgicals, London, Ontario, Canada) was stereotaxically implanted into the right hippocampus, according to the squirrel monkey brain atlas of Gergen and MacLean. A bipolar EEG electrode was also positioned subdurally over the ipsilateral temporal cortex. In one monkey, additional recording electrodes were placed in the contralateral hippocampus and temporal cortex. The surgical procedures, conducted under general anesthesia, essentially followed our previously described protocol for chronic electrode-implantation in the monkey temporal lobe (Ludvig et al.

J Neurosci Methods 2001;106:179–87). After a 2-week postoperative period, each monkey was seated in a primate chair without head-restraint, and the hippocampal and temporal cortical electrographic activities were recorded before, during and after the intrahippocampal microinjection of either 4.0 or 0.25 μg kainic acid (pH = 7. 4; injection volume: 1 μl; injection duration: 1 min). Behavioral monitoring was also conducted. Post-seizure antiepileptic drug administration (pentobarbital, 20 mg/kg, i.p.) was performed in one monkey.

Results: The single, unilateral microinjection of 4.0 μg kainic acid into the hippocampus of the first monkey induced brief, high-amplitude, local EEG bursts within 40 min that were transformed into continuous electrographic seizures in the subsequent 20-min period, spreading to the contralateral recording sites. These seizures were accompanied with oral automatisms and staring gaze and led to a lethal outcome 3 days later. The similar microinjection of 0.25 μg kainic acid in the second monkey induced repetitive, hippocampal/temporal cortical electrographic seizures also within 40 min, but these seizures were not accompanied with apparent behavioral abnormalities. Pentobarbital administration at the 60th minute of the EEG seizure activity halted the pathophysiological electrographic events and prevented lethal outcome.

Conclusions: Intrahippocampal kainic acid delivery (<1 μg) in squirrel monkeys can produce seizures within 1 hour that resemble those of human TLE. With further improvements, this model may become a useful tool in TLE research and therapy development.

2.058
GENE-ENVIRONMENTAL INTERACTIONS IN THE METABOLIC CONTROL OF MULTIFACTORIAL IDIOPATHIC EPILEPSY

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Rationale: Glucose uptake into the brain is greater during epileptic seizures than during most other brain activities suggesting a key role for glucose in the initiation and spread of seizure activity. Under conditions of fasting or caloric restriction (CR), however, brain cells can also derive energy from ketone bodies (acetoacetate and beta-hydroxybutyrate). The high fat, low carbohydrate ketogenic diet (KD) was developed as an alternative to fasting for seizure management. While the mechanisms by which fasting and the KD inhibit seizures remain speculative, ketone bodies and alterations in brain energy metabolism are likely involved. The metabolism of ketones likely produces multiple changes in gene expression that lead ultimately to reduced neuronal membrane excitability and seizure management. We previously showed that caloric restriction (CR) inhibits seizure susceptibility by reducing blood glucose in the epileptic EL mouse, a model of multifactorial idiopathic epilepsy. In this study, we compared the antiepileptic efficacy of the KD with that of CR in adult EL mice.

Methods: EL mice that experienced at least 15 recurrent complex partial seizures were fed either a standard (chow) diet unrestricted (SD-UR) or restricted (SD-R), and either a KD unrestricted (KD-UR) or restricted (KD-R). Each mouse served as its own control to achieve a 20% body weight reduction in the diet-restricted groups. Seizure susceptibility, body weights, and the levels of plasma glucose and ketone bodies (beta-hydroxybutyrate) were measured once a week over a ten-week treatment period in each diet group.

Results: Seizure susceptibility remained high in both UR diet groups throughout the study. Seizure susceptibility decreased significantly ($p < 0.001$) after three weeks in both R diet groups and was managed completely after ten weeks of diet therapy. Body weights and plasma glucose were similar over the ten-week testing period in the SD-UR and the KD-UR groups, but were significantly ($p < 0.001$) reduced in the SD-R and KD-R groups. Plasma ketone levels measured at the final week were significantly increased in the SD-R and KD-R groups compared to their respective UR groups ($p < 0.001$). RT-PCR and Western blot analysis will examine the expression profiles of various genes potentially involved in the seizure management under the restricted dietary conditions. The results of the gene and protein expression profiles as well as linear and multiple logistic regression analyses will be also presented.

Conclusions: A reduction in plasma glucose levels coupled with an increase in plasma ketone levels is predicted to manage EL epileptic seizures through multiple neurochemical and metabolic interactions. [Supported by the Epilepsy Foundation through the generous support of the R.F. and E.F. Evans Fund, NIH grant (HD39722), and the Boston College Research Expense Fund.]

2.059
SPECIFIC FAST OSCILLATORY THALAMOCORTICAL ACTIVITY IN BRAIN SLICES IN THE GAERS ABSENCE EPILEPSY MODEL

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Rationale: The genetic absence epilepsy rats from Strasbourg (GAERS) model is a well established model of generalised epilepsy. Electrophysiological abnormalities that occur in GAERS have been described *in vivo*, but underlying ion channel and network activities are incompletely understood. The aim of this study was to determine whether specific thalamocortical oscillatory activity recorded in GAERS brain slices differs from non-epileptic controls (NEC).

Methods: NEC or GAERS rats (12–14 weeks) were anesthetized with pentobarbitone, decapitated and the brain rapidly removed to perfusion with ACSF. Thalamacortical slices (300–450 micron) were cut in the axial plane. Bipolar electrodes were placed in the nucleus reticularis thalamus (nRt) and ventrobasal thalamus (VB) and nRt activity was evoked by electrical stimulation. In other experiments recording electrodes were used in both the neocortex and the VB. Spontaneous and electrically-induced activity were recorded, and effects of a non-selective K+-channel blocker, 4-aminopyridine (4-AP), and low Mg^{2+} artificial cerebral spinal fluid (ACSF) were studied.

Results: 17 and 11 slices from 6 GAERS and 4 NEC, respectively, were studied. Spontaneous bursts of oscillatory activity were apparent in slices from the GAERS animals and these activities were at distinct frequencies of 1.7 ± 0.1 Hz, 2.7 ± 0.1 and 5.4 ± 0.3 Hz ($n = 4$ for each). The duration of oscillatory bursts in these animals was averaged 12.9 ± 1.4 seconds ($n = 24$ bursts calculated from 20 different traces). In the NEC animals only very brief, transient discharges with low frequency were seen. In GAERS, application of 4-AP evoked highly organised fast oscillatory bursts of electrical activity. Bursts of oscillatory activity could also be evoked in thalamocortical slices from GAERS by electrical stimulation of the nRt/VB boundary. In some recording sequences, coincident thalamocortical oscillations were obtained. Preliminary experiments have shown that calcium transients in the VB, measured using calcium ion-sensitive fluorescent probes, can be regulated by electrical stimulation of the nRt.

Conclusions: Specific fast oscillatory activity was seen in thalamocortical slices from GAERS but not in NEC rats. Such aberrant activity could underly the seizures seen in this model. In future studies, optical imaging techniques will be used to characterize the ion channel activities associated with these GAERS-specific oscillations at both the cellular and network level. [Supported by NHMRC (Australia) and ARC (Australia).]

2.060
DYNAMICAL CHANGES IN THE RAT CHRONIC LIMBIC EPILEPSY MODEL

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Rationale: We have previously reported seizure prediction in human temporal lobe epilepsy (TLE) using Short Term Lyapunov Exponent (STL_{max}) and Average Angular Frequency (Ω) with a sensitivity of 80% (Iasemidis et al, 2003). These results have prompted us to apply the same techniques to a rat chronic limbic epilepsy (CLE) model described by

Lothman et al.(1990). The present study tests the hypothesis that similar dynamical changes exist in the CLE model.

Methods: Thirty, 2-hr epoch data sets from 6 CLE rats (mean seizure duration 74 ± 20 sec), each containing a grade 5 seizure and continuous intracranial EEG beginning 1 hr before the seizure were analyzed. Teager energy is calculated iteratively every 5-second epoch for each electrode and a detection is determined at an adaptive fixed threshold. Coherence is calculated for every 4-sec non-overlapping epoch for each electrode pair. Ictal and interictal periods were compared to estimate the change in synchronization between channels at seizure onset. STL_{max} measures the dynamical chaoticity of a signal and Ω measures how fast the local state of a system changes on average and are estimated for every 10.24-second interval. T-index, a statistical measure is used to quantify the convergence or divergence of STL_{max} and Ω before and after a seizure.

Results: Data analysis showed an abrupt increase in the energy profile of each channel and a significant increase in coherence values in multiple frequency bands between the area of ictal onset and other sites during a seizure. Nonlinear analysis shows multiple transient drops in STL_{max} values during the pre-ictal period followed by a significant drop during the ictal period. Ω values show transient peaks during the pre-ictal period followed by a significant peak during the ictal period. The channel corresponding to the stimulated side of the hippocampus had a consistently lower value of STL_{max} and a higher value of Ω compared to other channels. A convergence among electrode sites was also observed in both STL_{max} and Ω values (low T-index) before a seizure.

Conclusions: Results suggest that linear and non linear analysis can detect the dynamical change that precedes and accompanies seizures in rat CLE model. Furthermore, convergence in non-linear measures suggest that it is possible to identify the preictal transition. Thus, the rat CLE model may serve as a tool to further develop seizure prediction algorithms and implement real time closed-loop intervention techniques. (Supported by NIH grant R01EB002089, Children's Miracle Network, University of Florida Division of Sponsored Research and Department of Veterans Affairs.)

2.061

SYNAPYOPHYSIN AND GAP-43 IMMUNOREACTIVITY IN THE LITHIUM-PILOCARPINE MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: The lithium-pilocarpine (Li-pilo) model reproduces the main characteristics of human mesial temporal lobe epilepsy. This model is characterized by an acute status epilepticus (SE) followed by a latent seizure free period and spontaneous recurrent seizures. Extensive damage and neuronal loss are present in hippocampus, thalamus, amygdala and ventral cortices. Synaptopysin is a protein expressed at presynaptic vesicles and is known as a neuronal marker of synaptogenesis. GAP-43 is a specific marker for axons and growth cones. It is expressed at high levels during nervous system development, and its dramatic synthesis was observed in injured and regenerating tissue. Here, we examined the features of neuronal reconstruction after SE using these neuronal markers.

Methods: SE was induced by LiCl (3 meq/kg) 18 h before pilocarpine was injected (25 mg/kg) to adult male rats. Control rats received LiCl and saline instead of pilocarpine. Expression of synaptophysin and GAP-43 was examined at 7 days after SE. Sections were cut with a vibratome and free floating sections were stained with specific antibodies. Image analysis was performed using a CCD camera mounted onto a light microscope and connected to a computer. The optical density was measured by means of an image processing system.

Results: Immunoreactivity of synaptophysin was increased in piriform and entorhinal cortex of the Li-pilo group, compared to the control group, and that of GAP-43 decreased in the same regions. In medial and lateral thalamus and amygdala, GAP-43 immunoreactivity decreased in Li-pilo rats, while synaptophysin did not show any significant difference compared to control animals. In hippocampus, immunoreactivity of both synaptophysin and GAP-43 was similar in control and Li-pilo rats.

Conclusions: The higher expression of synaptophysin and lower expression of GAP-43 in ventral cortices may relate to severe neuronal loss. The decrease of GAP-43 expression in thalamus and amygdala occurs in regions less damaged but undergoing early neuronal loss as the ventral cortices. The expression of synaptophysin and GAP-43 was not altered in CA1 in which neuronal loss is delayed compared to the former regions. A time-dependent study of the expression of these proteins has been undertaken in order to clarify these regional differences and the potential relationship between time-dependent neuronal loss and the expression of these proteins. (Supported by INSERM U405.)

2.062

ENHANCED SUSCEPTIBILITY/SEVERITY TO EPILEPTIFORM ACTIVITY IN REELER HOMOZYGOUS MICE

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Rationale: Cortical malformations are frequently associated with epilepsy, cognitive impairment and other neurological disorders. Reeler homozygous mice (rl/rl) are a model of cortical malformation that exhibit anatomical and genetic alterations similar to that observed in humans with lissencephaly with cerebellar hypoplasia. However, it is currently unclear whether seizure susceptibility/severity is altered in rl/rl mice.

Methods: In vivo (minimal electroshock) and in vitro techniques (extracellular field potential recordings in hippocampal and neocortical brain slice preparations exposed to bicuculline methiodide) were used to assess whether the susceptibility to generate epileptiform activity or the severity of the epileptiform activity elicited is enhanced in rl/rl mice relative to controls. Males (2–4 months) were used in all experiments. In hippocampal slices, recordings were performed in the dentate gyrus (recording at the granule cell–molecular layer border), and in CA1 (both the superficial and deep layers of CA1 were examined in rl/rl mice). Additionally, since rl/rl mice exhibit an inverted lamination in the neocortex and only 4 primary layers, recordings were made in the deep layers from rl/rl mice and the superficial layers from controls.

Results: Minimal electroshock was delivered transcorneally using a Whalquist electroshock instrument (5 mA intensity; 60 Hz; 200 ms duration) and seizures were scored using a modified Racine's scale. Minimal electroshock elicited seizures ≥ class 3 in severity in 100% of rl/rl mice (n = 4), and in only 25% of controls (n = 4). Following application of 30 μm bicuculline, an increased probability of eliciting spontaneous prolonged negative field potential shifts (i.e. epileptiform activity) was observed in hippocampal slices from rl/rl mice relative to controls. Prolonged field potential shifts were observed in the dentate gyrus in 100% of slices from rl/rl mice and 0% from controls (25/25 vs 0/27 slices respectively). A similar increase in the probability of generating prolonged field potential shifts was observed in CA1 of rl/rl slices relative to controls (10/10 vs 4/10 slices, respectively). Furthermore, in 10 μm bicuculline, neocortical slices from rl/rl mice exhibited epileptiform events that were of longer duration than those recorded in controls (rl/rl: duration = 5.1 ± 0.7 s, n = 4; control: duration = 3.4 ± 0.4 s, n = 4).

Conclusions: Both in vivo and in vitro data indicate that rl/rl mice exhibit an enhanced susceptibility/severity to epileptiform activity. Although additional experiments are needed, these data suggest that the rl/rl mouse may be a suitable model for examining how global and naturally occurring (in comparison with injury induced) cortical malformations contribute to a change in seizure susceptibility/severity. (Supported by ORDA grant SIUC.)

2.063

ROLE OF ENDOTHELIAL AND NEURONAL NITRIC OXIDE (NO) IN THE CEREBROVASCULAR RESPONSE TO PARTIAL SEIZURES: A GENETIC APPROACH IN MICE LACKING NEURONAL OR ENDOTHELIAL NO SYNTHASE

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Rationale: NO is a potent vasodilator involved in the regulation of local cerebral blood flow (LCBF) in physiological and pathological situations. The mechanisms coupling the neuronal activity to the vascular response during seizures have to be clarified. The role of NO in the cerebrovascular response to generalized or focal seizures has been shown,

but the origin of NO (endothelial or neuronal) remains to be elucidated. We investigated LCBF in limbic areas in response to partial seizures in mice lacking the neuronal (nNOS-/-) or endothelial isoform of NO synthase (eNOS−/−).

Methods: nNOS−/− mice, eNOS−/− mice and their paired wild type controls, nWT- and eWT mice (Jackson Laboratory) received a unilateral injection of kainate (KA, 50 nl; 1nmol) or saline within the right dorsal hippocampus under equithesin anesthesia. Four monopolar electrodes were implanted over the frontal and parietal cortices for EEG recordings. LCBF was measured upon awakening from anesthesia during partial seizures (4–6h after KA injection) using the quantitative autoradiographic ^{14}C-iodoantipyrine method. LCBF was quantified in 14 limbic areas ipsi- and contralaterally to the injection site.

Results: In nWT- and eWT mice, KA seizures led to ipsilateral 23–52% LCBF increases restricted to the hippocampus. Contralaterally, seizures induced LCBF decreases (27–41%) in all hippocampal areas, cingulate and parietal cortices, and amygdala of eWT mice, and in CA3, subiculum, perirhinal and entorhinal cortices of nWT mice, compared to saline-injected animals. In seizing nNOS−/− mice, hippocampal LCBF displayed ipsilateral 31–88% increases but no contralateral change, compared to saline-injected nNOS−/− mice. Conversely, a significant 27–47% contralateral decrease was recorded in the other limbic areas of nNOS−/− treated with KA, compared to saline. In eNOS−/− mice, seizures induced no ipsi- or contralateral change in LCBF within the hippocampus. However, KA seizures induced significant 22–46% contralateral LCBF decreases in limbic cortices and amygdala of eNOS−/− mice.

Conclusions: The absence of LCBF increases in the ipsilateral hippocampus of eNOS−/− mice during seizures emphasizes the role of NO of endothelial origin in the vascular response within the epileptic focus. Contralaterally, the LCBF decreases during seizures in limbic cortices in both eNOS and nNOS−/− mice demonstrate the involvement of both isoforms of NOS in seizure-induced vascular changes within areas distant from the focus. Thus, NO appears to play a role in the redistribution of LCBF between the focus and the other brain regions during partial seizures. The specific involvement of endothelial and/or neuronal NO appears to depend on the structure. [Supported by Institut National de la Recherche et de la Sante Medicale (U398) and NATO grant 960716.]

2.064

TRACING OF MOSSY FIBER PATHWAY BY MANGANESE-ENHANCED MRI (MEMRI) IN EPILEPTIC RAT BRAIN

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Rationale: Mn^{2+} is a paramagnetic ion commonly exploited in Mn^{2+}-enhanced MRI (MEMRI). Mn^{2+} mimics Ca^{2+} and is taken up by living neurons, transported by axons across synapses, and can reflect functional properties of neuronal connections. We have used MEMRI to investigate the mossy fiber pathway in the kainic acid model of temporal lobe epilepsy. It was anticipated that MEMRI would reveal reorganization of mossy fibers during epileptogenesis *in vivo*, and consequently, be used as a candidate surrogate marker for development of epilepsy.

Methods: Status epilepticus (SE) was induced with kainic acid (11 mg/kg, i.p.) in 5 adult male Wistar rats. Controls (n = 6) received saline. Two weeks later, injections of Mn_2Cl (1M, 30–50 nl) were targeted to the caudal subfield of the entorhinal cortex (EC). MRI data was acquired 3, 5, 7, 9, and 10 d after $MnCl_2$ injection using a 4.7T magnet interfaced to a Varian console. T_1-weighted (TE = 2.7 ms, TR = 120 ms, flip = 70 deg) 3D gradient echo MRI was performed. A volume of $25 * 25 * 35$ mm^3 was covered with $192 * 64 * 256$ points. Signal intensities of the regions of interest were measured and normalized with adjacent muscle tissue. AVS Express software was used to create volume rendered 3D reconstructions from volumes enhanced by Mn^{2+}. After MRI, animals were perfused with Timm fixation to verify mossy fiber sprouting.

Results: All animals with SE developed spontaneous seizures within 3 weeks. In controls, MEMRI signal was detected in all subfields of hippocampus. In epileptic rats, signal was stronger than in controls in hilus and CA3 subfield, probably related to mossy fiber sprouting that was verified by histology. Unexpectedly, epileptic animals also had stronger MEMRI signal in the laterodorsal thalamus which may be due to spread of tracer substance to postrhinal cortex at the time of injection. Both in controls and epileptic animals the MEMRI signal enhancement was more pronounced ipsilaterally than contralaterally.

Conclusions: Our data indicates that the MRI detectable transneuronal tracer, Mn^{2+}, was transported from the EC via the perforant pathway to the granule cells of dentate gyrus resulting in the labeling of mossy fibers. Consequently, we could non-invasively detect an increase in the extent of mossy fiber pathway in epileptic brain. Our data also provide the first evidence that target cells of the postrhinal cortex-thalamus pathway may undergo reorganization during epileptogenesis. (Supported by Academy of Finland, Sigrid Juselius Foundation.)

2.065

ANDROGENIC NEUROSTEROID 3α-ANDROSTANEDIOL INDUCES CROSS-TOLERANCE TO ANTICONVULSANT ACTIVITY OF BENZODIAZEPINES

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Rationale: Neurosteroids are endogenous modulators of neuronal excitability with important roles in epilepsy. 3α-Androstanediol (3α-Diol) is a neurosteroid synthesized from testosterone in the brain, but the clinical importance of this steroid remains unclear. Recently, 3α-Diol has been shown to be a powerful anticonvulsant in several animal seizure models. 3α-Diol has been proposed as an endogenous protective neurosteroid in the brain, and thus could play a role in gender specific forms of epilepsy. The purpose of this study was to determine whether tolerance occurs to the anticonvulsant activity of 3α-Diol in the pentylenetetrazol (PTZ) seizure test and whether there is cross-tolerance with the benzodiazepine diazepam.

Methods: In acute studies, 3α-Diol and diazepam were tested for protective activity against PTZ-induced seizures in a dose-dependent fashion in mice. The median effective dose (ED_{50}) was determined by log-probit analysis. In chronic studies, mice were treated with two daily injections of a 3 × ED_{50} dose of 3α-Diol (108 mg/kg, s.c.), diazepam (1.5 mg/kg, i.p.), or vehicle for 7 days. On the day after chronic treatment periods, the anticonvulsant potencies of 3α-Diol and diazepam were determined.

Results: 3α-Diol had an ED_{50} of 36–44 mg/kg against seizures induced by GABA receptor antagonists PTZ, picrotoxin, and DMCM. However, it was inactive against seizures induced by glutamate receptor agonists, kainic acid, NMDA, and 4-aminopyridine. Consistent with allosteric modulation, acute treatment of mice with 3α-Diol potentiated the anticonvulsant potency of diazepam. The protective potency of 3α-Diol after 7-day treatment with 3α-Diol was not significantly different from that in control mice. In contrast, in animals that were treated chronically with 3α-Diol for 7 days, there was significant reduction in the anticonvulsant potency of diazepam. Chronic treatment with diazepam was not associated with a reduction in the potency of 3α-Diol, but there was a reduction in the potency of diazepam.

Conclusions: These results suggest that tolerance does not develop to the anticonvulsant activity of 3α-Diol during chronic treatment. However, 3α-Diol induces cross-tolerance to diazepam. Thus, endogenous androgenic neurosteroids could partly contribute to development of benzodiazepine tolerance during long-term clinical use for their sedative, anticonvulsant, and tranquilizing actions. The lack of tolerance suggests that 3α-Diol may be an efficacious anticonvulsant over longer time periods than most drugs targeting the benzodiazepine binding site of the GABA-A receptor. (Supported by NC State University.)

2.066

REDUCED EXCITATORY DRIVE IN FAST SPIKING INTERNEURONS IN EXPERIMENTAL CORTICAL DYSPLASIA

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Rationale: Cortical dysplasia (CD) has a strong clinical association with epilepsy. We have studied an animal model of CD, in utero

irradiation in rats. Previous studies have shown that the frequency of spontaneous and miniature inhibitory postsynaptic currents in pyramidal neurons in dysplastic cortex is decreased compared with control cortex. A reduction in excitatory drive on interneurons could contribute to this impairment of inhibition. The purpose of the present study is to address this hypothesis by measuring spontaneous and miniature excitatory postsynaptic currents (EPSCs) in fast spiking (FS) interneurons in dysplastic and control neocortex.

Methods: Pregnant rats were exposed to 225 cGy of external γ-irradiation at E17. The offspring consistently demonstrated diffuse CD. Whole-cell recordings were performed in neocortical slices from irradiated and control rats at age 21–28 d. Interneurons were identified by their morphology and firing pattern to suprathreshold current pulses. Data was obtained from interneurons showing high frequency action potentials with no or little adaptation (i.e., FS interneurons). We compared the frequency and amplitude of sEPSCs and mEPSCs from irradiated and control animals. We also assessed short-term plasticity (STP) of stimulus-evoked EPSCs using a 5-pulse stimulation protocol (20 Hz).

Results: The frequency of sEPSCs and mEPSCs was decreased in FS internurons in CD. The amplitude and kinetics were not different. On average, the frequency of sEPSCs was 0.9 ± 0.2 Hz in CD ($n = 16$) and 4.8 ± 0.7 Hz in control tissue ($n = 11$; $p < 0.01$). sEPSC amplitude was 13.3 ± 0.9 pA in CD and 13.6 ± 1.1 pA in control tissue ($p > 0.05$). The frequency of mEPSCs was 0.2 ± 0.1 Hz in CD ($n = 8$) and 0.7 ± 0.2 Hz in control tissue ($n = 5$; $p < 0.01$). STP showed depression in every interneuron in control, but a mixture of depression and facilitation among cells in CD. On average, the ratio of the second response to the first was 73 ± 8.6 percent in control tissue ($n = 7$), but 107 ± 11.6 percent in CD ($n = 8$; $p < 0.05$).

Conclusions: Our results show that the excitatory driving force, namely sEPSCs and mEPSCs, in FS interneurons in CD is largely attenuated. The absence of change in the amplitude and kinetics of sESPCs and mEPSCs implies a presynaptic locus. Reduced short-term depression of evoked EPSCs in CD interneuron indicates that a decrease in release probability of the presynaptic terminal could contribute to this reduced excitatory drive. Reduced numbers of excitatory contacts are another possible mechanism. This study further documents impairments in the inhibitory component of the neocortical circuitry in radiation-induced CD. [Supported by a grant from NINDS (2R01NS35651) to S.N.R.]

2.067

SURGICAL IMPLANTATION AND CHRONIC STIMULATION OF THE VAGUS NERVE (VNS) WITH EEG RECORDINGS IN THE RAT

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Rationale: Vagus nerve stimulation (VNS) has been previously shown to be effective for seizure control in some animal models of seizures and in patients with epilepsy. A standardized method for the implantation and the stimulation of the vagus nerve in the rat has not been previously described. Suboptimal seizure control in rats has been attributed to implantation problems. VNS is a highly researched field as a treatment modality for epilepsy and depression. We describe a surgical method of successful VNS implantation and stimulation of the left vagus nerve with EEG recordings.

Methods: Eleven adult male Sprague Dawley rats weighing 250–400 g were used according to a protocol approved by the CCF ARC. Under i.p. ketamine anesthesia (0.1 ml/100g), a spiral electrode lead (Cyberonics, Inc., TX, USA) was coiled around the left vagus nerve after isolation from the carotid artery. The 2 spiral contacts measured 5 mm in length and 1.5 mm in diameter, while the entire lead measured 11.5 mm. The 2 spiral electrodes were in a tandem orientation (5 mm apart). Using microsurgical tools, the spiral electrodes were carefully wrapped around the left vagus nerve, and a small piece of muscle tissue was sutured around both contacts. The lead was then run subcutaneously to the base of the skull and through an incision in the scalp. The incision in the left side of the neck was sutured. The rats were then placed on a stereotactic frame. For EEG recordings, 5 screw electrodes were implanted in bi-frontal and bi-parietal areas and 2 additional twisted electrodes were implanted in the left and right hippocampal formations. All of the 7 electrodes and the 2 VNS leads were connected to a socket cemented to the skull. EEG recordings were performed using the Vangard digital EEG system. The VNS leads were connected to a NCP model 101 stimulator (Cyberonics, Inc., TX, USA) which was placed over a Cyberonics programming wand. The programming wand was connected to a computer and the stimulations were controlled by Model 250 NCP Programming Software Release.

Results: Among the 11 rats that underwent the surgical VNS implantation, only one of them died 5 days after the surgery and prior to any stimulation. The other surgeries were successful, with 8 rats surviving for at least 2 months after surgery. During this period, there was no weight loss and no infection in any of the implanted rats. Left vagus nerve stimulation (on 30 sec, off 5 mn, 0.5 mA, PW 0.25 msec, F 50 hz) for periods of 2 hours each was done with concomitant EEG recording with no stimulus artifact recorded on the EEG.

Conclusions: These results show that the implantation of left vagus nerve stimulator in conjunction with epidural and intrahippocampal electrodes is safe in the rat. Vagus nerve stimulation using the currently used human paradigms is also safe. This method could be used for the testing of acute and chronic effects of VNS in various rat models of epilepsy and seizures. (Supported by a grant from Cyberonics.)

2.068

IDENTIFICATION OF QUANTITATIVE TRAIT LOCI FOR SUSCEPTIBILITY TO KAINIC ACID–INDUCED CELL DEATH IN INBRED STRAINS OF MICE

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Rationale: Inheritance patterns between mouse strains suggest that a robust genetic influence determines individual susceptibility to kainic acid-induced hippocampal cell death. FVB/N and C57BL/6 mice exhibit differential susceptibility to kainate-induced cell death, with FVB/N being sensitive and C57BL/6 mice relatively resistant. In previous studies, phenotypic assessment of cell death in (F1 X FVB/N)N2 backcross progeny suggested that differences in apparent cell death are conferred by a single gene locus (Schauwecker, 2003b). To define the genetic contributions affecting individual differences in kainate-induced cell death susceptibility, a genome-wide scan was performed on N2 backcross populations to map quantitative trait loci for kaiante-induced cell death susceptibility.

Methods: An N2 backcross was constructed using the C57BL/6 and FVB/N strains as progenitors. Mice were injected with kainate and observed for 3–4 hours for the onset and extent of seizures. To determine whether seizure severity correlates with excitotoxic neuronal loss, morphological analysis was performed. Seven days following administration of kainate, a total of 331 N2 offspring were perfused and assessed for susceptibility to kainate-induced cell death. Following the phenotypic testing, quantitative trait linkage analysis was performed using information derived from a genome scan of 87 polymorphic microsatellite markers spanning the whole genome, Chromosome Y excepted. Linkage between kainate-induced cell death susceptibility and marker loci was analyzed by the computer program MapManager QTX.

Results: Statistical mapping yielded significant evidence (LOD scores$>$2.3) for quantitative trait loci (QTLs) on Chromosomes 4, 15, and 18, which together explain roughly 25% of the phenotypic variance in this model. We detected the locus of greatest effect on distal Chromosome 18 (LOD = 4.9). We subsequently controlled for two markers that flank the Chr 18 locus and used composite interval mapping to search for other loci that may have additive effects. No additional QTLs were mapped in models that fix the identified QTL. In order to show conclusively that cell death susceptibility can simply be predicted by the genotype across one of our critical intervals when it is inherited, we constructed a congenic strain by moving the Chr 18 C57BL/6 region into the FVB/N strain. Damage was significantly reduced in the congenic strain that contained the C57BL/6 resistant region in a FVB/N strain.

Conclusions: This study provides evidence for the genetic control of seizure-induced cell death susceptibility in mice and identifies individual susceptibility loci. These QTLs may ultimately lead to the identification of genes influencing individual differences in kainate-induced cell death threshold in mice and aid in the discovery of novel neuroprotective agents. (Supported by NIH grant NS38696 to P.E.S.)

2.069

THE SEIZURE SUSCEPTIBILITY OF mGluR8 RECEPTOR KNOCKOUT MICE IN ELECTRICAL KINDLING AND CHEMICALLY INDUCED SEIZURE MODELS

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Rationale: Metabotropic glutamate mGluR8 receptors are located on the terminals of the lateral perforant path in the dentate gyrus. Stimulation of mGluR8 receptors is known to decrease the release of glutamate. The lateral perforant path - hippocampal pathway is part of the limbic seizure circuitry, and presynaptic mGluR8 receptors might be involved in dampening or terminating seizure propagation through this pathway by decreasing the release of glutamate onto neurons in the dentate gyrus. The purpose of the present studies was therefore to compare the seizure susceptibility of mGluR8 (−/−; KO) and wild type mGluR8 (+/+; WT) mice. We compared the differences between KO and WT mice in the amygdala-kindling model, as well as thresholds in electrically and chemically induced acute seizure models. In addition, we determined the anticonvulsant effects of carbamazepine and levetiracetam in kindled mice.

Methods: A bipolar electrode was stereotaxically implanted into the right amygdala of CD-1 WT and KO mice. Mice were given 15 daily stimulations (500 mA, 60 Hz, 1 sec). Behavioral seizure scores (Racine scale) and EEG after-discharge (AD) durations were recorded throughout. Post-kindling seizure thresholds and AD durations were also determined. After thresholds stabilized, the anticonvulsant effects of carbamazepine (30 mg/kg, IP) and levetiracetam (50 mg/kg, IP) were determined. Median convulsant currents (CC50s) were determined for producing electrically-induced clonic and tonic seizures (60 Hz, 0.2 sec) as well as limbic seizures (6 Hz, 3 sec). In chemically induced seizure models, kainate (20 mg/kg, IP) or pilocarpine (100 mg/kg, IP) were injected every 20 minutes until the first limbic seizure. The number of doses and minutes to onset of limbic seizures were recorded.

Results: During kindling development, KO mice had higher seizure scores but comparable AD durations compared to WT mice. Post-kindling, seizure thresholds were significantly lower in KO mice. Carbamazepine and levetiracetam increased the seizure thresholds both KO and WT. Electrical seizure thresholds did not significantly differ between KO and WT. In addition, the threshold doses of kainate and pilocarpine required to produce limbic seizures did not differ between KO and WT mice.

Conclusions: mGluR8 KO mice kindled more rapidly in the amygdala kindling model. However, seizure thresholds for electrically-induced clonic, tonic and limbic seizures as well as for kainate- and pilocarpine-induced seizures did not differ between KO and WT mice. The present results suggest that mGluR8 receptors may be involved in dampening kindling-induced sensitization of the lateral perforant path – hippocampal pathway, and as such might be a functional part of the dentate gate. (Supported by Eli Lilly and Company.)

2.070

ONTOGENY OF TEMPORAL LOBE EPILEPSY IN AMYGDALA-KINDLED CATS: AN UPDATE

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Rationale: To update previous work on age-related differences in spontaneous epilepsy after amygdala kindling in cats.

Methods: Amygdala kindled seizure development and the post-kindling course is described in 58 cats (29 males and 29 females), including 40 preadolescents between 2.5 and 6.5 months of age and 18 adults ≥1year of age at the beginning of kindling

Results: The results confirm and extend previous findings, as follows: 1) Young animals are far more likely than adults to exhibit spontaneous epilepsy, indexed by seizures that occur ≥1 h after stimulus-evoked seizures; 2) The youngest animals (≤5.0 months, n = 30) exhibit accelerated kindling rates (fewest elicited afterdischarges or ADs to the first generalized tonic-clonic convulsion or GTC) and rapid post-kindling onset of multifocal spontaneous epilepsy with a catastrophic clinical course. The profile includes a variety of EEG and/or clinical seizure manifestations and a progressive increase in the number and density of convulsive seizure clusters. Behavioral sequelae accompany seizure clusters and range from sensory or motor deficits (visual agnosia, sensory hypersensitivity, atonic episodes, restricted mobility) to social isolation and placidity. Developmental deterioration with spontaneous epilepsy need not be gender-related, rarely involves anatomical localization of kindling site and is substantially enhanced by recurrent or recent evoked seizures early in the post-kindling course. The post-kindling progression can be stopped or minimized by suspension of evoked seizure trials and/or by management of frequent spontaneous convulsions (>1 per h) with nembutal.

Conclusions: The findings suggested different factors in the onset vs. maintenance of spontaneous epilepsy at different ages and a favorable prognosis for the young following early detection and intervention. (Supported by Department of Veterans Affairs.)

2.071

NEUROPEPTIDE Y SUPPRESSES ABSENCE SEIZURES IN A GENETIC RAT MODEL OF GENERALIZED EPILEPSY

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Rationale: Evidence from genetic and pharmacological studies in rodents, and some data in humans, support an anti-seizure action of neuropeptide Y (NPY) in focal, acquired epilepsy. However, the effects of NPY on the seizures in generalized genetic epilepsy remains unexplored. We investigated the effect of exogenously administered NPY on seizures were in a model of genetic generalised epilepsy, Genetic Absence Epilepsy Rats of Strasbourg (GAERS).

Methods: Adult male GAERS were implanted with extradural electrodes and an intracerebroventricular (icv) cannula. After an initial dose-effect experiment (n = 3), saline, 6 and 12 nmol NPY were administered in a random order (n = 6). The effect of NPY on seizure activity was quantitated by a 90-minute EEG post-injection recording. The endogeneous regional brain content of NPY was compared between GAERS (n = 8) and non-epileptic control (NEC) rats (n = 8) using radioimmunoassay on tissue microdissected from the parietal cortex, thalamic ventrobasal complex and reticular thalamic nucleus.

Results: The icv injection studies demonstrated a rapid onset and sustained seizure suppression following NPY treatment compared to vehicle, with both 6 and 12 nmol NPY having a decreased median percentage time in seizure (4.7% and 5.3% vs. 12.4%, $p = 0.028$ and 0.043) and number of seizures per minute (0.5 and 0.3 vs. 1.1, $p = 0.028$ and 0.043), and 6 nmol NPY having a decreased average seizure length (6.1 vs. 7.5 sec, $p = 0.046$). There was no significant difference between the degree of seizure suppression between 6 and 12 nmol of NPY (all $p > 0.05$). Tissue NPY content did not differ between GAERS and NEC rats for any region examined.

Conclusions: These data study demonstrate that exogenous administration of NPY suppresses of absence seizures in the GAERS. This suggests that NPY modulates pathological oscillatory thalamocortical activity and may represent a new therapeutic approach for the treatment of generalized epilepsies. The lack of difference in the tissue content of NPY in thalamocortical brain regions between GAERS and NEC rats indicates that alterations in NPY expression is unlikely to be a major contributor to the GAERS phenotype. (Supported by The Royal Melbourne Hospital Neuroscience Foundation.)

2.072

INTERICTAL AGGRESSIVE BEHAVIOR IN EPILEPTIC RATS

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Rationale: In spite of anecdotal reports describing an association between chronic epilepsy and interictal aggressiveness (Geschwind, 1983), and of surveys suggesting that such an association is common in temporal lobe epilepsy (Bear and Fedio personality inventory), this concept has not been generally accepted by epileptologists. In the course of studies of the long-term consequences of untreated limbic status epilepticus (SE) in juvenile rats, we noticed that experimental animals, unlike littermate controls, could not be housed together because of severe fighting. We now report a study of interictal aggression in those rats.

Methods: Long-term behavioral consequences of lithium/pilocarpine SE were studied 3 months after SE had been induced in male Wistar rat pups at age 28 days. Chronic spontaneous seizures developed in 90% of animals. We tested rats for territorial aggression under the resident-intruder paradigm: an "intruder" rat is introduced into the cage of a "resident" rat for 15 min session. Each experimental animal was exposed to three different controls and three different experimentals as resident, and to three separate animals of each group. We measured the average number of episodes of dominant mount (ventral/dorsal contact and immobilization of opponent), pinning (ventral/ventral contact and immobilization of opponent), and agonistic behavior: attacks (lunging onto opponent), boxing (upright stance, facing opponent, pushing opponent with forepaws) and biting (direct dental contact of one rat with another).

Results: The experimentals, when observed together, showed less dominant behavior (0.8 ± 0.4 vs. 6.3 ± 2.8 mounts), more agonistic behavior (8.5 ± 3.3 vs. 0.5 ± 0.2 boxing episodes) than controls together. The experimentals exposed to controls, expressed more dominant behavior both as a residents and as intruders (14 ± 4.1 vs. 2.1 ± 1.7, 16.7 ± 3.0 vs. 2.3 ± 1.2 mounts, respectively), and showed more frequent agonistic behavior: boxing (4.7 ± 1.9 vs. 0.6 ± 0.2, 5.5 ± 1.2 vs. 0.7 ± 0.3, respectively) and biting (7.3 ± 3.1 vs. 0 or 5.8 ± 3.0 vs. 0) than controls. The experimental rats showed more dominant behavior toward controls than toward other experimentals, in mounts (15.5 ± 3.1 vs. 0.6 ± 0.4), attacks (5.4 ± 2.0 vs. 1.6 ± 0.5) and bites (6.5 ± 3.5 vs. 0). Controls that faced experimentals, expressed less dominant behavior (2.2 ± 1.5 vs. 6.3 ± 2.0 mounts) and showed tendency toward increased agonistic behavior (2.0 ± 0.3 vs. 0 attacks) compared to facing other controls.

Conclusions: The untreated lithium/pilocarpine SE induced a large increase in aggressive behavior, which involved all aspects of aggression in the intruder paradigm, when tested 3 months after SE. The experimentals were dominant toward the controls, as residents or as intruders, and showed episodes of biting and boxing rarely displayed by controls. They also displayed increased aggressiveness compared to controls when tested against each other. (Supported by VHA Research Service and by grant RO1 NS 13515 from NINDS.)

2.073
SEIZURE-INDUCED CHANGES IN ZEBRAFISH BEHAVIOR, NEURAL ACTIVITY, AND GENE EXPRESSION

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Rationale: Zebrafish represent an important model organism in genetics and neurodevelopment. Despite burgeoning interest, very little effort has been directed toward using zebrafish to study neurological disorders. Although seizures induced in rodents provided insights into epileptogenesis, many questions remain unanswered. To address this issue, we propose to establish a simple vertebrate model of induced seizures. Here, we hypothesize that zebrafish larvae which are small and can be produced in large numbers, can exhibit complex seizure activity. To highlight the usefulness of such a model we describe behavioral, electrophysiological and molecular changes that occur in zebrafish exposed to a common convulsant agent.

Methods: Experiments were performed on zebrafish (*Danio rerio*) larvae of the TL strain. To induce seizures, zebrafish larvae at 7 day post-fertilization (d.p.f.) were exposed to pentylenetetrazole (PTZ). For behavioral studies, zebrafish were monitored using locomotion tracking software (EthoVision 3.0). For electrophysiology studies, zebrafish were immobilized in agar. A field electrode containing 2 mM NaCl was placed in the tectum or forebrain. Electrical activity was monitored using a patch-clamp amplifier in current-clamp mode. For molecular studies, c-fos mRNA levels were examined by RT-PCR and whole-mount in situ hybridization.

Results: PTZ elicited seizure-like behavior in all zebrafish tested ($n = 34$). At 15 mM PTZ, rapid clonus-like movements followed by loss of posture were consistently observed (10 min). Video tracking analysis of this behavior indicated an average distance traveled (in cm) of 19.0 ± 1.3 and a "movement" score (in%) of 1.71 ± 0.22. These scores were significantly greater ($p < 0.0001$, ANOVA) than those obtained at baseline (Ringer's solution): 6.7 ± 1.0 cm and 0.11 ± 0.05%, respectively. PTZ-induced electrographic seizure activity could be simultaneously recorded in forebrain and tectum. Activity consisted of ictal- and interictal-like components and was highly synchronized between the two brain regions. RT-PCR analysis of c-fos expression at various time-points following PTZ exposure indicated a clear increase in expression. Findings were confirmed using in situ hybridization which showed significant c-fos mRNA in forebrain, tectum and cerebellum.

Conclusions: Here we demonstrate that zebrafish represent a valuable model for studying mechanisms of seizure generation and propagation. Analysis of behavioral, electrophysiological and molecular changes that occur with exposure to a common convulsant agent is but one step in our efforts to use zebrafish in the field of epilepsy research. Future studies incorporating forward-genetic and chemical screening, as well as application of morpholino or transgenic technologies will, no doubt, lead to a better understanding of epilepsy. [Supported by EFA (Holden Targeted Investigation Program), NIH and Klingenstein Fund.]

2.074
FOCAL AMYGDALAR GLUTAMATERGIC AGONIST INFUSION LEADS TO RAPID DIFFUSE CEREBRAL ACTIVATION

Madhumita Banerjee, Jeeva Munasinghe, Daryl Despres, Mary Angstadt, Martin Lizak, Alfonso Silva, Michael Rogawski, Alan Koretsky, and William H. Theodore (NINDS, NIH, Bethesda, MD)

Rationale: Glutamatergic receptors may play a significant role in epileptogenesis in the amygdala. The role of GluR receptor subtypes has not been elucidated. Agents such as kainic acid (KA) activate multiple glutamatergic receptors. Preliminary studies with amygdalar infusion of the specific KAr GluR5 agonist ATPA ((RS-2-amino-3-(3-hydroxy-5-tert-butylisoxazole-4-yl)propanoic acid) led to prolonged limbic seizures (10 mins–4 hrs) monitored behaviorally (Racine stages 1–5) and by EEG, suggesting that the KAr GluR5 receptor subtype could mediate ictal activity. In order to evaluate the physiologic effects of specific GluR5 activation, we used KA, AMPA and ATPA, and functional MRI to map the cerebral blood flow (CBF) response to seizures induced by amygdalar injection in rats.

Methods: Rats were anesthetized with ketamine/xylazine and an MR-compatible cannula was placed stereotactically in basolateral amygdala. After several days rest, they were intubated under isoflurane anesthesia. Body core temperature was maintained at 37 degrees with a heated water pad. Lines were placed in femoral artery to monitor blood pressure, and femoral vein for drug and fluid administration. Blood gases were analyzed at frequent intervals. MRI was performed on a horizontal 7T Bruker Avance scanner using a 72 mm diameter transmit-receive coil. A 2 mm axial slice containing the cannula was scanned for 10 minutes before and for approximately two hours after 10 nanomoles (5 μL) infusion of each convulsant. Regional cerebral perfusion was measured using arterial spin labeling techniques. MRI parameters: matrix size : 64×64, TR : 2 s, TE: 6.5 ms, 2 ms labeling pulse with power of 81 mG/cm. Field of View = 3.2 cm, Time per scan : 4.5 min. T2 weighted and Diffusion weighted images (in read) were acquired for five 1mm slices centered around the cannula. Parameters: 128×128, TR = 3000 ms, TE = 10 (T2) and 20 ms, (DWI), $\Delta = 20$ ms, FOV = 3.2 cm.

Results: The perfusion images for each drug showed bilateral cortical and subcortical increases in CBF beginning approximately 10 minutes after infusion, peaking at approximately 60 minutes, and lasting up to 2 hours. There was no significant difference in the intensity of CBF activation among the three agents. The time course of activation was similar in widely separated brain regions. Normal saline had no effect.

Conclusions: Focal Amgydalar infusion of glutamatergic agonists leads to rapid widespread bilateral cerebral activation. Selective GluR5 activation is sufficient to produce this response. The spread of activation is unlikely to have been due to physical diffusion of the infused agent. (Supported by NINDS Division of Intramural Research.)

2.075
THERE IS A CORRELATION BETWEEN STATUS EPILEPTICUS AND BRAIN LESION SEVERITIES

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Rationale: Status epilepticus (SE) has been associated with brain damage and plasticity in acute and chronic phases of temporal lobe epilepsy in animal models. It has been shown that SE duration correlates with the severity of consequent tissue alterations. In this work, we intended to investigate if there is a correlation between behavior scores presented by animals during self-sustained SE (SSSE) and the number of brain injured areas found after 3 hours, 24 hours or 14 days.

Methods: Adult, male Wistar rats, 240–320 g, were anesthetized with xilazine (0.7 mg/kg) and ketamine (1 mg/kg) and implanted with stainless steel coated electrodes in left amygdala (AMY) and hippocampus (HIP). EEG data was acquired from both AMY and HIP. A stainless steel screw attached to frontal skull was used as reference electrode. In order to induce SE, we applied to AMY 30 min of electrical stimulation (biphasic square waves, 100 ms duration, 300 μA, 60 Hz, each half a second). We only included in this study animals that presented SSSE after stimulation ($n = 22$). Additional 11 animals were not stimulated (controls). All animals were rescued (diazepam, 5 mg/kg) after 2 hours of SE. Based on video-EEG files, we classified each 5 min of SE using a Seizure Severity Index (SSI) proposed by Pinel and Rovner (*Exp Neurol* 1978; 58(2):190–202). Animals were perfused under deep anesthesia (thionembutal, 60 mg/kg) 3 hours, 24 hours or 14 day after SE onset. Nissl-stained and Neu-N immunohistochemistry slices (40 μm) were used to confirm electrodes tips position and integrity of tissue.

Results: Different types of SSSE were observed in stimulated animals: (i) SE-I (50%), with facial automatisms, neck and forelimb myoclonus, rearing and falling and tonic-clonic generalized seizures and (ii) SE-II (50%), with facial automatisms, neck myoclonus and concomitant exploratory behavior. Statistical analysis showed that SE-I is more severe than SE-II, when compared by SSI ($p < 0.05$; ANOVA on Ranks, Tukey test), during the 1.5 hour of SSSE between the end of electrical stimulation and the rescue. Analysis of Nissl and Neu-N protein showed that there is a positive correlation between the type of SE and the quantity of injured areas both 24 hours ($R = 0.873$) and 14 days ($R = 0.798$) after SSSE (Pearson correlation, $p < 0.01$). Qualitatively, there is evident neuronal loss in piriform cortex and HIP. Control animals did not present seizure behaviors or evident neuronal loss.

Conclusions: Those results indicate that, in addition to the duration of SE, severity of seizure during SE influences the subjacent brain alterations consequent to it. Based on our data, we suggest that further analysis of brain alterations subjacent to SE should be observed considering the type of SE presented by the animals. (Supported by FAPESP, PRONEX, PROAP-Capes, CNPq, and FAEPA.)

2.076

ANTICONVULSANT EFFICACY AND SAFETY PROFILE OF NUTMEG OIL OF *MYRISTICA FRAGRANS*

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Rationale: Currently available antiepileptic drugs (AEDs) are synthetic molecules with certain negative properties, which limit their utility and complicate patient management. It is generally estimated that up to 30% of patients diagnosed with epilepsy are refractory to available AED treatment. In this instance, the plant kingdom is undoubtedly a valuable source for the development of better and safer drugs for the treatment of epilepsy.

Nutmeg, the dried kernel of *Myristica fragrans* Houtt (Myristicaceae), has been used for the treatment of epilepsy in traditional medicine. Previous reports have indicted that the pharmacological activity of nutmeg mainly exists in its volatile oil fraction.

Methods: Volatile oil of nutmeg (nutmeg oil) was tested for its effects in maximal electroshock (MES), subcutaneous pentylenetetrazole (PTZ), strychnine (STN), bicuculline (BIC) and picrotoxin (PIC) seizure tests. At least three doses of nutmeg oil (50–300 μl/kg) were tested against each seizure tests. Safety profile of nutmeg oil was established by determining its acute toxicity and acute neurotoxicity.

Results: Nutmeg oil was found to possess significant anticonvulsant activity against hind limb tonic extension in MES test. It also showed dose dependent anticonvulsant activity against different patterns of PTZ-induced seizures. It delayed the onset of hind limb tonic extensor jerks induced by STN. It showed both pro- and anticonvulsant effects against PTZ, BIC and PIC induced clonic seizures. Nutmeg oil didn't induce motor impairment when tested up to 600 μl/kg in inverted screen acute neurotoxicity test. Furthermore, its HD_{50} (1265 μl/kg) i.e. dose at which 50% of the animals lose their righting reflex and LD_{50} (2150 μl/kg) values are much higher than its anticonvulsant doses (50–300 μl/kg).

Conclusions: Our results indicate nutmeg oil possesses anticonvulsant effect against generalized tonic clonic seizures. Moreover, potentiation and inhibition of clonic seizure activity can be due to the presence of both pro- and anticonvulsant compounds as well as dual activity. We conclude that nutmeg oil has higher margin of safety when tested in animal models of epilepsy and contains compounds that can be promising candidates of anticonvulsant drug development. (Supported by an Institutional grant from H.E.J. Research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Karachi 75270, Pakistan.)

2.077

NEURONAL ACTIVATION IN THE THALAMIC RETICULAR NUCLEUS CORRELATES WITH SEIZURE BURDEN BUT NOT CARBAMAZEPINE TREATMENT IN A RAT MODEL OF ABSENCE EPILEPSY

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Rationale: The mechanisms underlying carbamazepine (CBZ) aggravation of absence seizures are uncertain, but are thought to involve enhancement of neuronal activity within the thalamocortical circuitry. We utilised c-Fos immunohistochemistry (cFos-ir) to examine patterns of neuronal activation and the relationship to seizure burden following administration of CBZ to female Generalised Epilepsy Rats of Strasbourg (GAERS).

Methods: Female ovarectomised GAERS rats implanted with extradural EEG electrodes received, after one week, either 15 mg/kg of CBZ or vehicle i.p. The seizure burden post injection was quantitated by measuring the total duration of spike-wave discharges (SWD), the number and the individual burst length of the discharges over a 90 min EEG recording. Results of the EEG analysis were correlated with cFos-ir in thalamocortical slices.

Results: CBZ treated rats ($n = 5$) had significantly greater total duration of SWD vs. vehicle treated rats ($n = 5$) (17.9 vs. 8.8%, $p = 0.04$). The level of cFos staining did not differ between the treatment groups, however there was a positive correlation between staining intensity in the reticularis thalami (Rt) and both the total seizure duration ($r = 0.66$, $p = 0.04$) and mean burst length ($r = 0.68$, $p = 0.03$), but not with the number of bursts per minute ($r = 0.13$, $p = 0.71$). No significant correlation was found between seizure expression and cFos-ir for any other region examined.

Conclusions: The association between increased neuronal activation in the Rt and seizure burden in GAERS provides further support for the critical role of this structure in the generation and maintenance of absence seizures. The lack of difference in cFos activation patterns between CBZ and vehicle treated animals suggests that the mechanism for CBZ aggravation of absence seizures may not involve neuronal activation, but rather enhanced neuronal synchronisation. (Supported by EEG machine provided courtesy of Compumedics, Australia.)

2.078

SHORT- AND LONG-TERM ALTERATIONS OF GLYCOGEN METABOLISM IN THE RAT ENTORHINAL CORTEX AFTER STATUS EPILEPTICUS

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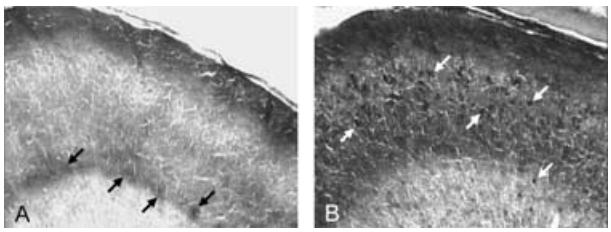
Rationale: The conversion of glycogen to glucose in astrocytes is thought to supply essential metabolic substrates to neurons during periods of heightened activity or stress. The breakdown of glycogen is catalyzed by glycogen phosphorylase (GP), which is found in 2 forms: active, phosphorylated (GP*a*) and inactive, dephosphorylated (GP*b*). We asked if status epilepticus, which involves extreme periods of neuronal activation, followed by gliosis in several brain areas, would produce alterations in glial metabolism that would be reflected by changes in GP. We focused on the entorhinal cortex (EC) because GP has striking pattern of expression, and our method to induce status produces highly reliable degeneration and gliosis in this area.

Methods: Male Sprague-Dawley rats (30–34 days old) were injected with 380 mg/kg pilocarpine i.p. 30 min after 1 mg/kg atropine methylbromide s.c. Controls received the same treatment but saline instead of pilocarpine. Status epilepticus was truncated by 5 mg/kg i.p. diazepam after 1 hr. Either 1 hr, 1 wk or 1 month after status, brains were flash frozen (−50 °C). Horizontal sections (35 μm) cut on a cryostat were processed concurrently for GPa and total GP (*t*GP; GP*a*+*GPb*) or were double-labeled immunocytochemically for neurons (NeuN) and astrocytes (GFAP). All procedures were performed on frozen, non-fixed tissue because perfusion fixation denatures GP protein.

Results: A clear pattern of reactivity was revealed by GP*a* and *t*GP in control rats that was highest in the superficial layers (see Fig. 1A for example of control condition; n = 17/17). GP*a* and *t*GP reactivity was reduced in a layer-specific pattern when examined 1 hr after status (n = 6/6) and irregular patches of apparent GP depletion occurred at 1 hr throughout the EC (n = 5/6). At later times GP reactivity was enhanced (1 wk, n = 5/5; 1 month, n = 4/6) and localized hot spots punctuated superficial layers, parasubiculum and to a lesser extent, deep layers (1 wk, n = 5/5, see arrows in Fig. 1B; 1 month, n = 6/6).



Typical GP*a* reactivity profile for control (A) and pilocarpine (B) rat 1 wk after status epilepticus. *Black arrows* (A) illustrate normal patches of heightened reactivity. *White arrows* (B) illustrate concentrated GP reactivity after status epilepticus and an overall increase in GP staining in EC.

FIG. 1. GP*a* histochemistry 1 week after status epilepticus.

Conclusions: GP histochemistry delineates the superficial layers of the EC in normal rats, and status epilepticus produces immediate (reduction) and long-term (enhancement)alterations in the pattern of reactivity. These data highlight the potential importance of GP to normal EC function, and its response to severe seizures. (Supported by an AES-Milken award to S.G.W. and NS 16102.)

2.079

VIRAL VECTOR DELIVERY OF THE Kv1.1 GENE TO HIPPOCAMPUS OF Kv1.1 KNOCKOUT MICE

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Rationale: Epilepsies due to a single gene mutation could provide a useful experimental condition in which to study the therapeutic efficacy of replacing a lost and/or non-functional gene. Mice lacking the Kv1.1α subunit (delayed rectifier potassium channel) develop recurrent behavioral seizures early in life associated with pathologies similar to temporal lobe epilepsy in humans. We examined the effects of injecting a viral vector carrying the deleted Kv1.1 gene into hippocampal neurons of Kv1.1 knockout (−/−) mice. We hypothesized that Kv1.1 channel protein would be expressed in transfected hippocampal neurons, and that spontaneous seizures (thresholds and/or frequencies) would be appropriately "normalized."

Methods: Wild-type and Kv1.1 −/− mice were prepared for a long-term video/EEG recording using a video/EEG telemetry system (Data Sciences International and Stellate). Animals were monitored two days prior to vector injections and then for 4–6 days after injections. The HSV1 amplicon vector (provided by Dr. Robert Sapolsky, Stanford University) contained the rat Kv1.1 gene and the E.coli lacZ gene (to express a reporter molecule, beta-galactosidase (β-gal)). Control vectors contained only the β-gal gene. Mice were stereotaxically injected with the viral vectors into the hippocampus. Injections (two sites per hemisphere) were placed bilaterally within the CA3 region of the middle hippocampus; injection volume was 1.2 μl/site. At the predetermined survival time, brains were fixed (4% paraformaldehyde) and processed for histochemistry of β-galactosidase (x-gal staining).

Results: Initial results of long-term video/EEG monitoring failed to demonstrate changes in seizure frequency, type or severity following the Kv1.1 gene transfer. General histological findings of brains from the Kv1.1−/− mice were consistent with previous results (hippocampal neuronal cell loss, reactive gliosis and mossy fiber reorganization). Hippocampi of animals injected with β-gal and/or β-gal + Kv1.1 vectors showed vector-mediated transfection (based on x-gal staining) limited to a few hundred hippocampal neurons. Peak expression was observed (4 days post injection. The majority of x-gal stained cells were neuronal, primarily granule cells.

Conclusions: Viral vector-mediated gene transfection (β-gal and Kv1.1 genes) in the hippocampus of Kv1.1 −/− mice results in infection of a limited population of granule cells and CA3 pyramidal cells. Thus far, this level of transfection has not been found to affect the seizure pattern in Kv1.1 knockout mice. [Supported by a grant from Citizens United for Research in Epilepsy (CURE).]

2.080

BILATERAL TETRADOTOXIN INFUSION AFTER ACUTE PILOCARPINE INDUCED STATUS EPILEPTICUS IN RATS

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Rationale: Status epilepticus (SE) results in cell loss and abnormal neuronal circuits. Following SE there is evidence that on-going aberrant neuronal activity results in these pathological processes. We postulated that suppression of electrical activity following SE at the site of the epileptic focus will reduce seizure-induced damage. To achieve this goal tetradotoxin (TTX) was used to suppress electrical activity in the hippocampi bilaterally following SE.

Methods: Adult Sprague Dawley rats (300–350g) (n = 13) experienced lithium-pilocarpine induced SE for 2 hours. Starting 12–18 hours after the SE 7 rats received continuous TTX (1 microM) infusions through cannulas implanted in the bilateral hippocampi for 5 hours for 4 days. EEG activity monitored continuously through intracerebral electrodes demonstrated that EEG activity was suppressed (from 200–300 μV to 40–60 μV). Attempts to suppress EEG activity further resulted in a high mortality rate. Six rats received normal saline (NS) for the same duration of time and had no EEG changes. Despite TTX or NS rats showed behavior and electrographic seizures during the first day of infusion. Rats had a progressive declince in spikes and sharp waves in the EEG during the course of the infusions. However, even on the last day of of the infusion interictal epileptiform activity was present in both groups. Rats were sacrificed 2 weeks after SE and the brains evaluated with Timm and thionin staining. Semi-quantitative scales were used to measure mossy fiber sprouting (0–5, from no sprouting to marked sprouting) and neuronal cell loss (0–4, from no cell loss to total loss of cellular architecture) in the hippocampi.

Results: There were no significant differences between TTX-treated and NS-treated rats in histology scores. Mossy fiber sprouting mean score for CA3 was 2.00 for TTX and 1.65 for the NS group. In the supergranaular region the score was 3.00 for TTX and 2.50 for the NS group. CA1, CA3 and hilus cell loss scores were 2.05, 2.05, 1.90 in the TTX groups versus 1.55, 1.55, 1.30 in the NS groups. There was a strong correlation between sprouting and cell loss scores.

Conclusions: Despite suppression of EEG activity, there was no reduction of cell loss and mossy fiber sprouting in the TTX-treated animals.

These results suggest that suppression of electrical activity following SE provides little neuroprotection for animals. In addition, our findings indicate that the majority of damage associated with SE occurs during or immediately after the SE. [Supported by Citizens United for Research in Epilepsy (C.U.R.E.) and NIH (NINDS) (NS044296).]

Human Genetics

2.081

CLINICAL AND MOLECULAR GENETIC CHARACTERIZATION OF TWO FINNISH FAMILIES WITH BENIGN FAMILIAL INFANTILE SEIZURES AND PAROXYSMAL DYSKINESIA

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Rationale: Benign familial infantile seizures (BFIS) and paroxysmal dyskinesias (PD) are clinically and genetically heterogeneous, autosomal dominant disorders. In some families BFIS occurs together with PD. We have identified and clinically characterized two large Finnish families with BFIS and PD linked to chromosome 16p12.1–16p11.2. Here we have used linkage and candidate gene analysis with the aim of further narrowing the disease gene region and of identifying the underlying mutation(s).

Methods: Medical records of 18 consenting patients were examined. Microsatellite markers were tested to evaluate the disease gene locus on chromosome 16. Haplotypes spanning the candidate region were constructed and LOD scores were calculated with MLINK and GENEHUNTER 2.1 programs. The gene content of the region of interest was examined with the NCBI genome browser. The coding regions and exon-intron boundaries of three candidate genes were amplified from genomic DNA by PCR and sequenced in 2 patients and 1 control.

Results: The affected individuals had variable phenotypes including infantile convulsions with favorable outcome and paroxysmal dyskinesia with onset later in life. The infantile convulsions started at the age of 3 to 8 months and subsided later. The onset of PD was at the age of 5 to 17 years and the PD symptoms had features of both kinesigenic and non-kinesigenic dyskinesia. The psychomotor development of all patients was normal. Significant linkage was detected to markers on chromosome 16p12.1–16p11.2. A maximum two-point LOD score of 4.95 (at $\theta = 0.000$) and multipoint LOD score of 4.80 were obtained at marker D16S3022 using a penetrance of 80% and a phenocopy rate of 2%. Meiotic recombinations defined a candidate region of 4.76 cM, where patients in the two families shared a common haplotype suggesting a common ancestor. This 4.60 Mbp region contains 140 known or predicted genes in NCBI sequence map. Three genes were considered as potential candidates due to their position, known or predicted function, and expression in the central nervous system. The genes were sequenced exon by exon from PCR-amplified genomic DNA. No disease-associated mutations were identified in the coding or immediate flanking intronic regions. Some previously described exonic polymorphisms were found.

Conclusions: The candidate locus on chromosome 16 contains 140 already known or predicted genes. By sequence analysis we were not able to identify a disease-associated mutation in three positional and functional candidates making these genes unlikely to underlie the BFIS-PD phenotype in our families. (Supported by Finnish State Grant TYH3239, The Folkhalsan Research Foundation, University of Helsinki.)

2.082

FAMILIAL MESIAL AND LATERAL TEMPORAL LOBE EPILEPSIES: IS THERE A COMMON GENETIC LINK?

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Rationale: The purpose of our study was to determine if mutations in the Leucine Rich Glioma Inactivated 1 gene (LGI1) contribute to the development of both lateral(LTLE) and mesial temporal lobe epilepsy(MTLE). Our hypothesis was driven by the 1) occasional reports of auditory symptoms in familial MTLE patients and 2) the presence of mesial symptoms such as deja vu and epigastric aura in familial LTLE patients with mutations in the LGI1 gene.

Methods: Genomic DNA was extracted from 34 temporal lobe epilepsy (TLE) patients. A preliminary cohort of 21 patients (18 probands, 3 LTLE, 17 MTLE and 1 IGE) were screened for LGI1 mutations. Each of the 8 LGI1 exons and the surrounding splice sites were amplified by PCR and sequenced directly.

Results: Age at seizure onset ranged from 1 to 52 years (mean 16.5years). Febrile seizures were present in 4 MTLE patients. Simple partial seizures were present in 94.4% of all patients. Autonomic auras, especially epigastric sensation and fear, were the most prevalent auras in the MTLE patients. Auditory auras were present in all 3 LTLE patients and in 4 familial MTLE patients in association with additional mesial symptoms such as experiential phenomena. Complex partial seizures were present in 73.3% of MTLE patients and 66.7% of LTLE patients. 66.7% of both MTLE and LTLE patients had secondary generalized tonic clonic seizures. Refractory seizures were present in more than half of the MTLE patients and in the 2 patients with sporadic LTLE. Imaging detected abnormal mesial structures in 7 patients, with the majority displaying hippocampal atrophy with or without amygdala involvement. EEG demonstrated epileptiform temporal lobe discharges in 13 patients.

No mutations were detected in the coding regions of the LGI1 gene. We did however detect 2 intronic single nucleotide polymorphisms (SNPs) in 3 patients (2 MTLE and 1 LTLE). One is a novel G to C polymorphism 56 base pairs upstream of exon 2. The second is a C to T polymorphism 18 bases upstream of exon 7.

Conclusions: To date, we did not find any known or novel LGI1 gene mutations in our preliminary cohort of 21 TLE patients. However, the significance of the two intronic SNPs found in three of our patients requires further investigation. Since LGI1 gene has now been associated with a wider range of epilepsy phenotypes, including idiopathic generalized epilepsy (Ottman et al., 2004), it is possible that SNPs in the intronic regions of the LGI1 gene could be acting as modifying factors leading to phenotypic variability in TLE families. (Supported by E.A.: Canadian Institutes of Health Research Grant; E.K.: Preston Robb Fellowship; D.D.: Savoy Foundation Fellowship.)

2.083

GENETIC INFLUENCES ON THE PHENOTYPIC EXPRESSION OF SEIZURES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Rationale: Identifying genes that influence the development of seizures in complex genetic medical disorders may provide valuable insights into mechanisms of epileptogenesis. Neurological involvement is a major manifestation of systemic lupus erythematosus (SLE), an autoimmune disorder with multiple genetic and environmental determinants. The objective of this study was to identify genetic loci influencing the expression of seizures in the setting of SLE.

Methods: SLE families with two or more affected individuals were ascertained for linkage. Following informed consent data collection and genotyping was performed using standard research protocols. All individuals affected with SLE met American College of Rheumatology revised criteria for SLE. Non-parametric genome-wide linkage analysis was performed using 318 microsatellite markers. The linkage model allowed the inclusion of clinical covariates as a method of accounting for genetic locus heterogeneity. Two clinical covariates were analyzed, one representing a history of seizures in a SLE-affected individual, and the other representing the number of family members affected with seizures.

Results: A total of 117 African-American (AA) and 228 European-American (EA) affected-relative-pairs in 340 pedigrees were analyzed. The study sample consisted of 769 individuals affected with SLE, of which 106 had seizures, a rate of 14%. Using the seizure covariate we

found linkage to two chromosomal regions in the AA population, 16p13-p12 and 17q21, not detected using the baseline model without covariates (maximum multipoint lod scores of 2.54 and 2.1, respectively). Similarly in the EA population, use of the clinical seizure covariate produced linkage to two regions not detected with the baseline model, 3p25 and 14q13 (maximum multipoint lod scores of 2.28 and 2.53, respectively).

Conclusions: These results suggest important genetic effects related to the development of seizures in SLE. Identifying such genetic determinants may shed light on epileptogenic pathways, as well as provide useful indicators of seizure susceptibility in SLE patients. These results also demonstrate the power of the covariate method to detect linkage in the setting of locus heterogeneity in complex genetic disease. (Supported by NIH.)

2.084

UNVERRICHT-LUNDBORG DISEASE TYPE 2: HOMOZYGOSITY MAPPING TO CHROMOSOME 12

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Rationale: Progressive myoclonus epilepsy (PME) has a number of causes, of which Unverricht-Lundborg disease (ULD) is the most common. ULD is due to mutations in the cystatin B gene on chromosome 21. We identified an inbred Arab family with a clinical pattern compatible with ULD, but mutations in the cystatin B gene were absent. We sought to characterize the clinical and molecular features of the disorder.

Methods: The family was studied by multiple field trips to their town to clarify details of the complex consanguineous relationships and to personally examine the family. DNA was collected for subsequent molecular analyses from 21 individuals. A genome wide screen was performed using 811 micro-satellite markers. Homozygosity mapping was used to identify loci of interest.

Results: There were 8 affected individuals. Clinical onset was at 7.3 ± 1.5 yr with myoclonic or tonic-clonic seizures. All had myoclonus that progressed in severity over time and seven had tonic-clonic seizures. Ataxia, in addition to myoclonus, occurred in all. Detailed cognitive assessment was not possible, but there was no significant progressive dementia. There was intra-family variation in severity; three required wheelchairs in adult life, the others could walk unaided. MRI, muscle and skin biopsies on one individual were unremarkable. We mapped the family to a 15 megabase region at the peri-centromeric region of chromosome 12 with a maximum lod score of 6.32.

Conclusions: Clinically, the phenotype of individual subjects was typical of ULD, but the mean age of onset (7.3 yr versus 11 years for ULD) was younger. The locus on chromosome 12 does not contain genes for any other form of PME, nor does it have genes known to be related to cystatin B. This represents a new clinical and molecular form of PME that we have designated ULD type 2. (Supported by AES, NHMRC, Bionomics Ltd.)

2.085

FREQUENCY OF HLA CLASS 2 ALLELES IN RASMUSSEN ENCEPHALITIS

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Rationale: Rasmussen encephalitis is a rare disease. In the original description, Rasmussen and co-workers attributed the disease to a possible viral infection. Later, the disease was associated with the presence of circulating anti-bodies (anti-GluR3 and anti-Munc-18) or a cytotoxic T-cell reaction against neurons. Despite all efforts in trying to better define the pathophysiology of the disease, its etiology remains quite obscure.

HLA (human leukocyte antigen) system is the human version of the major histocompatibility complex (MHC). This system encompasses genes divided in two classes, class I and class II, and both are involved in immune response. The function of these classes of molecules is the presentation of short, pathogen-derived peptides to T-cells, a process that initiates the adaptative immune response. Class I genes are expressed by most somatic cells, while class II genes are expressed by some types of immune cells like B-cells, activated T-cells, macrophages, and dendritic cells. A large group of diseases involves genes in the HLA region that are linked or associated to specific class I and class II alleles or combinations of alleles. These associations help not only to better understand some diseases but also serve as markers for several diseases, thus improving diagnosis.

So far, we were not able to find in literature HLA studies in Rasmussen encephalitis, in spite of this obvious need. This fact is probably related to the rarity of the disease. In this study we address the frequency of HLA class II antigen in all our cases of pathological confirmed Rasmussen encephalitis.

Methods: After research ethical committee approval, DNA of 10 patients with pathological confirmed Rasmussen encephalitis was isolated from a blood sample and the HLA class II was typed using sequence-specific primers hybridized with DNA amplified by polymerase chain reaction (PCR), using commercially available kits.

Results: The frequency distribution of HLA class II alleles were: 1) HLA-DRB1*01: 5%, 2)HLA-DRB1*15: 15%, 3) HLA-DRB1*03: 5%, 4) HLA-DRB1*04: 10%, 5)HLA-DRB1*11: 10%, 6) HLA-DRB1*13: 25%, 7) HLA-DRB1*08: 10%, 8) HLA-DQB1*05: 20%, 9) HLA-DQB1*06: 25%, 10) HLA-DQB1*02: 10%, 11)HLA-DQB1*03: 25%, 12) HLA-DQB1*04: 10%. No allele was found to be significantly higher in patients with Rasmussen encephalitis when compared with ethnically matched controls.

Conclusions: We did not observe any association of specific HLA class II genes and Rasmussen encephalitis. In spite of lack of any correlation, larger samples of patients would be necessary for a definitive conclusion. Because of the rarity of the disease, multicentric studies may be necessary. (Supported by FAPES 02/03743–0.)

2.086

STURGE-WEBER SYNDROME WITH LATE-ONSET EPILEPSY IN A PEDIGREE WITH PORT WINE STAIN

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Rationale: The genetic basis, pathophysiology, and spectrum of Sturge-Weber Syndrome (SWS) remain unknown. Epilepsy in SWS presents by age 5 years in 95% of cases (range 0–23 years). The vast majority of cases are felt to be sporadic, without any affiliated family history. We present an individual affected with SWS with an atypically late onset of epilepsy. Furthermore, he is one member of a pedigree in which several relatives exhibit vascular (including port wine) cutaneous lesions.

Methods: Clinical evaluation of the proband was performed and detailed pedigree information was obtained during inpatient and outpatient contacts at our Comprehensive Epilepsy Program. Clinical investigations included EEG, MRI ± gadolinium, MRA and diffusion-weighted imaging (DWI).

Results: A 48-year-old male with a congenital facial port wine stain (left V1 distribution) presented with a generalized tonic-clonic seizure and treatment was begun. He re-presented weeks later with focal status epilepticus, complicated by an ipsilateral occipital ischemic stroke evident with DWI. Imaging revealed calcifications in his left hemisphere with gadolinium enhancement consistent with leptomeningeal

angiomatosis and he was diagnosed with SWS. He also reported a family history of vascular cutaneous lesions. These were present in his daughter (cervical region), mother (cervical region) and maternal grandmother (arm and breast). None of his family reported epilepsy or glaucoma. SWS has not yet been shown to obey familiar Mendelian genetics. Although one family with SWS in both a father and son has been reported (Adamczak, 1979), virtually all cases are sporadic. Somatic mosaicism has been proposed as one possible pathophysiologic mechanism in SWS (Happle, 1987). Studies on fibronectin expression in fibroblasts from SWS patients (port wine vs. normal skin) are consistent with a somatic mosaic mechanism. Chromosomal analyses of port wine vs. normal cells have found other markers of mosaicism. Familial Port Wine Stain without epilepsy has been described in one kindred with unclear inheritance pattern (Berg et al., 2000). Our proband met clinical criteria for the diagnosis of SWS. His positive family history of cutaneous vascular lesions with a possible autosomal dominant inheritance pattern and atypically late expression of epilepsy are distinctive features.

Conclusions: This unique kindred with members expressing cutaneous vascular lesions alone or SWS suggests that these conditions may share a common genetic mechanism. One may interpret this kindred as an instance of hereditary Port Wine Stain, (with one member additionally displaying features of SWS) or as a kindred with hereditary SWS with phenotypic heterogeneity. Somatic mosaicism may provide one possible explanation for the inconsistent expression of cerebral abnormalities in this kindred. Future collaborative studies using this kindred may provide insights into the molecular genetic basis of this uncommon cause of epilepsy.

2.087

A DEFECT IN NEURONAL MIGRATION RESULTS IN A DYSLEXIA-LIKE PHENOTYPE

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Rationale: Patients with malformations of cortical development, a common cause of epilepsy, offer opportunities to characterize the effect of developmental disruptions on human cortical anatomy and function. Periventricular nodular heterotopia (PNH) is a neuronal migration disorder associated with seizures and, in most cases, normal intelligence. We sought to define the cognitive phenotype of PNH and correlate our results with the anatomical and clinical features of the disorder.

Methods: Ten consecutive PNH subjects, all with epilepsy, were studied with structural neuroimaging and neuropsychological screening. T1-weighted, T2-weighted, and 3D-MPRAGE MR images were acquired on 1.5T and 3T scanners. Cognitive testing assessed general intellect, executive function, attention/working memory, learning/memory, written achievement, and reading/phonology.

Results: Eight subjects (80%) demonstrated prominent deficits in reading abilities despite the presence of normal intelligence, attention, and working memory (Fig. 1). Affected subjects showed variability in the number, size, and location of their heterotopias (Fig. 2). However, more marked reading difficulties were seen in those with widely distributed heterotopias. There was no correlation with epilepsy severity.

Conclusions: Our results suggest that a generalized disorder of neuronal migration can lead to a specific functional deficit while sparing most global cognitive abilities. There is accumulating evidence that dyslexia, or specific reading disability, is a developmental disorder associated with subtle variations in structural brain anatomy. We demonstrate that a striking alteration in brain architecture can result in a similar pattern of cognitive deficits. (Supported by the Clinical Investigator Training Program of BIDMC and Harvard-MIT in collaboration with Pfizer. C.A.W. is an Investigator of the Howard Hughes Medical Institute and was supported by NINDS and the March of Dimes.)

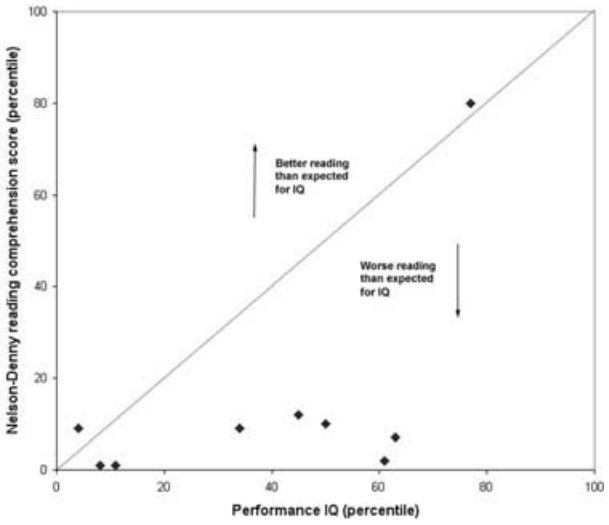

FIG. 1.

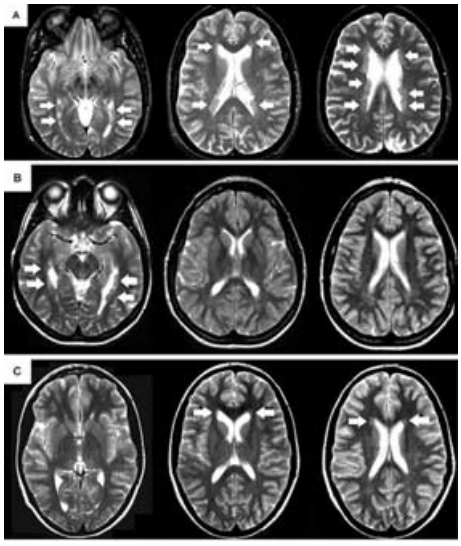

FIG. 2.

2.088

GENETIC FACTORS CONTRIBUTE TO RISK FOR FEBRILE STATUS EPILEPTICUS

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Rationale: Genetic factors have long been recognized as important determinants of risk for febrile seizures. Significant strides have been made towards an understanding of the factors that impact upon their risk of occurrence and the risk that a febrile seizure, if it does occur, will be greatly prolonged. However, the specific factors involved in determining risk for prolonged febrile seizures or febrile status epilepticus (FSE) remain to be identified. This study was undertaken to determine whether or not genetic factors contribute to risk for the occurrence of FSE.

Methods: The occurrence of FSE was determined in 13,506 unselected Virginia-born twin pairs who were ascertained from birth records and members of their families. Information on seizure history was obtained either by mailed questionnaire or telephone interview. History of FSE was validated using medical records, where available, and by

personal and/or parental interviews. Concordance-rate analyses were used to assess the contribution of genetic factors to FSE risk. The frequency of FSE among first degree relatives of FSE probands was also determined.

Results: Among 416 twins and 526 relatives with a verified history of seizures, febrile seizures (FS) were validated in 173 twins and 183 relatives. FSE was verified in 40 individuals included in 30 families. This included 22 twins in 21 [5 monozygotic (MZ) and 16 dizygotic (DZ)] twin pairs. The single FSE concordant pair was MZ. Probandwise concordance rates for FSE in this sample were 0.33 (95% CI: 0.43–0.777) for MZ and 0.00 for DZ twins. Analyses of the distribution of FSE, FS and epilepsy among the relatives of both twin and non-twin FSE probands included in this sample found FSE in 5% of siblings of FSE probands, 6% of probands' offspring, 6% of their mothers and none of their fathers. Neither FSE, FS or epilepsy were found to have occurred in any of the fathers of the probands included in the families identified.

Conclusions: The probandwise concordance rate estimate obtained for MZ twins is consistent with the existence of a contribution of genetic factors to risk for the occurrence of FSE. This, along with the increased frequency of FSE (5% or greater) observed among first degree relatives of FSE probands as compared to the 0.1%–0.25% frequency of FSE observed in the general population, suggests that genetic factors do contribute to FSE risk. [Supported by grants from the National Institutes of Health NINDS (NS25630 and NS31564).]

2.089

INFLUENCE OF GENETIC BACKGROUND ON SEIZURE OUTCOME AFTER TEMPORAL LOBECTOMY

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Rationale: Predictors of outcome after temporal lobectomy for mesial temporal lobe epilepsy (MTLE) remain controversial. In particular, family history (FH) of epilepsy as a prognostic factor has not been studied extensively. Our objective is to determine if FH predicts histopathological characteristics and outcome following temporal lobectomy.

Methods: Included were 186 consecutive patients who had resective epilepsy surgery for MTLE at a single tertiary center between 1990 and 2002. Retrospective review of medical records was performed for data on febrile seizure (FS), complex febrile seizure (cFS), major head trauma, and intracranial infection. Pedigree analysis was conducted by patient and family interview using a validated questionnaire for clinical seizure diagnosis. Outcome was determined by follow-up clinical interview using Engel's classification. Neuronal counts and immunohistochemistry were performed on the surgical tissue, and specimens were divided into the following subgroups: classical mesial temporal lobe epilepsy (MTLE), MTLE without evidence of dynorphin staining in the inner molecular layer (MTLE/DYN-), cell loss only in the CA1 region (CA1), mass lesions (MaTLE), or no visual evidence of sclerosis or immunohistochemical reorganization (paradoxical or PTLE).

Results: The 186 patients were 54% female and 22% had a history of simple FS, 20% of cFS, 10% of head trauma, and 14% of central nervous system infection. Positive FH was identified in 59 patients (32%), 16 with a first degree relative, 24 with a second degree relative and 19 with a third degree relative. Presence or absence of FH was not significantly related to surgical outcome ($p = 0.95$, OR = 1.02), nor was FH of a first degree relative with epilepsy ($p = 0.87$, OR = 0.91), or two or more relatives with epilepsy ($p = 0.42$, OR = 0.63). FH of FS was present in 14 patients (8%). Presence or absence of FH of FS was not significantly related to surgical outcome ($p = 0.77$, OR = 1.21). Pathology was available for 105 patients: 62 were MTLE, 9 were MTLE/DYN-, 9 were CA1, 7 were PTLE, and 16 were MaTLE. The Pearson Chi-Square test did not reveal a significant relationship of pathology with FH of epilepsy ($p = 0.75$) or FH of FS ($p = 0.21$).

Conclusions: FH of epilepsy or FS was not predictive of surgical outcome or pathology. Genetic influences on MTLE are heterogeneous and likely have a variable influence on these measures. Characterization of seizure type in relatives may be necessary. Further definition of the relationship between FH, pathology, and surgical outcome could provide a useful tool for counseling epilepsy surgical candidates. (Supported by The Epilepsy Foundation of America.)

2.090

MALIC ENZYME 2 (ME2) ON CHROMOSOME 18 IS LINKED AND STRONGLY ASSOCIATED WITH IDIOPATHIC GENERALIZED EPILEPSY

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Rationale: We previously reported strong evidence of linkage of IGE to chromosome 18 (lod = 5.2) (Durner et al., 2001). Our goal here is identifying the IGE-related locus indicated by the linkage result.

Methods: We typed 35 SNPs on chr.18 near D18S474 in 147 IGE patients + 126 controls. 96 families were used in family-based association tests (TDT).

Results: SNPs centromeric to D18S474 showed highly significant association with case control (Fig. 1) and TDT (Fig. 2) analyses ($p < .0001$). The strongest association was in the region of Malic Enzyme (ME2). The original linkage analysis supported recessive inheritance, so we tested IGE association with homozygotes vs. heterozygotes to test the mode of inheritance. SNP homozygotes were associated with the disease compared to heterozygotes. These association and linkage findings are in accord with the observation that enzyme-related diseases tend to show recessive inheritance. Also, at the 5′ end of ME2, there is a block (100–200 kb) of strong marker-marker disequilibrium.

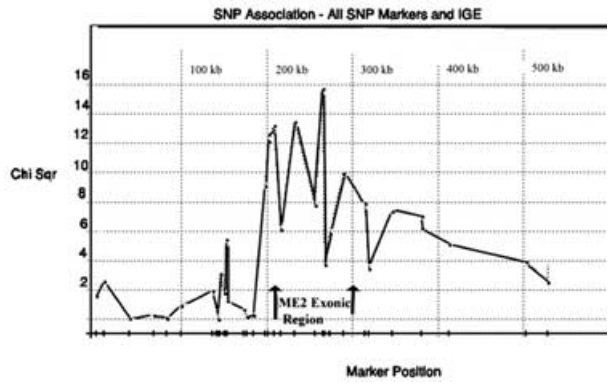

FIG. 1.

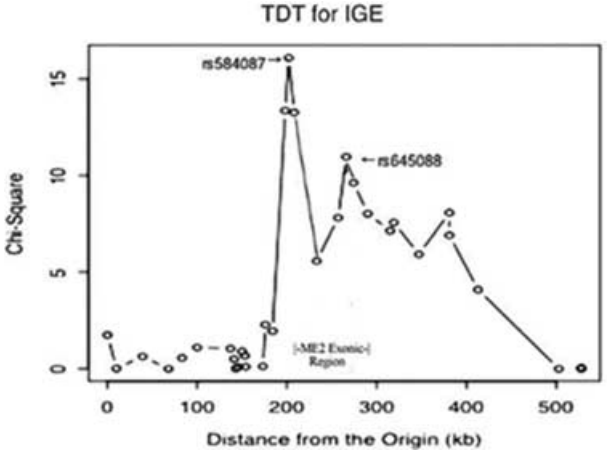

FIG. 2.

Conclusions: This report represents the second suggested IGE locus based on analysis of families collected specifically for common forms of IGE, and in a genomic region previously identified through linkage analysis. The association evidence suggests that ME2, or a close neighbor, is a major susceptibility locus for IGE and especially JME. There are no known channel genes in this region. ME2 is a genome-coded enzyme which localizes in the mitochondria. Thus, if ME2 is the susceptibility locus, then one might infer that variations in energy metabolism of the cell or pathways of apoptosis during brain development may be critical in susceptibility to common IGE. This notion supports etiologic mechanisms related to development previously suggested by the finding that BRD2, a nuclear transcription factor, is involved in the expression of forms of JME. (Supported by NS27941, DK31775, MH48858, and NS37466 from NIH.)

2.091

FAMILIAL PRIMARY HYPOMAGNESEMIA AND TEMPORAL LOBE EPILEPSY

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Rationale: Monogenic forms of epilepsy are rare but are increasingly recognized. Several forms of familial temporal lobe epilepsy have been described; however, a gene has been identified only in Autosomal Dominant Partial Epilepsy with Auditory Features. Hypomagnesemia is known to precipitate seizures and can occur on a hereditary (primary) basis from intestinal or renal wasting. The association between primary forms of hypomagnesemia and epilepsy has not been well-characterized. We describe the clinical and genetic characteristics of a family with primary hypomagnesemia and temporal lobe epilepsy.

Methods: Four members of the family had serum electrolyte and genetic studies performed. The proband and her sister underwent MRI and EEG studies.

Results: This non-consanguineous family has three affected members with primary hypomagnesemia: the proband, a 14 year old girl who presented in convulsive status epilepticus at age 12 years, now has medically-recalcitrant temporal lobe epilepsy; her sister, a 19 year old girl with temporal lobe epilepsy in remission; and her mother, who does not have epilepsy. The proband has frequent complex partial seizures characterized by an aura of diffuse paresthesias progressing to impaired awareness with oral-manual automatisms and garbled speech. The sister had 3 secondarily generalized seizures at age 10. One began with right arm clonic activity. She remained seizure-free on carbamazepine for three years, which was then successfully tapered off. Serum magnesium levels were low for the proband (0.8 mg/dL), sister (1.0 mg/dL), mother (1.0 mg/dL), but normal for the maternal grandmother (2.2 mg/dL); other serum electrolytes were normal. Urine magnesium was 4.5 mg/dL with a fractional excretion of 5%. Interictal EEGs in the proband revealed spike and slow wave discharges in the left frontal region and left temporal slowing in her sister. MRI with epilepsy protocol in the proband revealed bilateral hippocampal signal change on FLAIR and T2 weighted sequences. The sister's MRI was normal. Sequencing of genes known to cause primary hypomagnesemia including the Na+, K+-ATPase gamma-subunit (FXYD2) is in progress.

Conclusions: To our knowledge, this is the first description of familial primary hypomagnesemia in association with temporal lobe epilepsy with hippocampal changes on neuroimaging. Genetic disorders known to cause mesial temporal lobe epilepsy should be screened for by molecular and biochemical methods and may have an important impact on treatment and outcome. [Supported by American Epilepsy Society Fellowship (EJF).]

2.092

PROGNOSTIC VALUE OF THYMIDYLATE SYNTHASE GENE POLYMORPHISM IN EPILEPSY

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Rationale: Thymidylate synthase (TS) gene encodes a tightly regulated enzyme that catalyzes the conversion of deoxyuriylate to thymidylate, and contains a tandem repeat polymorphism, of which a triple repeat is associated with increased expression of TS. TS is key enzymes in the folate metabolism and compete with methylenetetrahydrofolate reductase (MTHFR) for limiting supplies of folate required for the remethylation of homocysteine. We studied to clarify the association between these genetic variations and prognosis in epilepsy.

Methods: A total of 125 epilepsy patients was included. All patients have been medicated with antiepileptic drug over at least one year. We investigated the TS promoter 28 bp polymorphism in serum of epilepsy patients using PCR amplification of genomic DNA. We obtained 2 different DNA fragments, which indicated triple-repeat (3R) and double-repeat (2R) type alleles.

Results: 68% of patients with epilepsy were 3R3R, 30.4% were 2R3R, 1.6% were 2R2R. In seizure frequency during one-year with medication, 3R3R was 7.94/year, 2R3R and 2R2R was 1.85/yr. Combined analysis of TS and MTHFR polymorphisms(C677T) revealed that CT/3R3R and TT/3R3R increase seizure frequency.

Conclusions: Epilepsy patients who were homozygous for the triple repeat had a poorer prognosis than those with other genotypes, especially when combined with mutant alle for MTHFR. So, our results suggest that the genotyping for the TS polymorphisms may become a useful indicator in determining prognosis of epilepsy.

2.093

FEBRILE SEIZURES IN DANISH TWINS: THE IMPORTANCE OF GENETIC FACTORS

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Rationale: The purpose of this study was to estimate the relative influence of genetic and environmental factors on the etiology of febrile seizures (FS) overall and of FS partitioned by subtype.

Methods: Twins with FS were ascertained from the population-based Danish Twin Registry by questionnaire. Twin pairs where both members had FS were considered to be concordant for seizures. Affected pairs were validated and classified according to the ILAE classification of epilepsies/syndromes (1989). Affected pairs with FS were subclassified into the following categories: simple febrile seizures (SFS), complex febrile seizures (CFS) and undetermined febrile seizures (UFS). Pairs where the FS of both twins were of the same type were classified as concordant for FS subtype, while pairs where the FS of pair members were not of the same type were classified as discordant for FS subtype. The similarity of monozygotic (MZ) and dizygotic (DZ) twins was assessed using probandwise concordance rates.

Results: It was possible to assign an FS diagnosis for a total of 526 individuals included in 446 complete twin pairs. For FS overall, the probandwise concordance rate for MZ twins was substantially higher than for DZ twins (MZ: 0.43 and DZ: 0.17, $p < 0.001$). For SFS, the probandwise concordance rate was also higher for MZ than for DZ twins (MZ: 0.44 and DZ: 0.13, $p < 0.001$). No significant differences were found in the concordance rates observed for MZ versus DZ pairs for either CFS or UFS (CFS: MZ: 0.06 and DZ:0.02, $p = 0.30$; UFS: MZ: 0.11 and DZ: 0.02, $p = 0.06$).

Conclusions: The finding of significantly higher probandwise concordance rates in MZ versus DZ twins with validated FS emphasizes the importance of the role that genetic factors play in the etiology of FS overall. The pattern of concordance rates observed for SFS, CFS and UFS in this sample (significant differences in probandwise concordance rates for SFS in MZ versus DZ twins and no significant differences in the MZ-DZ rates observed for either CFS or UFS) suggests that genetic factors play an important role in determining risk for the occurrence of SFS, but not as important or possibly not as straightforward a role in the etiology of CFS and UFS. [Supported by a grant from NIH NINDS (NS-31564).]

2.094

COMPLEX SEGREGATION ANALYSIS IN FAMILIAL MESIAL TEMPORAL LOBE EPILEPSY (FMTLE)

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Rationale: Recently, we described a large group of families segregating a distinct type of temporal lobe epilepsy with familial recurrence (FMTLE). Initial pedigree analysis pointed to a strong genetic predisposition for the development of hippocampal atrophy in these families. The objective of this study was to determine the type of inheritance that can most appropriately explain the recurrence of the disease in these families.

Methods: Complex segregation analysis was performed using the software POINTER(c). We used a series of 98 nuclear families, derived from 29 unrelated pedigrees. A total of 602 family members, including 147 patients were studied. Parameters estimated were: dominance (d), displacement (t), allelic frequency (q), multifactorial heritability (H). Different models were compared by likelihood coefficient tests.

Results: We rejected the absence of genetic effect ($\chi^2 = 59{,}480$; $p = 0{,}000$), absence of a main gene ($\chi^2 = 59{,}480$; $p = 0{,}000$), autosomal recessive inheritance ($\chi^2 = 17{,}766$; $p = 0{,}000$) and co-dominant model ($\chi^2 = 7{,}050$; $p = 0{,}029$). However, we could not reject the absence of multifactorial inheritance ($\chi^2 = 0{,}010$; $p = 0{,}920$) and autosomal dominant inheritance ($\chi^2 = 0{,}027$; $p = 0{,}987$).

Conclusions: To our knowledge this is the first segregation studied performed in FMTLE. Our results strength the evidence for genetic predisposition in this disorder. In addition our data provides additional evidence for the presence of a major gene, which could be involved in the development of hipocampal atrophy in these patients. Linkage studies are under way in order to identify the major gene involved in FMTLE. (Supported by FAPESP.)

2.095

PHENOTYPES AND GENOTYPES OF A COHORT OF PATIENTS WITH IDIOPATHIC GENERALIZED EPILEPSY IN HONDURAS

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Rationale: Idiopathic generalized epilepsies have been reported to constitute at least 8% of all epilepsies in population-based studies performed in Honduras [Medina et al. *Epilepsia* 1997;38(suppl 7):8]. A cohort of 25 families were evaluated in order to perform clinical/syndromatic classification and linkage studies to find chromosome loci.

Methods: Twenty five patients and families were recruited between 1993 and 2004 from one private and one public epilepsy clinic (University Hospital) at Honduras. The phenotype determination for both probands and non-proband members was done according to electroclinical criteria and the International League Against Epilepsy classifications for seizures and syndromes were applied. Previous IRB approval and consent form, all patients underwent video-EEG and at least two independent epileptological evaluations. Multiplex/multigenerational families were selected to perform a screen for nine IGE loci reported in medical literature for IGE with absence and myoclonias. Fluorescent microstelites and the linkage software by Jurg and Ott (*Am J Hum Genet* 1974; 28:528–9) were selected for loci study.

Results: Eleven families met criteria for classic juvenile myoclonic epilepsy (JME), 5 had childhood absence (CAE) evolving to JME, 4 had persiting CAE, one had CAE, one had idiopathic myoclonic astatic epilepsy, and two met criteria for generalized epilepsy with febriles seizures plus (GEFS+). Four families were simplex and 21 were multiplex/multigenerational.

Conclusions: Our results show the presence in Honduras of most the IGE reported in medical literature. Results on the linkage analyses on six JME loci, two CAE loci and one GEFS+ loci will be presented. (Supported by NINDS grant 5RO1NS042376–03 and local funds.)

2.096

SEGREGATION OF DYSLEXIA WITH BATHING EPILEPSY IN A LARGE FRENCH-CANADIAN FAMILY

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Rationale: We recently reported a large French-Canadian family with bathing epilepsy and X-linked transmission. All five affected members had reflex complex partial seizures occuring during the experience of bathing or induced by the contact of water. We noticed a high prevalence of learning difficulties in affected patients and sought to better characterize this observation.

Methods: Complete neuropsychological evaluation was performed for 3 of the 4 living individuals with bathing epilepsy.

Results: Complete neuropsychological testing of these three individuals with familial bathing epilepsy revealed severe deficits in writing and, to a lesser extent, in reading. These deficits contrasted with oral language abilities assessed in conversation and by the Boston Naming Test, which have been found to be normal, except for a limited verbal letter fluency. General intellectual level was low average, but without any significant difference between verbal and nonverbal scales. Both verbal (RAVLT and WMS-III logical memory and verbal paired associates) and visual (Rey-O figure, design and faces from WMS-III) memory functions were within normal limits. None of these patients presented deficits in executive functions. Taken together, these three profiles are compatible with a diagnostic of dyslexia. In addition, an initial questionnaire reveals significant learning difficulties compatible with dyslexia in the fourth living member with bathing epilepsy, but neuropsychological testing is pending.

Conclusions: These findings suggest an association between dyslexia/dysorthographia and reflex bathing epilepsy. Genetic studies are underway. Characterization of the genetic defect for bathing epilepsy may provide valuable insight into the pathogenesis of dyslexia. (Supported by CIHR, Epilepsy Canada, and Savoy Foundation. G.A.R. is supported by CIHR.)

2.097

PREDICTION OF LGI1 MUTATIONS IN FAMILIAL EPILEPSIES

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Rationale: We previously reported that mutations in LGI1 are present in 50% of families containing ≥ 2 individuals with idiopathic focal epilepsy with ictal auditory symptoms. However, mutations have not been found either in familial temporal lobe epilepsies without auditory symptoms, or nonfamilial epilepsies with auditory symptoms. Here we investigated mutation frequency in a different group: familial epilepsies in which one subject had ictal auditory symptoms. The results can be used to refine prediction of which families are likely to carry a mutation in this gene.

Methods: The study included 28 families each of which contained one subject with ictal auditory symptoms. Two neurologists classified partial seizure semiology in each affected individual in the families. To detect sequence variants in LGI1, the gene's eight coding exons were sequenced in DNA extracted from blood or EBV-transformed lymphoblastoid cell lines. For analysis of clinical and molecular data, the 28 newly studied families were combined with 14 previously reported families containing ≥ 2 subjects with auditory symptoms.

Results: The 28 families contained a total of 95 subjects with idiopathic epilepsy (average 3.4 per family), of whom 58 had focal epilepsy, and 28 (1 subject per family) had auditory symptoms. None of these

families had a mutation in LGI1. Excluding the original linkage family used to define this syndrome, we have analyzed 42 families for mutations in LGI1 (28 reported here and 14 reported previously), seven of which have had mutations. To detect family characteristics that might predict which have a mutation, we classified each family by the percent of affected subjects whose epilepsy was focal, the percent of subjects with focal epilepsy who had auditory symptoms, and the percent of subjects with focal epilepsy who had autonomic symptoms. Families with mutations did not differ from those without mutations in the total number of individuals with idiopathic epilepsy (4.3 vs. 3.6), or the percent whose epilepsy was focal (average per family: 80% vs. 73%). However, among subjects with focal epilepsy, the percent with ictal auditory symptoms was greater in families with mutations than in those without (average per family: 98% vs. 59%, $p = 0.001$), and the percent with autonomic symptoms was lower in families with mutations than in those without (average per family 19% vs. 50%, $p = 0.035$).

Conclusions: The families most likely to have mutations in LGI1 are those containing multiple subjects with idiopathic focal epilepsy, a majority of whom have auditory symptoms, and a minority of whom have autonomic symptoms. This symptom constellation reflects a high probability of a lateral temporal localization of the epileptogenic zone. (Supported by NIH R01 NS36319.)

2.098

FEBRILE SEIZURES AND RELATED EPILEPSY IN TWINS AND THEIR RELATIVES

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Rationale: The incidence of febrile seizures (FS) is estimated to be between 2 and 5% in North America and Europe. Complex febrile seizures (CFS) including status epilepticus (FSE) are estimated to occur in 20 to 35% of these children with approximately 5% being FSE. Although FS are generally benign, up to 5% go on to develop later seizures, wtih CFS, specifically FSE, having a greater risk of developing epilepsy. The occurrence of FS in first and second degree relatives has also been found to be associated with an increased risk of epilepsy.

Methods: Utlizing data from the Middle Atlantic Twin Registry (MATR), Norwegian Twin Panel (NTP) and the Danish Twin Registry (DTR), affected twins and relatives were classified as having FS (simple (SFS), CFS, FSE), as well as epilepsy. Medical information, including seizure history, was available on a total of 47,626 twin pairs ascertained from the three registries (17,112 MATR, 13,691 NTP, 16,823 DTR). Data was obtained through questionnaires and interviews with verification through medical records.

Results: Febrile seizures were validated in a total of 1,745 twins or family members. SFS or FS of unknown origin accounted for the largest proportion of cases identified (1,393, 79.8%). Total CFS equaled 352 (20.2%) with FSE in 119 (6.8%). Epilepsy was verified in 73 SFS or unknown cases (5.2%), while 43 were found to have had epilepsy following CFS (12.2%) and 19 of 119 subsequent to FSE (16%). In MZ twins with FSE, 8 of 18 developed epilepsy, whereas this was the case in only 5 of 46 DZ twins. The proportion is significantly increased in MZ twins compared to DZ twins ($p = 0.0026$).

Conclusions: These results verify that most cases of FS are benign and do not progress to epilepsy. A higher incidence of epilepsy followed CFS, especially in those with prior FSE. Clustering of FSE and epilepsy in some families, particularly in MZ twins, suggests a genetic component as a partial etiology. [Supported by grants from the National Institutes of Health NINDS (NS25630 and NS31564).]

2.099

LINKAGE ANALYSIS OF A FAMILY WITH FAMILIAL PARTIAL EPILEPSY WITH VARIABLE FOCI

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Rationale: Familial partial epilepsy with variable foci (FPEVF) is a recently described familial partial epilepsy syndrome. Linkage has been reported for FPEVF to chromosome 22q11–12 in two French-Canadian and one Dutch family. We have identified an extended Australian family with multiple members showing clinical characteristics of FPEVF. The familial inheritance of the epilepsy seen within this family is indicative of a strong underlying genetic component, with autosomal dominant inheritance. Here we report the results of genetic linkage analysis studies in this family.

Methods: We conducted a genome-wide scan using 400 microsatellite markers, followed by linkage analysis to identify regions of the genome likely to contain the causative gene.

Results: Two potential candidate regions on chromosomes 22 and 19 were identified. A significant lod score of 3.45 was obtained on chromosome 22q and a multipoint lod score of 2.63 was obtained on chromosome 19, both occurring at ~30 cM from the proximal end of the chromosome. The peaks span ~8 and ~9 cM on chromosomes 19 and 22, respectively. Fine mapping confirmed the region of linkage on chromosome 22 as falling within the candidate regions previously identified in two French-Canadian and Dutch FPEVF families (22q11–12).

Conclusions: We have identified linkage in an Australian family with the clinical phenotype of FPEVF to a region within that reported in three previous families on chromosome 22q. This result strongly supports the causative gene for this syndrome lying within this region. Additionally we have identified a second region of linkage on chromosome 19q that may represent the site of a modifier gene.

2.100

HIPPOCAMPAL SCLEROSIS IN FAMILIAL CASES WITH IDIOPATHIC GENERALIZED EPILEPSY

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Background: Hippocampal sclerosis (HS) is a common cause of refractory temporal lobe epilepsy (TLE) in Humans. In turn, HS has been rarely reported in patient featuring idiopathic generalized epilepsy (IGE). More recently, familial cases with partial epilepsy and HS have been reported, suggesting that genetics factor could play a role in the pathogenesis of this lesion.

Objective: To describe familial cases with epilepsy with both IGE and HS features.

Methods: We are systematically recruiting familial cases with epilepsy for the purpose of genetic studies, with an emphasis on idiopathic generalized epilepsy (IGE). We collected 58 IGE families, with at least 2 affected individual, for a total of 262 affected individuals (mean of 4,5 affected individuals per family). From this cohort, we identified 5 individuals featuring both IGE and HS. Seizure history, EEG and MRI from affected individuals of these families have been reviewed.

Results: We studied 20 cases belonging to 4 families, including 8 females and 12 males. Age of onset of seizures range from 6 month to 20 years (mean: 6,7 year old). In these families, the clinical manifestations were heterogeneous: 10 patients had only generalized seizures, 1 patient had only partial seizures, 4 patients had both partial and generalized seizures, 3 patients had only febrile seizures, 1 patients had post-traumatic seizures and 1 had undetermined seizure type. Eleven patients had an history of febrile seizure (55%). Five patients showed signs of HS, based on MRI or pathology. Interestingly, these five patients were found to have intractable seizures, including: 2 individuals with generalized seizures and EEG showing generalized epileptic activity, 2 individuals with partial and generalized seizures and EEG showing both focal temporal and generalized epileptic activity, and 1 individual with partial seizures and EEG showing focal temporal epileptic activity.

Conclusions: We report the association of both HS and IGE features in 4 French-Canadian families segregating idiopathic epilepsy. The clinical phenotype is heterogeneous, but compatible with IGE in many affected

individuals. Whether HS is the cause or consequence of intractable IGE remain to be determined. The identification of genes predisposing to the disease in these families should help to understand the pathogenesis of HS and IGE. (Supported by CIHR, Epilepsy Canada, and Savoy Foundation, G.A.R. is supported by CIHR.)

2.101
EPILEPSY AND MENTAL RETARDATION LIMITED TO FEMALES (EFMR): UNDERRECOGNITION OF A REMARKABLE PHENOTYPE AND CONFIRMATION OF LINKAGE

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Rationale: EFMR (Epilepsy and Mental Retardation limited to Females) is a rare disorder with a remarkable X-linked inheritance pattern with male sparing. A single large family has been previously described with the disease gene mapping to Xq22. EFMR is characterised by seizures beginning early in life, with developmental regression following seizure onset. Affected females have variable degrees of intellectual disability (ID). We describe 3 new families with EFMR where mapping is consistent with the Xq22 locus.

Methods: We ascertained 3 unrelated families where seizures in females were transmitted through unaffected males; two from Australia and one from Israel. Detailed electroclinical assessment was performed on 37 individuals. The segregation of Xq22 markers with the disease locus was examined.

Results: Onset of seizures was at a mean of 11 months (median 11, range 3–36). Affected girls typically presented with GTCS, often associated with fever. Some individuals had partial, absence, atonic and myoclonic seizures. Seizures often ceased by the second decade. Developmental regression occurred in 14 females, typically with seizure onset. Intellect ranged from normal to severe ID. Autistic features were prominent in one family, and one woman had schizophrenia. Brain imaging studies were normal (4 CT, 1 MRI). Although each family was of insufficient size to demonstrate linkage, haplotype analyses were consistent with the Xq22 localisation.

Conclusions: We report 3 new families with the remarkable condition of EFMR where females are affected with epilepsy and developmental regression, and carrier males are clinically unaffected. This disorder is characterized by an extraordinary pattern of inheritance where male sparing occurs and females with the same mutation show marked variability in severity. (Supported by NHMRC, Bionomics.)

2.102
A SINGLE-NUCLEOTIDE POLYMORPHISM IN THE *SCN2A* GENE IS ASSOCIATED WITH UNCONTROLLED EPILEPSY

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Rationale: The neuronal voltage-gated sodium channel is an important molecular target for several antiepileptic drugs (AEDs). Fundamental channel properties are conferred by a single α-subunit, which also contains the AED binding site. The $Na_v1.2$ subunit is the most widely expressed sodium channel α-subunit in human brain. Single nucleotide polymorphisms (SNPs) in the gene (*SCN2A*) encoding this subunit have the potential to influence the properties of the channel and its sensitivity to blockade by AEDs. We have investigated the prevalence of a specific SNP (R19K) in exon 1 of the *SCN2A* gene in responders and non-responders to AED treatment.

Methods: A total of 400 patients attending a specialist epilepsy clinic were recruited. Of these, 118 had idiopathic generalised epilepsy, 269 had localisation related epilepsy and in 13 patients, the epilepsy was unclassified. Genomic DNA was extracted from venous blood and a 400 bp fragment of the *SCN2A* gene containing the site of the R19K polymorphism was amplified by PCR. Presence of the R19K SNP was determined by restriction digest with ScrF1 endonuclease. Patients were categorised as responders (seizure free for 6 months) or non-responders by review of case notes and seizure diaries. Allele and genotype frequencies in each group were compared by logistic regression analysis.

Results: A total of 170 (42%) patients were classified as responders and 230 (58%) as non-responders. Genotype frequencies in the cohort were 88% GG, 11% GA and 1% AA. Variant genotypes (GA and AA) were present in 8% of responders and 16% of non-responders (OR 2.07, 95% CI 1.08–3.97, $p = 0.024$). The A allele was present in 5% of responders and 8% of non-responders (OR 1.71, 95% CI 0.95–3.09, $p = 0.067$). Sub-analysis on the basis of seizure classification did not influence the findings. As a diagnostic test for uncontrolled epilepsy, the variant genotype had a sensitivity of 16% and specificity of 92%, with test efficiency of 48%.

Conclusions: The R19K polymorphism in *SCN2A* is more prevalent in patients with uncontrolled epilepsy than in those with well-controlled epilepsy. The predictive power of the variant genotype is poor owing to low frequency of the polymorphic allele and the undoubtedly limited contribution of a single SNP to drug response. Identification of several SNPs correlating with response to drug treatment could provide sufficient predictive power to achieve the goal of genotype-based therapy.

2.103
EPILEPSY SYNDROMES IN FAMILIES

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Rationale: To study the occurrence of specific epilepsy syndromes in families with more than two affected individuals.

Methods: Participants in the Norwegian Twin Panel and the Mid-Atlantic Twin Registry were screened for a history of seizures among themselves and their family members by questionnaire. Based upon an evaluation of medical history information and detailed clinical and family interviews, seizures and epilepsy syndromes were classified in all individuals reporting a positive seizure history using the ILAE classification system.

Results: A history of epilepsy was confirmed in two or more members of 587 families. It was possible to classify the epilepsy syndrome in two or more family members in 445 families with 227 being concordant and 218 discordant for syndrome type. Among families concordant for localization-related epilepsies, four had idiopathic epilepsy, 14 symptomatic epilepsy and another 14 families cryptogenic epilepsy. We also identified 173 families who were concordant for special situation-related syndromes and 19 families for generalized idiopathic epilepsy. One family had undetermined epilepsy with both generalized and focal features, while three families had undetermined epilepsy without unequivocal generalized or focal features. After simplifying syndrome types in discordant families into four categories (generalized, localization-related, undetermined and special syndromes), we found that four families had a combination of all categories, 30 families a combination of three categories and 173 a combination of two categories. In 11 families, members had different forms of localization-related epilepsy. Both generalized and localization-related epilepsies were found in separate members of 42 families.

Conclusions: The importance of the contribution of genetic factors to risk for epilepsy has been well documented in twin and family studies. Our finding that among multiplex families, where it was possible to determine the epilepsy syndrome type of affected family members, approximately half were concordant and half were discordant for syndrome type provides further support for the existence of two classes of seizure susceptibility genes; those that are syndrome specific and those that are not. Of special interest are the families in which both generalized and localization-related epilepsies occurred. This large collection of families with verified epilepsy provides an important resource for identifying both specific epilepsy genes and more general seizure susceptibility genes. [Supported by NIH NINDS grant (NS-31564).]

2.104

FAILURE TO CONFIRM ASSOCIATION BETWEEN GABA(B) RECEPTOR 1 POLYMORPHISM (G1465A) AND TEMPORAL LOBE EPILEPSY

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Rationale: Genetic association studies have had an inconsistent record so far (Colhoun et al., 2003). A single nucleotide polymorphism (G1465A) in the GABA(B) receptor 1 gene has been reported to be associated with non-lesional temporal lobe epilepsy (TLE) in a study of 141 subjects (Gambardella et al., 2003). Subjects with the A allele were at higher risk of TLE. Population admixture was seen in this association study, thus cryptic population stratification remains a possibility.

As population stratification can cause spurious associations, independent replication of association studies is important to verify or refute published associations. We therefore performed a case-control replication study to confirm this association.

Methods: We recruited 200 subjects with non-lesional TLE using identical case definitions as the first study; 88 healthy subjects were used as controls. DNA was extracted with standard methods, and presence of the G1465A polymorphism assessed using restriction fragment length polymorphisms. Differences in allele frequencies between groups were compared using the chi-square test; reported p-values are two-sided.

Results: Our results showed that the A allele was absent in cases (0%, 95% CI 0–2.3%) and present in 0.8% of controls (95% CI 0.2–3.6%); this was not significantly different ($p = 0.55$).

We were unable to replicate the association despite a larger sample size and adherence to existing guidelines for genetic association studies. We suggest that the initial association may be due to uncorrected cryptic population stratification. Though the first study used logistic regression to minimise overt stratification, this does not minimise cryptic stratification, which can bias even well-designed studies (Freedman et al. 2004). Other possible reasons for non-replication such as inadequate sample size or genotyping errors are less likely.

Conclusions: We therefore suggest that new methods for correcting cryptic population stratification, such as genomic control, should be used routinely to verify positive findings in genetic association studies. Independent replication of genetic association studies remains an important method of verifying published associations, and cautious interpretation of association studies is emphasised.

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2.105

IS BENIGN ROLANDIC EPILEPSY GENETICALLY DETERMINED?

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Rationale: Benign rolandic epilepsy (BRE) is considered a genetically determined idiopathic partial epilepsy, but family studies of BRE probands show few family members have BRE. Whilst monozygous (MZ) concordant pairs with BRE are reported, our preliminary data showed an absence of concordant pairs. Our aim is to elucidate the genetics of BRE by systematically studying twins in a multi-center international collaborative twin study.

Methods: Large population-based twin databases in Melbourne (Australia), Odense, (Denmark), Oslo (Norway) and Richmond (USA) were reviewed for cases of BRE. Diagnosis of BRE was based on age of onset between 3–13 years, compatible clinical seizure pattern, absence of other neurological signs and centro-temporal spikes on EEG. All available information was reviewed to establish the diagnosis. Zygosity was determined clinically and confirmed where possible by polymorphic DNA markers.

Results: There were seventeen twin pairs (10 monozygous; 7 dizygous) with a definite diagnosis of BRE amongst a total sample of 1866 twin pairs. All pairs were discordant for BRE. The estimated MZ pairwise concordance of 0 (95% CI, 0–0.3) for BRE was significantly different to the estimated MZ pairwise concordance of 0.7 (95% CI, 0.5–0.9) for 26 IGE MZ pairs from our Australian cohort ($p < 0.001$).

Conclusions: The absence of any concordant MZ pairs from our multicenter collaboration of twin pairs with BRE strongly suggests that conventional genetic influences in BRE are considerably less than for IGE, where MZ twin concordance is high. The often-quoted misconception of an autosomal dominant gene for classical BRE should be expunged. A full understanding of the cause of BRE must look beyond traditional genetics and consider mechanisms such as environmental factors, somatic mutations and epigenetic influences.

2.106

PATERNAL UPD15 PREDICTS MILDER EPILEPSY IN ANGELMAN SYNDROME BUT HAS NO INFLUENCE ON EEG

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Rationale: Angelman syndrome (AS) is determined by different genetic mechanisms, affecting the maternal chromosome 15. One of these, paternal UPD, occurs in 1–3% of all AS patients, with strong evidence of a milder phenotype, constituting a putative subgroup that represents a challenge for clinical diagnosis. To date, electroclinical data in UPD is scarce and remains unknown whether the binomial epilepsy-EEG is similar to that reported in patients with DEL. We describe the electroclinical phenotype of four children with UPD and compare these findings to DEL patients.

Methods: We included 24 patients with DEL and 4, with UPD. We characterized epilepsy by history obtained with a pre-standard questionnaire, corroborated by medical records, personal contact with previous physicians, and video-EEG monitoring (mean 8 hours) in 21 patients. A total of 91 EEGs (mean 2.6 EEG/patient), ranging from 4 months to 22 years (mean 5y3mo), were analyzed. Suggestive EEG patterns for AS were classified according to Boyd et al. [1988] and were denominated: delta pattern (DP), theta pattern (TP) and posterior discharges (PD). We compared prevalence and severity of epilepsy plus the EEG features mentioned above between our UPD and DEL patients. For the purpose of statistical analysis, we added data of published UPD to our own patients and compared them with our DEL patients, using Fisher, Student t, x^2 and Mann-Whitney's tests with level of confidence of $\alpha = 0.05$.

Results: Our data showed that none UPD had refractory epilepsy compared to 19 DEL patients. Only one DEL patient (4.8%) had a normal age-related background, whereas three (75%) non-DEL had this feature. Suggestive EEG occurred in both groups. Our UPD patients presented infrequent and short runs of DP and PD, while DEL had prolonged and quasi-continuous/continuous patterns, as well as electrographic seizures and unspecific interictal epileptiform discharges. Analyzing our patients plus previous work, we observed that prevalence of epilepsy was significantly higher in patients with DEL ($p < 0.001$) than in those with UPD. Parameters indicating severity of epilepsy (earlier age of onset, higher occurrence of disabling or multiple seizures, SE, and refractoriness) were

also significantly higher in patients with DEL. In relation to EEG, the presence of an abnormal background and the higher frequency of posterior discharges in DEL were the only significant differences between groups.

Conclusions: The analysis of our and published patients showed that in UPD, when epilepsy occurred, it was milder compared to patients with deletion, although a suggestive EEG was observed in most patients. Although, UPD patients do not completely fit the scenario delineated for AS, suggestive EEG patterns were as helpful as in other groups to corroborate the diagnosis. (Supported by CNPQ and FAPESP.)

2.107

INCREASED EXPRESSION OF COMPLEMENT COMPONENT 5 AND GLIAL ACTIVATION GENES IN TISSUE AND PERIPHERAL BLOOD MONONUCLEAR CELLS IN PATIENTS WITH INTRACTABLE TEMPORAL LOBE EPILEPSY

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Rationale: To characterize the gene expression profile of peripheral blood mononuclear cells (PBMC) and brain tissue obtained from patients with intractable epilepsy due to mesial temporal sclerosis (MTS).

Methods: Candidates for temporal lobectomy were asked to participate in this study. PBMC were isolated using gradient separation on cell preparation tubes. Following temporal lobectomy, the hippocampus (HC) and neocortex (NC) removed were labeled and evaluated for specific pathology and for gene expression. The GeneFilters GF211 DNA array containing known named human genes were used. We compared PBMC gene expression differences between patients with TLE vs. patients with active relapsing remittent multiple sclerosis (RRMS) and normal controls (NL), as well as between the NC, HC and PBMC of MTS patients.

Results: Brain tissue and PBMC were available from 5 patients (4 M and 1 F) with MTS. Mean age was 33.6 years (range 16–53), and mean disease duration was 18.2 years (range 11–29). An increased expression of Complement Component 5 (CC5) an inflammatory anaphylatoxin recognized to be associated with peripheral and brain inflammation showed a 7 fold up regulation in the PBMC of epileptic patients compared to healthy controls and active untreated MS patients. Similar CC5 expression was seen in HC and NC. Seventeen genes were significantly increased in the HC compared with the NC, 214 different genes showed increased expression in NC vs HC while 1445 and 1885 genes were significantly different expressed in PBMC vs. NC and HPC respectively. An increase of two to three fold in gene expression of proteins associated with neural damage and glial activation such as Apolipoprotein D (Apo D), beta2 microglobulin and Glial fibrilary acidic protein (GFAP) were found in the HC compared to NC.

Conclusions: Our data suggest glial activation and inflammatory reactive response in the hyppocampus and neocortex. Similar increased gene expression was seen in animal models of Unverricht-Lundborg disease, probably associated with long standing epilepsy. The increased inflammatory gene expression seen in the PBMC as well as in the brain may suggest a neuroprotective role for anti-inflammatory therapies in intractable epilepsy. Additional corroborative gene expression data with control brain tissue and confirmatory tissue immunostaining for these specific genes are underway. (Supported by National MS Society Novartis.)

Pregnancy/Gender Issues

2.108

A SERVICE FOR PREGNANT WOMEN WITH EPILEPSY: 2 YEARS' EXPERIENCE

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Rationale: To provide a clinic and advisory service for pregnant women with epilepsy and to evaluate the care received by such women with regard to their epilepsy and antiepileptic drug therapy during pregnancy.

Methods: Arising out of our successful Preconception Clinic for women with epilepsy (Betts T, Fox C. *Seizure* 1999;8:322–7) we have set up a formal clinic for women with epilepsy who are pregnant. Some come from our continuing preconception clinic but an increasing number previously unknown to us are referred already pregnant by General Practitioners. In addition we provide an advisory service for other Birmingham maternity clinics and beyond. We have seen nearly 200 pregnant women in the 2 years the clinic has been open.

Results: Our early experience is that few women with epilepsy (unless they attend our preconception clinic) enter pregnancy in a planned way. Some are taking sodium valproate without any information about its pregnancy risks; nearly 30% turn out not to have epilepsy despite taking anticonvulsants; very few are taking an appropriate dose of folic acid. Our elective Caesarian section rate is less than 5% and we try to keep labour to 12 hours or less but recognise that we need to improve epilepsy education for obstetric doctors and midwives if birth plans are to remain intact.

Conclusions: Our early impression is that premature birth is more common in women with epilepsy as may be foetal loss in the early puerperium and we have set up a controlled comparison to evaluate this. The one maternal death appears to have been a sudden death in epilepsy.

2.109

BENEFICIAL EFFECTS OF LEVETIRACETAM ON PHOTO AND PATTERN SENSITIVITY

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Rationale: Levetiracetam, a new antiepileptic drug licensed for add-on therapy in partial epilepsy, is being increasingly used in our unit for patients with primary generalised epilepsy. It is used particularly in patients with juvenile myoclonic epilepsy (Krauss G, Betts T. Abou-Khalil B, et al. *Seizure* 2003;12:617–20) especially women withdrawn from sodium valproate before conception who cannot remain seizure-free on lamotrigine alone. Many of these patients have either photo or pattern sensitivity or both.

Methods: We have observed the effect of levetiracetam on photo or pattern sensitivity in over 40 patients in our clinic.

Results: Levetiracetam appeared very successful in controlling both pattern and photo sensitivity and will sometimes do so when no other drug has previously been able to. A small number of patients, however, retain photo or pattern sensitivity even if they have tried all three drugs (sodium valproate, lamotrigine and levetiracetam). The reason for this is not clear but suggests that photo and/or pattern sensitivity is not a single entity.

Conclusions: We have found levetiracetam to be successful in controlling photo and pattern sensitivity in patients with primary generalised epilepsy and speculate that it may become the drug of choice for photo and pattern sensitivity in women of child bearing age if our early experience of safety of this drug in pregnancy is confirmed.

2.110

GENDER DIFFERENCES AND MENSTRUAL CYCLE EFFECTS ON BRAIN EXTRACELLULAR GLUTAMATE AND GABA LEVELS IN EPILEPSY PATIENTS: A MICRODIALYSIS STUDY

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Rationale: Women with catamenial epilepsy have increased seizures, often prior to their menstruation. MRS studies (Epperson NC. *Arch Gen Psychiatry*, 2002) describe lower cortical GABA levels during the luteal phase of the menstrual cycle in healthy women. Since glutamate and GABA play role in seizure generation, we investigated whether the

extracellular levels of these neurotransmitters change over the menstrual cycle, and whether gender effects may exist.

Methods: Microdialysis studies were performed in 52 patients (32 F and 20 M) with CPS who were being evaluated for resective surgery. Menstrual cycle history was obtained in 19 female patients. Microdialysis probes attached to depth electrodes were implanted in the cortex (ctx) and hippocampus (hipp) and the epileptogenisity of the probe site was assessed with intracranial EEG recordings. The interictal basal levels of glutamate and GABA were measured using the zero-flow method and HPLC. Data was analyzed with Wilcoxon test.

Results: In the non-epileptic sites, the glutamate levels in the CTX (F 2.4 $\pm$ 0.4 μM, n12 vs. M 2.9 $\pm$ 0.4 μM, n10) and in the HIPP (F 3.0 $\pm$ 0.6 μM, n14 vs. M 2.9 $\pm$ 0.5 μM) were comparable for M and F. However the GABA levels were significantly higher in both the female CTX (F 0.3 $\pm$ 0.1 μM, n12 vs. M 0.1 $\pm$ 0.03 μM, n10, $p < 0.03$) and HIPP (F 0.4 $\pm$ 0.1 μM, n11 vs. M 0.2 $\pm$ 0.07 μM, $t < 0.05$). Moreover, while the glutamate levels did not change over the menstrual cycle (follicular phase 3.1 $\pm$ 0.5 μM, n 14 vs. luteal phase 2.4 $\pm$ 0.9 μM, n 5, $p > 0.5$), the GABA levels were significantly lower during the luteal phase (luteal 0.12 $\pm$ 0.1 μM, n5 vs. follicular 0.5 $\pm$ 0.1 μM, n14, $p < 0.02$).

Glutamate levels were significantly elevated in the epileptic CTX and HIPP in F and M (CTX F 13.7 μM, n9 vs. M 10.2 μM, n4, $p > 0.05$; HIPP F 12.1 μM, n10 vs. M 11.4 μM, n4, $p > 0.05$). However the GABA levels in the epileptic brain sites were not significantly different in neither gender ($p > 0.5$ for all tests), although there was a general trend for increased GABA levels in the epileptic regions.

Conclusions: While basal glutamate levels in the non-epileptic CTX and HIPP are comparable in men and women, the GABA levels are higher in women and fluctuate across their menstrual cycle. GABA levels are much lower during the luteal phase. In both genders, the basal glutamate levels are high in the epileptic CTX and HIPP, while GABA levels do not change significantly. Thus, while the ECF levels of glutamate are tightly regulated, and are not under sex hormone control, the GABA levels are influenced by the menstrual cycle. The decrease in GABA levels during the luteal phase may play role in the catamenial epilepsy. The elevation in the extracellular glutamate (and possibly the marginal increase in the ECF GABA) are a result of the underlying pathology in epilepsy. (Supported by NIH-PO1 NS 39092–01 and BIRCWH 1K12DA14038–01 for I. Cavus.)

2.111
FETAL HEART RATE DECELERATION DURING NONEPILEPTIC SEIZURES: A CASE REPORT

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Rationale: Fetal distress has been reported with partial and generalized epileptic seizures, and nonepileptic seizures have been associated with autonomic dysfunction. However, the consequences of nonepileptic seizures on the fetus have not been well described.

Methods: We evaluated a 20 year old right-handed Caucasian woman in the 28th week of pregnancy with a one-year history of possible seizures. Video/EEG monitoring was perfomed to make a definitive diagnosis of the clincal events, and continuous fetal heart rate monitoring was obtained to determine fetal distress.

Results: A typical event was recorded on video/EEG and continuous fetal heart tone monitoring. The event consisted of head bobbing, irregular truncal twitching with closed eyes that progressed to pelvic thrusting. Lorazepam 4 mg was emergently given. Upon review of the EEG, no electrographic correlate was found, and alpha rhythm was seen when the EEG was not obscured by myogenic artifact. The fetal heart rate by determined ultrasound was initially in the 140 s, but fell to the 60 s during this event. The patient's monitoring was discontinued and she was taken to emergent Caesarian section. In the operating room, the irregular motor activity stopped and fetal heart tone returned to the 140 s. She was brought back to the labor and delivery floor for continued observation. Review of the video/EEG by a board-certified electroencephalograper supported the diagnosis on non-epileptic psychogenic seizures. The fetal heart monitoring and simultaneuous video/EEG will be presented as supportive evidence.

Conclusions: Nonepileptic psychogenic seizures are often presumed to have minimal physiological effects, but associated autonomic dysfunction may have adverse consequences for some patients. Our observations support the potential for nonepileptic seizures to cause significant fetal distress during late pregnancy. Further research and vigilant clinical management may be indicated for pregnancy in woman with nonepileptic psychogenic seizures.

2.112
THE UK EPILEPSY AND PREGNANCY REGISTER: UPDATE OF RESULTS 1996–2003

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Rationale: To determine the relative risks for major congenital malformations (MCM) of in-utero exposure to anti-epileptic drus (AEDs).

Methods: Prospective, observational, registration and follow-up study. Subjects are women with epilepsy who become pregnant, whether or not they are taking an AED, either singly or in combination, who are referred before the outcome of the pregnancy is known. The main outcome measure is MCM rate for each AED regime. MCM rate is defined as the total number of live-births with an MCM plus the the total number of pregnancy losses with an MCM, divided by the total number of live-births plus the total number of pregnancy losses with an MCM.

Results: Full outcome data are available on 2829 pregnancies, with 560 outcomes awaited. Monotherapy exposures account for 71.9% (MCM rate 3.7% [95% C.I. 3.0%–4.6%]), polytherapy exposures for 21.0% (MCM rate 6.6% [95%C.I. 4.8–8.8%]), and no AED exposures for 7.1% (MCM rate 3.0% [95% C.I. 1.4–6.1%]). The crude MCM rate for carbamazepine [n = 775] at 2.3% (95% C.I. 1.5–3.6%) is significantly less than for sodium valproate [n = 619] at 6.0% (95% C.I. 4.4–8.1%). Although the crude MCM rate for lamotrigine [n = 476] at 2.9% (95% C.I. 1.4–4.9%) is less than for sodium valproate the difference is not statistically significant.

Conclusions: The UK Epilepsy and Pregnancy Register is proving an effective method of collecting outcome data on large numbers of pregnancies occurring in women with epilepsy. The results suggest there are differences in MCM rates between AEDs. Further cases are required to establish the degree of these differences and the influence of other confounding variables. [Supported by Epilepsy Research Foundation Grant (and donations from Glaxo-Smith-Kline, UCB-Pharma, Janssen-Cilag, Sanofi-Synthelabo, Parke-Davis to maintain database, run epilepsy freephone helpline, provide fliers).]

2.113
GESTATIONAL LAMOTRIGINE MONOTHERAPY: CONGENITAL MALFORMATIONS AND PSYCHOMOTOR DEVELOPMENT

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Rationale: The treatment of female epilepsy patients during gestation presents a considerable clinical dilemma. On the one hand, it is necessary to keep the patient free of seizures and, at the same time, try to maintain the patient on monotherapy with the lowest possible dose, because of the effects medication may have on progeny. The use of classic antiepileptic drugs (AEDs; eg, sodium valproate) during gestation is associated with a wide range of disorders in the growth and development of the child. Although there is relatively limited data on the effects of the newer AEDs (eg, lamotrigine, carbamazepine) on offspring, there are no evidence of similar developmental disturbances. Among these drugs, lamotrigine is the medication with which the most wide-ranging experience is available, and so far no greater incidence of congenital anomalies has been observed in comparison with the general population. The goal of our study has been to monitor children newly born to epileptic mothers receiving monotherapy with lamotrigine (LTG) during gestation.

Methods: Sixty-two children newly born to mothers diagnosed as having secondarily widespread partial complex epilepsy were studied. This patient population received monotherapy with lamotrigine. The

family and personal history of the parents were assessed together with the obstetric data on the pregnancy and delivery. Findings on the examination of each newborn child with regard to psychomotor development at the moment of birth and after 1, 3, and 6 months, and 1 year after birth also were evaluated.

Results: Among the patients examined in this study, no congenital malformation was evident. Seven patients presented seizures during gestation (2 in the first trimester, 1 in the second trimester, and 4 in the third trimester), without detectable impact on the fetus. It was not necessary to effect any adjustment in the habitual dosage of medication in the remainder of the subjects. No complications in relation to epilepsy arose during delivery or puerperium. The mean APGAR score was 8 at 1 minute and 9 at 5 minutes after birth. Weight, size, and cranial perimeter in all assessments were between the 50th and 75th percentiles. The psychomotor development of the children was appropriate throughout the study according to the Denver test. None of the newborn children suffered from seizures. All of them received artificial lactation.

Conclusions: Anthropometric growth and psychomotor development of children born to epileptic mothers under treatment with lamotrigine monotherapy during gestation are similar to those of the general population. These data indicate that the new AEDs present a considerable therapeutic advantage not only in the handling of epilepsy in different clinical situations, but also with the good results observed in the use of lamotrigine with female epileptic patients of child-bearing age.

2.114
SEXUAL DESIRE AND ANXIETY IN MEN WITH EPILEPSY

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Rationale: It is frequently asserted that men with epilepsy are hyposexual. The reasons for this observation are variously cited as dysfunction in hippocampal-hypothalamic complex leading to endocrinological changes at testicular level, and the effects of anti-epileptic drugs (AEDs) on testosterone levels. The profound psychosocial effects of epilepsy on sexual interest have not been so frequently studied.

Methods: Forty-five men aged between the ages of 18 and 60 were recruited form a district general epilepsy clinic(Leigh Infirmary). All took one AED only, and had not had any change in AED therapy in the previous 6 months. None of the men took anti-depressant medication. All lived independently in the community, did not suffer any progressive neurological condition nor from any endocrine dysfunction. Forty-five men in good health between the ages of 18 and 60 were recruited from the spouses of women with epilepsy attending the clinic, from friends of the men involved in the study, and from hospital personnel. There were no significant differences in age between patient and control groups. Men in the control group were more likely to be in regular employment.

Each man completed a battery of validated questionnaires. The Hospital Anxiety and Depression Scale(HADS), the WHOQOL-BREF(UK). In addition they completed 2 validated sexual function questionnaires; the Sexual Desire Inventory to explore their wish for sexual intimacy and activity and the Sexual Confidence/Competance Scale to examine confidence in performing sexual activities.

Results: Men with epilepsy had significantly higher anxiety scores than controls($P < 0.01$), but did not differ on the depression subscale of HADS. There were no significant differences in overall quality of life scores between the groups, but the men with epilepsy rated their health and social relationships as being less satisfactory than the controls($P < 0.05$). There were no significant differences between the groups in their desire for sexual intimacy, but men with epilepsy had significantly lower sexual confidence scores ($p < 0.05$) indicating that they were less confident than control men of their ability to initiate sexual activity with a partner or achieve orgasm.

Conclusions: Sexual function demands a complex interplay of both endocrinological/neurological systems as well as social and cognitive factors. Previous studies of men have tended to concentrate on endocrinological causes of hyposexuality in men with epilepsy and in particular to consider diminished libido purely in terms of these men's testosterone levels.This approach ignores the fact that recent work strongly suggests there is not a simple relationship between testosterone levels and sexual interest/activity in men and fails to take into account the profound effects on self confidence and social funtion that epilepsy causes.

2.115
BREAST MILK LEVELS OF LEVETIRACETAM AFTER DELIVERY

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Rationale: It is policy in our pregnancy and epilepsy clinic (about 100 deliveries a year) to suggest that post delivery, all women who were taking anticonvulsants at birth, breast feed (at least some of the time) for at least 4 days after delivery to prevent sudden withdrawal of the anticonvulsant from the baby at birth (the colostrum period) unless the baby is significantly premature. An increasing number of pregnant women in our clinic are taking levetiracetam either in combination with another anticonvulsant or as monotherapy. Levetiracetam is a new antiepileptic drug (AED) shown to be effective and well tolerated. However, there are still insufficient data on its use in pregnant and lactating women and so some midwives are reluctant to suggest advising the policy of breast feeding with levetiracetam because its concentration in breast milk is currently unknown.

We aimed therefore, to assess the levels of levetiracetam in breast milk post delivery.

Methods: We have therefore been trying to measure breast milk levels of levetiracetam at 4 days post delivery and 2–3 months post delivery in those mothers who continue to breast feed. Because stay in hospital is usually short this is not as easy as it sounds but we now have data on 12 women.

Results: The evidence so far is that breast milk levels of levetiracetam are significantly lower than blood levels in the mother.

Conclusions: Our results suggest that it is safe for women taking levetiracetam during their pregnancy and the puerperium to breast feed with this drug, particularly because there have been no concomitant clinical problems. (Supported by Educational Grant from UCB Pharma, UK.)

2.116
EFFECT OF HORMONE REPLACEMENT ON SEIZURE FREQUENCY IN MENOPAUSAL WOMEN WITH EPILEPSY

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Rationale: Previous reports have suggested that hormone replacement therapy (HRT) could increase seizure activity in women with epilepsy. We sought to determine whether adding HRT to the medication regimen of menopausal women with epilepsy was associated with seizure increase.

Methods: This is a randomized, double-blinded, placebo-controlled trial of the effect of HRT on seizure frequency in menopausal women with epilepsy taking stable doses of antiepileptic drugs (AEDs) and within 10 years of their last menses. After a three month prospective baseline, subjects were randomized to placebo, Prempro (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate) daily, or double-dose Prempro daily for a three month treatment period. Baseline characteristics between treatment arms were compared using univariate ANOVA. The proportion of subjects with increased seizure frequency in the treatment arm was compared with those whose seizures decreased or stayed the same relative to baseline (Chi-square). Bivariate correlations (Spearman's rank) were also used. Significance level set at 0.05.

Results: Twenty-one subjects were randomized after completing baseline. The subjects' age ranged from 54–62 years (mean = 53 years, SD = +/−5), number of AEDs used ranged from 1–3 (mean = 1.6,

SD = +/−0.8). Seven subjects had no seizures during baseline. No differences between treatment arms were present at baseline for age, number of AEDs used, and seizure frequency.

Four out of seven subjects had a worsening seizure frequency of their most severe seizure type on double-dose Prempro, compared to 3/8 on single dose Prempro and 0/6 on placebo. The association of increased seizure frequency with increasing Prempro dose was significant ($p = 0.032$, $r = 0.470$). The association of increased complex partial seizure frequency with increased Prempro dose was also significant ($p = 0.048$, $r = 0.436$). Chi-square analyses of seizure frequency vs. treatment arm revealed no significant results, however increased frequency of the subject's most severe seizure type was associated with increasing Prempro dose at a level that approached significance ($p = 0.089$).

Four subjects in the double-dose Prempro arm discontinued before completion of the treatment period; 2 due to HRT-related adverse effects, 1 due to seizure increase (met exit criteria) and one due to the WHI study results. One subject in the single-dose Prempro arm discontinued early, due to HRT-related effects; only one subject in the placebo arm discontinued early, due to the WHI study results.

Conclusions: Prempro is associated with a dose-related increases in seizure frequency in menopausal women with epilepsy. (Supported by RO1-NS38473.)

2.117
THE IMPACT OF EPILEPSY ON SEXUAL FUNCTION, BEHAVIOR, BELIEFS IN, AND ATTITUDES TOWARD SEXUALITY

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Rationale: Although epileptic dysfunction, antiepileptic drug therapy, and the stigma of having epilepsy/seizures can be expected to affect sexual function, this issue is largely taboo in the treatment and counselling of patients with epilepsy.

Methods: Sexual function, behavior and attitudes were assessed via self report measures in 118 patients with epilepsy (m/w: 54/64) as compared to 128 healthy control subjects (m/w: 55/73). The questionnaire comprised 6 parts evaluating: 1. frequency of sexual behavior, 2. beliefs in sexuality and epilepsy, 2. a need hierarchy, 3. attitude towards sex, 4. general sexual functioning, 5. sexual functioning during the last 4 weeks, 6. a symptom check list. Questionnaires were consecutively given to unselected inpatients. Completion was voluntary, which may have led to a response bias. Independent epilepsy variables were, localization and lateralization, seizure type and frequency, antiepileptic drug (AED) regimen, and onset and duration of epilepsy.

Results: With the exception of a poorer education, patients did not differ from controls in demographic variables. Patients had fewer partners and were less sexually active. Fifty six percent of patients claimed to be impaired in sexuality by epilepsy, 32% suggested an influence of AED, 43% expressed fears that sex may trigger seizures, and 65% to 70% were afraid that epilepsy or AED will damage the unborn child. As compared to controls, men and women with epilepsy more often rated sex as being holy, immaculate or controlled and both sexes ranked sexuality less significant than controls. Both sexes scored poorer on sexual drive, arousal, frequencies of sexual activities, and success in terms of orgasm and/or ejaculation. Multiple regression analysis indicated that in both sexes need, appetence, arousal, and sexual function were primarily determined by attitudes and fears. Generalized tonic clonic seizures, antiepileptic polytherapy, and a greater seizure frequency appeared to have an effect in some respect.

Conclusions: Epilepsy and its treatment appear to have some impact on sexual behavior and function, but sexuality in epilepsy appears primarily determined by psychological variables like attitudes and fears. Thus it is time to remove the taboo from sexuality and to clear up prejudice. Counselling, successful seizure control and AED monotherapy, may improve the situation significantly.

2.118
LACK OF ASSOCIATION OF HIGH SERUM ESTRADIOL LEVELS DURING PREGNANCY WITH SEIZURES

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Rationale: Catamenial epilepsy includes seizure exacerbation at the time of ovulation and perimenstrually ("Type 2" and "Type 1," respectively). Postulated mechanisms include the proconvulsant effects of high periovulatory serum levels of estrogens and the premenstrual withdrawal of the GABA-ergic anticonvulsant effect of progesterone. During pregnancy, serum levels of both estrogens and progesterone reach very high levels, 20-fold compared to the peak mid-cycle levels and 200-fold compared to the follicular levels. After parturition, levels of both drop 200-fold to early follicular levels within 24–48 hours. I examined the association of high estrogen levels during the last trimester of pregnancy and the post-partum progesterone withdrawal with seizure frequency in order to ascertain the role of estrogen and progesterone in seizure precipitation in a setting of hormonal fluctuation other than the menstrual cycle.

Methods: 6 women with epilepsy were followed prospectively with monthly visits through a full term pregnancy and for 2 months post-partum. Seizure count was determined with a seizure diary. Serum levels of estradiol, estrone, estriol and progesterone were determined monthly. Seizure frequency was compared during pregnancy months 1, 2 and 8, 9 and during the first 2 post-partum (PP) months and was correlated with hormone levels.Statistical analysis included Kurskal Wallis test and multivariate logistic regression analysis. Statistical significance was set at $p < 0.05$.

Results: Total of 29 seizures occurred during months 1, 2, 8 and 9 of pregnancy and PP months 1 and 2. Seizures were most common during months 1 and 2 ($n = 13$, mean 1.1 seizure/woman/month), least common during months 8 and 9 ($n = 6$, mean 0.5 sz/w/mo) and intermediate during the PP months ($n = 10$, 0.8 sz/w/mo), but the difference was not statistically significant.7/10 of the seizures during the post-partum period occurred within 11 days of delivery, making the PP month the most likely month for seizure occurrence (1.2 sz/w/mo). Mean serum estradiol levels were 437, 11957, and 35 pg/ml for months 1/2, 8/9 and for PP months 1/2, respectively. The mean serum progesterone levels for the same periods were 28, 158 and <1 ng/ml. There was no correlation between seizure frequency and serum estradiol levels or between serum estradiol/progesterone level ratios.There was a statistically non-significant suggestion of an inverse correlation between progesterone levels and seizures.

Conclusions: (1)Very high serum estrogen levels during pregnancy are not associated with seizure exacerbation. Therefore, high serum estrogen levels alone are not sufficient to cause seizure exacerbation. (2) By contrast, high progesterone levels may mitigate against seizures during pregnancy and progesterone withdrawal during post -partum period may facilitate seizures.

2.119
DO WOMEN WHO HAVE HORMONAL EVIDENCE OF THE POLYCYSTIC OVARY SYNDROME WHILE TAKING SODIUM VALPROATE LOSE IT IF THEY SWITCH TO ANOTHER ANTICONVULSANT?

Frances Lefevre and Tim Betts (Birmingham University Seizure Clinic, Queen Elizabeth Psychiatric Hospital, Birmingham, United Kingdom)

Rationale: In a previous study of the effect of 3 different anticonvulsants on ovarian function in a group of women with primary generalised epilepsy who had only ever taken one anticonvulsant (sodium valproate, lamotrigine or carbamazepine), we showed that women taking sodium valproate but not an oral contraceptive were significantly more likely to suffer from the polycystic ovary syndrome than women taking the other two anticonvulsants (who were no different from a group of women of comparable age who did not have epilepsy). We used the American hormonal definition of the polycystic ovary syndrome as it is more accurate. (Betts T, et al. *Seizure* 2003;12:323–9).

We have now investigated whether women taking sodium valproate and suffering with the polycystic ovary syndrome lose evidence of this disorder if their anticonvulsant therapy is changed.

Methods: All 16 women taking valproate, who had the polycystic ovary syndrome, were switched to a different anticonvulsant (11 to lamotrigine and 5 to levetiracetam).

Results: The initial anticonvulsant drug switch was from sodium valproate to lamotrigine but some later additionally received levetiracetam (and were withdrawn from lamotrigine subsequently) to preserve seizure freedom. All but one patient (on lamotrigine) lost the hormonal evidence

of the polycystic ovary syndrome during the switch. This patient achieved pregnancy after one treatment with clomiphene.

Conclusions: Our findings show that evidence of polycystic ovary syndrome is likely to be lost in women taking sodium valproate if they are switched to either lamotrigine or levetiracetam. It is possible therefore that the increased number of women with the polycystic ovary syndrome on sodium valproate is a property of the drug itself (possibly its effect on insulin metabolism) and not a permanent effect if the drug is withdrawn.

2.120

IRISH WOMEN WITH EPILEPSY: ARE THEY RECEIVING SATISFACTORY PRECONCEPTUAL COUNSELLING?

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Rationale: Pre-conceptual counselling is of vital importance for women with epilepsy of childbearing age. Women with epilepsy require advice, education and guidance to enable them to make informed choices and guide their decision-making abilities. This in return will improve their quality of life and self -management practices. This audit identifies specific pre-conceptual women's issues and identifies whether women with epilepsy are receiving satisfactory pre-pregnancy counselling and leads the way for the establishment of a pre-conceptual Epilepsy and Pregnancy Clinic.

Methods: This audit obtained its sample of women with epilepsy (n = 150) from a weekly outpatient epilepsy clinic in a Dublin-based teaching hospital. The data was collected via questionnaires, using a random selection of women of childbearing age with epilepsy.

Results: To date, 35 questionnaires have been returned. From the returned data, 51% (18) were between 18–30 years, 46% (16) between 31–40 years, and 3% (1) between 41–45 years. Forty six percent (16) of the sample were single women and 37% (13) were married. Thirty percent of these women have had epilepsy for 2–8 years, 18% for 8–14 years, 30% (10) for 14–20 years, and 18% for 20 years and more; only 3% (1) have had epilepsy for less than 2 years (6%(2) were of unknown epilepsy duration). Fifty one percent (17) attended the neurologist every 6 months while 44% (12) attended their GP every 6 weeks. Thirty one percent (11) had previous pregnancies. Of the women who had previous pregnancies 36% (4) are planning future pregnancies, and of the women who have had no previous pregnancy 62%(15) are planning to have children. Eighty two percent (29) of the women said they were currently taking folic acid, with 65% taking a 5mg tablet. Forty five percent (16) of the women said that they were not given advice on contraception while on anti-epileptic drugs. Yet 71% (25) of women said they were currently on some form of contraception, the oral contraceptive pill (OCP) being the most common form. When asked to rate their satisfaction with pre-pregnancy advice that they received, 20% (7) were very satisfied, 23% (8) were satisfied, 14%(5) were unsatisfied, 6% (2) were very unsatisfied, and 38% (13) don't know/not applicable/didn't answer.

Conclusions: The results of the audit to date identify specific pre-pregnancy issues for women with epilepsy. It identifies the overall satisfaction rate of a sample of Irish women with epilepsy of childbearing age and leads the way for the establishment of a pre-conceptual Epilepsy and Pregnancy Clinic. It recognizes neglected areas of pre-conceptual counselling and highlights existing practices which will be reinforced and add to the overall quality of care of women with epilepsy in Ireland. [Supported by a grant from Bord Altranais (Nursing Board of Ireland).]

2.121

USE OF PROGESTERONE IN SELECTED WOMEN WITH REFRACTORY SEIZURES: ONE EPILEPSY CENTER'S CLINICAL EXPERIENCE

Julie K. Martin, George L. Morris, Pamela Smith, Jennifer Burgos, and Susan Loveless (Regional Epilepsy Center, St. Luke's Medical Center, Aurora Health Care, Milwaukee, WI)

Rationale: To examine our center's experience with the off-label use of progesterone for refractory seizures in selected women.

Methods: Our center developed a protocol for progesterone supplementation and patient education materials. A commercially available dosage form of progesterone (Prometrium®) was used for patient convenience and for possible prescription insurance coverage.

In Oct 2003, female patients with medically intractable seizures that increased in frequency around or during menses were offered progesterone therapy in addition to their current antiepileptic medications. Each patient received extensive education from our center's clinical pharmacist including therapy rationale and expectations, instructions, and side effects. Each patient received standard follow-up care at our center.

In Apr 2004, the charts of patients offered progesterone therapy were retrospectively reviewed for efficacy, side effects, and reason for discontinuation of progesterone if applicable. Patients were contacted via telephone or interviewed at a clinic appointment if necessary.

Results: Between Oct 2003 and Apr 2004, 6 patients were offered progesterone therapy. By April 30, 2004, 33% (2/6) of the patients remained on progesterone, 50% (3/6) of the patients discontinued progesterone due to lack of efficacy (1 of these patients also experienced an intolerable side effect), and 17% (1/6) of the patients chose not to start therapy. All patients were maintained on individualized regimens of therapeutic antiepileptic medications.

The majority of patients who started on progesterone later discontinued it due to lack of effect on seizure frequency. Of the five patients who started progesterone therapy, four patients continued it for an adequate (at least 3 month) trial period, and one patient discontinued it after 1.5 months due to a noticeable increase in seizure frequency. Of note, all patients offered progesterone have been difficult to treat. Of the 5 patients who started progesterone, each failed an average of 9 medications (range: 5–17) prior to progesterone therapy. All patients had also been treated with non-medication interventions including surgery, vagus nerve stimulation, or both.

Of the five patients who started progesterone, four patients reported side effects. One patient reported improvement in mood (favorable). One patient reported tolerable dizziness and continued therapy. One patient with a history of sleep difficulties reported insomnia, and one patient reported excessive fatigue that contributed to progesterone discontinuation.

Conclusions: Overall, our center experienced limited success using a regimen containing progesterone (as Prometrium®) in female patients with medically intractable seizures that increased in frequency around or during menses. In patients refractory to other therapies, a regimen containing progesterone may be an option with a low risk of intolerable side effects.

2.122

ELEVEN-YEAR INTERIM RESULTS OF AN INTERNATIONAL OBSERVATIONAL STUDY OF PREGNANCY OUTCOMES AFTER EXPOSURE TO LAMOTRIGINE

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Rationale: This international registry is part of an epidemiologic safety program monitoring pregnancy outcomes in women exposed to lamotrigine.

Methods: Physicians report exposure to lamotrigine during pregnancy and subsequent outcomes on a voluntary basis. Prospective (before there is any knowledge regarding the outcome) reporting early in pregnancy is encouraged as only the prospectively reported cases can be used to estimate incidence rates for outcomes. Major congenital malformations (MCMs) are classified according to the US Centers for Disease Control criteria and are reviewed by a pediatrician. The percentage of MCMs is calculated for prospective first trimester lamotrigine monotherapy and polytherapy exposures. Conclusions are developed and endorsed by a scientific advisory committee

Results: As of September 30, 2003, 10 MCMs were observed among 360 lamotrigine monotherapy exposures in the first trimester, a risk of 2.8% (95% CI 1.5%–5.2%). This compares to risks of 2 to 3% in the general population and 3.3% to 4.5% in women with epilepsy on AED monotherapy. The current sample size is sufficient to detect, with 80% power, a 1.85 fold increase in the risk of major malformations at the

5% statistical level assuming a baseline risk of 3%. The observed risk among 76 lamotrigine and valproate polytherapy first trimester exposures was 10.5% (95% CI 5.0%–20.2%) and was 3.1% (95% CI 1.1%–7.4%) among 163 first trimester exposures to lamotrigine polytherapy without valproate. Although the registry is not powered to detect with any accuracy the risk of specific malformations, no consistent pattern of malformation types was observed.

Conclusions: This is one of the largest studies examining pregnancy outcomes in prospectively reported first trimester exposures to monotherapy with lamotrigine. The risk of MCMs following lamotrigine monotherapy exposure is similar to that in the general population, though the sample size is insufficient to allow definitive conclusions. The higher frequency of MCMs following lamotrigine-valproate polytherapy exposure is consistent with published data on valproate monotherapy, though the registry is not powered to determine the individual contribution of each medication or to determine the effect of lamotrigine on the pregnancy risk associated with other antiepileptic drugs. Continued registration of exposed pregnancies will further enhance the statistical power of the study. (Supported by GlaxoSmithKline Epidemiology.)

2.123
DEFINING FETAL EXPOSURE TO LAMOTRIGINE

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Rationale: Ideal treatment of women on AEDs during pregnancy involves achieving a balance between minimizing fetal exposure to medications while maintaining seizure control. Previous studies demonstrated marked increases in total LTG clearances during pregnancy (>330% of baseline), often necessitating dosage increases for seizure control. Free LTG concentrations are the more relevant measures for effects on maternal brain as well as for fetal exposure. This study extends previous findings by looking at alterations in free LTG clearance (Cl) during the course of pregnancy, and examines fetal exposure by measuring umbilical cord free LTG concentrations at birth.

Methods: Nine pregnant women (7 epilepsy, 2 bipolar disorder) treated with LTG were followed in a prospective observational study. After obtaining informed consent, serum samples were obtained monthly during pregnancy and up to 4 months postpartum (n = 51 samples). Maternal and umbilical cord samples were also obtained in 6 mother-child pairs at delivery. Samples were stored at –80 °C until assay. Free LTG was separated from bound using Centifree cartridges from Millipore Corp, and measured by an HPLC-UV assay from Chromsystems, Munich, Germany. Cl was calculated as LTG daily dose (mg)/body weight (kg)/free LTG concentration (mg/L). Comparisons were made across perinatal stages using an ANOVA with unbalanced repeated measures design. Umbilical cord/maternal free LTG concentration ratios were calculated and evaluated by regression analysis.

Results: Clearance data within each perinatal stage are reported in Table 1. ANOVA revealed a significant main effect of perinatal stage upon free LTG Cl ($p < .01$). Cl values peaked in the third trimester to 205% of baseline postpartum values. Umbilical cord/maternal free LTG concentrations demonstrated a mean placental passage of 1.20 (±0.29). Regression analysis showed a strong correlation ($r^2 = 0.962$). Outcomes for all pregnancies were devoid of major malformations.

TABLE 1. *Free LTG Clearance across Pregnancy*

Daily Dose (mg/kg)/ Serum Concentration (mg/L)	1st Trimester	2nd Trimester	3rd Trimester	Postpartum
# of samples	6	19	18	8
Free LTG Cl	3.40 (0.55)	4.41 (2.70)	4.96 (2.83)	2.42 (1.29)

Free LTG Cl reported as Mean (SD) for each perinatal stage, ANOVA, $p < .01$

Conclusions: Free LTG Cl progressively increases during pregnancy, but to a lesser degree than that described for total LTG. Free LTG is the more pertinent compound for seizure control and for fetal risk. Substantial *in utero* exposure occurs with complete placental passage of LTG at all maternal concentrations studied. Therapeutic drug monitoring of free LTG may be warranted throughout pregnancy to optimize maternal and fetal outcomes. (Supported by a Specialized Center of Research P50 MH 68036.)

2.124
PRESCRIBING OF ANTIEPILEPTIC DRUGS IN PREGNANCY IN A NONACADEMIC COMMUNITY

Robert Rezek and Pavel Klein (Epilepsy, Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD)

Rationale: Potential for AED-related teratogenicity is a concern in the management of pregnancy in women with epilepsy. AEDs with documented teratogenic potential include older AEDs such as valproate (VPA), Phenobarbital (PB), phenytoin (PHT) and carbamazepine (CBZ). Less is known about the newer AEDs, but recent data suggests that lamotrigine may be safer than VPA or PB (1, 2). The present study was performed to ascertain the pattern of AED prescribing to pregnant women with epilepsy in a non-academic, community setting.

Methods: We ascertained the pharmacy database of a community hospital in the Maryland suburbs of Washington, D.C. for all AEDs prescribed in 2003 to women with epilepsy at the time of delivery. The hospital, Holy Cross Hospital, has the largest obstetrical service in the state of Maryland. The database was searched by diagnostic codes for parturition and epilepsy. All women who delivered in the hospital and had AEDs dispensed by the hospital pharmacy were included. The data was reducted in order to delete all demographic identifiers.

Results: There were 7153 deliveries during the year 2003. 25 women with epilepsy received AEDs at the time of delivery (0.35% of all deliveries). In the order of frequency, the AEDs used were phenobarbital, 6/25 (24%), phenytoin, 6/25 (24%), valproate, 5/25 (20%), carbamazepine, 3/25 (12%), gabapentin, 3/25 and fosphenytoin, 2/25.

Conclusions: AEDs with significant teratogenic potential such as valproate and phenobarbital are commonly prescribed during pregnancy in non-academic, community setting. More education of community physicians concerning pregnancy and epilepsy is needed.

2.125
EURAP: AN INTERNATIONAL REGISTRY OF ANTIEPILEPTIC DRUGS AND PREGNANCY

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Rationale: EURAP aims at comparing risks of major malformations following intake of antiepileptic drugs (AEDs) in pregnancy.

Methods: EURAP builds on networks of reporting physicians in Europe, Asia, Oceania and South America. Women taking AEDs at the time of conception are eligible for inclusion. Only pregnancies registered before foetal outcome is known and within week 16 of gestation contribute to the prospective study. Information on drug therapy and other potential risk factors is collected prospectively online each trimester, at birth and at one year after delivery. Foetal outcome is classified by a committee unaware of the type of drug exposure.

Results: By May 2004 physicians from 37 countries have reported more than 4,800 pregnancies to the Central Registry. By the time of the latest interim report November 2003, 2330 pregnancies meeting the inclusion criteria had been completed. Of these, 73% were prospective. There were 24 stillbirths, 16 perinatal deaths, 46 induced and 114 spontaneous abortions, and 1501 livebirths among the prospective pregnancies. 81% used a single AED,16% were on two AEDs. The most frequently used AEDs in monotherapy were carbamazepine (n = 506), valproic acid (n = 354), lamotrigine (n = 228) and phenobarbital (n = 115).

Lamotrigine and valproic acid (n = 41) and lamotrigine and carbamazepine (n = 35) were the most common combinations. 98 cases with malformations have been identified, including 10 cases among induced abortions, two among stillbirths and three of the perinatal deaths. This represents a malformation rate of 6%. Of the birth defects, 65 were observed after monotherapy (4.7%) and 33 after polytherapy (10%). It should be emphasized that this is a preliminary classification of outcome based mainly on the follow-up three months after birth. A formal comparison of malformation rates between different AEDs will be made when sufficient statistical power has been obtained.

Conclusions: Intensive on-line interaction between the central registry and reporting physicians has proven effective in ensuring enrolment and follow-up on an international basis. Comparative data on risks with the most frequently used treatments is expected to become available soon. [Supported by Presentation on behalf of the EURAP study group (www.eurapinternational.org) Scientific Advisory Board: Bernd Schmidt and Martin J. Brodie.

Educational grants from GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Sanofi-Synthelabo, and UCB SA.]

2.126

AUSTRALIAN PREGNANCY REGISTRY OF WOMEN ON ANTIEPILEPTIC DRUGS (AEDS): 5-YEAR RESULTS

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Rationale: Established in 1999, the Australian Registry enrolls women with epilepsy treated with AEDs, untreated women with epilepsy and those taking AEDs for other indications. It is a centralized observational study, with ethical committee approval and patient consent. Here we report the five year data from the Registry.

Methods: Four telephone interviews are conducted, and patients are enrolled prospectively as well as retrospectively. To date 830 women have contacted the registry, 630 have been enrolled, 565 pregnancies reached completion, including 10 sets of twins.

Results: There were 165 patients on valproate (VPA), 209 on CBZ, 129 on LTG, and 38 on PHT. The indication for the AED was predominantly for epilepsy (542 out of 555 women). Folic acid intake preconception was noted in 378.Truly prospective enrolment comprised 233, prospective 252 and retrospective 80 patient. Primary generalized epilepsy was present in 253 women, partial in 266, the remainder were unclassified. Live births with no defects comprised 89%, live births with defect 5%, spontaneous abortions 3%, stillbirths, induced abortion with defect and lost to follow-up 1% each. The categories of malformations comprised neurological (12), cardiac (11), craniofacial (7), skeletal (15) and genitourinary (15). Drug therapy with valproate had a significant increase over untreated patients in the incidence of malformations: in monotherapy (16.1%) vs. untreated. patients (2.5%: $p < 0.05$). On further analysis it was striking that the increase in VPA treated patients was related to dose, with greater than1100 mg per day associated with a high risk, ($p < 0001$). Lamotrigine was not associated with a single defect in monotherapy (61 patients), carbamazepine and phenytoin were similarly not significantly different from untreated patients. All seizure types were observed more frequently when patients were taking lamotrigine, than compared to VPA. The incidence of convulsive seizures was 5.3.% on VPA and 21,.3% on LTG ($P < 0.0029$). Seizure control on carbamazepine was not significantly different from VPA. Seizure control did not appear to related to teratogenicity, but did contribute to foetal loss.

Conclusions: The Registry is providing important information regarding pharmacotherapy for women who are pregnant or planning to become pregnant. The most striking finding is the relationship to higher dose VPA (>1100 mg) with a markedly increase risk of fetal malformations. However, it is also important to not that VPA was associated with better seizure control that other drugs. (Supported by Unrestricted research grants from The Epilepsy Society of Australia, Sanofi Synthelabo, Novartis, Janssen-Cilag, GlaxoSmithKline, UCB, and Pfizer.)

Nursing/Psychosocial/Health Services 2

2.127

PUBLIC AWARENESS AND PERCEPTION OF EPILEPSY IN BOSNIA AND HERZEGOVINA (B&H)

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Rationale: Social stigma is one of the unfortunate realities facing persons with epilepsy. Socio-cultural differences are key determinants of this process, and diligent effort is necessary to alleviate this aspect of suffering. However, periodic public surveys in the USA have shown that despite the unchanged level of public knowledge about epilepsy over time, public attitude has improved considerably. Targeted educational campaigns aimed at further improving public attitude towards epilepsy may be designed effectively based on current public knowledge and perception of epilepsy in a given community. This study was aimed at assessing, for the first time, public knowledge and perception of epilepsy in B&H, and represents the first step towards instituting a public health awareness campaign.

Methods: One thousand adults living in B&H (~4 mil.) were randomly selected according to region and size of community as part of a larger omnibus survey. The randomness was ensured in the three steps: a random choice of a community, random choice of initial points for "random walk," and using Troldahler-Carter method within a household. The participants were asked 12 questions about epilepsy by those trained in survey techniques. Standard statistical methods were used for data analysis.

Results: 91% of the respondents had either "read" or "heard" about epilepsy. Epilepsy was ranked the least severe among 8 diseases (schizophrenia, heart attack, AIDS, stroke, depression, peptic ulcer, lung cancer, and epilepsy). 41% knew someone with epilepsy, 32.5% had witnessed a seizure, and 33.1% did not know the main symptoms of epilepsy. The main symptoms were identified as foaming (29%), loss of consciousness (25%), fall (12.5%), convulsions (6.7%) and stiffening (5.9%). A moderate affective distance from epilepsy patients was expressed, as compared to a person with one of the other listed diseases, and, on average, interviewees were ready to accept a patient as a friend or coworker. Approximately 15% would object if their child played with a child with epilepsy, and 39% believed that a child with epilepsy could not succeed as a healthy child. According to this sample, the worst aspect of epilepsy is seizures (28.5%), followed by injuries (24.3%), fear of seizures (19.8%), and rejection by others (15.3%). While 55.9% would approach a seizing person and help, 25.9% would call "911" and 12.4% would "just yell to get help".

Conclusions: General awareness about epilepsy in B&H appears somewhat lower than in more developed countries. Surprisingly, epilepsy was perceived as a less severe disease than peptic ulcer. The majority of the population would accept a coworker or friend with epilepsy, and would approach and help a seizing person. The detailed context, specific confounding factors for these outcomes, and the utility of the data as a strategic basis for a public health intervention campaign are discussed. [Supported by PULS agency (Zagreb, Croatia) performed this survey as a part of its public work.]

2.128

SCHOOL COUNSELORS AND EPILEPSY: ARE NEEDS BEING MET?

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Rationale: The prevalence of epilepsy in the general population of children and adolescents in New York State is 2.7% (CDC, National Health Interview Survey, 1994–95). Also, 23–26% of youths with epilepsy suffer from depression, which may explain the increased suicides in this population (*Epilepsy Behav* 2003;4:S39–45). Unrecognized, their development is impaired and a poor long-term psychosocial prognosis is projected. Early detection and intervention is effective in reversing this outcome. The school guidance counselor represents a critical component in the care of these students.

Methods: A 10-item survey was sent to 1,471 schools in New York State. 177 (12%) school counselors, responsible for a total of 132,602 students, responded with information about their current caseloads of 53,104 students.

Results: 67 counselors reported having 174 students with epilepsy from their caseloads of 17,431 students with a total student body of 49,525. The survey asked them to weight 15 identified conflicts as to prevalence, with points being assigned to each conflict, 1 being the least prevalent and 5 being the most. In descending order, these conflicts predominated as follows: School achievement, 205 (10.0%); Depression, 166 (8.1%); Medication side-effects, 164 (8.0%); Fear, 162 (7.9%); Seizures, 158 (7.7%); Stigmatization, 149 (7.3%); Restrictions 144 (7.1%); Anger Management, 138 (6.8%); Disclosure, 134 (6.6%); Denial, 130 (6.4%); Additional Disabilities, 120 (5.9%); Driving, 111 (5.4%); Alcohol Abuse, 98 (4.8%); Narcotic Abuse, 88 (4.3%); Pregnancy, 73 (3.6%). For the question as to whether students with epilepsy were regularly screened for depression, 79% of these 67 counselors answered "No."

Conclusions: Statistically there is the potential of 1,337 students with epilepsy in our survey respondents' student population. Allowing for the fact that approximately 30% of students with epilepsy live with intractable seizures, and that those students would most likely present to counselors, approximately 401 students with epilepsy might be expected. Our study accounted for only 174. Despite the perceived prevalence of depression among the small percentage of students they see with epilepsy (it ranks second only to school achievement), counselors seem unaware of the co-morbidity of depression and epilepsy. An education program to apprise them of this disorder will help them to detect potential damage and intervene. (Supported by Epilepsy Foundation of Southern New York.)

***Abstract 2.129 has been withdrawn.**

2.130
PREDICTION OF THE APPEARANCE OF NONEPILEPTIC SEIZURES DURING EEG MONITORING

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Rationale: Neurologists must frequently make decisions as to whether or not referral for EEG monitoring is likely to produce fruitful results such as whether or not the attacks recorded are likely to be epileptic or nonepiletic. Data to guide making such decisions are frequently lacking.

Methods: 191 adults with reported spells underwent EEG monitoring for an average of 5.6 days. Of these, 163 demonstrated attacks which were either epileptic only (n = 116) or nonepilelptic (NES; presumed psychogenic) only (n = 47). The remaining cases were indeterminant or had both epilepsy and NES. Predictors of epileptic vs. nonepileptic attacks were as follows: 1) report to the social worker of physical, emotional, or sexual abuse from the patient's perspective during the developmental years (0 = no report of abuse; 1 = abuse reported in one of the three areas; 2 = abuse reported in more than one area); 2) age at onset of repetitive spells (0 = before age 21; 1 = after age 20); 3) reported frequency of attacks (0 = less than 1/d; 1 = 1/d or more; 4) psychiatric history (0 = negative; 1 = positive); and 5) gender (0 = male; 1 = female). A stepwise, buildup, linear regression model was employed.

Results: The first four predictors were entered by the computer into the prediction equation in the order described. History of abuse was the most potent predictor (R = .368), but this prediction was significantly improved with the stepwisse additions of early vs. late onset of attacks (R = 508), frequency of spells (R = .596), and history of psychiatric problems (R = .619). Gender did not add significantly to this predictive equation. Of interest was the fact that the four predictors were not greatly different in predictive power. Also, surprisingly, the predictors were almost uncorrelated with one another (median intercorrelation = .06). Therefore, a predicitve system was devised by simply adding up the scores from the four predictors (range 0–5 for summary score). This summary score was associated with percentages of epileptic and nonepileptic cases, respectively, as follows: score of 0: 100%, 0%; score of 1: 94%, 6%; score of 2: 69%; 31%; score of 3: 35%, 65%; score of 4: 23%, 77%; score of 5: 0%, 100%. With scores of 2 and less identified as epilepsy and scores of 3 and more identified as characteristic of NES, 82% of patients were correctly classified overall (90% epilepsy; 64% NES).

Conclusions: Not surprisingly, the prediction of whether epileptic or NES will be recorded at monitoring remains imperfect. Nevertheless, the predictive formula identified here is easy to use, and the necessary information can be obtained noninvasively at any clinic visit in very few minutes. As such, it should be of value in presaging the likely outcomes of EEG monitorings. The importance of the abuse variable is evident in this study involving NES patients, and it clearly requires additional attention in the future.

2.131
USE OF A STATEWIDE ADMINISTRATIVE DATASET TO DETERMINE NUMBER OF SEIZURE AND EPILEPSY CASES

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Rationale: This study examines whether statewide administrative billing data can be used for surveillance of seizure and epilepsy cases in South Carolina (SC). A critical issue is whether seizure and epilepsy diagnoses are accurately coded in such a database. Inpatient and emergency department (ED) ICD-9-CM discharge codes indicating possible seizure or epilepsy are being reviewed for accuracy.

Methods: We utilized a dataset of all 2001 inpatient and ED discharges from non-federal hospitals in SC. This database is housed at SC Office of Research and Statistics (ORS). A sample of approximately 35% of 345.x (epilepsy) diagnoses, 5% of 780.3 (convulsions), 1% of 780.2 (syncope and collapse), and 5% of 293.0 (acute delirium) was selected—approximately 3000 charts. If an individual had multiple visits, the highest-level diagnosis chronologically listed first was chosen. 2543 charts (85%) were abstracted by SC Department of Health & Environmental Control. Data was de-identified at ORS and sent to the Medical University of South Carolina (MUSC). At MUSC epilepsy specialists reviewed the data for appropriateness of diagnostic coding according to International Classification of Epileptic Seizures from the International League Against Epilepsy. The data presented is based on information from 547 (22%) of the abstractions reviewed thus far.

Results: In 43% of the cases, the reviewer agreed with the listed seizure- or epilepsy-related code, in 47% the reviewer felt the code was incorrect, and in 10% of the charts there was insufficient information to determine correctness. Of the 47% incorrect, however, most (86%) had a 780.39 code (seizure not otherwise specified) and a history of seizures, but not enough information to characterize the type of epilepsy. It is felt that these could have been more properly coded as 345.9 (epilepsy, unspecified). Whether a seizure was new onset is critical in determining incidence. 17% were new onset, 73% had a history of seizures, and in 10% of the charts there was insufficient information to make a determination.

Conclusions: Preliminary analysis appears to indicate an under diagnosis of epilepsy. While administrative data has limited information,

it has the advantages of representing the entire state and ease of use. While the present data does not include outpatient visits, there are additional outpatient datasets ORS may access that represent approximately one-third of the state population. It is planned to include this data to estimate incident and prevalent cases of seizure and epilepsy in SC. This study will help determine an accurate estimate of the number of cases of seizure and epilepsy, which will inform public policy on the appropriate allocation of resources. (Supported by Cooperative agreement with CDC, U36/CCU319276.)

2.132
EVALUATING EPILEPSY EDUCATION PROGRAMS
Novette S. Green, Laura Ponticello, Susan Sucic, Jung Hahm, Syed A. Hosain, Cynthia Harden, Andy Dean, and Douglas Labar (Comprehensive Epilepsy Center, New York Presbyterian Hospital-Weill Cornell Medical College of Cornell University, New York, NY)

Rationale: The Comprehensive Epilepsy Center provides educational seminars on epilepsy to community based organizations, businesses and corporations in New York City. The purpose of the educational program is to enhance general awareness and to educate the public about epilepsy, seizure safety and first aid. A study was conducted to evaluate the effectiveness of the program.

Methods: Nurse Clinicians from the Epilepsy Center provided epilepsy educational in-services to 6 organizations. Presentations were given based on an epilepsy education handbook created by the Center. A survey was performed after the presentation. Information was gathered on gender, age, prior knowledge of epilepsy, knowledge of understanding the information presented, and personal experiences related to epilepsy.

Results: 162 people completed the survey. 72% of the audiences were female, 26% were male and 2% did not indicate. 50% of the audiences were above the age of 50, 18% were ages 40–49, 21% were ages 30–39, 9% were ages 20–29 and <1% were below the age of 20.84% of the audience knew about epilepsy prior to the presentation and of those 77% indicated that they had a better understanding of epilepsy. All of the respondents (16%) that did not have prior knowledge of epilepsy indicated that they acquired knowledge, however, as a result of the program they stated that in retrospect, they realized that previously they had actually seen a seizure or know someone with epilepsy.

Conclusions: Epilepsy education is a welcomed choice even for those who have had prior knowledge. Conducting these educational programs have proven to be successful in educating the public about epilepsy, seizure safety and first aid.

2.133
UNDERSTANDING EPILEPSY PATIENTS THROUGH A PATIENT CONFERENCE SURVEY
Jung Hahm, Laura Ponticello, Susan Sucic, Novette Green, Luydmila Jovine, Cynthia Harden, Blagovest Nkolov, and Douglas Labar (Comprehensive Epilepsy Center, Weill Medical College of Cornell University, New York, NY)

Rationale: Our Comprehensive Epilepsy Center hosts an annual free educational patient conference for people with epilepsy and their families. The purpose of the educational program is to provide the latest information on epilepsy to people affected by this condition. In order to develop better understanding of the epilepsy patients who attend our conference, and their future educational interests, a survey was performed after the conference this year.

Methods: A written survey was given to the entire audience in the beginning of the conference and collected upon conference completion. Information was gathered on gender, age, understanding of the presentations, topics of interest, and how the attendees heard about our conference. The conference was open to everyone, but attendees were required to register. Seven speakers covered various epilepsy-related topics, which included memory, bone health, new research, stress, burn safety, and health insurance. Speakers were physicians, nurses, a social worker, a neuropsychologist, a government official, and a patient.

Results: 192 people attended the conference. 93 surveys were returned. 68% of respondants were female. 47% were above the age of 50. 72% responded that they understood all or most of the presentations. Topics of interest suggested by the audience for future conferences were epilepsy issues related to: children, women, diet, alternative medicine, and the workplace.

Conclusions: Our findings suggest women are more likely to seek out new health information than men. This may represent women's traditional familial role. Future topics suggested also seem to reflect women's epilepsy-related interests at home and at work.

***Abstract 2.134 has been withdrawn.**

2.135
TWO HELPFUL PREDICTORS OF PSYCHOGENIC SEIZURES IN AN EPILEPSY CLINIC: A SPELL IN THE CLINIC AND A HISTORY OF CHRONIC PAIN OR FIBROMYALGIA
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Rationale: Psychogenic nonepileptic seizures (PNES) are found in 20–30% of patients seen at epilepsy centers for intractable seizures. The diagnosis of PNES requires EEG-video monitoring, but for this to happen, clinicians must first *suspect* PNES in the clinic. We analyzed two independent "red flags" that we felt might predict an eventual diagnosis of PNES: 1) an antecedent diagnosis of "fibromyalgia" or "chronic pain; " and 2) the occurrence of a seizure in the clinic.

Methods: We reviewed the records of all patients evaluated in a single epilepsy clinic for refractory seizures over 5 years, who eventually underwent EEG-video monitoring. We collected two groups:

1) Group 1: Patients who carried a diagnosis of "fibromyalgia" or "chronic pain." These diagnoses had to be stated as such and patients had to be under the care of a pain specialist.
2) Group 2: Patients who had an episode during their visit, either the waiting area or the examining room.

We then looked at their final diagnosis following prolonged EEG-video monitoring.

Results: Group 1: We identified 28 patients with a diagnosis of "fibromyalgia" and 8 patients with a diagnosis of "chronic pain," for a total of 36 patients. After EEG-video monitoring, 27 ended up with a diagnosis of PNES. Five were found to have epilepsy, 2 other organic spells, and 2 received no diagnosis. Thus the positive predictive value of a diagnosis of "fibromyalgia" or "chronic pain" was 27/36 = 75%.

Group 2: We identified 13 patients who had a "seizure" during their clinic visit. After EEG-video monitoring, 10 ended up with a diagnosis of PNES, and 3 with a diagnosis of epilepsy, for a positive predictive value of 10/13 = 77%.

Conclusions: Both red flags, a history of "fibromyalgia" or "chronic pain" and the occurrence of an episode during the visit, have a high predictive value for an eventual diagnosis of PNES.

2.136
QUALITY OF LIFE, COPING, AND CHRONIC SORROW IN FAMILIES OF CHILDREN WITH EPILEPSY
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Rationale: The diagnosis of epilepsy in a child affects not only the child's quality of life (QOL) but also impacts on other family members. Parents use different coping behaviors to assist in dealing with their child's diagnosis. Chronic sorrow has been described in parents of children with other chronic health conditions. This is an ongoing study which aims to measure QOL in children with epilepsy, compare it with parental perceptions of their child's QOL, quantify chronic sorrow and study different coping behaviors in parents. A second aim is to delineate the relationships between health related QOL, coping and chronic sorrow in parents of children with epilepsy and to compare these variables with a population of children with migraine.

Methods: Children and their parents were enrolled from an outpatient neurology practice at a tertiary care children's hospital. All children who were able to were asked to complete a pediatric quality of life questionnaire (Peds QL^{TM}). Parents, in addition to completing the parent version of the Peds QL^{TM} also completed a coping health inventory (CHIP: Coping Health Inventory for Parents) and the Adapted Burke Questionnaire (a questionnaire to quantify chronic sorrow).

Results: Sixty-seven children with epilepsy (mean age 9.7 yrs) and 9 children with migraine (mean age 12.8 years) have been enrolled to date. Paired sample correlations of QOL data between 43 parent-child pairs show a good degree of correlation (0.6–0.8) across all domains which is highly significant ($p < 0.0001$). Paired sample t-test does not demonstrate significant differences between parent and child. The most significant impact on QOL is in the physical and psychosocial aspects. Chronic sorrow is highly prevalent with a mean score of 10.45 (maximum score = 24) with a standard deviation of 7.9 in parents of children with epilepsy. Chronic sorrow also correlates highly with coping style 2 (maintaining social support, self esteem and psychological stability) and with physical measures of QOL but has a negative correlation with the psychosocial measures of QOL. T- tests of QOL scores between patients with epilepsy and migraine demonstrate significant differences in the psychosocial and physical aspects, even with the small number of migraineurs enrolled so far.

Conclusions: There is good agreement between parent and child perception of the impact of epilepsy on the child's HRQOL. Chronic sorrow is highly prevalent in parents of children with epilepsy and correlates with specific coping behaviors. Structured interventions to influence these coping behaviors may decrease chronic sorrow and thus have a positive impact on parental perception of their childs HRQOL (Supported by St. Christopher's Foundation for Children.)

2.137
THE CONTRIBUTING FACTORS TO UTILIZE COMPLEMENTARY AND ALTERNATIVE MEDICINE IN KOREAN PEOPLE WITH EPILEPSY

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Rationale: To determine which factors are influential in complementary and alternative medicine (CAM) utilization in Korean people with epilepsy

Methods: The 246 Korean adult people with epilepsy (53.7% male, mean age 33.6 years) were recruited from out-patient clinic of a tertiary care hospital. Data about CAM utilization in the last five years and willingness of CAM use in the future were collected via a face-to-face semi-structured interview. To determine which factors contribute to CAM use, multivariate analysis using logistic regression was performed on variables that were significant ($p < 0.05$) in univariate analysis.

Results: (1) The utilization rate of CAM among Korean people with epilepsy was 31.3% during the last 5 years. Herb and health supplements were the most commonly used. On univariate analysis, the following variables were significantly associated with CAM utilization in the past: men, younger age, shorter epilepsy duration, higher educational level, higher economic status, and the belief in safety of CAM use. Multivariate analysis identified men ($p = .021$, OR = 2.3 [95% CI = 1.1 to 4.9]), higher economic status ($p = .010$, OR = 2.5 [95% CI = 1.2 to 5.0]), and the belief in safety of CAM use ($p = .001$, OR = 1.9 [95% CI = 1.3 to 2.9]). (2) About half of patients who had CAM utilization reported to be satisfied with their CAM use as a whole although only 28.6% of patients with CAM use said their seizure frequency decreased after CAM use. In 2 patients, their seizures were reported to be getting worse. (3) Out of our participants, 30.5% reported that they were willing to utilize CAM for their epilepsy in the future. Univariate analysis showed that experience of CAM use in th past, higher economic status, and the belief in safety of CAM use were related to willingness of CAM use in the future. Multivariate analysis identified experience of CAM use in th past ($p = .000$, OR = 8.4 [95% CI = 4.0 to 17.7]) and the belief in safety of CAM use ($p = .002$, OR = 1.7 [95% CI = 1.2 to 2.6]).

Conclusions: Each one third of Korean people with epilepsy reported to have CAM utilization in the past or to have willingness of CAM use in the future although only minority of CAM user reported the effectiveness in seizure frequency. The important factors contributing to CAM use were gender, economic status, experience of CAM use in the past, and the belief in safety of CAM use, but not seizure-related variables.

2.138
EVALUATION OF AN EPILEPSY EDUCATION PROGRAM FOR GRADE 5 STUDENTS: A CLUSTER RANDOMIZED TRIAL

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Rationale: Increasing awareness and decreasing stigma about epilepsy are priorities of the World Health Organization (WHO). There has been one published evaluation of an epilepsy education program for healthy children. This evaluation examined knowledge change following the program. There are no published studies of children's attitudes toward people with epilepsy, nor any evaluations of programs aiming to change attitudes. The objective of this study was to evaluate an epilepsy education program designed for grade five students to improve their knowledge and attitudes about epilepsy.

Methods: A stratified cluster randomized trial was conducted. Schools from 2 Ontario school boards were randomized to either the intervention (education) arm or delayed intervention control arm. Analyses were conducted using linear regression adjusted for clustering.

Results: Pilot study results indicated that the evaluation questionnaire has acceptable reliability (intra-class correlation coefficients ≥ 0.70; Cronbach's alpha > 0.70) and validity. The full study randomized a total of 24 schools (783 individuals). At baseline, on average, 40% of knowledge questions were answered correctly and attitudes were neutral (32/50 mean score where 50/50 would be most positive attitudes). One month following an epilepsy education program there was a highly significant increase in the intervention group compared to the control group in both knowledge ($p < 0.0001$) and positive attitudes ($p < 0.0001$). Significant predictors of post-intervention knowledge were "heard of epilepsy prior to program" and "seen TV commercial about epilepsy prior to the program." Significant predictors of post-intervention attitudes were sex, language spoken at home, knowing someone with epilepsy and having seen a seizure prior to the program.

Conclusions: The epilepsy education program evaluated was successful in improving knowledge and increasing positive attitudes about epilepsy. Future research could investigate if these changes hold over a longer period of time. Ideally, future research could investigate whether these changes translate into decreasing the stigma felt by people with epilepsy. [Supported by The Social Sciences and Humanities Research Council of Canada (SSHRC), the Research Alliance for Children with Special Needs (RACSN; fellowships), the Child Health Research Institute and Lawson Health Research Institute (internal research grants).]

2.139

RELATIONSHIPS BETWEEN FAMILY VARIABLES AND HEALTH CONDITION IN A NEW-ONSET SAMPLE

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Rationale: Childhood chronic illness can impose a burden in the lives of families. The purpose of the study was to explore the relationships among family variables and health condition in children with new-onset seizures and a control group of children with asthma. The specific research question was: How do family variables change over time in relation to health condition group (no additional seizures, additional seizures, or asthma)?

Methods: We followed 3 groups of children (101 had no additional seizures between 3–24 months, 95 had at least one additional seizure between 3–24 months, and 103 with asthma) age 8 to 14 years over a 2-year period. Baseline data for the previous six months were collected within 6 weeks of a child having a first seizure or being placed on daily asthma medications. Repeated measures analyses of variance were done to investigate the effect of health condition variables on the family variables of environment (mastery, satisfaction with family relationships, esteem/communication), parent behaviors (child autonomy, family life/leisure, child support, condition management confidence, child discipline), and parent affect (stigma, mood, needs for information/support, worries/concerns) over time (baseline, 6, 12, and 24 months).

Results: Parents of children with no recurrent seizures had the fewest worries/concerns and needs for information/support, and the lowest perceptions of stigma at all four times compared to parents of children with recurrent seizures or asthma. Family life/leisure was highest in the families of children with no additional seizures at all times. Across time, parent mood was lowest in the additional seizures group and highest in the no additional seizures group. At 6 months, parent confidence in disciplining their child was significantly higher in the asthma group than in the no additional seizure group, but at 24 months was significantly higher in asthma group than in the additional seizure group.

Conclusions: Epilepsy and asthma are chronic conditions of childhood that can be difficult for families. Our findings show that families of children who have no additional seizures are generally doing better than families of children with either recurrent seizures or asthma. These families have the fewest problems related to the family environment and parent behavior and affect. The recurrent seizures and asthma groups were relatively similar with the exception that parents of children with recurrent seizures had less confidence in their ability to discipline their children at 24 months. In the clinical setting parents of children with recurrent seizures should be assessed for mood and concerns related to disciplining their child. (Supported by NINDS 22416.)

2.140

SELF-DISCONTINUATION OF ANTIEPILEPTIC DRUGS DUE TO COST IN PATIENTS WITH REFRACTORY EPILEPSY

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Rationale: Self-discontinuation (SD) of AEDs is a subject that has received little attention. Most studies focus on noncompliance in situations, such as pregnancy or medication withdrawal after epilepsy surgery. There are no data on SD of AEDs due to lack of affordability. This study aimed to identify disease-related and socioeconomic factors associated with SD of AEDs due to its cost in a population of patients with refractory epilepsy.

Methods: We studied a group of 338 patients with refractory epilepsy admitted to the Cleveland Clinic Foundation Adult Epilepsy Monitoring Unit. Patients were asked to volunteer information regarding SD of AEDs due to cost. Seizure severity, type of therapy, health care utilization, income, major daily activity and coverage for payment was compared between the group admitting to SD of AEDs due to cost (SD group) and those who did not (control group). Fourty patients who did not provide adequate information were excluded. Chi square, t-test and regression analysis were used in the statistical analysis.

Results: The sample was comprised of 298 epileptic patients (52.7% female) between 15–73 years of age (mean = 36.14 years; +/−11.36). 34 patients (11.4%) had paroxysmal non-epileptic seizures (PNES) in addition to epilepsy. Only 28 patients (9.4%) admitted to SD due to cost. This group had more seizures with loss of bladder control [18 patients (66.7%) vs. 92 patients (40.6%); $p = 0.004$] and more accidents during seizures [22 patients (81.5%) vs. 169 patients (65.3%); $p = 0.001$] than the control group. Postictally, patients in the SD group had more restrictions for activities of daily living [19 patients (67.9%) vs. 115 patients (44.2%); $p = 0.014$] than the control group. SD group had more hospital admissions within the prior year [14 patients (53.8%) vs. 96 patients (36.9%); $p = 0.05$] and was more likely to be disabled [8 patients (29.6%) vs. 40 patients (14.9%); $p = 0.048$] than the control group. SD patients were less likely to have private insurance to pay for AEDs [8/28 patients (28.6%) vs. 162/270 patients (60%); Standardized Coefficient B (SB) = −0.17; Unstandardized Coefficient B (UB) = −0.10; Standard Error (SE) = 0.04; $p = 0.012$] and was more likely to be supported by drug assistance programs [6 patients (21.4%) vs. 12 patients (4.5%); SB = 0.19; UB = 0.23; SE = 0.73; $p = 0.002$]. No differences between the groups was found in age, gender, age of seizure onset, duration of epilepsy, seizure frequency, presence of other chronic diseases, type of AED therapy, number of AEDs, gross monthly cost of AEDs or source of income.

Conclusions: 9.4% of the patients with refractory epilepsy admitted to SD of AEDs due to cost. This group had more severe epilepsy (as expressed by accidents, health care utilization and life restrictions) and socio-economic disadvantages (as expressed by more disability and less coverage for treatment). We suspect that this number is an underestimate since some patients may fail to disclose noncompliance to their physicians.

2.141

PATIENT COMPLIANCE WITH TOPIRAMATE VS. OTHER ANTIEPILEPTIC DRUGS: A CLAIMS DATABASE ANALYSIS

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Rationale: Successful long-term management of epilepsy depends on patient compliance with antiepileptic drug (AED) regimens. Noncompliance resulting in suboptimal seizure control may increase healthcare costs. Noncompliance can also be a marker of patient satisfaction with therapy. We used refill data from a national managed care database of medical and pharmacy claims to assess patient compliance with phenytoin (PHT), carbamazepine (CBZ), valproate (VPA), and topiramate (TPM).

Methods: Data for patients with epilepsy, identified by ICD-9 codes, were collected from a database containing claims from 57 managed care health plans covering 33 million patients, providing a nationally representative sample. For each AED, prescription activity during a 1 yr period was used to calculate the "AED compliance ratio" based on days of medication possession—i.e., total days for which AED had been prescribed/filled divided by days between first detected prescription and last prescription for that AED during 1-yr follow-up. Assumptions with this method are that 1) patients continued AED therapy throughout follow-up period and 2) all AEDs prescribed were consumed. Patients with ratio $\geq$0.80 were deemed compliant. A logistic regression model quantified differences across AEDs, controlling for age, gender, comorbidities and combination therapy.

Results: A total of 20,774 patients with epilepsy and $\geq$1 yr data following an initial prescription for PHT, CBZ, VPA, or TPM between January 1, 1998 and July 30, 2003 were identified. 53% were male; mean (SD) patient age was 38.6 (12.7) yrs. The TPM cohort included significantly more women than men (58% vs. 46%, $P < 0.0001$). Compliance ratios: PHT, 0.78; CBZ, 0.78; VPA, 0.73; TPM, 0.82. Proportion of

compliant patients: PHT, 63%; CBZ, 63%; VPA, 53%; TPM, 68%. Based on logistic regression model, TPM was associated with 30% greater likelihood of compliance (≥0.80) compared with other AEDs (Odds Ratio = 1.30; P = 0.002).

Conclusions: Compliance with TPM was superior to that with PHT, CBZ, and VPA. Greater compliance suggests greater patient satisfaction with TPM therapy, with the potential for better outcomes in epilepsy. (Supported by Ortho-McNeil Pharmaceutical.)

2.142

RELATIONSHIPS BETWEEN FAMILY VARIABLES AND CHILD BEHAVIOR PROBLEMS IN A NEW-ONSET SAMPLE

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Rationale: Epilepsy introduces a challenge to the family unit that may be further complicated by the presence and extent of behavioral problems. Most previous research exploring relationships among family factors, child illness factors and child behavioral problems have been cross-sectional studies done with a chronic sample. This study addresses a gap in the literature by measuring the associations among family factors and child behavior problems in children experiencing new-onset seizures over a 24 month period. The study is strengthened by comparing those families whose children had no additional seizures after the onset period (N = 95) with those families whose children had at least one additional seizure (N = 101).

Methods: Data were collected four times (baseline, 6, 12 and 24 months) using structured telephone interviews with the primary caregiver. Child behavior problems were measured using the CBCL. The associations between twelve family variables and child behavior problems were analyzed over time using a repeated measures ANCOVA model after adjusting for (1) prior unrecognized seizures, (2) recurrent seizures between 3 and 24 months, (3) child age, (4) taking AED(s) and (5) recurrent seizures by time interaction effects.

Results: All twelve of the family factors in the investigation were related to total behavior problem scores in the expected direction. Seven factors demonstrated no differences between the two groups. Four family factors had relationships in both groups, but the relationships were significantly stronger in the additional seizures group. These were (1) family life and leisure, (2) parental stigma, (3) parental mood, and (4) parental need for support and information. Finally, one family factor (confidence in seizure condition management) was related to child behavior problems in the additional seizure group only. There were no differences in associations between family factors and behavior problems over time.

Conclusions: Although all family factors were significantly associated with child behavior problems in this sample, relationships between child behavior problems and several parent measures were stronger in families having a child experiencing recurrent seizures, suggesting that intervention may be especially important for these families. Regular assessment of child behavior and parental response to the child's condition should be part of the clinical management of the child experiencing a seizure disorder and his or her family. (Supported by grant PHS R01 NS22416 from NINDS to J.K.A. and NINR T32 NR007066.)

2.143

USEFUL ON-LINE COMPLEMENTARY MEDICINE SURVEYS IN EPILEPSY ARE PRODUCTIVE AND MAINTAIN PRIVACY

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Rationale: On-line patient surveys are a concern to practitioners in regards to state and federal regulations [Health Information and Patient Privacy Act (HIPPA)] governing the use and disclosure of individually identifiable health information (PHI). We sought to develop an on-line survey requesting information on patient's current therapies, quality of life and interest in complimentary medicines but void of any PHI.

Methods: With more than 2.5 million people having been diagnosed with epilepsy and over 180,000 new cases being diagnosed annually in the United States, the Director of the Regional Epilepsy Center of Aurora Healthcare, determined a complimentary medicine assessment in epilepsy was needed.

An on-line survey was designed for use by patients or anyone who knows someone with a diagnosis of epilepsy. The information included exposure to, interest in, and willingness to use Acupuncture, Massage, Aromatherapy, Chiropractic Care, Energy Work, Herbs and Supplements, Prayer, and Mind/Body Technique.

Discussions with the local IRB determined that PHI was not being accessed so therefore, IRB approval was not necessary. The survey was posted on the facility web site.

An informational letter from the practitioner was sent to his patient population directing patients to the Internet access or offering use of an "Internet Kiosk" at their next office visit. Verification from marketing and public affairs confirmed that an informational letter sent in this manner is not a HIPPA violation.

At the completion of the survey, if patients wanted additional information on complimentary medicine, the responsibility was placed on them to contact us. Therefore, PHI was not accessed.

Results: Forty six responses were obtained in two weeks. Prayer was reported as used, and with success, in the largest number of respondents (9/46). Prayer was also identified as the most likely of the Complimentary Medicines to be used in the future (14/46) followed by Aromatherapy (4/46), Mind/Body Techniques (4/46) and Herbs and Supplements (3/46).

Conclusions: On-line surveys for patients can be developed and used if no PHI is accessed. We created and are collecting survey information consistent with federal regulations. Complimentary Treatments can be assessed for interest and research planning. (Supported by Novartis Pharmaceuticals.)

2.144

UTILITY OF THE PERSONALITY ASSESSMENT INVENTORY (PAI) IN THE EVALUATION OF PATIENTS ON A LONG-TERM MONITORING UNIT

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Rationale: Despite increasing use in epilepsy centers as a measure of psychological functioning, the Personality Assessment Inventory's (PAI) utility has not been formally examined within this population. Past studies have used other objective measures of psychological functioning in an effort to discriminate between epileptic and nonepileptic seizure patients. This study examines differences between these patient groups using the PAI.

Methods: Sixty consecutive long-term monitoring patients completed the PAI as part of a comprehensive neuropsychological evaluation. Forty-five percent (n = 27) were discharged from the monitoring unit with a diagnosis of epilepsy only (EO), 32% (n = 19) with a psychogenic nonepileptic seizure diagnosis (PNES), and 23% (n = 14) of the patients had spells that were indeterminate in nature or did not have a typical event during monitoring (IS). Age, education, gender distribution, and WAIS-III Full Scale IQ were not significantly different between the three groups.

Results: PNES and IS patients scored significantly higher than the EO group on the Somatic Complaints scale on the PAI (p = .034). Specifically, these patients scored, as a group, in the clinical range on Somatic Complaints subscales measuring Conversion (p = .041) and Somatization (p = .034) symptoms. The subscale measuring Health Concerns measured in the clinical range for all three groups, but was not significantly different between diagnostic categories. Mean scores for all three groups fell within the normal range on all other clinical scales, with the

exception of the Depression scale. On this measure, IS and PNES patients scored in the clinical range at the group level while EO patients did not, but this difference did not reach significance. There were no differences on validity scales between the three groups, all of which fell within acceptable ranges.

Conclusions: The PAI appears to be a useful measure when evaluating patients on an epilepsy long term monitoring unit, and may aid in identification of patients who do not have epileptic seizures. Patients with documented PNES and those with indeterminate spells tend to report a higher number of somatic complaints, relative to patients with documented epilepsy only. Interestingly, patients with indeterminate spells produced PAI profiles quite similar to PNES patients. Future studies should examine the PAI's ability, in conjunction with other measures, to predict diagnostic group membership.

2.145
VAGUS NERVE STIMULATION IN THE DEVELOPMENTALLY DISABLED

[1,2]Susan A. Vitale and [2]Mary R. Andriola ([1]School of Nursing; and [2]Epilepsy Management Program, State University of NY, Stony Brook, NY)

Rationale: Vagus nerve stimulation (VNS) with the neuro cybernetic prothesis (NCP) is an approved treatment for epilepsy. It is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over twelve years of age with seizures refractory to antiepileptic medications. Clinical experience of developmentally disabled or mentally retarded patients with epilepsy indicates they benefit from VNS, however understanding their unique experience challenges traditional methods of evaluation. Supervised community residential staff and/or family members are uniquely involved with this category of patients, providing pre and post implant evaluations of patient status. The purpose of this study was to gain a better understanding of VNS, as a treatment in a developmentally disabled population who were living at home or in a supervised residential community setting.

Methods: A retrospective chart review was conducted on (N = 48) patients with an NCP implanted. There were 39% (19/48) with a diagnosis of developmental disability. Data were reviewed for age, gender, seizure classification, seizure frequency, VNS settings, side effects of VNS, duration of VNS therapy, antiepileptic medications, magnet use, and reports from family or supervised community residential care-givers.

Results: A total of (N = 19) patients were entered into the analysis. Age range was (3 to 54 years). and gender (M = 17 and F = 3). The majority had generalized seizures or complex partial with secondary generalization. Duration of VNS treatment ranged from 6 months to over 5 years. Lennox Gastaut was diagnosed in (N = 4). There were (N = 9) living at home with their families and (N = 10) living in a supervised group residential setting. One died due to complications not related to VNS, after one year of treatment. Only (N = 6) were capable of understanding the indications for VNS implantation and treatment effects. Only (N = 5) were capable of learning magnet self-use. The majority received magnet assistance from residential staff and family members. Staff of community group homes received inservice training on VNS treatment and offered suggestions for long-term monitoring of their residential clients. Staff followed a variety of residential VNS protocols designed for seizure recording and magnet use in their clients.

Conclusions: VNS appears well tolerated in this small group of developmentally disabled patients. Family and care-givers are significant to patient adjustment to living with VNS and their long-term treatment follow-up. VNS may be an important treatment consideration for this population of refractory patients.

2.146
PATIENTS WITH EPILEPSY: ARE THEY RECEIVING TIMELY AND ADEQUATE ACCESS TO SPECIALIST EPILEPSY SERVICES?

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Rationale: Since the late 1990's audit has gained considerable importance and is now a necessary component in the efficient planning and delivery of care to patients. We identified several issues which needed to be resolved before introducing a unique electronic patient record (EPR) system.

Methods: An audit of 10 adult neurology clinics (with a particular emphasis on epilepsy) over a 3 month period in a Dublin hospital was undertaken. Apart from basic demographic details, specific record was taken of diagnosis, waiting time and intellectual development. In a subset of patients, (20% of return epilepsy patients) appointment patterns, drug levels and educational issues relating to epilepsy were further evaluated

Results: Main results show that 85% of 'new' patients seen in the clinic had established epilepsy and these new patients waited on average 17 months for an appointment. The actual time waited in the clinic was 90 minutes.

Of the 25% of patients who had blood tests carried out, only 20% had any comment or intervention on the result recorded on the following out patient visit.

It was documented in 80% of charts that current driving regulations were discussed with the patient. The risk of sudden unexplained death in epilepsy (SUDEP) was not documented as being discussed in any of the charts biopsied.

Conclusions: The results of the study allow us to plan for various modules prior to the introduction of the EPR which may improve the efficiency of the clinic for example scheduling specific times for patients to reduce waiting times and integration with the hospital system laboratory results to avoid duplication of blood tests.

Clinical Neurophysiology–Adult 2

2.147
HEALTHCARE COSTS ASSOCIATED WITH NEWER ANTIEPILEPTIC DRUG THERAPY

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Rationale: Newer antiepileptic drugs (AEDs) offer many alternatives in the treatment of epilepsy, including broad spectrum efficacy, unique mechanisms of action, and tolerable adverse effect profiles. Data for patients newly initiated on AEDs were retrospectively assessed to examine differences in overall healthcare costs (inpatient, emergency room, outpatient, prescriptions) including treatment costs, monitoring, and costs related to adverse events.

Methods: The 1999–2003Q1 MarketScan Commercial Claims and Encounter Database of health insurance claims for employees/dependents affiliated with large Fortune 500 companies was used to identify adult patients diagnosed with epilepsy and newly initiating on newer AEDs (lamotrigine, oxcarbazepine, levetiracetam, topiramate, felbamate, gabapentin, tiagabine, and zonisamide). Patients were followed from initiation of AED treatment until termination of enrollment or administrative close of the database. Demographics, comorbid conditions, healthcare resource utilization, and healthcare costs were collected and compared between AED and versus matched non-epileptic patients.

Results: The study sample (n = 7,050) was 38% male, with a mean age of 44 years, and had an average length of follow-up of 1.5 years. Amongst the newer AEDs, median annualized total healthcare costs were significantly lower (t-test, all $p < 0.05$) for lamotrigine ($5,592), as compared to oxcarbazepine ($7,480), levitiractam ($9,829) topiramate ($9,309), and the other newer AEDs ($13,127). The primary drivers of differences in costs between AEDs were variances in outpatient care and pharmaceutical expenditures. For comparison, the median annualized healthcare costs for a matched non-epileptic population was ($1,726).

Conclusions: Compared to the non-epileptic population, healthcare costs are approximately 5 times higher for persons with epilepsy newly initiating anewer AED. Among newer AEDs, annual healthcare costs vary substantially by type of treatment prescribed. Research is underway to further examine these costs, including controlling for differences in baseline demographic and comorbidity characteristics across newer AED therapies—this work will be presented. (Supported by GlaxoSmithKline Inc.)

2.148
YIELD OF VIDEO/EEG MONITORING IN PATIENTS OVER THE AGE OF 50
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Rationale: Patients over the age of 50 represent the fastest growing segment of the population with new onset epilepsy. Co-morbid illnesses and variability of seizure semiology often lead to initial diagnostic uncertainty in older patients with spells or epilepsy, making video/EEG (VEEG) monitoring a useful diagnostic procedure. However, the yield of VEEG monitoring in patients over the age of 50 is not well characterized.

Methods: Following approval from our Institutional Review Board, all patients over the age of 50 admitted to the Iowa Comprehensive Epilepsy Program Epilepsy Monitoring Unit (EMU) were retrospectively identified. Patients were monitored in an inpatient setting with simultaneous VEEG recording. Events were identified with patient/observer event marking, computerized seizure and spike detection and review by a board certified clinical neurophysiologist. Data collected included age, sex, seizure types, interictal epileptiform discharges, ictal EEG patterns, and discharge diagnosis.

Results: Of 2,054 admissions to the EMU between January 1, 1995 and March 30, 2004, 326 (15.9%) admissions for patients over the age of 50 were identified. Patients were monitored for an average of 4.4 days (range: 1–19 days). 5 (1.5%) were diagnosed with primary generalized epilepsy and 90 (27.6%) with partial epilepsy. 77 (23.6%) patients had no spells recorded during their monitoring session, while 17 (5.2%) other patients had a non-diagnostic video/EEG. 129 (39.6%) patients were diagnosed with non-epileptic spells. 8 (2.5%) patients had multiple diagnoses following VEEG.

Conclusions: Patients over 50 years of age constituted a minority of patients monitored in our EMU. Our retrospective analysis demonstrates that 71.2% of monitored patients over age 50 had clinical spells recorded. Of these, 31.6% were diagnosed with epilepsy, while 39.6% had non-epileptic spells. VEEG is helpful in diagnosing epilepsy or establishing an alternative spell diagnosis in a majority of patients over age 50.

2.149
OCCURRENCE OF PSYCHIATRIC DISORDERS IN TEMPORAL EPILEPSY PATIENTS THAT UNDERWENT SURGERY IN A DEVELOPING COUNTRY
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Rationale: The aim of this study is to determine the current and past history of psychiatric disorders, in patients with refractory temporal lobe epilepsy included in the epilepsy surgical program, and determine the psychiatric outcome after surgery.

Methods: Twenty nine patients with standardized presurgical psychiatric assessment underwent temporal lobectomy for refractory epileptic seizures, and followed up for 6 month to four years after surgery. Psychiatric assessment included: Structural Interview, SCID I and II of DSM IV for past and current psychiatric disorders, psychopharmacological history, suicide attempts, and psychiatric institutionalization.

Results: Three different groups of patients were presurgical determined: nine patients (31%) without psychiatric disorders, nine patients (31%) with not severe psychiatric compromise and eleven patients (38%) with severe psychiatric compromise: current psychiatric disorders at the moment of presurgical assessment, psychiatric history, Axis I and Axis II co morbidity. This last group had a higher range of other psychiatric variables like suicide attempts (63%), psychiatric institutionalization (54,5%) and psychopharmacological history(45,5%). After surgery 31% developed a psychiatric disorder codified in Axis I of DSM IV, while most of them were total relief of seizures: Engel class I was observed in 89% of patients. Most patients without psychiatric co morbidity (89%), and patient with not severe psychiatric co morbidity (77%) did not have psychiatric complications after surgery. The third group showed controversial results; while some patients developed other and de novo psychiatric disorders (55%), like conversion, mania, psychoses and depression, other patients with both co morbid disorders in Axis I and II, were completely relief of symptoms in Axis I, and secondary get better in Axis II (45%).

Conclusions: Psychiatric disorders after epileptic surgery seem to be more common in patients with more severe presurgical psychiatric compromise, but some patients with both Axis I and Axis II co morbidity and severe psychiatric compromise, get better in both Axis symptoms after surgery.

2.150
THE ELECTROGRAPHIC DIFFERENTIATION OF TRIPHASIC WAVES WITH GENERALIZED NONCONVULSIVE STATUS EPILEPTICUS: NOT ALWAYS EASY
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Rationale: Triphasic waves (TWs) and generalised nonconvulsive status epilepticus (GNCSE) may share electrographic morphological features that create diagnostic ambiguity. The three phases of TWs are easily mistaken for the spike, trough and wave of epileptiform discharges. Both conditions are seen in patients with altered consciousness. The managment of the two conditions is quite different (treatement of the underlying metabolic encephalopathy for TWs and anticonvulsant drugs for GNCSE). A formal electrographic comparison of these two entities has not been performed.

Methods: We compared retrospectively the EEGs of two groups of patients: TWs associated with proven metabolic encephalopathy and GNCSE confirmed clinically. All EEGs were done over a period of five years at the same institution. Several EEG morphological features were analysed.

Results: We reviewed 63 EEGs (54 patients) with TWs and 22 EEGs (10 patients) with GNCSE. Decreased consciousness was present in all patients. When compared to TWs, epileptiform discharges had a higher frequency (mean = 2.6 Hz vs 1.9 Hz) ($p < 0.01$), showed more often extra-spikes components (60% vs 0%), ($p < 0.01$) and had less generalised background slowing (92.6% vs 20%) ($p < 0.01$). Lag of phase two was absent in all cases of GNCSE but present in 42.6% of patients with TWs ($p < 0.01$). Relative amplitude predominance of phase 2 within complexes (more than 50% of other phases) was present in 42.6% of patients with TWs versus none of the GNCSE patients ($p < 0.01$). Noxious or verbal stimulation frequently increased the amount of TWs (47.4%) while it had no effect on epileptiform patterns ($p < 0.01$). Electrode of highest voltage, distribution and duration of phase one were not helpful differentiating features in this study.

Conclusions: This study confirms the usefulness of some electrographic features to correctly differentiate TWs from GNCSE. Low frequency (<2 Hz), relative amplitude predominance of phase two, lag of phase two, background slowing and increased amount of complexes with stimulation were all suggestive of TWs.

2.151
MEG ULTRA-SLOW ACTIVITY IN EPILEPSY PATIENTS
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Rationale: Slow activity in the frequency range of 0.5–4 Hz has been described in the MEG of patients with brain tumors and ischemic lesions. DC MEG recordings have also been performed in migraine patients. To date there is no information in the literature on ultra-slow activity (0.1–0.5 Hz) in epilepsy patients. This study intended to explore to what extent these frequencies can be demonstrated and their relationship to ictal activity and the EEG.

Methods: The data were obtained on a Neuromag system. In the early cases 122 gradiometer sensors were available. In later ones 204 gradiometer and 102 magnetometers were used and the EEG was co-registered on 30 or 60 channels. The data were acquired with a bandpass from 0.1–90 or 0.1–120 Hz. Offline data analysis was performed with the BESA software. Ictal recordings were available in three patients and interictal in ten.

Results: Background ultra-slow activity, as defined above, was present in all recordings with an amplitude ranging between 6–113 fT (corresponding EEG amplitude was 5–16 μV). There was also intermittent focal increase in amplitude in various brain regions but these did not always correlate with the areas of interictal spike activity. In 9 patients continuous rhythmic activity of 4–5 second duration was present in the occipital or frontal areas which tended to wax and wane suggesting a biologic phenomenon but its nature is unclear at this time. Intermittent burst activity into the pT range was observed in 10 patients. These bursts were also visible in the usually sampled frequency range of 1–90 Hz but much shorter in duration. Relationships to seizure onset could not be observed and the mentioned MEG bursts had no consistent EEG correlates.

Conclusions: Since MEG is less contaminated by skin currents ultra-slow activity may be more reliably recorded by MEG than EEG. These currents exist as background activity but can show also widespread burst discharges in epilepsy patients. The relationship of focal and paroxysmal ultra-slow activity to other parameters needs further investigation as well as the nature of continuous rhythmic activity, which may be related to respiration. Further studies, which include the DC range, are indicated since they may demonstrate the internal milieu of the brain involved in epileptogenesis.

2.152
ANALISYS OF ICTAL AND POSTICTAL SEMIOLOGY IN PATIENTS WITH HIPPOCAMPAL SCLEROSIS AND PATIENTS WITH HIPPOCAMPAL SCLEROSIS PLUS

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Rationale: Magnetic resonance imaging (MRI) demonstrates abnormalities in the temporo-polar region in 1/3 to 2/3 of patients with hippocampal sclerosis (HS) that had been named HS- Plus.The aim of this study is to compare ictal and postictal clinical symptoms in patients with temporal lobe epilepsy (TLE) and pure HS, and patients with HS-Plus, diagnosed by MRI.

Methods: Blinded to clinical details, we reviewed ictal video-EEG recordings from patients with HS, and from patients with HS-plus. We analyzed all ictal and postictal symptoms. We reviewed 104 seizures in 32 consecutive patients. Patients were differentiated in 2 groups: group 1: HS patients, and group 2: HS-plus patients. Variables (symptoms) were analyzed by Chi-square or Fisher exact tests. To identify the variables that significantly contribute to differentiate the 2 groups we performed a binary logistic regression.

Results: Group 1: 18 patients, 51 seizures, and group 2: 14 patients, 53 seizures. The following symptoms were significantly more frequent in group 1: non-versive early head turning ($p = 0.013$), non-verbal ictal speech ($p = 0.002$), well-formed ictal speech ($p < 0.001$), hyperpnoea ($p = 0.032$); and in group 2 the more significantly frequent symptoms were: presence of an aura ($p = 0.003$), presence of more than one type of aura ($p = 0.017$), forced ocular version before (<10 s) secondary generalization: ($p = 0.034$), non-versive late (>10 s) head turning ($p = 0.005$), forced head version before (<10 s) secondary generalization ($p = 0.018$), forced unilateral mouth deviation ($p = 0.015$), unilateral clonias ($p = 0.037$), bilateral eye blinking ($p = 0.007$), postictal nosewiping ($p < 0.001$), and hyper salivation ($p = 0.031$). Using binary logistic regression, the strongest variables selected to differentiate the two groups were: non-versive late head turning (>10 s), forced head version before (<10 s) secondary generalization, bilateral eye blinking, non-verbal ictal speech and postictal nosewiping.

Conclusions: These observations suggest that different networks may be involved during seizures of patients with HS and HS-plus. Preoperative diagnosis of the entire temporal lobe pathology may be relevant for the surgical approach (ie, a temporal lobectomy as opposed to an amygdalohippocampectomy). (Supported by Buenos Aires University.)

2.153
THE ROLE OF EEG IN THE CRITICAL CARE SETTING

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Background: Non-convulsive status epilepticus (NCSE) is believed to be common in comatose patients and is presumed to increase morbidity and mortality. While the electroencephalogram (EEG) remains the only method of diagnosis, considerable disagreement exists regarding the definition of EEG criteria for NCSE. In addition, substantial resources are required to maintain 24-hour EEG coverage. The objective of this project was to determine whether EEG findings influenced acute management or were predictive of outcome in comatose patients.

Methods: EEGs and clinical charts were reviewed in 86 consecutive patients for whom EEGs were ordered during admission to a tertiary-care ICU. Patient outcomes were correlated with EEG findings, historical factors, and acute therapies.

Results: Of the 86 subjects: 9 (10.5%) had Periodic Generalized Epileptiform Discharges (PGEDs) or triphasic waves, 25 (29.1%) had interictal epileptic discharges, 1 (0.1%) had Periodic Lateralized Epileptiform Discharges (PLEDs), 7 (8.1%) had burst suppression pattern, and the remaining 44 (51.2%) had background disturbance without paroxysmal activity. Three (3.5%) of 86 had seizures recorded during the EEG. All 3 of these patients had clinical convulsions during their admission to hospital; 2 presented initially with clinical status epilepticus. Two of the 3 patients had both clinical and electrographic seizures during the EEG. None of the patients were found to have continuous seizure activity (NCSE). Thirty-three (38.4%) patients died, 35 (40.7%) were transferred to subacute hospitals or nursing homes and 18 (20.9%) were discharged home. Medical management was modified in 14 (16.3%) patients based on EEG findings. EEG findings and use of antiepileptic drugs (AEDs) did not correlate with patient outcome. Worse outcome was correlated with history of cardiac arrest and the presence of motor activity other than clonic seizures. Better outcome was correlated with convulsive status epilepticus and clinical evidence of convulsive seizures.

Discussion: Our finding of improved outcome in comatose patients with clinical evidence of seizures as compared to those without was unexpected based on the assumption that seizures are detrimental. These observations suggest that while patients presenting with convulsive seizures are likely to respond to AEDs, EEG changes and motor activity resulting from severe brain injury such as cardiac arrest may be manifestations of different underlying pathophysiology, which are unlikely to respond to AEDs.

2.154
LOCALIZATION OF ICTAL ONSET WITH DC SOURCE LOCALIZATION

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Rationale: Ictal discharges contain frequency components that are substantially below conventional recording bandwidth (<0.5Hz). We have previously shown that such slow activity may, on occasion, lateralize seizure origination better than the conventional EEG. In this study we expand on these observations by performing long-term (24–72 hour) direct current EEG recording with 27 channels, followed by analysis of the ictal recordings by principal component analysis.

Methods: A total of 65 seizures in 15 patients with focal epilepsy were recorded using a commercial system (NuAmps, Compumedics Neuroscan). A full array of Ag/AgCl electrodes was applied using the 10:10 system. A special connector was used so that conventional long-term video EEG monitoring could continue simultaneously with the DC recording. Afterwards, ictal events were exported to an EEG analysis software package (BESA 5.0, Megis Software). Segments for the 60-second interval preceding AC electrical seizure onset were decomposed into principal components, and current sources were modelled to correspond to the dominant components. This analysis was applied for sequental short intervals, studying the evolution of current sources. Ictal onset was determined to be when and where a current source first became dominant, being stationary for at least 5 seconds.

Results: Our results show that, for sources with high signal-to-noise ratio, and not obscured by slow artifact, clear localization consistent with other clinical data can be determined. In such patients, localization of the dominant DC component (PCA weighting >90%) can be discerned up to 20 seconds before apparent AC onset, even when lateralization via traditional EEG techniques was inconclusive. When available, subsequent invasive monitoring confirms the DC localization.

Conclusions: DC-EEG recordings can give useful additional information to noninvasively localize the epileptogenic focus. The value of this method is increased by mathematical analysis that can reveal highly localized changes not apparent on direct visual inspection.

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2.155
AMYGDALA ONSET SEIZURES: CLINICAL, ELECTROPHYSIOLOGIC, AND PATHOLOGICAL FINDINGS

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Rationale: To define amygdala onset seizures in relation with the clinical, electrophysiological, neuroimaging and pathological changes.

Methods: Clinical, extracranial EEG, MRI, and pathological findings, as well as surgical outcome were retrospectively analyzed in 13 patients with intractable temporal lobe epilepsy and focal AOS defined by depth electrode studies (D-EEG). All underwent temporal lobectomies with amygdalohippocampectomy. The amygdala and the hippocampus were removed en bloc in seven.

Results: A presumed etiology was present in 8 patients, and included meningoencephalitis with or without febrile convulsion (FC), isolated FC, and parasitic infection. Seizures were complex partial only in 6 (46%) and complex partial with secondary generalization the other 7 (54%). Extracranial EEGs failed to lateralize the ictal onset zone. Low voltage fast activity was the most common electrographic pattern at ictal onset on D-EEG (9 patients, 69%). *Ictal discharges propagated first to the contralateral temporal lobe in 2 (15%).* MRI abnormalities were seen in 10 patients, and suggested simultaneous sclerosis of amygdala and hippocampus in 6 (46%), isolated hippocampal sclerosis in 3 (23%), and parahippocampal gliosis in one (8%). The imaging abnormality was always concordant with the side of resection. Amygdaloid sclerosis was present in all patients on histopathology, being mild in 9 (71%), moderate in 2 (14%) and severe in the other 2 (14%). Ten patients are seizure free, one is almost seizure free, and the other two had a worthwhile improvement after operation, after mean follow-up of 59 months.

Conclusions: AOS are arise from sclerotic amygdala of varying severity, can only be confirmed through D-EEG studies, and may first propagate to the contralateral temporal lobe, potentially leading to mislateralization of ictal onset on scalp-sphenoidal EEGs. Surgical outcome was excellent in the majority of patients.

2.156
MEASURING SYNCHRONIZATION AND DIRECTIONALITY IN EEG TIME SERIES FROM EPILEPSY PATIENTS: AN APPLICATION TO SEIZURE PREDICTION

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Rationale: An unresolved question in epileptology is whether epileptic seizures can be predicted by characterizing measures of the EEG. In a recent comparison of univariate and bivariate measures we have shown the latter to be superior (unpublished date). However, so far only symmetric bivariate measures for synchronization were evaluated. In this study a comparison of 16 different measures for both synchronization and directionality was carried out with respect to their capability to discriminate pre-seizure from seizure-free intervals with special emphasis placed on statistical validation (Kreuz et al. *Physiol Rev* E, in press). Furthermore, we investigated to which extent different measures carry non-redundant information.

Methods: We analyzed continuous multi-day, multi-channel EEG (total duration: 860 hrs., 66 seizures) recorded intracranially from 9 patients with focal epilepsies. Symmetric measures included cross correlation, mutual information, and phase synchronization (based on Hilbert and wavelet transform, respectively); asymmetric measures comprised transfer entropy, non-linear interdependencies, and event synchronization. Time dependent measure profiles were evaluated using a statistical approach (Receiver-Operating-Characteristics; ROC). The analysis was performed as in our previous work (unpublished data) allowing different lengths of the pre-ictal interval and testing for both a pre-ictal decrease and increase. Two different evaluation schemes were designed focussing either on global or local effects. The statistical significance was estimated using seizure times surrogates (Andrzejak et al. *Physiol Rev* E, 2003). Finally, redundancies between these measures were quantified using correlation analysis.

Results: In the first evaluation scheme all measures yielded poor performances and no measure proved to be significant. In the second evaluation scheme performances were considerably higher and, more importantly, for the most part significant. Maximum values were obtained for phase synchronization, minimum values for the symmetric non-linear interdependencies. While the measures of directionality covered the same range as the measures of synchronization, correlation analysis showed that both groups provide non-redundant information.

Conclusions: While no significant global effect could be observed, some measures of synchronization as well as some measures of directionality proved capable to detect significant local effects. Due to their non-redundancy a combination of these different approaches appears

promising. However, more research has to be carried out to evaluate whether these statistical results allow to yield an acceptable performance for broader clinical applications. (Supported by Deutsche Forschungsgemeinschaft.)

2.157
SEIZURE PREDICTION: MEASURING EEG PHASE SYNCHRONIZATION WITH CELLULAR NEURAL NETWORKS
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Rationale: Anticipation of epileptic seizures is, among others, the most challenging aspect in epileptology. Recent studies have shown that particularly measures which characterize the degree of synchronization between two EEG signals allow an improved differentiation between the seizure-free interval and the pre-seizure period. Despite the conceptual simplicity of a number of these bivariate measures, real-time applications are currently limited by calculations for large number of combinations of electrodes. In this study we examine the ability of Cellular Neural Networks (CNN) to accurately approximate the degree of synchronization (as defined by the mean phase coherence R) between two EEG signals. CNN have a massive computing power, are capable of universal computation, and are already available as analog integrated circuits.

Methods: In order to find optimum network settings we performed an in-sample supervised training using 24 randomly selected pairs of EEG epochs (epoch duration: 23.6 sec.) recorded intracranially during the seizure-free interval and the pre-seizure period from three epilepsy patients along with the corresponding values of the mean phase coherence R. For an out-of-sample validation and in order to study the long-term behavior of our CNN-based approximation for phase synchronization, network settings were then tested on multi-day, multi-channel EEG recordings.

Results: CNN with polynomial weights allowed to approximate the temporal evolution of mean phase coherence R with a stability and an accuracy (more than 90%) that can be regarded sufficient to distinguish between the seizure-free interval and the pre-seizure period. Interestingly, the obtained CNN allowed to approximate R values even from the ictal and post-ictal state with a comparable accuracy although we did not use data from these states for the training.

Conclusions: CNN allow an accurate and stable approximation of the degree of phase synchronization between two EEG signals. This ability along with the high computational power and the small energy and space requirements render CNN attractive for future implementations in a hardware environment to be used as a miniaturized supercomputing device for real-time applications. (Supported by The Deutsche Forschungsgemeinschaft.)

2.158
ICTAL NEGATIVE MOTOR PHENOMENA ASSOCIATED WITH FAST EPILEPTIC DISCHARGES
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Rationale: Focal motor negative phenomena have been described in seizures primarily involving negative motor areas (opercular pre-motor and medial pre-motor regions) and the rolandic region (post-central or pre-central). The localizing value of such signs and the mechanisms by which an epileptic discharge may generate negative phenomena remain debated. Our objective is to study the localizing value of ictal facial paralysis and possible mechanisms of ictal negative motor phenomena.

Methods: A 32-year-old right-handed woman underwent a presurgical evaluation for medically intractable epilepsy by Stereo-Electro-Encephalography (SEEG). During the video-SEEG and EMG recording both negative and positive motor seizures were observed. We compare the spatial and temporal characteristics of the epileptic discharges associated with positive and negative motor signs.

Results: Nine positive and 27 negative motor seizures were recorded. All were generated within the same area (right opercular central area, Brodmann Area 4). All the seizures started with a slow and sharp wave followed by a rhythmic discharge. The 2 different types of clinical seizure were differentiable by their power/frequency spectrum: positive motor seizures were associated with an alpha-beta band discharge while negative motor seizures were associated with a gamma band discharge.

Conclusions: Both negative and positive ictal motor phenomena may be produced in the primary motor cortex. We propose that within the primary motor cortex, high frequency sustained discharges (>40 Hz) may disrupt the ongoing excitatory drive to the peripheral motoneurons while sustained lower frequency discharges (<40 Hz) may activate the cortico-nuclear or cortico-spinal pathway and produce positive motor signs.

2.159
DIAGNOSTIC YIELD ON INPATIENT INTENSIVE SEIZURE MONITORING
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Rationale: The yield on intensive inpatient monitoring depends on, among other variables, the reasons for admission and the duration of monitoring. The latter variable is linked to the length of patients hospital stay (LOS), which in turn is closely monitored by third party payors and hospital administrators. We undertook this study to assess the yield of intensive inpatient seizure monitoring in the context of short term LOS.

Methods: We retrospectively reviewed our database of adult patients electively admitted to the Epilepsy Monitoring Unit (EMU) at Westchester Medical Center for further diagnostic evaluation and management, during a 5-year period February 1999-February 2004. All cases were evaluated by one of two adult epileptologists as outpatients prior to EMU admission. The reasons for EMU admission included: 1) to document event, 2) to establish specific diagnosis, 3) to classify seizure type, 4) to localize seizure focus, 5) pre surgical evaluation and 6) antiepilepsy drugs (AED) adjustment. Pre and post EMU variables to be analyzed included seizure diagnosis, EEG interictal and ictal abnormalities, documentation of habitual or new clinical events, and AED treatment. Admitting diagnosis was sub classified as follows: clinical diagnosis of established epilepsy, probable epilepsy, suspected nonepileptic psychogenic seizures (NEPs), or simply to rule out (r/o) seizure disorder. Activation procedures consisted of sleep deprivation, hyperventilation, photic stimulation, and aggressive AED taper.

Results: 123 subjects were identified. The age range was 18 from 86 years (mean 38 years) 43 male, 80 female. Mean length of stay was 3.0 days. Initial admitting diagnosis: established epilepsy 56/123, probable epilepsy 30/123, NEPs 22/123, r/o seizure disorder 15/123. Clinical events were recorded in 81/123 (65.8%). Out of 81, 54 (66.6%) had ictal EEG correlate. 25/81 subjects (30.8%) were diagnosed as definite NEPs. In two subjects, the study was inconclusive due to failure to capture the habitual clinical events.

Conclusions: In our study, positive diagnostic yield (specific diagnosis established) was obtained in 79/123 (64%) in contrast to a negative yield or inconclusive study in the remaining 44 patients. We consider that the reasons for the high positive yield despite the short restrictive LOS include careful and consistent adherence to admission criteria and a systematic approach with activation procedures implementation. Our experience has demonstrated that carefully planned intensive seizure monitoring is a cost effective procedure in a restrictive managed care environment.

2.160
SLOW CORTICAL POTENTIAL CHANGES IN PATIENTS WITH EPILEPSY AFTER GALVANIC SKIN RESPONSE (GSR) BIOFEEDBACK TREATMENT
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Rationale: Biofeedback is one behavioral intervention that allows representation of unconscious physiological processes in a consciously accessible form (e.g. by means of a visual display), allowing patients

to be trained to modulate these processes. A number of biofeedback approaches have been suggested for the management of epilepsy. In a previous study, we have shown a robust effect of Galvanic Skin Response (GSR) biofeedback treatment in reducing frequency of seizures in patients with epilepsy. The rationale of this approach is based on a previous study in which we demonstrated an inverse relationship between GSR and the amplitude of the contingent negative variation (CNV) in healthy subjects, in that increases in peripheral sympathetic activity were associated with reduction in an EEG index of cortical neural excitation. Furthermore, an imaging study has demonstrated that generation of CNV involves a thalamo-cortical circuit and that peripheral GSR activity modulates this circuit. Together, these findings suggest that GSR biofeedback may influence, directly or indirectly, thalamo-cortical sensory regulation circuits, and modulate the seizure threshold by altering thalamic excitatory input to the cortex. Thus it is worthwhile to pursue such treatment related modulations of the CNV in patients with epilepsy.

Methods: Eighteen patients with drug refractory epilepsy were randomly assigned either to an active GSR biofeedback group ($n = 10$) or to the sham control biofeedback group ($n = 8$). Patients participated in a total of 12 sessions over 4 weeks, during which they received either real GSR biofeedback training, where they were trained to decrease skin resistance using biofeedback, or sham training, where the feedback was unrelated to the subjects' GSR. Contingent Negative Variation (CNV) was measured before and after the biofeedback and sham control treatments.

Results: Biofeedback training significantly reduced patients' seizure frequency in the active biofeedback group ($p = 0.004$), but not the control group ($p > 0.10$). This was manifest as a significant between group differences in seizure reduction ($p = 0.007$). The CNV amplitude was significantly reduced after training in the GSR biofeedback (active) group, but not in the sham control group.

Conclusions: Our findings support the hypothesis that GSR biofeedback training can lead to both a reduction in seizure frequency and CNV amplitude in patients with epilepsy. (Supported by Bial Foundation and Raymond Way Fund.)

2.161
TIME DOMAIN SOURCE LOCALIZATION (TDSL) BASED ON ICTAL EEG RECORDINGS

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Rationale: 3D source localization of an epileptic seizure using non-invasive EEG recordings often suffers from inaccuracies resulting from other activity generators not related to the epileptic zone. These generators may be active for only short time intervals in parallel to the source activity, shielding epileptic-relevant information. Localizing the epileptic zone using methods as BESA is based on extracting features related to the spatial form of the wave in a given very short time interval. In contrast, our new method, TDSL, is based on identifying ictal epileptic-relevant information on a much longer time scale, reducing the influence of other sources. In cases of a single epileptic focus we aim at isolating the activity resulting from that source, and then by applying a dipole source localization algorithm, identify the exact location.

Methods: We analysed three scalp ictal EEG recordings from patients with temporal lobe epilepsy. These patients were known to have a single temporal epileptic focus confirmed by MRI scan and a subsequent surgical procedure. Scalp EEG was digitally recorded with electrodes placed according to 10/20 system, using 23 channels. An interval of 4–6 seconds from the onset of each ictal scalp recording was sliced as an input data to the TDSL algorithm for identifying source-related typical rhythmic waveform in each electrode during the time interval. The result of this process, namely, the epileptic activity in each electrode, was used as an input to the localization process based on solving the EEG inverse problem.

Results: In these three patients our algorithm has accurately identified the ictal onset zone in accordance with raw EEG analysis and the subsequent surgical outcome.

Conclusions: The results of this preliminary study illustrate the possible contribution of a time domain source localization analysis of ictal EEG epileptic activity. TDSL methods may also be used to evaluate the propagation of the epileptic activity to cortical areas distant from the source.

2.162
DETECTION OF SEIZURE PRECURSORS IN THE EEG WITH CELLULAR NEURAL NETWORKS

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Rationale: Despite a number of approaches that have been introduced to the field of seizure prediction the detection of features predictive of an impending seizure remains unsolved. Recent studies have shown that nonlinear feature extraction algorithms may be useful for the detection of precursors that exhibit distinct changes in the pre-seizure period. In previous investigations we have proposed algorithms for signal prediction based on multi-layer discrete time Cellular Neural Networks (DTCNN) and Volterra systems. Furthermore, we introduced a so called Pattern Detection Algorithm (PDA) for standard CNN which is based on the analysis of the level-crossing behavior of the EEG. In this contribution recent results for the CNN prediction algorithm and for the PDA will be discussed in detail.

Methods: Firstly, PDA is based on a binary input-output CNN with linear weight functions. A CNN with 72x72 cells is used to map an EEG segment of 30 seconds duration (5184 data points) to the CNN output activity. Depending on the neighborhood range of the considered network a so called window pattern is defined, e.g. as a 3×3 binary pattern, which is obtained from the binarized EEG. As will be shown later, one or more patterns, that show distinct changes in their rate of occurrence before seizure onset, can be found for each patient. Secondly, based on multi-layer DTCNN with polynomial weight functions, the nonlinear prediction of the EEG is discussed. The coupling weights and the prediction error of the obtained predictors have been analyzed in order to find appropriate features which may be used for a pre-seizure state identification.

Results: Using the PDA our results show that for each patient one or more patterns can be found, showing distinct changes in their rate of occurrence before seizure onset. Two types of patterns can be found for all patients that are defined by their type of occurrence. A first overview of the results obtained from a nonlinear prediction of the EEG using DTCNN shows that the prediction error and a measure derived from the coupling weights exhibit distinct changes before and at seizure onset. Applying these techniques to long-term EEG recordings we observe a decrease of the linear weights over a period of several hours which is accompanied by an increase of the nonlinear weights.

Conclusions: Our preliminary results underline the importance of CNN-based feature detection algorithms for a realization of a miniaturized seizure prediction device. CNN-based analog cellular computing is a unified paradigm for universal spatial-temporal computation. CNN-based realizations with stored programmability show an enormous computation capacity with trillions of operations on a single chip. (Supported by the Deutsche Forschungsgemeinschaft.)

2.163
SPATIAL SYNCHRONIZATION MAPS FROM INTRACRANIAL EEG RECORDINGS ALLOW DIFFERENTIATION OF ANATOMICALLY AND FUNCTIONALLY DISTINCT BRAIN STRUCTURES

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Rationale: Patients suffering from intractable focal epilepsy may benefit from neurosurgical resection of the epileptic focus if this focus can be identified via electroencephalographic recording of the seizure onset. In cases where the seizure origin can not be identified unequivocally

from surface EEG recordings, implantation of intracranial electrodes can be indicated to achieve a better spatial resolution. Exact knowledge of the location of the implanted electrode contacts is crucial for evaluating these recordings. Electrode positions are usually verified by MRI scans, which are sometimes difficult to interpret due to artifacts caused by the electrode material. In this study we evaluated spatial synchronization maps calculated from intracranial EEG recordings to detect structural and functional boundaries and thereby supply additional information about electrode positions.

Methods: We analyzed intracranial EEG recordings from the seizure-free intervals of 19 patients with medically intractable medial temporal lobe epilepsy undergoing invasive presurgical diagnostics. EEG signals were recorded via bilateral intrahippocampal depth electrodes, each equipped with 10 recording contacts and implanted stereotactically along the longitudinal axis of the hippocampal formation. The total recording time comprised more than 40 hours. As a measure for phase synchronization, the mean phase coherence R was calculated for all channel combinations within each hemisphere using a moving window technique resulting in a time series of spatial synchronization maps for each hemisphere. After evaluating the temporal stability of the maps, an automated cluster analysis was performed to track boundaries characterized by a spatial gap in synchronization along the hippocampal formation. Findings were then compared to post-implantation MRI scans.

Results: Spatial synchronization maps from both hemispheres proved stable over time. Synchronization gaps obtained from the automated cluster analysis corresponded well to anatomical boundaries of the hippocampal formation as evidenced by post-implantation MRI scans.

Conclusions: Spatial synchronization maps obtained from intracranial EEG recordings can provide valuable information about electrode placement with respect to anatomical and functional boundaries. Due to the temporal stability of these maps, even short recordings provide a robust estimation of these boundaries. (Supported by The Intramural Research Fund BONFOR of the University of Bonn and the Deutsche Forschungsgemeinschaft.)

2.164
VERBAL MEMORY IN PATIENTS WITH LATERALIZED RIGHT TEMPORAL LOBE SEIZURES: RELATIONSHIP TO THE INITIAL PRECIPITATING INJURY AND SURGICAL OUTCOME

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Rationale: In the surgical candidate with intractable complex partial seizures, a neurocognitive profile that lateralizes to the suspected temporal lobe (TL) provides confirmatory evidence of the primary seizure focus. In some patients, however, there is cognitive evidence of involvement of the contralateral hemisphere. The etiologies of the collaborative lateralized cognitive changes have been well addressed; however, little information is known regarding the cognitive changes in the contralateral temporal lobe. Our research addresses a) the relationship of bilateral cognitive changes in patients with documented lateralized temporal lobe onset to presence and type of initial precipitating injury (IPI) and b) the surgical prognostic value of the bilateral neurocognitive deficits.

Methods: Subjects were 316 surgical candidates with intractable epilepsy whose primary seizure onset was localized to the left (140) or right TL(176). Independent variables were presence or absence of IPI and type of IPIs (i.e., prolonged seizure, brief seizure, or a nonseizure event). The preoperative neurocognitive data included Verbal IQ (VIQ), Performance IQ (PIQ), the Boston Visual Confrontation Naming Score, and a Hard Word-Pairs Verbal Learning score from the WMS. Seizure outcome after surgery was based on a 1–4 rating scale, with R1 being seizure free, R2 fewer than 6 seizures per year, R3 between 0.5 and 2 seizures per month, and R4 more than 2 seizures per month.

Results: The group of patients with LTL seizures, as compared with the group of with RTL seizures, had lower VIQs ($p < .02$), Naming scores ($p < .002$), and Verbal Learning scores ($p < .0001$). In the LTL group, neither the presence or absence of an IPI or the type of IPI related to the cognitive scores. However, in the RTL group, a prolonged seizure as the type of IPI related to lower Verbal Learning scores, but not to the Naming scores or IQ scores. In RTL patients, an IPI of a prolonged seizure was more predictive of lower Verbal Learning scores than either brief seizures ($p = .05$) or nonseizure injuries ($p < .03$). Also, in the RTL group, using a logistic regression model, Verbal Learning scores had stronger predictive value of surgical outcome than a history of a prolonged seizure. Lower Verbal Learning scores in RTL patients were associated with a lower probability of surgical seizure control ($p < .03$).

Conclusions: A history of a prolonged seizure as the IPI is associated with the presence of poorer verbal learning scores in patients with RTL seizures. This finding suggests that the precipitating seizure event resulted in bilateral hippocampal damage. The extent of verbal learning loss in the RTL indicates the degree of contralateral LTL involvement and relates to a poorer surgical seizure outcome. [Supported by RO1NS31277 (R.R.); RO1NS38992 (G.W.M.); PO5NS02808 (G.W.M.).]

2.165
IMPAIRED FUNCTION OF ASSOCIATION CORTEX DURING TEMPORAL LOBE SEIZURES

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Rationale: Temporal lobe epilepsy (TLE) may cause impaired function of extratemporal association cortex during seizures. Prior neuroimaging using ictal SPECT has demonstrated decreased perfusion in frontoparietal association cortex during temporal lobe seizures, suggesting impaired function in these regions. Using intracranial EEG in patients with surgically confirmed mesial TLE, we sought to investigate remote electrographic effects of temporal lobe seizures on the association cortex.

Methods: We selected 11 consecutive patients with mesial TLE and hippocampal sclerosis who had no seizures during a follow-up period of one year following surgery. Secondarily generalized seizures were excluded and up to 3 seizures were analyzed per patient (31 seizures total). Electrode contacts were assigned to one of nine cortical regions based on MRI surface reconstructions. EEG during seizures was analyzed for specific patterns including low voltage fast (LVF), rhythmic polyspike, spike-wave, irregular slowing, and post-ictal suppression. Behavioral analysis was also performed based on review of videotapes during seizures. Statistical analyses were performed by concordance of parametric (ANOVA followed by two-tailed t-tests) and nonparametric (Friedman followed by Wilcoxon) tests with a Bonferroni corrected significance threshold of 0.05.

Results: 31 seizures were analyzed in 11 patients (6 left temporal onset, 5 right). Significant increases in ictal EEG patterns (LVF and polyspike activity) were observed in mesial and lateral temporal contacts ipsilateral to seizure onset, followed by post-ictal suppression. Interestingly, bilateral frontal and ipsilateral parietal cortex exhibited large amplitude irregular slow waves during seizures which persisted into the post-ictal period. Peri-Rolandic and occipital cortex were relatively spared. These EEG patterns were accompanied by bland staring, minor automatisms, and unresponsiveness in the majority of patients.

Conclusions: Prominent irregular intracranial EEG slowing was observed in bilateral frontal and ipsilateral parietal association cortex during and following temporal lobe seizures. We propose that this irregular slowing does not represent ictal activity, but rather, more closely resembles the EEG slowing seen in coma, sleep, or encephalopathy. EEG slowing in the frontoparietal association cortex may signify physiological impairment that contributes importantly to altered cerebral function during complex partial seizures. [Supported by Dana Foundation Clinical Hypotheses in Neuroscience award (H.B.).]

2.166
ICTAL ASYSTOLE WITH CONVULSIVE SYNCOPE MIMICKING SECONDARY GENERALIZATION: A DEPTH ELECTRODE STUDY

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Rationale: Unlike tachycardia, ictal bradycardia is rare, and its localizing value is debated. Bradyarrythmias are clinically important because of their potential morbidity, and ability to affect clinical seizure manifestations. Cerebral hypoperfusion induces loss of consciousness, at times with myoclonic jerks, whose clinical differentiation from a generalized convulsive seizure may prove difficult.

Methods: We compared 2 invasive to 5 surface monitored seizures recorded over 2 years in a 49-year-old woman with post-traumatic epilepsy. Phase II recording included bilateral medial temporal depth and right frontal subdural electrodes. Seizures involved somatosensory phenomena and altered awareness, with occasional "generalization" described as diffuse limb jerks and prolonged unresponsiveness.

Results: All 7 seizures showed left temporal onset. Both intracranially recorded events appeared to start in the left amygdala and rapidly involved the adjacent hippocampus. They spread to the contralateral hippocampus in 35 and 25 seconds respectively; then, within 10 seconds, EKG showed asystole lasting 22 and 28 seconds, associated with loss of all recorded cerebral electric activity, apart from a polyspike-suppression pattern in the left hippocampus. Clinically, the patient was motionless until 20 and 8 seconds after the beginning of asystole, and then, concomitantly with cerebral suppression, had myoclonic twitches of the limbs. 4/5 surface recorded seizures showed bradycardia, with pauses of 2–4 seconds; mild tachycardia to 100–130 BPM preceded the bradycardia in 2/5 seizures.

Interictal EKG and echocardiography were normal. A dual chamber cardiac pacemaker was implanted. After seven months, the patient has experienced only infrequent partial seizures, with none involving falls or shaking.

Conclusions: Left temporal lobe seizures produced apparent convulsions that most likely represented convulsive syncope initiated by ictal asystole, which occurred shortly after the seizure had spread from the left to the right hippocampus. Similar spread was briefly mentioned in two previous reports of intracranial recordings, although the exact timing was not specified. These observations suggest that intertemporal spread is necessary, though probably not sufficient, to produce asystole. While intracranial recording is needed to precisely analyze EEG/EKG relationships, our surface recorded seizures demonstrate how variable ictal arrythmias may be, even in electrographically and clinically similar seizures. Furthermore, pacemaker implantation may be not only potentially life-saving, but also may decrease seizure severity. (Supported by the Swiss National Science Foundation and the SICPA Foundation.)

2.167
EEG DIPOLE SOURCE LOCALIZATION OF INTERICTAL SPIKES IN NONLESIONAL TEMPORAL LOBE EPILEPSY WITH AND WITHOUT HIPPOCAMPAL SCLEROSIS

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Rationale: There is controversy as to whether non-lesional temporal lobe epilepsy (NLTLE) without hippocampal sclerosis (HS) is a variant of NLTLE with HS (i.e. mesial temporal lobe epilepsy, MTLE), but with less marked hippocampal damage, or represents a different clinicopathological syndrome. The aim of this study was to determine whether EEG dipole source localisation of the interictal spikes differs between patients with NLTLE with and without hippocampal sclerosis (HS+ and HS−).

Methods: Sixteen spike foci from five consecutive HS+ and eight HS- NLTLE patients were analysed with EEG dipole source localisation utilising a MRI based finite element model (NEUROSCAN 4.3 Source 2.0 software). EEG data was acquired during prolonged routine video-EEG monitoring using 29 electrodes including an inferior temporal row. Dipole localisations of averaged spikes were assessed for each individual patient and also averaged for the HS+ and HS- groups.

Results: 13/16 dipoles (81%) localised to the temporal lobe, varying considerably in their intralobar site. Source localisation of the averaged spikes from each group calculated a dipole in a very similar region in the anteromesial temporal lobe for both the HS+ and HS− groups. A t-test of the differences in the scalp distribution of averaged spikes potentials showed higher spike potentials in the anterotemporal electrodes in the HS+ group, while the HS group showed higher potentials in the mid to posterior temporal electrodes. The largest difference between the groups was at electrode FT9 ($t = 2.247$).

Conclusions: We conclude that, despite the fact that the topographic pattern of distribution of the spike potentials on the scalp differed between HS+ and HS− groups, the source localisation data suggest that the site of the intracerebral generator of the interictal epileptiform spikes does not differ between the two groups of patients. (Supported by Stefanie Meckes-Ferber was supported by a research fellowship grant from GlaxoSmithKline and Janssen-Cilag. The study was supported by equipment and software loaned by Compumedics Limited, Australia.)

2.168
EEG RECORDING AFTER SLEEP DEPRIVATION IN A SERIES OF PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY

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Rationale: Seizures in Juvenile Myoclonic Epilepsy (JME) are dependent on the sleep-wake cycle and precipitant factors, among which sleep deprivation is one of the most important. Still an underdiagnosed syndrome, misinterpretation of the EEGs has been reported to contribute to diagnostic delay in one to two thirds of misdiagnosed cases. Despite this, a proper quantitative EEG investigation of sleep deprivation effects has not been performed. The aim of this study was to investigate the effect of sleep deprivation on EEGs in a series of 41 JME patients who had not yet had syndromic diagnosis.

Methods: 41 patients, 16–50 yr. (mean 25.4) who had not had the diagnosis of JME after a delay of 8.2 yr. (12 days to 24yrs), had 2 EEG recordings separated by a 48-hour interval without any changes in their medication. The exams were always taken at 7 a.m. preceded by a period of 6 hours of sleep (called routine EEG) and after sleep deprivation (sleep-deprived EEG). The same protocol was followed in both exams and included a rest wakefulness recording, photic stimulation, hyperventilation for 5 minutes and a post-hyperventilation period. Sleep was not necessarily recorded. The EEGs were analyzed as to the effect of sleep deprivation on the number, duration, morphology, localization and predominance of epileptiform abnormalities in the different stages. The paroxysms were counted in isolation as well as in bursts, independent of their duration. The discharge index per minute in all different phases was calculated. Statistical analysis was done with the t-test and the McNemar test.

Results: Out of the 41 patients, 4 presented normal EEG recordings on both occasions. In 37 (90.2%) there were some epileptiform discharges (ED). The number of patients with ED ascended from 26 (70.3%) in the routine EEG to 32 (86.5%) in the sleep-deprived exam. The presence of generalized spike-wave (considered the most commonly seen pattern in JME) and multispike-wave (considered the most specific) increased from 20 (54.1%) and 13 (35.1%) in the first EEG to 29 (78.4%) and 19 (51.4%) in the second, respectively (McNemar test $p < 0.005$ and $p < 0.01$). As to localization, the number of generalized, bilateral and synchronous discharges with frontocentral predominance increased from 21 (56.8%) to 30 (81.1%) ($p < 0.01$). The discharge index also increased; while 8 patients (21.6%) presented greater rate in the routine EEG, 25 (67.6%) did so in the sleep-deprived EEG; this was seen mainly during somnolence and sleep ($p < 0.001$). Moreover, the paroxysms were also longer in the sleep-deprived EEG.

Conclusions: Sleep-deprived EEG is a powerful tool in JME and can significantly contribute to the syndromic characterization of this syndrome. [Supported by FAPESP (Fundação de Amparo a Pesquisa do Estado de São Paulo), CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).]

2.169
NONCONVULSIVE STATUS EPILEPTICUS INDUCED BY CEFEPIME

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Rationale: Nonconvulsive status epilepticus (NCSE) is underdiagnosed in critically ill patients, because decreased level of consciousness may be erroneously attributed to toxic-metabolic encephalopathy. Antibiotics, especially penicillins, cephalosporins, imipenem and quinolones have been implicated in seizures and NCSE. Recently, cefepime, a fourth generation cephalosporin, has been reported to induce NCSE, specially in association with renal failure.

Methods: Case series, describing clinical and EEG findings in seven patients with NCSE treated with cefepime.

Results: Mean age of patients was 52 years (24 to 74), all were women. Six patients presented abnormal renal function while on cefepime treatment. Three were under dialysis, and the other, hepatic failure after liver transplant. Cefepime was started for sepsis in 3, pneumonia in 1, severe skin infection in 1 and fever of unknown origin in 3. Doses ranged from 2–4g/day. Two patients had neurological disease prior to introduction of cefepime. One patient had herpes encephalitis treated with acyclovir without consciousness impairment until cefepime was started. Another patient had an external ventricular shunt due to brain hemorrhage. When cefepime was started the patient was alert, with global aphasia. The interval between initiation of antibiotic therapy and first neurological signs (confusion, impaired level of consciousness in all patients, and myoclonic jerks in two) ranged from 24 to 96 hours. One patient had excessive drowsiness and brief staring periods. The EEG showed electrographic status epilepticus, characterized by continuous generalized sharp and slow waves in 6 patients. The EEG of the patient with milder clinical features (excessive drowsiness) showed diffuse background slowing and bursts of slow delta activity. All patients underwent CT scan and extensive metabolic and clinical work-up to rule out other causes of acute encephalopathy. Neurological improvement was observed 24 to 72 hours after discontinuation of cefepime, confirmed by repeat EEGs, showing resolution of electrical status epilepticus. One patient died of systemic complications several days after neurologic improvement.

Conclusions: Cefepime is the possible culprit of nonconvulsive status in all cases in this series. Level of consciousness and responsiveness should be carefully monitored in patients receiving cefepime, specially in patients with renal failure. Early EEG diagnosis and cefepime withdrawal influence outcome in these cases.

2.170
ELECTROENCEPHALOGRAPHIC EVALUATION OF PATIENTS WITH CHRONIC HEPATIC DISEASE SUBMITTED TO LIVER TRANSPLANTATION

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Rationale: Hepatic encephalopathy (HE) encompasses a wide spectrum of neuropsychiatric disturbances, usually reversible, observed in patients with significant liver dysfunction.

Methods: In order to better asses the electroencephalographic changes found in patients with chronic hepatic failure submitted to liver transplantation (LT) at the ServiÇo de Transplante Hepatico do Hospital de Clinicas da UFPR, Curitiba, the authors prospectively followed 20 patients, the youngest one being 15 years old, who had all underwent LT. The variables included physical examination, classification of HE and liver disease, electroencephalogram (EEG) and assessment of cognitive functions with the following neuropsychological tests (NPTS): Mini-Mental State, Trail Making Test Part B, Digit Span subtest used in the Wechsler Adult Intelligence Scale – Revised (WAIS-R), Word Fluency (FAR) and Category Fluency and the Clock Drawing Test. The severity of HE was graded according to the findings of the physical examination, neuropsychological testing and EEG. Subclinical HE was diagnosed when the EEG disclosed a diffuse slowing of background activity or at least two neuropsychological tests were abnormal in the absence of clinical findings. EEG was prospectively evaluated, with a baseline recording in the pre-transplantation period (pre-LT) and 30 and 90 days after the transplant (post-LT).

Results: Mean posterior baseline rhythm frequency (PBRF) was of 8.8 $\pm$ 1.9 Hz in the pre-LT period, 9.8 $\pm$ 1.7 Hz at 30 days post-LT and 9.9 $\pm$ 1.7 at 90 days post-LT and this increase in the PBRF was considered significant ($p > 0{,}0001$). Mean PBRF in the transplantation group was lower than in the control group. Nine patients (45.0%) had a diffuse slowing of background activity in the EEG in the pre-LT period, with 4 patients (44.4%) presenting with a IIA slowing, 4 patients (44.4% with a IIIA slowing and one with a IIIC slowing. Fifteen patients were evaluated 30 days after LT, and 3 of them (20.0%) had a slow EEG: 1 with a IIA slowing, 1 with a IIIA and one with a IIIB. EEG recording of 14 patients 90 days after LT disclosed a IIIA slowing in just one patient. All the patients who presented with slowing in their initial EEG had a significant improvement of background activity following LT ($p > 0,\ 0001$). Three patients also had triphasic waves in their EEGs. The diagnosis accuracy of PBRF, background slowing and the occurrence of triphasic waves were evaluated in comparison with NPTS as the gold standard for the diagnosis of HE. As a result, EEG parameters had a good specificity and positive predictive values (PPV), with low sensitivity and negative predictive values (NPV).

Conclusions: Final assessment of improved HE in the post-LT period considered NPTS as the gold standard, but also demonstrated that EEG abnormalities have high specificity and PPV, but low sensibility and NPV.

Clinical Neurophysiology–Pediatric

2.171
AUTOMATIC SPIKE DETECTION FOR SOURCE LOCALIZATION IN CHILDREN AND NEONATES

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Rationale: Interictal spikes, in children, and Positive Rolandic Spikes (PRS), in preterms, are transient abnormal activities indicating specific pathologies (i.e. epilepsy and Periventricular Leukomalacia (PVL)). EEG source localization gives new insights for identification of the brain area where focal activities originate. Spike shape classification is essential for good dipole fit accuracy.We designed an automated method that extracts spikes and detects the clusters of neuronal activities for EEG source localization in epileptic children and preterms.

Methods: We used template matching to extract spikes to discriminate individual neuronal activities. The desired spike is captured as the reference spike template, then all spike candidates are scanned for waveforms matching the template within a specified error range. The sum of squared error (SSE) is used as a criterion for the goodness of fit. When SSE reaches a value below the preset detection-threshold, detection is reported. To track changes in the shape of the spikes, matched spikes are averaged during template matching in order to adapt the reference spike template. The above mentioned method is applied to spontaneous EEG data sets, collected from epileptic children (64 channels) and preterm (21 channels) with PVL. The Dipole Fit method (ASA, ANT Software) is used to localize the equivalent dipoles for all extracted spikes. The spatial topography associated with the sources was calculated using a realistic head model.

Results: Spike clustering was carried out in temporal and spatial domains for interictal and PRS activities. The source localization shown below resulted from our spike clustering method in a newborn with PRS. In this case, mean and variance of SSE were 0.5886 and 0.1460 for the selected spikes, and respectively 0.7167 and 0.1854 for the rejected ones. Then, the localized dipoles were selected to be in the same cluster by comparing the distance between the center of cluster and dipoles with the predetermined threshold (Figs. 1 and 2).

Conclusions: Lack of a unique definition for specific age-dependant cerebral activities (normal: delta brush, frontal transients, and abnormal: PRS) in preterm makes the template matching method very useful in extracting the spikes. This method allows a better discrimination between different sources of activities by using contextual information. [Supported by French Ministry of Research, Region Picardie, University of Picardie (HTSC Project & ACI "Integrative and Computational Neurosciences" Project).]

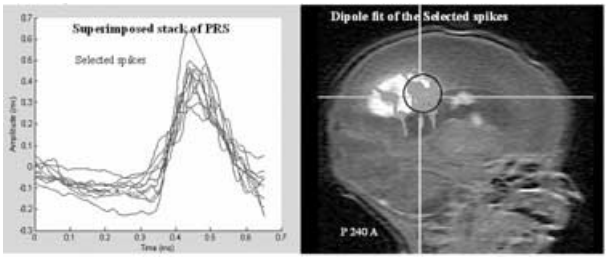

FIG. 1 and 2.

2.172
ANALYSIS OF INTRACRANIAL ELECTROCORTICOGRAPHY IN CHILDREN WITH EPILEPTIC SPASMS
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Rationale: Ictal electrographic patterns associated with epileptic spasms have not been well studied on chronic intracranial electrocorticography (ECoG) recording. Ictal ECoG changes were assessed in children with medically-refractory epileptic spasms.

Methods: We have studied a consecutive series of 13 children (age: 5 months to 13 years; 7 girls and 6 boys; 8 had tuberous sclerosis complex, 3 had developmental malformations) where epileptic spasms were captured during a prolonged intracranial ECoG recording for subsequent cortical resection. Ictal onset zones were objectively delineated, using spectral analysis (Gotman et al. *Electroencephalogr Clin Neurophysiol* 1993;87:206–14; Asano et al. *Clin Neurophysiol* 2004, in press). The relationship between the ictal onset zone for epileptic spasms and that for focal seizures was assessed individually.

Results: Spasms were associated with widespread fast wave bursts exceeding 30 Hz over the neocortical regions on intracranial ECoG recording in all cases. Such spasm-related fast wave bursts were obscure on scalp EEG recording in 4/13 cases but well recognized on intracranial ECoG recording in all cases. Spasm-related fast wave bursts were superimposed on a delta wave activity on intracranial ECoG recording always in 11/13 cases and occasionally in 2/13 cases. Fifteen types of concomitant focal seizures were captured during the prolonged intracranial ECoG recording in 10/13 cases. Ten of the 15 focal seizures involved the neocortical regions, whereas the other five focal seizures mostly involved the medial- to sub-temporal regions. In a single child with tuberous sclerosis complex, both spasms and focal seizures originated from the same brain region along a massive frontal tuber. In the other nine children, there was no or minimal spatial overlap between the cortices showing a focal seizure onset and spasm-related fast wave bursts, although there was a close spatial and temporal relationship between the spasms and focal seizures in the majority of the patients.

Conclusions: Cortical regions responsible for epileptic spasms may be, for the most part, distinct from those responsible for focal seizures. Further studies using other modalities such as diffusion tensor imaging or cortico-cortical evoked potential techniques may reveal the underlying connection between the cortices showing a focal seizure onset and spasm-related fast wave bursts as suggested by the temporal relationship between the two seizure types.

2.173
ANALYSIS OF SHARP AND SPIKE–WAVE TRANSIENTS IN NEONATAL POLYSOMNOGRAPHY
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Rationale: To identify and quantify sharp and spikes wave transients found in neonatal polysomnography of healthy term newborn babies throughout different sleep-stages.

Methods: Thirty-two neonatal polysomnographic studies of term babies from the Hospital de Clnicas da Universidade Federal do Paraná (UFPR) were reviewed. The babies were term, healthy, legal age of two days and with adequate monitoring during pregnancy. Polygraphic studies were performed in a 21 channels EEG machine, with montages internationally accepted standards for the neonatal period and without sedation. Quantify sharp and spikes wave transients and analyzed in each sleep-stages.

Results: The mean duration of the polygraphic studies was of 57 minutes. The total number of sharp and spikes wave transients was 206 (6.4 per exam), of which 106 were in quiet sleep, 55 in active-sleep and 41 in transitional sleep. Showed a total of 0.1 sharp and spikes wave transients per minute. In quite sleep were 0.17 sharp and spikes wave transients per minute, in active-sleep 0.07 per minute and in transients sleep 0.19 per minute. The Kruskal-Wallis test shows that sharp and spikes wave transients are more frequently in sleep-quiet.

Conclusions: In the normal term babys sharp and spikes wave transients mostly during quiet-sleep. Even thus, sharp and spikes wave transients per minute were more frequentlly in sleep transients. In newborn healthy we found the number of sharp and spikes wave transients during one minute in each sleep-stages. The clinical significance of Sharp and spikes wave transients(ST) for both preterm and fullterm infants needs more investigation. Sporadic sharp wave may be either normal or anormal, depeding on clinical context, the EEG background activity, location, morphology and age postconceptional.

2.174
A NEW EXPERIMENTAL LIPOSTEROID (DEXAMETHASONE PALMITATE) THERAPY FOR INTRACTABLE EPILEPTIC SEIZURES IN INFANCY
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Rationale: West syndrome (WS) is a severe age-dependent intractable epilepsy in infants that frequently results in mental retaldation. ACTH or glucocorticoids are among several effective treatments in WS, but the advantages and disadvantages of these two therapies are still unknown. In the past study, liposteroid (dexamethasone palmitate) has been used for the treatment of WS and compared with ACTH therapy in relation to therapeutic effect and adverse reactions. Then, the initial effects observed are the same as for ACTH therapy. In this study, liposteroid (dexamethasone palmitate) therapy was tried in new protocol for WS and its related syndrome to shorten the therapeutic period and to reduce the relapse rate.

Methods: A single intravenous injection of liposteroid(0.25mg/kg) was administered twelve times in one month(total dosage = 3.0mg/kg) to one patient with WS aged 5 months and two patients with WS's epileptic sequelae after ACTH therapy aged 12 and 25 months. All three patients had uncontrollable daily seizures by the conventional antiepileptic drugs, such as VPA, CZP, or ZNS.

Results: Nodding spasm and hypsarrhythmia on EEG disappeared in one patient with WS within six doses, a 50% decrease of seizures and EEG improvement were found in another patient. No notable effects were seen in the other patient. There were no notable adverse reactions throughout the therapy. Efficacy can be determined in this new experimental liposteroid therapy earlier than with conventional liposteroid therapy.

Conclusions: The liposteroid therapy under the new protocol can be performed safety and is useful for those susceptible for the adverse reactions by the conventional treatment or those without effective treatment.

2.175
FEBRILE SEIZURE: RETROSPECTIVE ANALYSIS OF CLINICAL DATA AND EEG FEATURES IN 100 CHILDREN
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Rationale: Febrile seizure is a bening condition in childhood, but 2–4% of the children will have epilepsy in the future. Analyzing the clinical

and EEG features of these children can help future genetic studies to understand the epileptogenesis of this condition.

Methods: Retrospective analysis of clinical and EEG data of 100 children who comprehend NIH (1980) FS definition. The following aspects were analyzed: 1) EEG features; 2) family history of FS and/or epilepsy; 3) FS recurrence and/or epilepsy.

Results: We analyzed 100 children with FS who were seen at the epilepsy out-patient unit between January 1993 and August 2003. Most of the patients had normal EEG (70%), 20% focal discharges, 5% generalized abnormalities, and 5% other EEG patterns (generalized plus focal, multifocal). Among the patients with normal EEG, 51,3% had family history of epilepsy and 35% of FS, and those with focal EEG abnormalities, 30% had family history of epilepsy and 25% of FS, while patients with generalized EEG patterns, 60% had family history of epilepsy and 40% of FS. All patients with focal plus generalized EEG abnormalities had family history of epilepsy, and only 50% of FS. The one child with multifocal EEG activity did not have family history of seizures. FS recurrence was common, it occurred in 68,5% of patients with normal EEG, and in those with abnormal EEG in 73,3%. The outcome with epilepsy occured only in 8,5% of the patients with normal EEG, and in 40% of those with abnormal EEG, which were diagnosed focal epileptic syndrome in 65%.

Conclusions: Most FS patients had normal EEG. The patients with focal abnormalities had less family history of epilepsy or FS, than those with generalized EEG abnormalities or normal EEG. These observations could suppose a genetic difference between these groups. FS recurrence was similar in patients with normal (68,5%) and abnormal EEG (73,3%), while the outcome with epilepsy was more frequent in those with abnormal EEG (40%), than in those with normal EEG (8,5%). In this series of patients with FS, the abnormal EEG showed to be better indicator of epilepsy outcome than of FS recurrence.

2.176
STATISTICAL PROPERTIES OF NONLINEAR DYNAMIC SYSTEMS MEASURES IN THE PEDIATRIC-AGE PATIENT

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Rationale: The tools used for quantitative analysis of the EEG have expanded to include methods used it physical sciences, including nonlinear dynamical systems measures. These tools have been used to 1) distinguish seizures from non-seizures, 2) perform seizure prediction and 3) to determine whether EEG segments include chaotic behavior. Despite the promise shown by these methods, a number of fundamental properties of the measures have not been described. The purpose of this paper is to describe the probability density functions for a number of nonlinear systems measures of dimensionality, entropy, global non-linearity and eigenvalues. We are especially interested in these functions as seen in the pediatric aged patient.

Methods: Participants included both neurologically normal children (10) and those with epilepsy (17). Ten segments, five from sleep and five from awake, were procured from each subject. Each segment consisting of thirty seconds of EEG sampled at 400hz. The values were calculated for eigenvalue, Kolmogorov entropy, maximum likelihood correlation dimension, least squares correlation dimension and a Z score. The thirty second window was then shifted by one second and the values re-calculated (moving thirty times to produce a thirty second moving window). Data from each of ten electrodes were calculated (F3, F4, C3, C4, O1, O2, T7, T8, P7 and P8). Distributions were then constructed of 1) the absolute values of each of the non-linear metrics, 2) the number of consecutive samples changing in the same direction, 3) the magnitued of sample to smple change and 3) the percentage change from sample to sample. Measures of control tendency and variability were then calculated for each distribution and the distribution were fit with normal or gamma distributions.

Results: The trial to trial differences in consecutive values for normals were normally distributed for eigenvalue, dimensionality (both measures), entropy and the Z score with means all near zero (0.02, −0.125, 0, 0 and 0) with eigenvalue showing the narrowest distribution. The trial to trial change did not show a strong dependence on electrode location or state, but the distribution of the absolute values had a strong dependence on both variables. The distributions of absolute values for awake (0.56 and 0.75) and asleep (0.88 and 0.8) eigenvalues were bimodal and the distributions of entropy and Z during sleep were best fit by poisson distribution. The distributions of the number of samples showing n consecutive increases or decreases matched that expected if each consecutive sample were independent. The distributions of percent change from sample to sample were all normally distributed.

Conclusions: There are significant differences in the shapes of the underlying distribution of the variables studied. This information must be taken into account when performing statistical comparison. (Supported by Falk Medical Trust Foundation.)

2.177
GABAPENTIN MONOTHERAPY IN PEDIATRIC EPILEPSY: A RETROSPECTIVE REVIEW

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Rationale: Gabapentin (GBP) was first introduced as an anticonvulsive agent in 1993, with an indication for use as an adjunctive therapy for patients with complex partial epilepsy, with or without secondary generalization. Although in adults GBP been shown to be effective in randomized, double-blinded, placebo controlled studies, the effectiveness of GBP monotherapy in pediatrics has not yet been established. This retrospective review was conducted to evaluate both the efficacy and safety of GBP monotherapy in pediatric epilepsy.

Methods: We conducted a retrospective review of GBP treatment in patients followed through the Massachusetts General Hospital pediatric epilepsy program from January 2002-March 2004. The data include patients that were started on GBP as first anticonvulsant medication in new onset epilepsy, as well as patients who were initially on combination therapy with GBP and other ACD and then converted to monotherapy with GBP. Data collected included patient age, gender, seizure type and etiology, GBP dosages, reported side effects, and effect of GBP on seizure frequency (as percentage reduction from baseline prior to GBP treatment).

Results: Twelve patients were treated with GBP as monotherapy during the study period. These had complex partial epilepsy, with or without secondary generalization. Seizure etiology included Sturge Weber Syndrome, Tuberous Sclerosis Complex, and cortical dysgenesis; 60% of the subjects had abnormal brain MRI findings. Dosage of GBP was based on mg/kg for each patient, with an average dose of 45 mg/kg. GBP was discontinued in one patient who developed behavioral problems. Of the twelve patients on GBP monotherapy, nine (75%) became seizure free, and two reported a greater than 50% reduction in seizure frequency. One patient with a history of hypoxic ischemic injury following prematurity continues on GBP monotherapy, but also receives frequent diazepam administration due to seizure activity.

Conclusions: In our population of children with epilepsy, GBP appears to be an effective and well tolerated medication in the treatment of complex partial epilepsy. Gabapentin can be effective as monotherapy in pediatric epilepsy, including symptomatic epilepsies.

2.178
FAINTS OR FITS: EEG WITH OCULAR COMPRESSION IN DISTINGUISHING BREATH HOLDING SPELLS AND SYNCOPE FROM EPILEPTIC SEIZURES

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Rationale: Brief episodes of loss of consciousness pose a diagnostic dilemma. Episodes of syncope or breath holding spells (BHS) are often misdiagnosed as epileptic events. The purpose of this study is to assess the usefulness of EEG with ocular compression (OC) to distinguish BHS/syncope from seizures.

Methods: OC is routinely performed in our EEG laboratory if the clinical history is suggestive of either BHS or syncope. A retrospective

analysis was performed on EEG records of all children on whom OC was performed from 2000–2003. Data from 116 (mean age 9.4 years ± 5.8 SD) patients with a clinical diagnosis consistent with syncope or BHS were compared with a control group of 46 patients (mean age 7.5 years ± 4.7 SD) who had EEGs requested for indications other than syncope or BHS. A physician performed 10 seconds of forceful OC during EEG and EKG recording for both groups of children.

Baseline RR (RR-B) interval was measured with the patient at rest and was compared to the maximum prolongation of RR interval during ocular compression (RR-OC).

Results: At baseline, the BHS/syncope group had a lower RR-B than controls (means ± SD = 0.73 ± 0.2 and 0.8 ± 0.22 respectively; $p = 0.043$ by unpaired t-test).

The RR-OC was significantly higher in BHS/syncope group than controls (means ± SD = 0.88 ± 0.32 and 1.73 ± 1.53 respectively; $p < 0.005$ by Mann Whitney U).

Using the accepted standard of 2 seconds of asystole as the cut off, the sensitivity of OC was 26% with 100% specificity. Setting the threshold of RR-OC at 1.3 seconds increased the sensitivity to 45% while maintaining a specificity of 93%.

The change in RR interval from RR-B to RR- OC also distinguished patients from controls. A 1.36 second increase in RR interval achieved a sensitivity of 25% with a specificity of 100%. Even a small increase of 0.2 seconds in RR interval demonstrated a sensitivity of 71% with a specificity of 89%.

No complications were noted during, or subsequent to performance of OC.

Conclusions: OC during EEG is useful in distinguishing patients with BHS/syncope from those with epileptic seizures. A requirement of a 2 second period of asystole with OC excludes many patients. Our data indicate that RR interval increase of 0.2 seconds over baseline identifies additional patients with increased vagal tone. Prompt and accurate diagnosis of the etiology of loss of consciousness may preclude the need for further extensive and expensive evaluation and reduce both patient and parental distress.

2.179
EFFICACY OF THE KETOGENIC DIET IN MYOCLONIC EPILEPSY OF DOOSE

Linda C. Laux, Kelly A. Devonshire, Kent R. Kelley, Joshua Goldstein, and Douglas R. Nordli, Jr. (Children's Memorial Epilepsy Center, Children's Memorial Hospital, Northwestern University, Chicago, IL)

Rationale: Myoclonic-astatic epilepsy of Doose (MAE) is classified by the International League Against Epilepsy (ILAE) as a specific cryptogenic/symptomatic epilepsy syndrome. Nevertheless, this syndrome is often under recognized and confused with Lennox-Gastaut syndrome. Patients with MAE typically have normal development with an unremarkable examination at seizure onset. Seizures typically begin in the preschool age (one to five years of life). Seizure types include a mixture of generalized seizures including myoclonic-astatic, atonic-astatic, myoclonic, absence, generalized tonic-clonic, and tonic/vibratory seizures. The EEG shows irregular fast spike wave discharges. A monomorphic 4–7 Hz parasagittal rhythm is also seen. Seizures are often difficult to control and prognosis for seizure resolution and cognitive outcome is variable. However, Oguni et al. in *Neuropediatrics* (2002;33(3):122–32) found that the ketogenic diet has marked efficacy in seizure resolution for patients with MAE.

Methods: Twenty eight patients placed on the ketogenic diet in the past two years were retrospectively reviewed. Of these 28 patients, 10 had a clinical/electrographic diagnosis of MAE, 16 had a diagnosis of a symptomatic generalized epilepsy (including Lennox-Gastaut Syndrome, periodic spasms, and a diffuse encephalopathy with multifocal seizures), and 2 patients had a cryptogenic localization epilepsy. The patients were identified in the following groups: 1. Excellent outcome (seizure-free or >90% seizure reduction), 2. Good outcome (>50% seizure reduction), and 3. Poor outcome (<50% seizure reduction). The majority of the patients in the "poor outcome" group had no change in seizure frequency.

Results: For the 10 patients with MAE, 70% of the patients had an excellent outcome with initiation of the ketogenic diet with 30% having a good outcome. However, of the 16 patient with symptomatic generalized epilepsy, 81% of the patients had a poor outcome to the diet with only 6% with an excellent outcome and 13% with a good outcome. Both patients with cryptogenic localization-related epilepsy had a poor outcome with initiation of the ketogenic diet.

Conclusions: Myoclonic-astatic epilepsy of Doose is a poorly recognized epilepsy syndrome with seizures that are often difficult to control. This retrospective review suggests that the ketogenic diet is particularly efficacious treatment in children diagnosed with this particular epilepsy syndrome. The ketogenic diet should be considered early in the course of therapy for children with myoclonic-astatic epilepsy.

2.180
RISK FACTORS OF POSTNEONATAL EPILEPTIC SEIZURES IN NEWBORNS WITH EEG-CONFIRMED NEONATAL SEIZURES

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Rationale: Confirmation of neonatal seizure is frequently difficult without EEG because neonatal seizure is quite different from other epileptic seizures in many aspects including seizure semiology, electrographic finding and long-term prognosis. We investigated to determine the prognosis and risk factors of postneonatal epilepstic seizure in the newborns that have neonatal seizures.

Methods: We retrospectively examined 71 infants who had neonatal seizures confirmed by EEG seizure with duration more than 10 seconds in regular EEG. Among 52 survivors, we examined the clinical and electrographic variables of 35 infants who were followed for more than 18 months. We divided these infants into two groups with postneonatal epileptic seizure and without postneonatal epileptic seizure.

Results: Postneonatal epileptic seizure developed in 43% (group A, 15 of 35). There was no postneonatal epileptic seizure in 67% (group B, 20 of 35). Among clinical variables, conceptional age at EEG seizures was older in A group (42.0 ± 4.4 weeks) than that of group B (39.4 ± 3.7 week) ($P = 0.036$). There was no significant difference in sex, gestational age, chronologic age at first seizure, Apgar score at 1 and 5 minutes, and the number of drugs administrated to control the neonatal seizure between two groups. Among EEG variables, abnormal EEG background and the duration of electrographic seizure affect the occurrence of postneonatal epileptic seizure. Abnormal EEG background activity occurred in group A (67%, 10 of 15) more often than in group B (35%, 7/20) with a tendency ($P = 0.063$). The duration of EEG seizure tended to be longer in group A (124 ± 224 seconds) than in group B (43 ± 52 seconds) ($P = 0.063$). Number of EEG seizures, number of seizure onset zone and predominant frequency of EEG seizure were not significantly different between two groups. Developmental delay was noticed at the follow up in 77% (27 of 35). All the infants in group A showed developmental delay (15 of 15), while 40% of group B showed normal development (8 of 20) ($P = 0.005$).

Conclusions: Our results suggest that older conceptional age at neonatal seizure, abnormal EEG background activity and the longer duration of EEG seizure predict postneonatal epileptic seizures. Infant who have both neonatal EEG seizures and postneonatal epileptic seizures have a high risk of developmental delay.

2.181
THE RELATIONSHIP BETWEEN SURFACE AND INTRACRANIAL NONLINEAR DYNAMIC CHANGES DURING SEIZURES

Sunila O'Connor, Jennifer Dwyer, Angela N. Song, Fengmei Liu, Seoan Marler, Michael Kohrman, Arnetta McGhee, and Kurt E. Hecox (Pediatrics, University of Chicago, Chicago, IL)

Rationale: The introduction of dynamic nonlinear systems tools into the field of EEG analysis has shown great promise in the areas of seizure prediction, seizure detection and in constructing large scale models of nonlinear interactions amongst removal populations. While both surface and intracranial recordings have been used for these purposes there are few direct comparisons of the two data sets. Generally speaking intracranial data has proven to be a more powerful predictor and detector of seizure activity than surface recorded data. This raises the question of the degree to which intracranial activity is accurately reflected in extracranial recordings. The purpose of this study was to determine the

degree to which intracranial nonlinear dynamic changes are accurately reflected on the surface of the scalp and to determine the surface and intracranial spatial distribution of those dynamic changes.

Methods: Ten pediatric aged patients were included in this University of Chicago IRB approved protocol. Three seizures were selected from each patient. eigenvalues, correlation dimensions (least squares and maximum likelihood), Kolmogorov entropy and Z (a measure of global non-linearity) were calculated for each of thirty consecutive thirty second epochs, separated by one second (moving window approach). The software package RRCHAOS was used to calculate the above named measures. These moving windows were calculated for involved and uninvolved intracranial leads (12 to 34 electrodes) and cross correlated to eight surface electrodes (four on each side). The spatial distributions of these correlations were then analyzed. Delays between surface and intracranial changes were also calculated, as were delays attributable to propagation across the intracranial grid.

Results: Values of cross correlation varied considerably as a function of intracranial electrode location, extracranial electrode and the dependent variable. The highest correlations were observed for eigenvalues, where the values for the highest correlation usually exceeded 0.90. Kolmogorov entropy also demonstrated relatively high (0.75 to 0.95), but more variable results. The lowest cross correlation were found for the least squares cross correlations and the Z score was intermediate in value. As expected correlations were generally lowest for distant and contralateral electrodes, although there were some notable, but consistent exceptions. In general the waveform delays between surface and intracranial data were minimal as expected.

Conclusions: The surface recorded waveform of the temporal evolution of nonlinear dynamic changes accurately reflects the behavior of intracranial resources. The degree to which surface recorded activity is distorted or diminished by the intervening tissues depends upon the dependent variable and the geometric relationship of the recording electrode to the source. (Supported by Falk Medical Trust Foundation.)

2.182
DOES GENERAL ANESTHESIA AFFECT MEG SPIKES IN YOUNG CHILDREN WITH INTRACTABLE EPILEPSY?

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Rationale: Magnetoencephalography (MEG) has been increasingly used in patients with intractable localization-related epilepsy. The accuracy of MEG source localizations onto MRI depends upon the ability of patients to keep still in the dewar. Thus, uncooperative children with epilepsy require general anesthesia (GA) for the MEG and MRI studies. GA has been known to either eliminate or provoke epileptic discharges. We evaluated MEG and simultaneous EEG spikes under GA in young children with intractable epilepsy in comparison with prolonged video-EEG (VEEG) results.

Methods: A total of 185 pediatric patients with epilepsy underwent MEG study with simultaneous 19-channel scalp-EEG at The Hospital for Sick Children in Toronto. These patients also had VEEG for 16–96 hours with 19-scalp electrodes. Twenty-one of 185 children (11%) underwent GA for MEG and MRI studies. Propofol and remifentanil were used for GA. Whole-head 151-channel gradiometers were used for MEG recording (VSM MedTech Ltd., Port Coquitlam, BC, Canada). We performed MEG dipole analysis using single moving dipole modeling. We compared MEG spikes and dipoles with interictal spikes of VEEG and simultaneous EEG.

Results: We studied twenty-one children consisting of 10 girls and 11 boys. Age at time of MEG study ranged between 7 months and 9 years (mean $\pm$ SD, 4.7 ± 2.6 years). Age of seizure onset ranged from one day of life to 3 1/2 years (0.9 ± 1.0 years). Eighteen children had MRI abnormalities. There was a positive correlation among number of MEG dipoles, number of interictal epileptiform discharges per minute on VEEG and number of EEG spikes under GA. The more frequent spikes VEEG showed, the more frequent EEG spikes and MEG dipoles we obtained under GA. Fifteen patients showed ≥ 10 MEG dipoles. Their VEEG findings were as follows. Three patients had regional interictal epileptiform discharges, 5 had hemispheric, 2 had bilateral, 4 had multiple, and one with no interictal epileptiform discharges. Six patients showed <10 MEG dipoles. Their VEEG findings consisted of bilateral and generalized discharges in 4 patients, generalized or bilateral interictal epileptiform discharges in one each.

Conclusions: MEG under GA is a useful procedure to perform in young children with frequent focal epileptiform discharges during VEEG. The patients with generalized interictal epileptiform discharges on VEEG did not provide sufficient MEG dipoles because the generalized interictal epileptiform discharges disappeared under GA.

2.183
SELECTIVE REORGANIZATION OF LANGUAGE SUBTASKS IN A CHILD WITH A LEFT PARIETAL TUMOR

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Rationale: Language mechanisms are multiple, and subserved by different brain regions. In this case of a 15 year-old bilingual girl, functional MRI (fMRI) revealed a pattern of language representation that differed from the results of stimulation mapping and Wada testing

Methods: As part of clinical evaluation, Wada testing, stimulation mapping of language during surgery using an object naming task, and langugae fMRI was performed. The language fMRI used both a semantic (meaning related) task and a phonologic (rhyme related) task. Both stimulation and fMRI studies used both English and Spanish.

Results: Wada testing in Spanish revealed a strong left lateralization for language. Stimulation mapping disrupted object naming just anterior to the tumor in both langauges. Functional MRI in both languages revealed left sided activation for the semantic task, but right sided activation for the phonologic task, in the homologous region from the tumor. She tolerated surgery well with no language deficits, even transient.

Conclusions: Language lateralization can be dependent on task. Semantic tasks appear to drive the results of both Wada testing and stimulation mapping. [Supported by NS41272 (JGO).]

2.184
USEFULNESS OF VIDEO-EEG MONITORING IN THE DIFFERENTIAL DIAGNOSIS OF PAROXYSMAL MOTOR PHENOMENA IN ALTERNATING HEMIPLEGIA OF CHILDHOOD

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Rationale: Alternating hemiplegia of childhood is a rare neurologic disorder presenting in infancy or early childhood with abnormal eye movements and paroxystic motor phenomenae of alternating hemiplegia. Epilepsy is associated in up top 50% of cases, which may cause diagnostic difficulty between seizures and hemiplegic episodes in these cases.

Methods: We discuss the role of video-EEG monitoring in the diagnosis of epileptic and non-epileptic events in two cases of alternating hemiplegia of childhood and discuss implications in management.

Results: Two unrelated boys with developmental delay and ataxia presented with paroxysmal spells in the first year. In the first patient, intermittent nystagmus and dystonic posturing started at age 6 months, followed by episodes of alternating transient hemiplegia lasting hours to days, worsened by stress. At age 2, brief blinking episodes and loss of body tone. Flunarizine was started. Video-EEG documented episodes of hemiplegia and complex focal seizures. Brain MRI disclosed left mesial temporal sclerosis, which had not been seen in a previous, good quality exam. Antiepileptic therapy was started, with reduction of seizure frequency. The second patient presented episodes of global hypotonia and abnormal eye movements at age 4 months. At age 2, these symptoms disappeared, and episodes of alternating or bilateral hemiplegia ensued. Antiepileptic drugs were started, with poor response. The child had two ICU admissions for presumed status epilepticus. At age 2 1/2, video-EEG

monitoring was performed. Typical events of hemiplegia were registered, during which no epileptiform activity was seen.Brain MRI was normal. Antiepileptic drugs were stopped and flunarizine was introduced, with clinical improvement.

Conclusions: Video-EEG monitoring may provide useful information in establishing a precise diagnosis of paroxysmal epileptic and nonepileptic events in patients with alternating hemiplegia, with impact in management.

2.185
SLEEP AND EEGs IN CHILDREN

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Rationale: EEGs are most useful when they reveal abnormalities supporting the clinical suspicion of epilepsy or when they provide evidence of a specific epilepsy syndrome. Recording sleep during an EEG is one way to try and provoke abnormalities that improve the test's diagnostic yield. We reviewed the likelihood of recording sleep and the usefulness of sleep for provoking abnormalites not present in wakefulness and drowsiness.

Methods: All outpatient EEGs performed over a 13 month period on children less than 19-year-old were reviewed. They were scored for presence of awake, drowsy, and stage II sleep samples. The presence or absence of epileptiform discharges (ED's) in the awake/drowsy state or sleep state was noted along with the specific type of discharge.

Results: 259 EEGs met the criteria for review. All included wakefulness. Drowsiness was recorded in all but 3. Forty (15%) EEGs did not include stage II sleep. Therefore 219 EEGs (85%) included both wakefulness and stage II sleep.

79 records (30%) revealed ED's.

Of the 40 EEGs where no sleep was recorded, 12 (30%) contained ED's.

Of the 219 EEGs with both awake and sleep states recorded, 67 (31%) contained ED's. 6 (3%) of these recordings revealed ED's in wakefulness but not during sleep. 11 (5%) revealed ED's in sleep but not in wakefulness. 50 (23%) showed ED's in EEG samples from both wakefulness and sleep. Of the 11 children with spikes only during sleep, 10 had symptomatic epilepsy; the remaining patient had nonepileptic staring spells and two brief irregular generalized spike wave bursts in sleep (suggesting a seizure diathesis but no supporting the clinical suspicion of absence epilepsy).

Conclusions: Most EEGs recorded in children in our outpatient EEG laboratory included sleep without resorting to sedation. Preparation with sleep deprivation and performing the study in a quiet, darkened room with appropriate technologist techniques was usually sufficient to get children to fall asleep. In only 5% of cases where a child did fall asleep did the EEG reveal ED's in sleep but not in wakefulness. While this is not a trivial number, it would only have added 2 "positive" cases among the 15% of our patients who did not achieve stage II sleep. In other words, EEGs performed on a pediatric outpatient population were "false negatives" about 5% of the time.

At the same time, 3% of recordings showed ED's only in the awake state. In this case there would be a 3% false negative rate. This raises a concern for EEGs obtained only in the sedated state, since wakefulness may not be present at all. The best diagnostic yield for a single EEG from a pediatric patient will come from recordings obtained with the child in the awake and asleep states, but repeating the EEG with sedation obtain sleep adds little additional diagnostic information. (Supported by Harman Clinic Fund at Lucile Salter Packard Children's Hospital.)

2.186
UTILITY OF INTERMITTENT BEDSIDE ELECTROENCEPHALOGRAPHIC MONITORING IN THE PEDIATRIC INTENSIVE CARE SETTING

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Rationale: When patients receive paralytic medications, seizure activity cannot be readily detected clinically. Intermittent bedside EEG monitoring can detect clinically occult seizure activity in these patients. We sought to determine the occurrence of recurrent seizures or status epilepticus in a series of monitored pediatric patients receiving paralytics during mechanical ventilation, and to look for patient and/or EEG characteristics that might identify which patients are at highest risk for developing these complications.

Methods: The Baylor IRB approved our protocol for a retrospective review of consecutive bedside monitoring studies performed between January 2001 and December 2003 on pediatric ICU patients receiving paralytic agents. We divided patients into four groups based on indications for monitoring. Within each group we recorded the occurrence of electrical seizures, the presence of interictal epileptiform activity and the timing of the first recorded electrical seizure.

Results: We reviewed ninety-eight monitoring sessions recorded from 82 patients aged 6 weeks to 24 years. Five patients had two sessions and two patients had three sessions. Monitoring duration ranged from 6 hours to 48 days, mean 150 hours. Twenty nine sessions were performed for a history of epilepsy, 24 for occurrence of seizure within 24 hours prior to monitoring, 26 for status epilepticus, and 19 for other conditions thought to increase risk for seizures. Thirty of the 98 monitoring sessions captured seizure activity. Six of these 30 positive studies captured only one seizure, one captured 2 seizures and one captured 6 seizures; twenty-two captured status epilepticus. Fourteen of 26 patients (54%) monitored because of status epilepticus manifested status during monitoring, compared to 5 monitored for seizure within 24 hours (21%), 1 monitored for other conditions (5%), and 2 monitored for history of epilepsy (7%). Eleven patients had ongoing status epilepticus at the onset of monitoring. Latency to development of status in the remaining 11 cases ranged from 3 hours to 20 days, with 5 occurring in less than 72 hours. The absence of interictal epileptiform activity predicted that no seizures would be captured with a negative predictive value of 84%.

Conclusions: The yield of intermittent bedside EEG monitoring in paralyzed pediatric patients is highest in patients who are monitored because of recent seizure activity or status epilepticus. Patients without interictal epileptiform activity were unlikely to develop status epilepticus, and patients monitored due pre-existing epilepsy or due to an acute illness or insult rarely did. We plan to investigate the patients in these low-risk groups to identify factors that might guide the utilization of this costly and labor-intensive procedure.

2.187
COMPARISON OF MEG AND EEG BEFORE AND AFTER TOTAL CALLOSOTOMY

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Rationale: Outcome of callosotomy depends on whether the transcallosal pathway is involved in the generation of bilateral synchronized discharges (BS). For true transcallosal propagation, the time lag between the leading and following hemispheres must be longer than the minimal transcallosal transfer time of 20 ms. We have demonstrated the superior definition of the leading spike focus by MEG compared to scalp EEG. The goal of this study was to find out whether MEG can provide an additional information for callosotomy cases.

Methods: Pre- and postoperative EEG and MEG were simultaneously recorded in a 15 yrs old F with Sturge-Weber syndrome (Case 1) and a 9 yrs old M with non-lesional epilepsy (Case 2) who presented with drop attacks (DAs). All discharges were classified into BS and unilateral independent discharges (UI). Interhemispheric time lag (ITL) was calculated for BS with "primary peaks" (most prominent peak for a single spike or first prominent peak for a burst) defined in each hemisphere by MEG or EEG.

Results: Case 1. UI discharges did not show laterality before callosotomy. ITL was calculated in 62% of BS by MEG and in 36% by EEG. BS appeared first in the right hemisphere in 74% by MEG, but in 52% by EEG. Average ITL in MEG was 25.9 ms, 7.1 ms longer than by EEG. The frequency of DAs reduced and MEG showed no BS after callosotomy. The proportion of right UI increased. Case 2. Right and left

UI accounted for 11% and 6%, respectively, before callosotomy. ITL was calculated in 88% by MEG and in 32% by EEG. BS appeared first in the left hemisphere in 50% by MEG and in 87% by EEG. Average ITL was 8.3 ms by MEG and 12.7 ms by EEG. DAs reappeared two months after surgery. MEG also indicated persistent BS. ITL was calculated in 38% by MEG and in 22% by EEG. Average ITL increased to 109.1 ms by MEG and to 95.8 ms by EEG. BS appeared first in the right hemisphere in 84% by MEG and which hemisphere was leading in generating of BS was impossible to clarify by EEG because of inconsistent values.

Conclusions: ITL of BS before surgery in Case 1 corresponded to the minimal transcallosal transfer time and most BS appeared first in the right hemisphere. Marked decrease of DAs and the absence of BS after surgery also suggested the dominant role of the transcallosal pathway in drop attacks. In contrast, ITL before callosotomy in Case 2 was too short to be explained by a simple transcallosal transfer and no hemisphere was dominant in the generation of BS. Recurrence of DAs and persistent BS after surgery indicated an underlying non-callosal mechanism in Case 2. However, the postoperatively prolonged ITL suggested that the corpus callosum was partially involved in synchronization before surgery. MEG showed better correlation with the clinical outcome than EEG. MEG is useful for evaluation of patients with DAs and BS.

2.188

PATIENT-SPECIFIC SEIZURE-ONSET DETECTOR TO OPTIMIZE ICTAL SPECT

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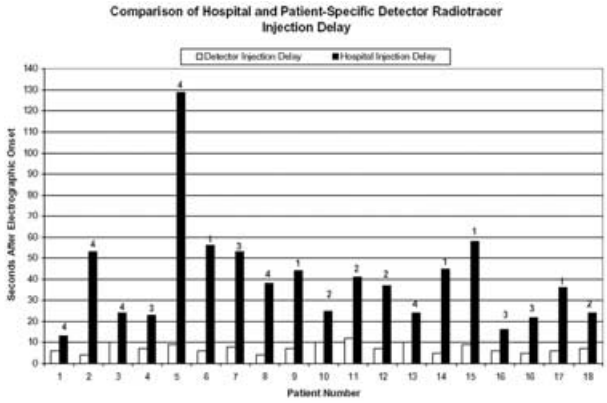
Rationale: Prompt administration of radiotracers following the *electrographic onset* of a seizure may enhance the localization of epileptogenic foci using functional imaging modalities such as SPECT. In our experience, ictal SPECT protocols that rely on a caregiver for visual recognition of a seizure's onset result in injection of the radiotracer 20–55 seconds after the *clinical onset*. This delay leads to poor localization of the seizure focus. To achieve consistent and prompt injection of radiotracers we developed an automated patient-specific method for the detection of seizure onsets from non-invasive EEG. The detector can alert staff of a seizure's electrical onset, or automatically activate a drug infusion pump that delivers the radiotracer.

Methods: Our *patient-specific* detector exploits the consistency of seizure and non-seizure EEG within patients. The detector uses a wavelet decomposition to construct a feature vector that captures the morphology and spatial distribution of waveforms in a 2 second EEG epoch. Next, the detector determines whether that feature vector is representative of a patient's seizure or non-seizure EEG using a classifier (a support-vector machine) that has already been trained to recognize that patient's seizure and non-seizure activity. When the detector notes seizure activity for six seconds it declares a seizure event.

Results: The detector was tested on EEG from forty-six pediatric subjects. It detected 160 of 168 seizure events within 7.9 +/− 3.0 seconds following the electrographic onset, and declared 22 false-detections in 75 hours of clinical EEG. The figure below compares the delay incurred by starting injection of the radiotracer using existing hospital protocols with the delay that would be incurred provided injections were triggered by the detector. The numbers over each bar indicate how many seizures the detector was trained on before attempting to detect the seizure on which an ictal SPECT was attempted.

Conclusions: We have developed a patient-specific method that detects the onset of epileptic seizures from non-invasive EEG. That method is well suited for triggering time-sensitive clinical procedures like injection of a radiotracer following seizure onset for the purpose of seizure focus localization. [Supported by Center for Integration of Medicine and Innovative Technology (CIMIT) and the MIT Project Oxygen Partnership.]



2.189

THE SIGNIFICANCE OF POSITIVE TEMPORAL AND CENTRAL SHARP WAVES IN NEONATAL EEG

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Rationale: The significance of positive temporal (PTS) and central sharp waves (PCS) in neonatal EEG has remained unclear. PTS and PCS have been associated with a non-specific injury to deep white matter. PTS has been associated with intracerebral hemorrhage in one study but not in another study. We aim to identify the significance of PTS and PCS.

Methods: Retrospective review of the 228 EEGs from 164 neonates, done between Junel 2002 to September 2003. We correlated the presence of PCS and PTS with neuroimaging (US, CT or/and MRI).

Results: PCS and PTS were reported in 184 EEGs of 144 neonates. Seven neonates were excluded, as they did not have neuroimaging done. We correlated the presence of PCS and PTS in 175 EEGs of 137 neonates with neuroimaging pathology.

The number of sharp waves varied from many i.e. >2.5/min (30%), some (40%) to few i.e. <10 (30%). Normal imaging was found in 26% of neonates; Ischaemic pathology was found in 46% of neonates and hemorrhaghic pathology was found in 13% of neonates. The location of sharp waves did not lateralize the pathology. The number and localization of sharp waves did not correlate to a specific pathology. There was some correlation between the number of sharp waves and abnormal imaging. If an EEG had many (>2.5/min) positive sharp waves, the imaging was abnormal in all neonates. However only 30% of EEGs with few (<1/min) positive sharp waves had normal imaging.

Conclusions: Positive central and temporal sharp waves are reported frequently in neonatal EEGs and they may be consistent with a non-specific brain abnormality especially when frequent (>2.5/min).

Clinical Epilepsy–Adult 2

2.190

CLINICAL-ELECTROENCEPHALOGRAPHIC CORRELATION AND OUTCOME OF PATIENTS PRESENTING TO THE EMERGENCY ROOM WITH POSSIBLE STATUS EPILEPTICUS

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Rationale: The rapid and accurate assessment of patients presenting to an emergency room (ER) with altered consciousness represents a special challenge. Early detection and treatment of status epilepticus in these types of patients is essential and the electroencephalogram represents a crucial diagnostic test. We retrospectively investigated the clinical

features and outcome of a subset of patients for whom an EEG was requested in the ER to assess the possibility of status epilepticus (SE).

Methods: An EEG database and a paper log of all EEGs performed from 5/97–4/2004 were reviewed. All patients who had an EEG performed in the ER at Parkland Memorial Hospital were identified. This preliminary report is based on the analysis of records obtained from the database which represented 27% of the total identified records. Medical records were reviewed and clinical information abstracted. Patients were excluded if 1) insufficient clinical information was available 2) the patient was a prisoner 3) the EEG indication was not possible SE. Clinical SE was defined as ≥30 minutes of continuous seizure activity or two consecutive seizures without interval return to baseline consciousness. EEG SE was defined as an EEG demonstrating ongoing ictal activity in a patient with altered consciousness.

Results: EEGs were performed in the ER for 206 patients. Medical records of 56 patients were analyzed and 11 patients were excluded (5 prisoners, 3 inappropriate EEG indications, 3 with insufficient information). A total of 45 patients met inclusion criteria with a mean age of 51.4+/− 19 years, and 45% were females. Twelve patients did not have epileptic seizures, 3 had provoked epileptic seizures, 1 was uncertain, and 29 had unprovoked epileptic seizures. Among the patients with unprovoked epileptic seizures, 13 were new onset. Seventeen patients met clinical criteria for SE (Epilepsia Partialis Continua = 3, Myoclonic = 1, Tonic = 1, tonic-clonic/other = 12) preceding or during the ER evaluation. A single patient was in electrographic SE. Nine of 17 patients with SE were intubated compared with 8 of 28 who were not in status. Of the 16 patients in SE with known outcome, 14 were discharged at or near baseline neurologic condition, 1 had severe disability, and 1 died.

Conclusions: While 38% of patients met a clinical definition of SE, only 2% showed evidence of EEG SE. This is considerably less than a previously reported figure of 37% (Privitera et al. *Epilepsy Res* 1994; 18(2):155–66). This may reflect research design differences, sampling errors, or reflect the current strategy of an aggressive approach toward possible SE. Although 53% required intubation, there were no associated complications or additional morbidity and 88% of patients had a good outcome. (Supported by Once Upon A Time Foundation.)

2.191
RECOGNITION OF EPILEPTIC VERSUS NONEPILEPTIC SEIZURES BY HEALTHCARE PROVIDERS

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Rationale: Psychogenic, non-epileptic events, conversion disorder, or pseudo-seizures are all terms given to a disorder that resembles an epileptic seizure, but has no electrographic correlates. Patients with this diagnosis may be treated for years without the proper testing for an accurate diagnosis. Long term video-electroencephalographic (EEG) recording is the only procedure that can definitively diagnose non-epileptic events for appropriate treatment. Since many patients are seen and treated based on their seizure presentation and self-report, misdiagnosis frequently occurs. The purpose of this study is to assess the ability of health care providers to differentiate between epileptic and non-epileptic seizure activity. A secondary purpose was to compare seizure identification scores between nurses and physicians.

Methods: A convenience sample of 118 health care providers (nurses, physicians, psychologists, medical students, and EEG technicians) who care for individuals with seizure disorders participated in this descriptive study. The majority of participants were nurses (38%) and physicians (41%). Videotapes with 10 randomly sequenced seizure-like events (50% epileptic) were viewed individually by all participants and scored as an epileptic or non-epileptic event. Each correct response was assigned 10 points. Points were summed for a total score. Higher seizure identification scores reflected more correct answers. Scoring was completed immediately after each participant completed the study.

Results: 118 participants completed the study. Scores for identification of epileptic and non-epileptic seizure activity ranged from 10 to 90 (M = 51). Mean scores by groups of participants were: physicians = 55.4, psychologists = 51, medical students = 49.6, EEG technicians = 55, and nurses = 46.2. It is notable that all these scores are close to chance levels (chance = 50). A one-way analysis of variance (ANOVA) was conducted to compare physician and nurse seizure identification scores. Physicians scored significantly higher than nurses ($F(1, 117) = 6.24$, $p = .01$).

Conclusions: Findings from this study suggest that visualizing seizure activity may not be the best way for health care providers to correctly identify epileptic vs. non-epileptic seizure activity. Long-term video EEG should be considered as an appropriate means for differentiation between epileptic and non-epileptic events.

2.192
LONG-TERM PROGNOSIS OF REFRACTORY EPILEPSY IN ADULTS

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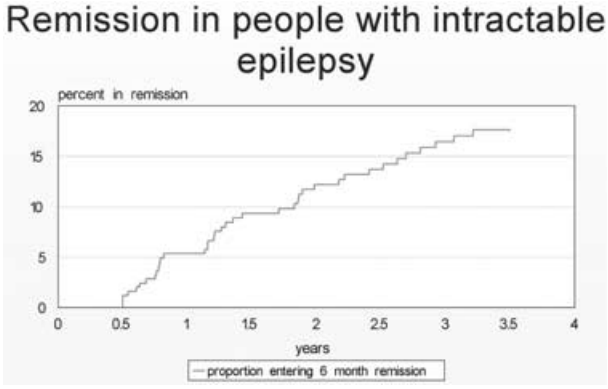
Rationale: A recent study in newly diagnosed epilepsy patients indicated that after failure of one AED due to lack of efficacy the likelihood of seizure control was 11%. No studies have been performed in adults that have become treatment refractory to determine if remission is possible. We wished to determine the likelihood of remission as well as any predictors of remission in patients that meet a strict definition of refractory epilepsy.

Methods: From the 3224 charts at the University of Pennsylvania Epilepsy Center, we identified 246 patients followed from 2000 who met the following criteria: 1) were having at least one seizure per month and 2) had failed at least two antiepileptic drugs (AEDs) at the index date. Records were reviewed to identify baseline characteristics such as seizure type and frequency, duration of epilepsy, epilepsy syndrome, current AEDs, AEDs failed, presence of developmental delay, and history of status epilepticus. We used Kaplan Meier methods to estimate the rate of achieving a 6-month terminal seizure remission over the next three years and evaluated clinical predictors for seizure remission.

Results: Syndromes in the study population epilepsy included: localization related 80.5%, symptomatic generalized 11%, primary generalized 6.9% and other syndromes 1.6%. The median duration of follow up from index date was 3.10 years. The overall rate of 6-month terminal remission at 3 years was 15.5% (localization related: 16.7%, symptomatic generalized: 0%, and idiopathic generalized: 29.4%) (Fig. 1). Negative predictors for remission included a history of status epilepticus, the presence of mental retardation, and Lennox-Gastaut syndrome. Duration of epilepsy, age of onset, and number of AEDs failed were.



Conclusions: In our refractory adult population there was a 5% per year remission rate, a frequency comparable to that shown in studies in children. Prospective studies with long term followup to refine these findings are needed.

2.193

ACETYLCHOLINESTERASE INHIBITORS IN THE TREATMENT OF PATIENTS WITH ALZHEIMER DISEASE AND ASSOCIATED SEIZURE DISORDERS WHO MAINTAIN AN ANTICONVULSANT DRUG THERAPEUTIC LEVEL

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Rationale: Acetylcholinesterase (AChE) inhibitors are known to lower the seizure threshold in patients suffering from Alzheimer's disease and associated epileptic seizures, but little is known if seizures can be prevented in these patients if they maintain a therapeutic level of their antiepileptic drug (AED).

Methods: In a retrospective study, patients were selected if they fulfilled the NINCDS-ADRDA Work Group criteria for Alzheimer's disease and if associated complex partial and secondarily generalized seizures were demonstrated clinically and by electroencephalogram (EEG) in the same patients who had simultaneous treatment with AChE inhibitors and AEDs which were maintained within therapeutic range.

Results: From June 12, 2000 to March 12, 2004, fourteen patients fulfilled the selection criteria. There were eleven female and three male patients. Age varied from 52 to 86 years. Five patients had complex partial and nine patients had secondarily generalized seizures. One patient with secondarily generalized seizures had underlying Down syndrome. Eight patients were taking phenytoin, four patients were taking carbamazepine and two patients were taking valproic acid. The AEDs were kept within therapeutic level. Thirteen patients were taking donepezil and one patient was taking rivastigmine. After the AChE inhibitors were withdrawn, all patients achieved control of their seizures.

Conclusions: Despite maintaining an AED therapeutic level in patients with Alzheimer's disease and associated epileptic disorder, simultaneous treatment with AChE inhibitors (donepezil, rivastigmine and likely galantamine) threatens an optimal seizure control.

2.194

LATE-ONSET PSYCHOGENIC NONEPILEPTIC SEIZURES

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Rationale: Psychogenic nonepileptic seizures (PNES) represent 20–30% of patients evaluated at specialized epilepsy centers. Like psychogenic symptoms in general, PNES are typically seen in young adults. Our objective was to describe a series of patients with PNES of late onset.

Methods: We reviewed our database of patients diagnosed with PNES by EEG-video monitoring, and selected patients with late onset, defined as age 60 or later.

Results: Between January 2002 and March 2004, a total of 94 patients were diagnosed with PNES. Of these, 9 (9.6%) had PNES of late onset. Eight patients had a spell induced by activation, while one had a spontaneous event. Ages ranged from 60 to 78 (mean of 65.5). Eight of nine patients were women. "Seizure" type was heterogeneous, ranging from mild tremors to full convulsion with loss of consciousness. Frequency was once weekly to two to four times daily. Four of nine patients had a diagnosis of mood or anxiety disorder and were on an antidepressant, anxiolytic, or both. Five patients were receiving an anticonvulsant.

Conclusions: PNES with onset after age 60 is not common but does occur. Patient's psychosocial characteristics appear otherwise similar to younger patients with PNES.

2.195

PREVALENCE AND TREATMENT OF VITAMIN D DEFICIENCY IN PEOPLE WITH EPILEPSY AND MULTIPLE RISK FACTORS FOR BONE DISEASE

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Rationale: Vitamin D deficiency may be common in people with epilepsy (PWE) treated with antiepileptic drugs (AEDs). It is not clear when to evaluate PWE for vitamin D deficiency. There is almost no information regarding treatment of Vitamin D deficiency in this situation.

Methods: Serum 25 OH Vitamin D levels, total alkaline phosphatase, total calcium, and phosphorus were obtained in all PWE with 2 or more risk factors for osteoporosis or osteomalacia seen at an outpatient clinic by one of the authors. If Vitamin D deficiency was present (25 OH Vitamin D < 20 ng/ml), parathyroid hormone (PTH) levels were obtained in some subjects and 1200 IU Vitamin D daily was prescribed to all. Serum 25 OH Vitamin D levels and other chemistries were repeated approximately every 3 months.

Results: 91/307 PWE seen during 6 months had multiple risk factors for bone disease. 32/91 (35%) had 25 OH Vitamin D levels < 20 ng/ml including 7 (8%) with 25 OH Vitamin D < 10 ng/ml. No subjects had hypocalcemia. Only 5/15 with Vitamin D deficiency had elevated PTH (>65 pg/ml). 10/32 Vitamin D deficient subjects and 13/59 subjects with normal Vitamin D had abnormally elevated alkaline phosphatase ($p = 0.41$). 26/32 Vitamin D deficient subjects and 41/59 subjects with normal vitamin D were treated with one or more inducing AEDs ($p = 0.22$). Age, sex, body mass index, and fraction residing in group homes also did not differ in PWE with and without Vitamin D deficiency. 25 OH Vitamin D levels after >3 months of treatment with 1200 IU of Vitamin D are currently available in 15/32 subjects presenting with Vitamin D deficiency. 25 OH Vitamin D increased from a mean 14ng/ml to a mean 43ng/ml. All subjects had levels >20 ng/ml, 8/15 had levels >35 ng/ml and 2 had levels $>$ 60ng/ml (maximum 69) following treatment. Mean alkaline phosphatase prior to $(102 + -48.5)$ and following $(97 + -26)$ Vitamin D treatment didn't differ significantly ($p = 0.62$); alkaline phosphatase remained abnormally elevated in 5/15. Serial 25 OH Vitamin D and alkaline phosphatase determinations are ongoing to evaluate the possibility of cumulative toxicity and the impact of seasonal variation of light. Impact of other risk factors for bone disease will be discussed.

Conclusions: Vitamin D deficiency is common in PWE treated with AEDs who have multiple risk factors for bone disease; however it appears to be relatively mild. 1200 IU Vitamin D normalized Vitamin D levels in all subjects in this study. Higher doses may be needed at higher geographical latitudes or to achieve optimal levels ($>$35ng/ml) in some patients. Persistently elevated alkaline phosphatase following correction of Vitamin D deficiency suggests that abnormalities in Vitamin D metabolism are not the only cause of bone disease in PWE. (Supported by MINCEP Epilepsy Care.)

2.196

ARE PATIENTS WITH FAMILIES IN THE HEALTH CARE FIELD MORE LIKELY TO DEVELOP PSYCHOGENIC SEIZURES?

[3]Kirsten A. Bracht ([1]Epilepsy Center, CNI, Englewood, CO)

Rationale: Psychogenic seizures may be impossible to differentiate from epileptic seizures on the basis of history and clinical features alone. We wondered whether patients were more likely to have non-epileptic seizures if they had a prior close relationship to the medical field. Exposure could be through occupation, education, chronic pain/disability or a family member with epilepsy.

Methods: Using our database, we performed a retrospective chart review on patients evaluated at the Colorado Neurological Institute Epilepsy center between January 1, 2002 and April 1, 2004. Study subjects underwent inpatient video-EEG monitoring and had psychogenic seizures recorded. Only patients with complete medical, psychiatric, occupational and educational histories were included.

Results: A total of 45 patients fulfilled study criteria with 35 females and 10 males. Ages ranged from 16 to 77 years. Seven patients (15.6%) worked in or were trained healthcare related fields. Another twelve (26.7%) were on disability and/or receiving treatment for chronic pain. Five patients (11.1%) had close family members with epilepsy. Ten patients (22.2%) had been sexually/physically abused and four (8.9%) carried psychiatric diagnoses (e.g. bipolar disorder). One patient had undergone successful temporal lobectomy. Two patients were developmentally disabled. Another had concurrent complex

partial seizures. Four patients had negative histories and no obvious risk factors.

Conclusions: Familiarity with the medical field may be an independent risk factor for the development of psychogenic seizures. This is especially true of the patients without a history of physical/sexual abuse or psychiatric illness. Detailed occupational, educational and family histories can assist in the evaulation of these patients. (Supported by Colorado Neurological Institute.)

2.197

HIGH-DOSE VITAMIN D SUPPLEMENTAION REQUIRED FOR NORMALIZATION OF VITAMIN D LEVELS IN A PATIENT WITH MULTIPLE FRACTURES AND LONG-TERM PHENYTOIN THERAPY

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Rationale: Population based studies of fractures consistently identify anticonvulsants as a risk factor for osteoporotic related fractures. Phenytoin and phenobarbital have been shown to accelerate bone loss and carbamazepine has also been implicated. The mechanism for this adverse outcome is believed to be due to cytochrome P-450 enzyme induction that causes an increased clearance of vitamin D. Reduced vitamin D levels results in activation of parathyroid hormone and subsequent mobilization of calcium from bone and over time may lead to osteopenia and increased fracture risk. Supplementation with vitamin D has been recommended to limit demineralization. Doses of 400–2000 internation units (IU) daily are recommended for patients on anticonvulsant therapy. However there is no data that describes changes in vitamin D levels with supplements of vitamin D in the presence of enzyme inducers.

Methods: From January 2003 to March of 2004 levels of 25-hydroxy vitamin D were assayed by the Nichols chemiluminescent immunoassay in a patient on escalating doses of ergocalciferol.

Results: Initial supplementation at a dose of vitamin D of 400 IU daily found the 25-hydroxy vitamin D level at 16ng/ml. At 50,000 IU biweekly the Vitamin D level was 34ng/ml.

Conclusions: This institutionalized 41 year-old female with a lifelong history of epilepsy and exposure to multiple anticonvulsants including phenobarbital, phenytoin and divalproex, had suffered multiple fractures. She was found to be osteopenic, likely related to long-term exposure to vitamin D-depleting anticonvulsants. Normalization of vitamin D may limit her ongoing risk. Serial increases in vitamin D were necessary to normalize her level. Doses of 50,000 IU of vitamin D in healthy individuals would appear to be excessive, but may be required in the presence of enzyme inducers.

2.198

OBSERVATION OF THE COURSE OF INTRACTABLE SEIZURES IN PATIENTS WITH DELAYED OR POSTPONED INVASIVE RECORDINGS

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Rationale: In cases of medically intractable epilepsy, invasive monitoring is used to further determine the localisation of epileptogenic tissue when a) the Scalp EEG does not adequately localise the epileptogenic area; b) When EEG and neuroimaging are non-concordant suggesting an abnormality in more than one region or c) when seizures arise from functionally important areas of the brain. We retrospectively audited the history of seizure control in patients initially approved for invasive recordings but in whom the procedure was unavoidably delayed or postponed.

Methods: The Epilepsy Unit at Beaumont hospital houses the only epilepsy surgery programme in Ireland. A total of 11 patients were on a waiting list for invasive monitoring at our centre up to early 2002 when due to a large-scale redevelopment of the unit, the procedures could not be carried out. During the following 2-year hiatus, despite being approved for invasive monitoring, all eleven patients were managed medically. Using an audit of patient's clinical charts after close clinical supervision in the out-patient department and with telephone interviews for incomplete data, we recorded the seizure types, frequency and outcome after 2 years, as well as all pertinent clinical, neurophysiological and radiological data in this highly specific group.

Results: Of the 11 patients, we found 4 were seizure free for over a year; Two patients, although still having seizures, perceived their control as improved or acceptable; 3 patients had further minor improvements in seizure control. One patient continued to have seizures at the same rate and is now awaiting a device insertion. One patient was lost to follow-up. Among the reasons for improvement was optimisation of medication regime (including the introduction of leveteracetam in 3 of the 4 seizure free cases). There was no common clinical, historical or pathophysiological mechanism in the cases reviewed.

Conclusions: This interesting group of patients allows for a serendipitous observation of the course of intractable seizures in patients who, were it not for the forced hiatus in invasive monitoring, might otherwise have had epilepsy surgery. The fact that more than half had enjoyed either a complete remission in seizures or a worthwhile reduction in attacks suggests the need to constantly re-configure new medications and drug optimisation regimes into any decision to proceed to invasive recordings. (Supported by Epilepsy Surgery Programme, Beaumont Hospital, Dublin, Ireland.)

2.199

FACTORS OTHER THAN SEIZURE DURATION PLAY AN IMPORTANT ROLE IN THE DEVELOPMENT OF REFRACTORY STATUS EPILEPTICUS

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Rationale: Refractory status epilepticus (RSE) is a severe form of status epilepticus (SE) that does not respond to first and second anticonvulsant treatment efforts. Understanding what causes RSE may provide important insights into the prevention and treatment of this condition. Seizure duration prior to treatment has been suggested to play a role in the development of RSE. This study was initiated to evaluate the role of seizure duration and other factors in the development of RSE.

Methods: This study identified 148 cases of RSE in a data base of 539 cases of adult SE. These patients were identified prospectively in a population based study in the Richmond NIH SE data base. SE was defined as seizure activity lasting 30 minutes or longer or intermittent seizure activity lasting 30 minutes or longer without regaining consciousness. RSE was defined as SE patients that did not respond to the first and second treatements of anticonvulsant medications. Definitions of etiology, seizure types, and other variables and statistical methods have been described previously (*Neurology* 1996;46:1029–035).

Results: The effects of seizure duration prior to the initial treatment in influencing the development of RSE were analyzed. Univariate and multivariate analysis of seizure duration prior to first treatment as a predictor of the development of RSE indicated that seizure duration prior to first treatment did not have a statistically significant effect on the development of RSE. Other variables, including age, gender, race, seizure type, location of seizure onset, etiologies, previous seizure history, and laboratory values were evaluated. Specific variables including nonconvulsive SE, location of onset, and previous seizure history were statistically significantly contributing to the development of RSE using both univariate and multivariate statistical analysis. Unexpectedly, etiology did not statistically effect the development of RSE. Further analysis suggests that innovative strategies are needed to elucidate the causes of RSE.

Conclusions: Understanding the factors that contribute to the developent of RSE may play an important role in developing novel strategies to prevent and better treat this major neurological condition. Results from this study indicate that time to initial treatment may not play a major role in the development of RSE. Future studies on larger data bases are needed to expand these studies and more clearly dissect out the underlying contributing causes of RSE. Although these studies do not completely rule out time to treatment as a factor contributing to the development of RSE, they indicate that other factors clearly contribute to the development of RSE independent of time to first treatment. (Supported by P50NS25630 from the National Institutes of Health.)

TABLE 1. *Smoking status in risk of seizure/epilepsy (1995–2001)*

Current Smoking Status	Never	Past	Current
Number of Cases	46	13	14
Person-time yrs	274,877	99,925	38,696
RR (95% CI)*: Age-adjusted RR†	1.00 (reference)	0.81 (0.44, 1.52)	2.24 (1.22, 4.11)
RR (95% CI): Multivariate-adjusted‡	1.00 (reference)	0.80 (0.42, 1.50)	2.11 (1.13, 3.95)
RR (95% CI): Multivariate-adjusted + brain tumor	1.00 (reference)	0.79 (0.42, 1.48)	2.18 (1.17, 4.08)
RR (95% CI): Multivariate-adjusted + stroke	1.00 (reference)	0.72 (0.37, 1.37)	1.77 (0.91, 3.42)

*RR (95% CI) = Relative Risk (95% Confidence Intervals)

2.200

PROSPECTIVE STUDY OF SMOKING AS A RISK FACTOR FOR SEIZURES OR EPILEPSY: EVIDENCE FROM THE NURSE'S HEALTH STUDY II

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Rationale: Nicotine has been shown to cause convulsions at high doses. No prospective studies have directly related smoking to development of seizures or epilepsy, though it is a strong risk factor for stroke, which is a cause of late onset seizures/epilepsy. We investigated the relation between smoking and incidence of seizures/epilepsy among women prospectively followed in the Nurses' Health Study II (NHSII).

Methods: NHSII participants have been followed since 1989 with biennial questionnaires requesting lifestyle and health information. In 2001, participants were asked about occurrence and dates of seizures/epilepsy. For confirmation and classification of self-reports, we administered supplementary questionnaries to women reporting incident seizures/epilepsy occurring from 1995 to 2001. We compared rates of seizures/epilepsy across categories of smoking (never, past, current) among 70,000+ women, aged 30–52. We adjusted rates for age and other potential confounders such as alcohol, caffeine, diabetes, hypertension or high cholesterol using Cox proportional hazards models. In alternate analyses, rates were adjusted for stroke.

Results: From 1995 through 2001, during 413,497 person-years of follow-up, we identified 73 incident cases of seizures/epilepsy; the most frequent type was symptomatic partial epilepsy (37%). Preliminary medical record validation of self-reports confirmed epilepsy diagnosis. Compared to never smokers, age-adjusted relative risk (RR) of seizures/epilepsy for past smokers was 0.80 (95% CI = 0.42, 1.50) and for current smokers, 2.24 (95% CI = 1.22, 4.11); in multivariate analyses, for current smokers, the RR was 2.11 (95% CI = 1.13, 3.95) (Table 1). With further adjustment for strokes, we observed some attentuation in RR for current smokers: RR = 1.77 (95% CI = 0.91, 3.42). Trends were not detected with increasing smoking dose ($p = 0.22$).

Conclusions: In this population-based study, we found that cigarette smoking increases risk of seizures or epilepsy with a trend toward a relationship independent of stroke.

(Supported by CA50385, the main Nurses' Health Study II grant.)

2.201

BONE LOSS IN EPILEPSY: BARRIERS TO PREVENTION, DIAGNOSIS, AND TREATMENT

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Rationale: In treating epilepsy in the inner city, there are numerous barriers to prevention, diagnosis and treatment of metabolic bone disease. Anti-epileptic drugs (AEDs) lead to a loss of bone density of up to 35% compared to normals. Supplementation with a multivitamin/mineral (MVI), folate and calcium (w/vitamin D) is critical for bone health, especially for persons with epilepsy. Bone density screening by DEXA scan is required for diagnosis. The goal of this study is to elucidate these barriers.

Methods: Standard of practice in our clinic is to address bone health and nutrition with all patients and to communicate treatment issues to referring primary care physicians (PCP). We screened 101 consecutive patients (women n = 56, men n = 45) seen in our clinic over 4 months to determine the most frequent barriers to osteoporosis prevention. Data on each subject included: age, gender, seizure type, neurologic co-morbidities, years on AEDs, supplementation patterns and DEXA screening results. A problem list was compiled.

Results: This was an adult epilepsy population: Mean age: 44 years (SD = 14.8, range 19 to 78), Average length of AED exposure: 21 years (SD = 16, range 0.25 to 54).

Common barriers for prevention were compliance-related: of 87 subjects prescribed supplements, 47 patients took a MVI and 34 took calcium. In this population, the cost of over the counter (OTC) medications and supplements is a limitation. Some had difficulty remembering to take supplements.

DEXA scan was recommended for 47 of 101 subjects; 28 of 47 obtained DEXA. 23 subjects had abnormal results(osteopenia n = 13, osteoporosis n = 8, kyphosis n = 2). One of the most common barriers to screening was related to managed care; 55% of subjects had HMOs requiring referrals for DEXA scans. This process is time consuming. Physical/mental impairment preventing DEXA scan was also a barrier.

Conclusions: This retrospective review identified important issues in nutrition and epilepsy. It has been established that there is significant metabolic bone loss due to AEDs. The addition of supplements to a patient's program is relatively easy. However, issues of cost and compliance are common barriers. Potential solutions include: coverage of OTC medications by insurance, a cost/value summary of supplements and nutritional counseling of dietary sources of calcium to aid decision making.

"Compliance" is a term that tends to blame the patient. The idea of partnership in medicine can foster a sense of personal health responsibility in the patient. Despite routine communications to PCPs regarding need for screening/supplementation for bone health, in the epilepsy population, the recognition of its importance is still overlooked. Health behaviors related to lifestyle are struggles that require individual, community and nationwide approaches.

2.202

LAMOTRIGINE IN PATIENTS WITH EPILEPSY AND COMORBID DEPRESSIVE SYMPTOMS: PRELIMINARY REPORT

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Rationale: The prevalence of depressive complaints in people with epilepsy (PWE) ranges from 20 to 55% with ~8% to 48% (mean of 29%) meeting criteria for a Major Depressive Disorder (MDD). Several authors have noted the importance of milder depressive, dysthymic-like complaints in PWE. In addition, the single most significant predictive factor in the quality of life of PWE appears to be depressive complaints. Antiepileptic drugs (AEDs) have both negative and positive psychotropic features. Lamotrigine (LTG) has recently been approved for the maintenance treatment of depression in patients with bipolar disorder. The purpose of this study is to further evaluate the antidepressant qualities of LTG in PWE.

Methods: This is a multicenter open label study. Lamotrigine was added onto a stable AED regimen in the adjunctive and maintenance phases and became a single agent in the monotherapy phase. Patients were eligible for the study if they had refractory epilepsy, exhibited depressive symptoms [Center for Epidemiological Studies Depression Scale (CES-D) $\geq$ 12] but were excluded if they had a MDD as determined by a Mini International Neuropsychiatric Interview (M.I.N.I.) evaluation. One hundred fifty-nine patients with epilepsy have been entered into the study and results are available for 58 completing the adjunctive phase and 33 completing the monotherapy phase. Patients were evaluated using the Neurological Disorders Depression Inventory in Epilepsy (NDDI-E), Beck Depression Inventory (BDI-II), CES-D, Cornell Dysthymia Scale Self-Report (CDRS-SR) and the Profile of Mood States (POMS) at baseline, at the end of the adjunctive phase (Week 19) and the monotherapy phase (Week 36). Preliminary results are reported.

Results: Results of the depression psychometrics used are as follows: Mean baseline, end of adjunctive and monotherapy scores for weeks 19 and 36 for the NDDI-E were 14.0, 12.4 and 10.6; for the BDI-II, 20.2, 12.4, 8.8; for the CES-D, 26.7, 15.6, 12.6; for the CDRS-SR 62.1, 54.3, 49.6; and for the POMS were 63.0, 40.1, 25.8 respectively. All change scores were significant at $p \leq 0.0001$ except for the NDDI-E at the end of adjunctive therapy where $p \leq 0.0014$. Convergent validity appears to exist between all the measures. Seizure–free rates were 38% at baseline, 50% after adjunctive therapy and 69% after monotherapy. Changes in seizure frequency did not significantly correlate with changes in mood states.

Conclusions: It appears from preliminary data that LTG has antidepressant activity for PWE with low to moderate levels of depression that do not meet criteria for a MDD as measured by the M.I.N.I. Since this is an open label study with no control group the extent of this effect is unclear, but does not appear to be due to changes in seizure frequency. (Supported by GlaxoSmithKline.)

2.203

SEIZURE-ACTIVATION MANEUVERS IN EPILEPSY MONITORING UNITS

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Rationale: Simultaneous video-EEG monitoring in epilepsy monitoring units (EMU) is the goal standard to determine the etiology of spells (seizures vs. non seizures), and to evaluate patients with refractory epilepsy prior to epilepsy surgery. Reimbursement for EMU admissions, especially prolonged ones, by third party payers continue to be very challenging. Applying more aggressive "activation maneuvers," may trigger events early during admission to EMUs and may shorten duration of hospitalization. We conducted a survey to determine how different activation procedure including anti-epileptic drug (AED) withdrawal, sleep deprivation, hyperventalitation, and phtoic stimulation are utilized in different epilepsy centers.

Methods: A 19 question EMU survey was e- mailed to epileptologists in the United States. Only one survey was sent to each epilepsy center that was surveyed. The survey asked questions regarding EMU hours of operation, fellowship program, activation procedures prior and during hospitalization, and management of AEDs prior and during EMU hospitalization.

Results: At the time of submitting this abstract, data from 18 epileptologists were collected and analyzed. In 67% of all EMUs, operation hours were seven days a week, and those were mainly in epilepsy centers that offer neurophysiology or epilepsy fellowships. Prior to admission to EMU, 28% of correspondents ask patients all the time to start to discontinue anti-epileptic drugs (AED), but none asks patients to be sleep deprived the night prior to admission. During EMU hospitalization, 78% sleep deprived patients, 67% hyperventilate patients and 61% do photic stimulation. Discontinuation of AEDs begins on the first day of admission by 72% of the correspondents. Excluding benzodiazepines and barbiturates, 56% decrease AEDs at a rate between 35–50%, and 11% stop AEDs abruptly. In patients taking more than on AED, 55% discontinue more than one AED simultaneously.

Conclusions: Although most epileptologists used activation maneuvers to trigger seizures, the timing and methods of applying them vary significantly. Studies to determine the safety and the efficacy of such activation maneuvers may help to establish guidelines that can offer better patient care, shorten EMU admissions and may improve reimbursement.

2.204

ICTAL AND POSTICTAL DYSPROSODIAS: CLINICAL FEATURES AND DOCUMENTATION BY ACOUSTIC ANALYSIS

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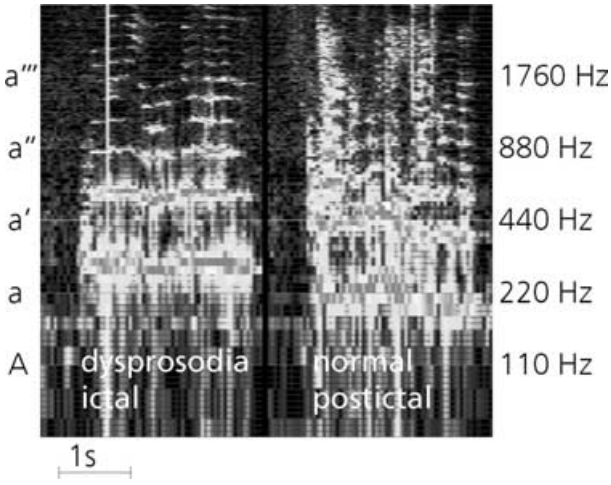
Rationale: Ictal and postictal dysprosodias are rarely reported but a phenomenon which is probably recognized too infrequently. In other neurological conditions dysprosodias are reported mainly after lesions of the right hemisphere, and so seizure-related dysprosodias may serve as a clinical lateralizing sign to the non-dominant hemisphere. Aim of this study was to collect the clinical features of patients with seizure-related dysprosodias and to characterize dysprosodic symptoms.

Methods: We identified retrospectively 26 patients with a seizure-related dysprosodia who had undergone presurgical evaluation. We documented EEG seizure patterns and epilepsy syndromes and we differentiated between postictal and ictal dysprosodia. We also analyzed available video recordings of seizures and classified by listening to the recordings and using Fourier spectral analysis.

Results: In 69% of the patients dysprosodia was found as an ictal symptom, in 31% postictal. The syndromes were 8% focal epilepsies without clear lateralization, 69% right and 12% bilateral temporal lobe epilepsies, 8% right frontal lobe epilepsies and one (3%) suspected left frontal epilepsy. Seizure patterns in 92% were on the right hemisphere, 8% of the patients showed no EEG seizure pattern during ictal dysprosodia, including the patient with the left frontal lesion.

Each patient had stereotyped patterns of dysprosodia, but there was a big variability between the patients (Fig. 1). Changes occur on four axes: 1) Pitch: We saw an exaggeration of a likely normal pitch course, a continuous increasing of pitch during one utterance or a flattened pitch course (see figure). 2) Volume: especially in ictal speech we found an increased intensity of speech, but decreased intensity of speech down to aphonia also occured. 3) Time course: We found some syllables prolonged or stops after each syllable, which could have resulted in a phase of stuttering. 4) Resonances: A few patients showed changes in the harmonic spectrum resulting in an abnormal nasal or in hollow speech.

Often the pathology of prosody was only obvious in comparison with the interictal speech.



Conclusions: Seizure-related dysprosodias are not uncommon and seem to occur nearly exclusively in right hemisphere seizures originating in the frontal and temporal lobe. Nevertheless, the value as a clinical lateralizing sign still has to be determined prospectively, for dysprosody may be underdiagnosed in patients with aphasic speech disturbances. Fourier analysis can especially help to measure pitch changes. Seizure-related dysprosodias may serve as a model for changes of prosody because they allow comparisons within single subjects.

2.205
CLINICAL EXPERIENCE WITH LEVETIRACETAM IN ADULTS WITH INTRACTABLE EPILEPSY
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Rationale: Levetiracetam is an antiepileptic drug approved as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. The purpose of this study was to review our clinical experience with levetiracetam in the different epilepsies in the adult population referred to an academic center.

Methods: Adult patients with persistent seizures despite adequate exposure to other AED(s) were started on 500 mg BID and titrated levetiracetam up to 3 gm per day. These patients were followed for efficacy (>50% seizure reduction) and adverse effects.

Results: 45 patients who range in age from 16 to 88 years were entered into the study. Seizures were classified as primary generalized (N = 3) and partial (N = 21). 2 Patients had Lennox-Gastaut syndrome (LGS). Associated conditions included schizencephaly, CVA, Cavernous angioma, HIV,SLE, Hx of intracranial hemorrage, and an astrocytoma. 8 patients had Vagal Nerve Stimulators. All patients were on two or three AED(s) when levetiracetam was added. Mean duration of treatment at the last clinic visit was 12.2 months. 37 patients had improvement in their seizure frequency. Four achieved 100% seizure control, and one patient developed a rash leading to discontinuation. Efficacy of >50% seizure control was reported in 33% of the patients using levetiracetam as adjunctive therapy to one or two other AED(s). Six out of the ten patients showing improvement were also receiving Dilantin. Seven out of the eleven were receiving carbamazepine. Only one out of the eleven were receiving both phenytoin and carbamazepine. No patients demonstrated worsening of their seizures while on levetiracetam. The most common reported side effects were fatigue, dizziness and confusion. No patients with primary generalized epilepsy showed benefit. One patient with VNS showed improvement on levetiracetam. One patient was tapered off all other AEDs.

Conclusions: Levetiracetam is well tolerated in the majority of patients (82%) in this population of adults with generalized and partial onset epilepsy. Approximately 59% had had significant decrease in seizure severity and frequency. One patient with LGS showed improvement. The remaining patients who showed improvement had partial epilepsy. One patient with VNS showed improvement as well. None of the patients with primary generalized epilepsy showed improvement.

2.206
PARTIAL-SEIZURE DURATION DURING SLEEP AND WAKEFULNESS IN MESIAL TEMPORAL EPILEPSY
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Rationale: Previous studies have suggested longer partial seizure duration in sleep, possibly due to NREM facilitation of neuronal hypersynchrony, but have lacked precise localization of the epileptogenic focus. We studied seizure duration in well-localized mesial temporal epilepsy, hypothesizing that partial seizures are longer during sleep than wakefulness.

Methods: We identified consecutive seizure-free patients following anterior temporal lobectomy (ATL) from 1993–2001 with video-EEG captured seizures in both wakefulness and sleep. We analyzed each seizure for seizure onset time by first clinical or ictal EEG change (whichever was earliest) and seizure offset time by end of the ictal EEG discharge. Seizure types were defined as simple or complex partial, or complex partial with secondary generalization.

Results: 23 (10 men and 13 women) seizure-free ATL patients had a total of 335 (176 right and 159 left) temporal onset seizures. 106 (32%) arose from sleep. Mean simple partial seizure duration was somewhat longer during sleep (45.80 seconds) than wakefulness (43.71 seconds), but the difference did not approach statistical significance ($p = 0.80$). There was a trend toward shorter mean complex partial seizure duration during sleep (57.06 seconds) than during wakefulness (66.61 seconds, $p = 0.07$). Secondary generalized tonic-clonic seizures were also slightly shorter during sleep (118.6 seconds) than wakefulness (120.2 seconds).

Conclusions: We found no significant difference in seizure duration between sleep or wake onset partial seizures of mesial temporal lobe origin. One possible explanation for this difference could be that sleeping patients may not awaken prior to ictal EEG onset, as compared to awake patients who could consciously experience clinical aura symptomatology and thereby mark their events prior to evolution of ictal EEG alterations. Given our methodology, this could have lead to an underestimation of true seizure duration in sleep-onset seizures. We conclude that mesial temporal onset simple and complex partial seizures with or without secondary generalization are not longer during sleep than in awake states. Future studies of sleep and wake seizure durations in other surgically-established localizations should be conducted.

2.207
INTRAVENOUS VALPROATE (VPA) IS EFFECTIVE IN STATUS EPILEPTICUS/SERIAL ATTACKS IN ADULTS
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Rationale: Intravenous VPA has recently been approved for treatment of benzodiazepine-resistant status epilepticus (SE) in Norway, as the first country in Europe. We have started a prospective registration of the effect of i.v. VPA in SE and serial attacks (SA) from 8 Norwegian hospitals.

Methods: Data have been obtained from the first 26 adult patients, 15 women and 11 men, treated with i.v. VPA for benzodiazepine-resistant SE/SA. The protocol suggested a VPA loading dose of 25 mg/kg over 30 min, followed by continuous infusion of 100 mg/hour for 24 hours.

Results: 16 patients were diagnosed with SE, 10 with SA. 14 had generalised tonic-clonic while 8 had complex-partial seizures as their main SE/SA seizure type. 4 had mixed or other type of seizures. Median VPA loading dose was 1200 mg (range 200–2514). Median time to treatment of SE/SA for all patients was 2.5 h (range 0.3–72 h). For patients with complex partial SE/SA, median time to start of VPA treatment was 2.4 h (range 0–72). Effect, defined as the lack of need of anaesthesia (barbiturates or propofol), showed that VPA was effective in 18 of 26 cases (69%). Of the 8 cases requiring anaesthesia, 4 had a significant delay before starting treatment (24 to 72 hours). Moderate hypotension during loading dose infusion was seen in one patient, but corrected easily with i.v. saline without complications. Otherwise, no side-effects were reported.

Conclusions: VPA seems to be safe and effective in the treatment of benzodiazepine-resistant SE/SA. Lack of effect may be related to delayed treatment. In addition, some of the patients also got a too low loading dose. Our preliminary results suggest that VPA is as effective as fos-phenytoin which is used as an alternative drug in Norway. However, randomised and blinded studies are needed.

2.208
REVERSIBLE LIMBIC ENCEPHALOPATHY INDUCED BY CHROMIUM PICOLINATE: NOVEL RISK FACTOR OF EPISODIC CONFUSION
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Rationale: Chromium picolinate is popular dietary supplement for weight reduction. We experienced a case of reversible partial seizure and limbic encephalopathy, worth attention in medical communities.

Methods: A 59 year old veteran visited our outpatient neurology clinic for intermittent episodes of deja vu, gasoline smell, and rage attack. The symptom started since he started ingesting dietary chromium picolinate pills at least once a day since five years ago. The patient has never experienced clinical seizure spells and had no previous history of seizure disorder. Neurological examination and brain MRI study were normal. Serial EEG studies were done.

Results: Initial EEG study demonstrated frequent interictal sharp discharges (IID) in the bilateral inferior temporal electrodes (T1 and T2) independently, but more preponderent in the left as a few spikes per page. The background activity was consistent with 10Hz alpha activity. Hyperventilation induced a single isolated high amplitude epileptiform discharge with maximum negativity at T3. Decision was made not to start

anticonvulsant but to discontinue habitual use of chromium picolinate. In the subsequent clinical follow up, the patient reported no recurrence of olfactory aura, deja vu, and mood swings. The EEG in 3 month showed decreased number of IID in left temporal electrodes at T1 and T3 but much less in frequency as one spike per 20 pages. The EEG in 6 month was negative in IIDs.

Conclusions: A case of reversible partial seizure due to chromium picolinate is described. The EEG findings were not only suggestive of the secondary epileptogenesis with bilateral independent discharges, but also indicative of reversible recovery process which was gradual after discontinuation of chromium picolinate. This supplemental form of organic chromium has been used as an active ingredient for weight reduction pills and diet beverages. Although its underlying pathophysiological mechanism has not been studied, chronic use of chromium picolinate should be counted and ruled out as a cause of new onset of reversible limbic encephalopathy in our modern community.

2.209

EXCITABILITY OF THE MOTOR CORTEX DURING OVULATORY AND ANOVULATORY CYCLES: A TMS STUDY

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Rationale: Even though about one third of female epileptic patients show anovulatory cycles, apparent seizure clustering in those cycles is not well understood. The aim of this study was to further investigate changes in cortical excitability during anovulatory as compared to ovulatory cycles using transcranial magnetic stimulation (TMS).

Methods: Using single- and paired- pulse TMS, 12 healthy women were investigated during ovulatory cycles (progesterone levels in luteal phase >5 ng/ml, age: 25.5 ± 4.9 years, BMI: 21.0 ± 1.3 kg/m^2, cycle length: 26.9 ± 1.9 days) and 8 during anovulatory cycles (progesterone levels <5 ng/ml, age: 24.1 ± 2.2 years, BMI: 22.5 ± 2.5 kg/m^2, cycle length: 29.0 ± 1.1 days). On days 8, 14, 21 and 2 of the cycle, resting motor threshold (RMT), cortical silent period (CSP), intracortical inhibition (ICI, averaged values of interstimulus intervals (ISI) 2 and 3 ms) and facilitation (ICF, averaged values of ISIs 10 and 15 ms) were investigated in the dominant hemisphere. Friedman and Wilcoxon tests were used for intraindividual comparisons over time within each group. Two-sample Mann-Whitney U tests were used to detect differences between groups at each point of measurement:

Results: ICI varied during anovulatory cycles ($p = .040$), mainly due to an increased inhibition at day 2 (median (range): day 8: 50% (32–98%); day 14: 39% (20–74%); day 21: 49% (33–59%); day 2: 29% (17–64%)). There were no differences in ICI during ovulatory cycles ($p = .564$, median (range): day 8: 64% (30–97%); day 14: 80% (35–129%); day 21: 63% (33–90%); day 2: 57% (30–100%)). Comparing ICI in ovulatory and anovulatory subjects inhibition was less pronounced in ovulatory cycles at day 14 ($p = .025$), day 21 ($p = .043$) and day 2 ($p = .007$). RMT, CSP and ICF showed no significant changes during ovulatory or anovulatory cycles.

Conclusions: The results suggest that fluctuations of cortical excitability exist also during anovulatory cycles. As estrogen withdrawal initiates bleeding in anovulatory cycles, the increased inhibition at this time may be caused by lowered proconvulsive estrogen levels. Decreased inhibition in ovulatory as compared to anovulatory cycles may reflect the estrogen peak preceding ovulation on day 14 and possibly higher estrogen levels during the luteal phase.

2.210

SEIZURE CLUSTERING: CREATING AN OPERATIONAL DEFINITION

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Rationale: Seizures often occur in clusters or flurries, but a specific definition of clustering and robust estimates of its frequency are lacking. Conceptually, seizure clustering implies that the probability of a seizure is increased by the occurrence of recent prior seizures. In a prospective seizure diary study, we applied a widely used clinical definition of clustering, and compared the results to a statistical definition derived from testing the empirical distribution of seizures for homogeneity (constant rate over time), to provide a foundation for better detection and management of seizure clustering.

Methods: Subjects were recruited from the Epilepsy Management Center and neurology clinics at MMC. Inclusion criteria: Age ≥18 years; localization-related epilepsy; ≥1 seizure within the prior 12 months; ability to maintain a daily seizure diary. Seizure clustering was defined using a standard clinical definition (3 or more seizures in 24 hours) and a statistical definition based on deviation from a Poisson distribution (variance of observed numbers of seizures that was significantly greater than the mean) utilizing a formula described by Boots and Getis (Point Pattern Analysis, 1988).

Results: Data were analyzed for the first 55 subjects completing the study. Mean follow up was 227 diary days. Nine subjects (16%) had no seizures, 19 (35%) were non-clusterers by either criterion, 26 (47%) met the definition of clustering by the clinical definition while 12 (22%) had a seizure distribution which met the statistical definition. All subjects identified by the statistical method also met the clinical definition. Review of the 14 discrepant cases (meeting the clinical but not the statistical definition) revealed that these subjects usually had a high baseline seizure frequency with occasional episodes of 3 sz. in 24 hrs by chance, or had a typical pattern of single seizures with a rare occurrence of 3 or more sz. in 24 hrs. All subjects identified as clusterers had at least one isolated single seizure.

Conclusions: The relative frequency of seizure clustering among our patients was 22% using a statistical definition and 47% using a clinical definition. Analysis of discrepant cases suggests that the clinical definition generates false positives. While the clinical definition of clustering may have utility (i.e. assessing seizure independence for presurgical evaluation), the statistical approach appears to be a more robust method of identifying a subset of patients who truly cluster. The results also suggest that even in individuals who meet a statistical definition of clustering, isolated seizures do occur. Optimal management will require clinical methods for the identification of individuals at high risk for seizure clustering. [Supported by K23NS02192 (PI: Dr. Haut).]

2.211

A MALIGNANT VARIANT OF STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) has been estimated to be refractory to first-line anticonvulsants in 30–50% of cases. The further management of such patients usually requires the administration of anticonvulsant anesthetics. In an as yet undefined number of cases even this aggressive approach fails to terminate SE. We have coined the term *malignant status epilepticus* (MSE) for this most severe variant and looked at frequency, risk factors, and outcome.

Methods: A retrospective analysis was performed including all patients that were treated between 1993 and 2002 on the neurological intensive care unit (NICU) of the Charité - University Medicine in Berlin with SE that was refractory to first-line anticonvulsants. MSE was defined as SE that persisted 5 days or more after tapering of the maximal dosage of anesthetic anticonvulsants that had been titrated to a burst suppression pattern (BSP) in the EEG before. Refractory status epilepticus (RSE) was defined as continuing epileptic activity not responding to benzodiazepines and (fos)phenytoin in adequate dosages, excluding episodes of MSE. Frequency distributions of epidemiological, etiological, therapeutic, and prognostic features were compared in MSE and RSE in order to identify characteristics of MSE, and were calculated by the Chi-square-test.

Results: In the current study, 34 patients were included. There were 7 episodes of MSE and 28 episodes of RSE. A female preponderance was found in both groups with 85.7% in MSE and 57.1% in RSE but

the difference was not significant. Patients with MSE had a mean age of 38.7 ± 13 years and were significantly younger compared to patients with RSE (55,4 ±18,2; $p < 0.01$). Pre-existing epilepsy was found in one episode of MSE and in 8 episodes of RSE (28.6%). Infectious encephalitis was the primary cause of status epilepticus in 71.4% of cases in MSE and in 10.7% of cases in RSE ($p < 0.01$). Inadequate levels of antiepileptic drugs as main cause for SE were neither seen in MSE nor in RSE. The anesthetic was titrated to a BSP per definition in all cases with MSE, 35.7% of RSE episodes were treated with an anesthetic ($p < 0.01$), and in 40% of these cases anesthetics were titrated to a BSP ($p < 0.01$). Duration of SE was 17 days in MSE and 2 days in RSE (median; $p = 0.061$). Length of stay on the NICU was 53 days in MSE and 10 days in RSE (median; $p < 0.01$). In-hospital mortality was comparable in both groups with 14.3% in MSE and 17.9% in RSE.

Conclusions: We have coined the term malignant status epilepticus to denote a most severe variant of SE. In the current series the condition is not rare. The underlying pathophysiological processes are elusive but our study indicates that female sex, young age (patients in their fourth decade of life) and infectious encephalitis without previous history of epilepsy represent important risk factors. Such patients should be treated aggressively in the early course of SE to prevent the development of MSE.

2.212

ANXIETY AND DEPRESSION PROFILES OF OUR REFRACTORY EPILEPSY PATIENTS WITH SELF-REPORT OF SEIZURE FREQUENCY AND CLUSTER "HIGH FREQUENCY" PARTIAL SEIZURES ON LEVETIRACETAM ADD-ON THERAPY

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Rationale: In a previous open-label prospective study we evaluated the efficacy of levetiracetam (LEV) treatment in patients with high frequency refractory partial or secondary generalised seizures. The aim of this study was to evaluate the effect of LEV on the potential risk of anxiety or depression development in these patients by using psychiatric rating scales.

Methods: We evaluated 53 patients (25 female, 28 male), mean age 33.5 ± 9.1 years, with refractory partial epilepsy and high frequency partial seizures, mean seizure frequency per month was: SPS (9.7), CPS (17.3) with or without secondary generalisation SGTC (1.1). Patients were recieving one or 2 other AEDs (for at least 4 weeks at stable doses) before commencing LEV as add-on therapy. Our patients were not diagnosed or treated for anxiety or depressive disorder before LEV treatment. In a subgroup of these patients ($N = 44$) we evaluated in detail the presence of 'de novo' anxiety and depressive symptoms (using clinical psychiatric examinations, Hamilton Rating Scales for anxiety HAMA 17 and depression HAMD 21) both at baseline and study end.

Results: 48 patients completed the study, a retention rate of 90.5% (48 pts. of ITT = 53 pts.), mean daily LEV dose was 2291.7 ± 617.4 mg.

Seizure freedom was achieved in 21% ($N = 11$) of patients, 49% were responders (≥50% seizure frequency reduction), with the main seizure reduction relatively rapid in the first month of therapy.

HAMA 17 and HAMD 21 scores were obtained for 44 patients (of 48 patients who completed the study). A global reduction in HAMA 17 and HAMD 21 scores was seen in all of these 44 patients at study end compared with baseline, responders showing a better improvement.

However, 4.2% ($N = 2$) patients experienced mild 'de-novo' anxiety and depressive symptoms and 4 patients (responders) showed mild signs of irritability and insomnia. Three of these patients were also treated with lamotrigine. There were no psychiatric reasons for LEV treatment discontinuation in any of our patients.

Statistical evaluations will be presented.

Conclusions: Our results show that LEV treatment was associated with mood improvement in our patients with frequent partial seizures, mainly in responders.

2.213

PSEUDO–FRONTAL LOBE SEIZURES IN PARIETAL LOBE EPILEPSY (PLE): A STEREO ELECTROENCEPHALOGRAPHIC (SEEG) STUDY

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Rationale: As opposed to seizures of temporal, frontal or occipital origin, the semiology of parietal seizures (PS) is not well known. This is partly due to their rarity since they represent less than 5% of partial seizures reported in surgical series. We believe that PS are actually underestimated because a number of them is unrecognized : if the ictal symptomatology is dominated by somato sensitive or painful symptoms, these presence is not nevertheless compulsory. Our study illustrates this fact by reporting two patients cases followed for frontal lobe epilepsy (FLE) and whom seizures originate from parietal lobe.

Methods: Ten to fifteen patients suffering from FLE benefit annually in our pre surgical unit evaluation from SEEG exploration. During last year, we were forced to repeat the exploration of two of them because the frontal lobe exploration was unable to localize the epileptogenic zone (EZ) but indicated the retro rolandic origin of seizures. The second exploration in these two patients was focused on the parietal lobe.

Results: Seizures in the first patient began with a sudden assumption of a fixed posture of left upper arm abducted at the shoulder and with left head and eye deviation and speech arrest. In the second patient, seizures began suddenly with complex motor automatism taking a frenetic agitation aspect without loss of consciousness, often occurring in nocturnal cluster. No somato sensory sensations were reported by any of the two patients. The SEEG exploration showed the discharge development in a extended frontal network but did not allow the precise origin of seizures. These two patients benefited a second SEEG exploration centered on the post central areas and the parietal lobe. In the first case, seizures originated in the right supra marginal gyrus, propagating in the internal aspect of the parietal lobe to reach the homolateral supplementary motor area. In the second patient, seizures originated in the left angular gyrus and propagated in the external homolateral pre frontal cortex.

Conclusions: Our study demonstrated that the PS could present in very different ways and in the absence of any somato sensitive symptomatology. The indentification difficulties could explain why parietal epilepsy cases are so rarely reported in litterature. These seizures could be of frontal type and in the absence of an adapted intracranial EEG exploration, explain some surgical failures in patients treated by inadequated corticectomy for unrecognized PLE.

2.214

SEIZURE-PROPAGATION PATTERNS IN PATIENTS WITH ICTAL SPEECH DURING LANGUAGE-DOMINANT, LEFT TEMPORAL LOBE COMPLEX PARTIAL SEIZURES

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Rationale: Preservation of speech during a complex partial seizure strongly supports seizure localization to the non-dominant hemisphere (*Neurology* 1988;38:634; *Ann Neurol* 1989;25:82). We previously reported a small group of patients who had ictal speech despite seizure origination in the left, language-dominant temporal lobe (*Neurology* 1995; 45(suppl 4):A180). To better explain these exceptions to the rule, we reviewed seizure propagation patterns obtained during intracranial monitoring in one of the reported patients and two patients monitored subsequently.

Methods: We reviewed records of 83 patients from our 1987–2002 database who met the following criteria: (1) language-dominant, left temporal lobe determined by Wada test, (2) ictal EEG onset from the left temporal lobe with resolution of seizures following epilepsy surgery. The video/EEG telemetry records of all patients were reviewed for the presence of ictal speech. Speech was defined as clear, comprehensible words. Patients who spoke only during the aura or the post-ictal period were not included.

Results: Ictal speech was observed in six out of 83 (7%) patients (including the four reported previously). Three patients required intracranial recordings for localization. During the intracranial recordings, one patient's seizures demonstrated rapid propagation of the ictal discharges

to the contralateral temporal area where the seizure evolved. The left temporal discharges abated quickly. The other two patients had ictal discharges that remained confined to the left inferior and medial temporal areas for approximately 120 seconds after the seizure onset without spread to classical language areas.

Conclusions: Ictal speech is very rare in patients with complex partial seizure arising from the language-dominant, left temporal lobe. When it occurs, it is likely explained by the preservation of language areas due to unusual seizure propagation patterns.

2.215
ESTABLISHMENT OF NEW FIRST SEIZURE SERVICE IN THE UK: LESSONS AND CHALLENGES
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Rationale: Provision for first seizure review inthe UK has traditionally been patchy. In order to cut misdiagnosis rates and address important social and medical issues, NHS board in Glasgow set up a First Seizure Service in 2002 to allow rapid assessment of all new onset loss of conciousness.

Methods: Information on diagnostic profile, outcomes and investigation results were collected for all previously untreated patients attending the North Trust First Seizure service between January 2003 and May 2004.

Results: 470 patients have been seen and assessed so far. Referral s had come mostly from General Practitioners and Emergency Room physicians.

23% of patients referred had their episode diagnosed as syncope. In these patients, AED treatment was therefore avoided and investigation with imaging and EEG was used more sparingly.

25% had an ictal cause of their loss of conciousness confirmed. Appropriate counselling and investigation was used in these cases.

18% gave a history of previous ictal events (complex partial seizures, nocturnal generalised tonic clonic seizures, or myoclonic jerks) when directly asked which had not been elicited by the referring generalist; in these patients, treatment was able to be started as the diagnosis of epilepsy was confirmed.

55 patients had been started on AEDs by the referring clinician; in 83% of these, treatment was either withdrawn (as inappropriate or dangerous).

Conclusions: First seizure clinics prevent misdiagnosis of epilepsy and allow for far more appropriate use of investigations and AEDs. Generalists and Emergency Room physicians should not be starting treatment with AEDs.

2.216
ING: A DIARY-BASED VALIDITY STUDY
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Rationale: Epilepsy management typically relies on patient report of seizure frequency and temporal pattern. To evaluate their accuracy, we compared these reports with the patterns observed in a one-year, prospective, clinic-based seizure diary study.

Methods: Subjects $\geq$18 years with localization-related epilepsy and $\geq$1 seizure during the prior year were recruited from the Epilepsy Mgmt Center/Neurology clinic at MMC. A comprehensive interview at recruitment included a full epilepsy history, with detailed questions regarding typical seizure frequency per week and month prior to the intake interview, and typical seizure pattern. Subjects were asked to maintain a yearlong daily seizure diary, including dates and times of all seizures. Patients who completed $\geq$30 days of the diary were eligible for analysis. We compared the initial self-report of patients to the daily reports turned in by the patients. Seizure clustering by self-report was defined as those subjects who initially reported that they typically experienced 3 sz in 24 hrs. Actual seizure clustering from diary data was defined by both this definition (clinical definition), and by a statistical analysis of the pattern of seizures for each subject in which clustering was defined as greater than expected variability from a Poisson process model that assumed no clustering (Boots & Getis, Point Pattern Analysis, 1988) (statistical definition).

Results: Of 55 subjects who completed the study, 9 subjects had no seizures. In comparison with diary-based frequency estimates, correlations of self-reports of average weekly ($\rho = 0.63$) and monthly ($\rho = 0.62$) seizure frequency were high. Using the diary-based clinical definition of clustering as the gold standard, self-reported clustering had a sensitivity of 62%, specificity of 79%, PPV of 73% and NPV of 70%. Using the diary-based statistical definition of clustering as the gold standard, self-reported cluster had moderate sensitivity (67%), high specificity (88%), a good positive predictive value (PPV, 62%) and an excellent negative predictive value (NPV, 90%).

Conclusions: Patient self-report provides relatively accurate estimates of seizure frequency and clustering and provides a sound basis for initial management. Some of the observed differences between self-reported and recorded seizures may reflect changes in therapy during the observational phase, and correlations may actually be higher. Though weekly and monthly estimates of seizure number by patients correlate well with diary-based estimates of seizure rates, diaries provide more accurate information that could improve patient management. In those who report lack of clustering, diaries rarely reveal it (as reflected by the high NPVs). Those who report clustering are likely to have it (as shown by the high PPVs) though diary confirmation is recommended. [Supported by K23NSO2192 (PI: Dr. Haut).]

2.217
INTRACTABILITY THAT OCCURS IN ELDERLY-ONSET EPILEPSY
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Rationale: Older persons with new onset epilepsy have a relatively good chance to achieve excellent seizure control, but some become intractable. In this study we investigated clinical risk factors related to becoming intractable in this population.

Methods: This is a retrospective analysis of data from VA Coop Study 428, "Treatment of Seizures in the Elderly Population." We looked at patients from our Denver site who completed at least 12 weeks of the study. Intractability was defined as one or more seizures a month. Controls were from the national multicenter database, and our local nonintractable patients.

Results: 11/50 of our enrolled patients were intractable, as were 11/36(31%) of those completing 3 or more months. 10/11(90%) had complex partial seizures as compared with 38% of the 593 national controls ($p < 0.01$). No other seizure types were significant. 6/11(66%) had a history of neoplasm upon entry (not expected to be fatal in 2 years) as compared to 22% of national controls ($p < 0.01$). No other concomenent diseases were significant, including history of alcohol abuse, cerebral vascular disease, cardiac disease, hypertension, or diabetes. Clinical notes suggesting poor phamacoadherence occured in 7/11(77%). This was significantly higher ($p < 0.01$) compared to 2/25(8%) of our patients who completed at least 12 weeks, were not intractable, but were also not pharamacoadherent. Age, sex, suspected etiology,brain imaging, and EEG were not significant. Specific drug treatment was not analyzed.

Conclusions: Risk factors for intractability when epilepsy begins in the elderly are a history of neoplasm, complex partial seizures, and poor pharmacoadherence. Clinical suspicion of poor pharmacoadherece may be indicated when intractable epilepsy begins in an older person. (Supported by VA Cooperative Study Program.)

2.218
SENIOR ADULT CONCERNS: LIVING WITH EPILEPSY
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Rationale: Older adults with epilepsy can expect to face many challenges living with this chronic health condition. Although increasing attention has been directed towards understanding the diagnosis and treatment of epilepsy in this age group limited information is available

about specific quality of life concerns. This study investigated patient-determined quality of life concerns in older adults with chronic epilepsy.

Methods: 33 community dwelling older adults (18 males/15 females; mean age = 65.6, range 60–80) with partial onset epilepsy (mean age at seizure onset = 37) were surveyed as to concerns of living with epilepsy. Patients were included in study if having at least 6 years of education, no history of alcohol/drug abuse, no life threatening illness, or serious illness within past three months. Participants were given a blank sheet of paper and asked to list any concerns they had about living with epilepsy. They were instructed to list their most important concern first. They were able to list as many concerns as they wanted. Concerns for seven participants were obtained through retrospective review of transcribed case study forms.

Results: A total of 31 different concerns were identified (range 1–6). Most frequently identified concern was driving/transportation restrictions (64%) followed by medication side effects (56%), safety issues (44%), cost of medications (29%), keeping job (26%), fear of embarrassment (21%), and memory loss (21%). Driving/transportation restrictions (36%) and medication side effects (21%) were listed as two most important concerns. Other concerns included restricted grandparenting role, sexual dysfunction, and recreations restrictions.

Conclusions: Quality of life issues in older adults with chronic epilepsy appear similar to younger epilepsy groups (Gilliam et al., 1997). Driving/transportation, role restriction, employment, social embarrassment, and safety are major concerns. Medication side effects appear more concerning compared to previous studies of younger adults. This study highlights the substantial burden of living with epilepsy in older adults and points to the challenges clinicians have toward addressing them. (Supported by Centers for Disease Control and Prevention.)

2.219
PATIENTS WITH INTRACTABLE EPILEPSY SECONDARY TO HEAD TRAUMA WITH ABNORMAL IMAGING STUDIES: HIGH RESPONSE RATE WITH ADD-ON LEVETIRACETAM

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Rationale: Head trauma is a well-known cause of epilepsy. It is the leading known cause of epilepsy in the 15–34 year age group. Several trials have shown lack of efficacy with the established antiepilepsy drugs (AEDs) in preventing the development of seizures following head trauma. However, very few trials have looked at use of a specific AED after the onset of seizures following head trauma.

Methods: Between the time period of Dec 1, 2002 and June 30, 2003, patients at Penn State, Milton S. Hershey Medical Center's Adult Epilepsy Center were evaluated for etiology of uncontrolled seizures. Inclusion criteria included a clear history of head trauma preceeding onset of seizures, abnormal imaging study, uncontrolled seizures despite trial of at least 3 other AEDs, and use of only 1 or 2 additional AEDs at the time of the study. Exclusion criteria included: head trauma complicated by other factors such as infection or shunt placement; additional risk factors such as febrile seizures, family history, prior history of seizures; or prior history of another head trauma. Patients meeting criteria had levetiracetam (LEV) added to pre-existing AEDs. Dosage of levetiracetam was titrated upward based on adverse events and response to treatment. Patients maintained a diary with seizure counts and adverse events.

Results: Seven patients met the criteria for the study. Onset of seizures following head trauma ranged from 2 weeks to 12 years with the age at the time of injury ranging from 4 months to 51 years. Duration of epilepsy ranged from 3 years to 34 years. Six of the 7 patients became completely seizure-free following the addition of LEV. The 7th patient had a 75% reduction in seizures. The dose of LEV ranged from 1000 mg/day–5000 mg/day. Four patients were on one additional AED and 3 were on 2 additional AEDs. Treatment ranged from 10 months to 16 months. Response to therapy did not change over time. No patients discontinued LEV. One patient listed "short temper" as an adverse event. No other behavioral side effects were noted.

Conclusions: Addition of LEV to existing AEDs produced a very high response rate in patients with intractable epilepsy that was related to head trauma. Future trials in a closed-label manner would be necessary to further evaluate the response to LEV in this group of epilepsy patients. Additional areas to investigate that would be of interest would include titrating to LEV monotherapy, specific response rates to region of brain injured or cause of injury, inclusion of patients with head trauma but no imaging abnormalities, and preventative therapy of LEV in head trauma patients prior to development of epilepsy.

2.220
OCCURRENCE OF OSTEOPOROSIS AND RISK FACTORS IN PATIENTS WITH EPILEPSY

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Rationale: Patients with epilepsy are predisposed to falls resulting in dislocations and fractures. Those with osteopenia and osteoporosis have an increased risk of fracture. Osteoporosis is a disorder characterized by decreased bone mineral density and deterioration of bone microarchitecture, leading to fragility. Several older antiepileptic drugs (AED) have been associated with osteopathies.

Methods: Data was collected from two geographically diverse epilepsy centers. In evaluation 1, a 30-question survey was given to over 150 epileptic patients on AEDs at the University of Miami clinics. Questions addressed risk factors for bone loss, diagnosis of epilepsy and prior treatment with AEDs. In some of these patients, bone mineral density (BMD) at the femoral neck was evaluated by dual energy x-ray absorptiometry (DXA). In the second evaluation, determinations of serum 25-OH vitamin D (25-OHD) concentrations as well as DXA scans at the proximal femur were done in patients over 50 years of age, receiving monotherapy with an enzyme inducing AED. In both evaluations, osteopenia was defined as DXA T-scores between -1 and -2.4, and osteoporosis at T-score greater than -2.5. Optimal 25-OHD concentration was considered to be $\geq$30ng/ml.

Results: Evaluation 1, mean age of those surveyed was 41.4 years with 44% being male. From the survey, indicators of potential bone disease were loss of height (10%), and fractures as an adult 27 (30%). Generalized or localized bone aching was reported in 43.3% of patients. Falls occurred in 40% with significant injuries reported in 22% during the prior year. DXA scans were obtained in patients taking phenytoin (47%), carbamazepine (34%), valproate (24%) and primidone (4%). DXA measured at the femur, in 21 patients (66% male, mean age: 65 years) revealed 42.8% with osteopenia and 28.6% with osteoporosis. A diagnosis of osteoporosis had previously been given to only 12.2%.

In Evaluation 2, a mean 25-OHD of 24.4 ng/ml was measured in 30 male patients (mean age: 76 years). 57% of these patients were receiving phenytoin (25-OHD = 23.4 ng/ml), and 43% carbamazepine (25.6 ng/ml). 30% of patients had 25-OHD $<$ 20 ng/ml. DXA scans were performed in 23 patients. 39.1% had osteopenia and 17.4% had osteoporosis. None had previously been diagnosed with a bone disorder.

Conclusions: These results indicate a high prevalence of decreased BMD in this population. These observations also suggest that many patients may have less than optimal 25-OHD concentrations. Importantly, our observations suggest that bone disorders may go unrecognized in many patients. These results emphasize the importance of proactive investigation of this potential disorder, particularly in those patients reporting previous fractures or perhaps bone pain.

2.221
LEVETIRACETAM ADD-ON THERAPY EFFICACY IN REFRACTORY EPILEPTIC PATIENTS WITH "HIGH-FREQUENCY" PARTIAL SEIZURES

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Rationale: Levetiracetam (LEV) is a new antiepileptic drug (AED) drug licensed and marketed for the add-on treatment of partial epilepsy. In our open-label prospective study we evaluated the efficacy of LEV in patients with 'high frequency' refractory partial or secondary generalised seizures.

Methods: We evaluated 53 patients-ITT (25 female 28 male), mean age of 33.5 ± 9.1 years, with refractory partial epilepsy and high frequency partial seizures, mean seizure frequency per month: total (29.8), SPS (10.4), CPS (18.4) with or without secondary generalisation SGTC (0.9). Patients were receiving one or 2 other AEDs (for at least 4 weeks at stable doses) before commencing LEV as add-on therapy. The follow-up period was 4 months, during which no changes of baseline AEDs were made.

Results: LEV mean daily dosage was 2291.7 ± 617.4 mg and 48 patients completed the study (retention rate 90.5%). 21% (N = 11) of patients achieved seizure freedom, the responder rate (≥50% seizure frequency reduction) was 49%. The significant main seizure reduction was relatively prompt in the first month of therapy. 3 pts. were discontinued due to treatment unefficacy. Mild to moderate adverse events were observed in 26% (14 patients, leading to therapy discontinuation in 5.7% (3) of patients. 4.2% (2) patients experienced mild anxiety and depressive symptoms, in 4 patients (responders) we found mild signes of iritability and insomnia, 3 of these patients were also treated with lamotrigine. There were no psychiatric reasons for LEV treatment discontinuation in the group of our patients. Statistical evaluation will be presented.

Conclusions: Our results confirm the efficacy and tolerability of levetiracetam as add-on therapy in patients with high frequency refractory partial seizures with a relatively rapid treatment response (in the first month).

2.222
ICTAL NYSTAGMUS BY EPILEPTIC ACTIVATION OF CORTICAL SMOOTH PURSUIT SYSTEM: A CASE STUDY WITH NONCONVULSIVE SIMPLE PARTIAL STATUS EPILEPTICUS PRESENTING AS ICTAL NYSTAGMUS

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Rationale: Ictal nystagmus is a rare sign of seizure activity and has been reported very rarely. We studied an 29 year male patient with nonconvulsive simple partial status epilepticus arising from right posterior temporo-occipital area presenting as a pure ictal nystagmus with left homonymous hemianopsia, which gave us a good opportunity to make it clear to understand the underlying mechanism of epileptic activation of ictal nystagmus.

Methods: EEG including electrooculogram and electronystagmogram was done during ictus. Brain MRI, ^{99m}Tc-ECD SPECT and ^{18}F-FDG PET were done during ictus and repeated after clinical improvement. Comparison between the area of glucose uptake and those of blood hyperperfusion was done through subtraction image in each of the study.

Results: Pure horizontal nystagmus without conjugate deviation or head turning to one side showed clear focal EEG onset from right posterior temporo-occipital electrodes without spread to contralateral hemisphere. The electronystagmogram during ictus revealed typical linear slow phase with midline cross of the eyeball clinically, which meant epileptic activation of cortical smooth pursuit system. Subtraction images from SPECT and PET revealed clear distribution of epileptic activation in the right posterior temporo-parieto-occipital lobe, but the area of glucose uptake was much wider than those of hyperperfusion.

Conclusions: We reports the case with ictal nystagmus by activation of cortical smooth pursuit system who had nonconvulsive partial status epilepticus presenting as a pure ictal nystagmus. The neuroimages reveals the relevant area of epileptic activation from smooth pursuit system is the posterior temporo-parieto-ooccipital area. This case suggests that activation of cortical smooth system could be directed to pulse generator in pontine independent of connection to frontal eye field, could result in ictal nystagmus.

2.223
HEMIFACIAL MOTOR SEIZURES OF MEDIAL TEMPORAL LOBE ONSET

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Rationale: To document a case of isolated hemifacial movements due to epileptic seizures of medial temporal onset, and document the probable neuroanatomical pathways responsible for ictal semiology.

Methods: A 28 year-old right-handed man presented with onset of epilepsy at age 8. Seizures began with a "tightening" feeling over the right side of the face. During these symptoms, the patient reported that the right side of his face "drew up" which would sometimes progress to involve "twitching." During these symptoms, he was unable to speak, but did not lose consciousness. Typical seizure duration was 15–30 seconds. Occasionally, more prolonged seizures involved "grunting" respirations, and a degree of loss of consciousness. At presentation, his simple partial seizures were occurring 3–4 times per day. His seizures were refractory to multiple AEDs.

Results: Neurological examination was non-focal. Routine interictal EEG showed left fronto-temporal epileptiform discharges. Video EEG telemetry monitoring revealed multiple seizures, beginning with tonic contraction of the right hemi-face, lasting 15–30 seconds, with preservation of consciousness. Scalp ictal EEG showed onset of left anterior temporal theta range slowing approximately 10 seconds after clinical seizure onset. MRI was normal. FDG-PET showed hypometabolism in the left anterior and medial temporal regions. Extensive subdural electrode coverage over the left frontal and temporal regions localized the epileptogenic zone to the medial temporal region, and showed propagation of the ictal discharge to the ipsilateral cingulate region. Clinical onset of contralateral hemi-facial movements correlated with propagation of the ictal discharge in the cingulate gyrus in all recorded seizures. The patient underwent a left anterior temporal lobectomy with resection of the amygdala and adjoining hippocampus, with sparing of hippocampal body. Post-surgical pathology revealed focal glial nodules and patchy neuronal loss in the amygdala. The patient has been seizure-free for 4 years postoperatively.

Conclusions: This case respresents a rare example of epileptic seizures of medial temporal onset presenting with isolated somatomotor manifestations, successfully treated with epilepsy surgery, which stresses the importance of this semiologic presentation. Anatomo-electro-clinical correlations of this case with cortical regions controlling facial movements (Morecraft et al. *Brain* 2001;124:176–208) are highly suggestive that this case represents secondary activation of M3 an M4 (rostral and caudal cingulate motor cortex), giving rise to focal hemi-facial movements.

2.224
THE SIMULATION OF DESMETHYLDIAZEPAM (DMD) CONCENTRATIONS AFTER MISSED DAILY DOSE(S) OF TRANXENESDand TRANXENE T-TAB

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Rationale: Clorazepate (Tranxene) is a long-acting benzodiazepine used as an adjunctive treatment for epilepsy. After oral administration, clorazepate is rapidly and completely converted to its active metabolite, desmethyldiazepam (DMD). It is available as two formulations, once daily (Tranxene®-SD™) and immediate release (T-Tab®) tablets. The purpose of this study was to simulate DMD concentrations over time to characterize the effect of missed daily dose(s) ± replaced doses for both formulations. The following serum concentrations-time profiles were simulated: 1) steady-state (SS) without missed doses, 2) missed daily dose(s) without replacement, and 3) missed daily dose(s) with replacement at the next scheduled dose.

Methods: Simulations were performed using WinNonLin® (Pharsight Corporation, version 4.0) using a 2-compartment, first order, oral absorption pharmacokinetic model. The dosing schedule was determined from the package insert as follows: Tranxene®-SD™ 22.5 mg given once daily and Tranxene® T-Tab® 7.5 mg given every 6 hours for 3 doses. The maintenance regimen was repeated for 20 days to ensure SS conditions.

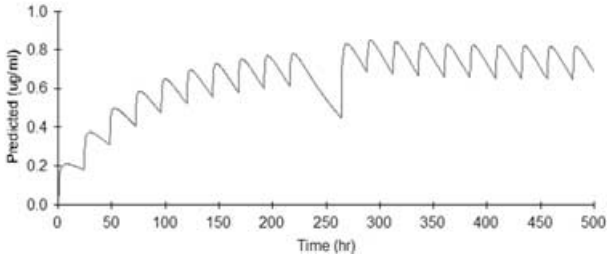
Results: For the T-Tab® and SD™ tablets under SS conditions, the times to maximum concentrations were 2.43 and 8.25 hours, the average concentrations were 0.65 and 0.85 μg/ml, and the average trough to peak differences were 0.13 and 0.17 μg/ml, respectively. The impact of a missed day's dose(s) was determined by calculating the difference in

TABLE 1. *Impact of Missed Daily Dose(s) on DMD Concentrations*

Formulation	Tranxene®-SD™			T-Tab®		
Simulation Scheme	No Missed Daily Dose	Missed Daily Dose	Replaced Daily Dose	No Missed Doses	Missed Daily Doses	Replaced Daily Doses
Peak/Trough Difference (Cmax-Cmin) at Css (ug/ml)	0.17	0.17	0.17	0.13	0.13	0.13
Peak/Trough Difference (Cmax-Cmin) after MDD (ug/ml)		0.18	0.38		0.18	0.42
% Change of Peak Concentrations [$(Cmax_{Css} - Cmax_{MDD})/Cmax_{MDD} \times 100$]		↓24.1%	↑5.9%		↓27.1%	↑9.6%
% Change of Trough Concentrations [$(Cmin_{Css} - Cmin_{MDD})/Cmin_{MDD} \times 100$]		↓38.9%	↓36%		↓56.1%	↓48.8%

Css = steady state, MDD = missed daily dose(s).

peak/trough concentrations at SS vs. the peak/trough concentration after the missed day's dose(s) ± the replaced dose(s), as well as the percent change in peak and trough differences between SS conditions and missed daily dosing conditions (see Table 1 and Fig. 1).



Conclusions: Despite DMD's long half life (>48 hours), a missed day's dosing results in altered trough to peak concentrations. The T-Tab® formulation had greater decreases in trough concentrations regardless of dose replacement. After a missed daily dose, the SD™ formulation maintains higher trough concentrations, which hypothetically may better prevent breakthrough seizures. (Supported by Ovation Pharmaceuticals, Inc.)

2.225
EFFICACY AND SAFETY OF LEVETIRACETAM IN ELDERLY PATIENTS WITH EPILEPSY

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Rationale: To compare the efficacy and safety of add-on treatment of levetiracetam (LEV) and lamotrigine (LTG) in late onset epilepsy.

Methods: LEV or LTG were randomly assigned (1:1) to 40 elderly patients with epilepsy previously clinically uncontrolled on antiepileptic drug (AED) monotherapy regimens. Patients were assessed for a 12 month follow-up period, using individual diaries (for efficacy) and Ward scale for side-effects; EEGs, routine bloods and neuropsychological tasks were also evaluated. Interim data are presented here.

Results: To date, 14 of 40 patients aged 65–85 (mean 73.1) years have completed 12 months follow-up. At 3 months : 5/20 (25%) LEV-treated (daily dose 1000 to 3000 mg) patients were seizure-free compared to 1/20 (5%) treated with LTG (daily dose 150 to 500 mg). Seizure reduction ≥50% was seen in 14/20 (70%) patients receiving LEV and 4/20 (20%) patients receiving LTG. After 6 months the percentage seizure-free was unchanged for LEV, 2 LTG-treated patients became seizure-free, the percentage of patients with ≥50% seizure reduction remained unchanged for both treatments. 2 patients prematurely discontinued LEV (due to side effects) and 5 discontinued LTG (2 for lack of efficacy, 3 for side effects). No significant changes in clinical, haematological or neuropsychological profiles were observed.

Conclusions: Our results suggest that the efficacy and safety of add-on LEV in elderly patients may be in some instances superior to those observed for LTG. LEV could have substantial potential use in the elderly due to its efficacy, safety, easy and fast titration programme and lack of drug interactions.

2.226
UNRECOGNIZED STATUS EPILEPTICUS IN THE ELDERLY

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Rationale: Status epilepticus is associated with significant morbidity. In the elderly, non-convulsive status epilepticus (NCSE) poses a particular problem given the frequency of associated cognitive impairment and the failure to consider, identify and appropriately treat this disorder.

We undertook this study to better understand seizures that present as confusional spells in the elderly.

Methods: A retrospective chart review of successive elderly pts presenting acutely to the ER or office with NCSE was undertaken at two institutions in order to better characteristize semiology, determine underlying EEG and imaging patterns and clinical outcomes.

Results: Time to diagnosis was delayed in all 22 patients. 14 women & 8 men (70 ± 11 yrs) presenting with confusion for 1–120 hours (mean 31 ± 30 hours) were found to have NCSE. 15 with prior NCSE had a average of 29 hours compared to 35 hours for 7 patients with the first episode of NCSE. For these 15 pts NCSE had occured between 1 and 10 times. Despite prior seizures or NCSE, family members did not seek evaluation for many hours. For 9 pts with prior seizures confusion was present for 22.3 h before a diagnosis of NCSE was made compared to 37 h for 13 pts without a prior seizures ($p = 0.13$). For this later group the initial diagnosis included dementia, TIAs, metabolic disease, or a psychiatric illness before NCSE was recognized. NCSE was much more frequently focal (frontal or central in 10, temporal in 4 patients or 8 anteriorly dominant diffuse epileptiform activity) whereas only 2 had primary generalized NCSE. 9 patients had normal MRIs, 13 had lesions (in only 5 patients did the lesion correspond with EEG focality, in the remainder the MRI showed non-specific small vessel disease or atrophy). Time to diagnosis was considerably longer (34 hours) if MRI was normal versus 21 hours if MRI showed lesion. NCSE required multiple medications administered acutely and 2 patients required pentobarbital to control status. All 22 patients eventually recovered from NCSE and could be discharged home.

Conclusions: Confusional NCSE lasted 1 to 140 hrs before epilepsy was considered. Surprisingly, this delay existed despite prior NCSE or seizrues. Furthermore, once brought to medical attention, the possibiltiy of NCSE was not considered early in the evaluation, with a wide variety of other diagnosis entertained before NCSE. Once established, NCSE was difficult to control and required multiple medications including theraputic coma. Unlike NCSE presenting with coma or NCSE in an ICU setting, all elderly patients presenting with confusional NCSE eventually recovered and were discharged home. Unlike NCSE in younger age groups, frontal or frontocentral epilepsy was the commonest type. Accordingly, caretakers and physicians need to be made aware that in the ambulatory elderly patient NCSE can present with confusion, this is particularly true of non-lesional NCSE.

2.227
PROSPECTIVE OUTCOME AFTER DIAGNOSIS OF NONEPILEPTIC SEIZURES

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Rationale: Retrospective series reported that only 35% of adults diagnosed with psychogenic nonepileptic seizures (NES) became free of seizures. A prospective study is indicated to learn of seizure and social outcomes, and factors that might predict outcome.

Methods: Since 1995, all adult patients diagnosed to have NES by successful video-EEG recording of typical attacks are prospectively followed by a medical social worker by telephone or by person at 3 months and 12 months after diagnosis. The contacts promoted patient education on the diagnosis of NES, encouragement to obtain mental health treatment (counseling, therapy, psychotropic medications), and assessment of NES activity and social function. Only patients with a sole diagnosis of NES were included in this study. Excluded were patients with concomitant epilepsy, or physiologic non-epileptic events. Through 2002, 94 patients have been enrolled. 23 patients (24%) dropped out from loss of contact, leaving 71 with complete follow-up at 3 and 12 months. A majority (86%) were women.

Results: At one year, 41 (Group I, 58%) were free of NES, 11 (Group II, 15%) had a major reduction to rare NES, but 19 (Group III, 27%) showed no improvement. The results at 3 months predicted outcome at one year. The NES free rates at 3 months were: Group I, 62%, Group II, 20%, Group III, 0%. There were no significant differences in the duration of disease, psychological diagnoses, and history of physical or sexual abuse, or rape amongst the groups. Group I patients verbalized self report of extreme situational stress more often (80%) as compared to the other groups. All Group I and II patients indicated an understanding of the diagnosis of NES by being able to verbalize what their diagnosis was at 3 and 12 months, but only 42% of Group III patients were able to do so. Social function at 1 year reflected NES outcome with return to work/school: Group I 90%, Group II 56%, Group III 5%, and with driving status: Group I 84%, Group II 36%, Group III 26%. Premorbid social function also predicted NES outcome. The proportions at work/school before diagnosis were: Group I 83%, Group II 45%, and Group III 26%, while the proportions dependent on disability-based income were: Group I 17%, Group II 36%, and Group III 58%.

Conclusions: In this prospectively followed series of NES patients who received post-diagnosis education and encouragement as the main intervention, 58% became free of attacks. Predictors of 1 year outcome with regards to NES and social function are: premorbid work and disability status, an ability to verbalize an understanding of NES diagnosis, and seizure status at 3 months.

2.228
HERBAL STIMULANT–INDUCED SEIZURES: A CASE SERIES

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Rationale: The U.S. Food and Drug Administration (FDA) has prohibited the sale of ephedra (often referred to as ma huang) containing dietary supplements as of April 12, 2004. This was based on review of available clinical evidence regarding safety and efficacy of ephedra in weight loss and performance enhancement (RAND Corporation report, 2/2003). Despite published warnings to the public since the RAND report, the sale of herbal stimulants has grown exponentially. Ephedra continues to be advertised, sold and widely used. Supposedly "safer" alternatives have been substituted. These stimulants are "standardized" for common ephedra doses and often mixed with other stimulants. In the past year we have seen 6 patients in our out patient clinics who appeared to have seizures directly linked with taking this type of dietary supplement.

Methods: Patients were gleaned from clinic visits on the basis of history at intake. History of supplement use was elicited through standard history taking techniques. All of the patients had routine laboratory work, an EEG, and either CT or MRI of the brain. Follow up in clinic in each case was carried out to track seizure freedom off of supplements.

Results: A total of 6 patients were identified. Ages were between 21–49 years. Only one patient had a prior history of seizures and significant medical illness. He had been seizure free, on monotherapy for more than one year prior to use of the supplement. Each subject used a different supplement. Only one contained the actual ephedra alkaloid. The others were "ephedra free." All subjects had witnessed generalized tonic-clonic convulsions. None of the subjects have had recurrent seizures following discontinuation of the supplement (4–12 months follow up).

Conclusions: In spite of FDA prohibition, patients continue to obtain and use ephedra and ephedra like compounds. Utilizing a Web search engine yields over one million responses from a query on ephedra. Many are informational with appropriate warnings and many offer the substance for sale. It is estimated in surveys that up to 42% of patients[1] will use some form of "alternative medicine" and that fewer than 35% will report[2] this use to their physician. It is important therefore, to actively seek a history of use in order to properly assess the need for initiation of anti-epileptic drug (AED) therapy in the case of new onset seizures, and to confirm the need for alterations in AED doses in patients who may be experiencing exacerbation of seizures solely on the basis of the use of ephedra compounds. Eliciting history of alternative therapies is paramount and physicians must maintain a high index of suspicion regarding the use of these in their patient population.

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2.229
CARDIAC DISEASE AND EPILEPSY: TREATMENT AND DIFFERENTIAL DIAGNOSES

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Rationale: Symptoms of heart disease affecting the level of consciousness is sometimes very difficult to distinguish from epilepsy. Even when the anamnestic information is good and all supplementary tests are performed, uncertainty may still exist. Furthermore, some antiepileptic drugs may affect cardiac electrophysiology which might lead to malignant arrhythmias. The aim of the study was to investigate the relationship between cardiac diseases, epilepsy and antiepileptic drugs (AEDs), using new methods for evaluating cardiac electrophysiology before and after the introduction of AEDs.

Methods: Twenty-six patients aged 20–60 years (mean age 32 years; 19 women, 7 men) with newly diagnosed epilepsy, were consecutively included. No patients used AEDs before inclusion, and they had no known heart disease. The patients received either carbamazepine ($n = 10$) or lamotrigine ($n = 15$). Blood parameters (electrolytes, creatinine, SR, Hb, thrombocytes and leucocytes) were analysed, and a 12-channel ECG and signal averaged ECG (for identification of ventricular late potentials) were performed before initiation of the AED treatment and after 3–9 months.

Results: One female patient had episodes with unconsciousness, generalized seizures and involuntary voiding. EEG showed epileptic activity, while cerebral MRI and resting ECG were normal. However, positive late potentials suggested right ventricular dysplasia, which was confirmed by cardiac MRI. This patient was not included in the rest of the study. All blood parameters including antiepileptic drug levels were within normal/therapeutic range. The serum electrolytes remained unchanged. Neither heart rate, PR interval, QRS- and QT-duration and the appearance of the T waves nor the parameters in signal averaged ECG were changed by AED treatment. However, one 20 years old female patient developed positive late potentials after introduction of lamotrigine. She is referred to further examinations in the department of cardiology.

Conclusions: This study illustrates that serious cardiac diseases in epileptic patients may remain undiagnosed if not examined properly. Changes in signal averaged ECG with development of late potentials was found in one patient after introduction of lamotrigine, but significant arrhythmic events were not observed in this limited study group. All epilepsy patients should have an ECG examined by a cardiologist, and in certain cases specialised investigations may be helpful.

2.230
MEASURING DEPRESSION IN SEIZURE DISORDERS
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Rationale: Patients with seizure disorders frequently suffer from comorbid depression. The degree of clinical depression is usually measured with Beck Depression Inventory - II (BDI-II), but research studies have also used Profile of Mood States depression/dejection subscale (POMS) to evaluate the mood state and the response to treatment. Although both measures are useful in evaluating the presence and the degree of depression, POMS is a research tool for which clinical application is unclear. The goal of this study was to provide data that would allow the use of POMS in patients with seizure disorders and to establish a formula for conversion of POMS scores into BDI-II. This would provide a beginning basis for the use of this instrument for clinical purposes.

Methods: 89 patients admitted to the Epilepsy Monitoring Unit of the University Hospital in Cincinnati completed BDI-II and POMS. We used bivariate correlation methods to determine the agreement between POMS and BDI-II.

Results: Data on 89 subjects ages 18–77 were available. Mean BDI-II score was $16.5 \pm$ SD 11.3 (min. $= 0$; max. $= 47$); mean POMS score was $14.9 \pm$ SD 13.4 (min. $= 0$; max. 53). Pearson correlation between BDI-II and POMS scores was $r = 0.77$; $p < 0.001$ indicating strong agreement between these measures. The following formula for conversion of the POMS scores to BDI-II scores was based on a regression equation with POMS as a predictor of BDI-II: BDI-II $= 6.85 + 0.65 * \text{POMS}$ ($R^2 = 0.59$) where 6.85 is intercept and 0.65 is the slope or effect coefficient of the relationship.

Conclusions: In our sample of seizure patients, the scores for POMS and BDI-II are highly correlated, suggesting concurrent validity for the POMS, and the possibility that either measure could be used to evaluate the degree of clinical depression in this population. A score of 16 on BDI-II, which is considered a cut-off point for mild depression requiring treatment, corresponds to POMS score of 14. These preliminary findings should of course be replicated in other studies before POMS is routinely used for clinical purposes.

2.231
NATIONAL AND REGIONAL PREVALENCE OF SELF-REPORTED EPILEPSY IN CANADA
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Rationale: Epidemiological estimates of epilepsy in Canada are sparse. No national data have been published. We assessed the point-prevalence of self-described epilepsy in the general population, nationally, provincially, and in different demographic segments.

Methods: We analyzed data from two national health surveys, the National Population Health Survey (NPHS, 49,000 respondents) and the Community Health Survey (CHS 130,882 respondents). Both surveys captured socio-demographic information, as well as age, sex, education, ethnicity, household income and labor force status of participants. Epilepsy was ascertained with one question in both surveys. (Do you have epilepsy diagnosed by a health professional? in the NPHS) and (Do you have epilepsy? in the CHS). Weights for probability sampling were applied in the CHS. Prevalences were age-adjusted using national standard population data at the time of each survey.

Results: In the NPHS, 241 subjects described themselves as having been diagnosed with epilepsy, yielding an adjusted point prevalence of 4.9 per 1,000 (95% CI 4, 6). In the CHS, 835 described themselves as having epilepsy, yielding a weighted point prevalence of 5.6 per 1,000 (95% CI 4, 6). Epilepsy prevalence was statistically significantly higher in groups with the lowest educational level, lowest income, and in those unemployed in the previous year. Prevalence was also higher in non-immigrants than in immigrants, and in provinces nearer to the Atlantic Ocean.

Conclusions: This is the first study exploring the prevalence of epilepsy in Canada and in different demographic groups. The overall and group-specific results are in keeping with those obtained in other developed countries, and using different ascertainment methods. In addition, heretofore unrecognized geographic variations emerged. We discuss methodological aspects related to the ascertainment of epilepsy in both surveys, and the possible implications of our findings.

2.232
TOLERABILITY OF LEVETIRACETAM IN DEVELOPMENTALLY DELAYED PATIENTS
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Rationale: Leveiracetam is an effective drug for generalized and focal seizures and can be used in a variety of seizure types and epilepsy syndromes. Because of the broad-spectrum nature of the drug, it is often used in the developmentally delayed population with severe seizure disorders and multiple seizure types.

Methods: We have retrospectively reviewed medical records of 30 patients who are developmentally delayed and were treated with levetiracetam. This population often suffer from psychiatric and/or behavioral difficulties. We were particularly interested in the reason for discontinuation of the drug, particularly if this was related to psychiatric or behavioral difficulties. We also assessed whether patients with psychiatric/behavioral difficulties prior to the use of levetiracetam had a higher discontinuation rate due to worsening of their previous condition.

Results: Thirty patients with developmental delay were assessed for their ability to be maintained on levetiracetam. The majority of patients were able to be maintained on levetiracetam without significant deterioration in psychiatric or behavioral difficulties. This proved true of patients whether or not they had had previous behavioral or psychiatric problems. Rare instances of other types of side-effects were noted, resulting in the need to discontinue the drug.

Conclusions: Levetiracetam is well tolerated in the developmentally delayed population and has proven to be an effective anticonvulsant in this group. Psychiatric/behavioral difficulties are not commonly precipitated or worsened with levetiracetam, including patients who have previous, recurrent, or continuing problems in this realm.

2.233
COMPARISON OF QUANTIFIED IPSILATERAL AND CONTRALATERAL HEAD MOVEMENTS IN PATIENTS WITH FRONTAL AND TEMPORAL LOBE EPILEPSIES
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Rationale: To compare the lateralizing significance of ipsilateral and contralateral head movements during seizures in patients with frontal (FLE) and temporal lobe epilepsy (TLE).

Methods: We inlcuded only EEG and video recorded seizures ($n = 45$) of patients with temporal lobe ($n = 18$) and frontal lobe epilepsies ($n = 16$) considered for resective epilepsy surgery, in whom the camera position was perpendicular to the head facing the camera in an upright position. FLE and TLE were diagnosed based on neuroimaging (MRI, PET, ictal SPECT), and interictal and ictal EEG. Head turning in a reaction to outside stimuli was excluded. Ipsi- and contralateral head versions were defined according to the side of ictal EEG seizure patterns. Head movements were quantifed for speed analysis on the videos by selecting the movement of the nose in relation to a defined point on the trunk (25/s) in the inner 90° angle facing the camera. The analysis of the duration was independent of the camera angle. The angular speed, the duration of the movements, and the duration from seizure onset to occurrence of the ipsilateral and contralateral head movements were computed (Mann-Whitney-Test).

Results: Ipsilateral head movement was always preceding contralateral head movement in FLE and TLE. Contralateral head movement occurred significantly earlier in FLE (median 5s $\pm$ 7.4) than in TLE (median 20s $\pm$ 16.3) ($p < 0.001$), whereas ipsilateral head movement occurred similarly early in the seizure evolution in FLE (2s $\pm$ 5.8) and

TLE (3.5 ± 14.2). The duration of the contralateral head movement was significantly longer in TLE (7s ± 3.1) than in FLE (4s ± 2.3) ($p < 0.01$). The angular speed of the ipsilateral (7.9deg/s ± 8.3 vs. 10.3deg/s ± 11.5) and contralateral (9.9deg/s ± 6.6 vs. 11.8deg/s ± 9.1) head movements was similar in TLE and FLE.

Conclusions: The quantitative analysis of ipsilateral and contralateral head movements shows differences in the movement characteristics and seizure evolution, which provide helpful information for the differentiation of patients with frontal and temporal lobe epilepsies considered for resective epilepsy surgery.

Clinical Epilepsy–Pediatric 2

2.234
EPILEPSIA PARTIALIS CONTINUA CAN REVEALED AN NADH-COENZYME Q REDUCTASE DEFICIENCY: REPORT OF THREE PATIENTS

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Rationale: Epilepsia partialis continua (EPC) is a condition characterized by continous myoclonic or clonic jerks repeated at short intervals followed by a slowly progressive neurological disorder and eventual progressive brain atrophy of the involved hemisphere. We report three patients with EPC associated with a defect of complex I of the mitochondrial respiratory chain.

Methods: We report the clinical, neuroradiological, biochemical and pathological features of our three patients. To study the mitochondrial respiratory chain complexes, muscle samples were analysed spectrophotometrically with a normalisation to the activity of citrate synthetase.

Results: Three patients (two boys, one girl) started to present continuous myoclonic jerks at age of 8 months, 11 months and 6 years, respectively. Two of three had a previous developmental delay. Neurological examination ad first admission revealed extrapyramidal symptoms (choreoathetosic movements) in our three patients. There was no symptom of myopathy. Two patients presented initially a hepatic cytolysis. Initial biological investigations suggested a possible mitochondrial dysfunction (lactacte in blood and in CSF, lactate/pyruvate ratio, ketone bodies). Initial EEG showed in two of three patients, a continuous discharge of right occipital periodic spikes (0.5–1 Hz). MRI studies were initially normal and progress to cerebral hemiatrophia. EEG revealed an absence of correlations between spikes or sharp waves and myoclonic jerks. The morphological investigations and ultrastructural examinations of muscle samples were normal. The activity of NADH-coenzyme Q reductase (complex I) was reduced (inferior to 80% of the normal activity) in the muscle samples of the three patients. No mutation of mtDNA was found in our patients. Two patients died during the year after the admission.

Conclusions: Our report establish that EPC can be due to mitochondrial disorders. In the literature, we found three case reports of EPC due to mitochondrial respiratory chain deficiency. In our study, some historical details, clinical findings and initial biological data were indicative for a disorder of mitochondrial metabolism. A previous development delay or extrapyramidal symptoms and others organs involvements in initial presentation should suggest a possible mitochondrial etiology of EPC. Our report emphasizes the importance of studying mitochondrial energy metabolism in patients with EPC.

2.235
COST EFFECTIVENESS OF STIRIPENTOL IN DRAVET SYNDROME

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Rationale: Dravet syndrome is one of the most severe and medically intractable forms of childhood epilepsy. Stiripentol (STP) has been shown to have a unique efficacy in this syndrome. The manufacturer of STP had provided this medication as "compassionate release," however effective February 2004, families have been required to cover the costs for this medication. Third party insurance will not cover these costs, as this medication is available only through the Special Access Programme of Health Canada. This study compares the medical costs in children with Dravet syndrome, pre and post STP initiation.

Methods: The medical costs of all four children (aged 18 mos to 11 yrs 11 mo) with Dravet syndrome followed in the Refractory Epilepsy clinic at the Alberta Childrens Hospital who were treated with STP were assessed over three time periods:

1. Pre-treatment: the year preceding STP initiation (or in children commencing STP prior to 1 year after seizure onset, the time from seizure onset to STP initiation)
2. Titration: the month following initiation during which titration to therapeutic dose was achieved
3. Post-treatment: the first year following the Titration period (or in children who have not yet been treated for a one year period, the total duration of follow-up available).

Costs assessed included hospitalization and clinic fees, ER visits, ambulance/EMS costs and physician billings, but medication costs were excluded. Families also completed a QOLCE for the pre and post-treatment periods.

The mean monthly medical costs for the Pre-treatment and Post-treatment periods were calculated for each patient.

Results: All 4 children showed a significant reduction in seizure frequency on STP (with benzodiazepine). Three of the four children have been treated with STP for at least one year, while the fourth has only completed 2 months of the Post-treatment period to date. The average monthly medical cost was lower post-treatment (mean of $93, range $40–160) compared to pre-treatment (mean of $2573, range $215–8415). Cost reduction was most dramatic in the 3 younger patients (ages 18 mos–4 yrs 2 mos at initiation, range $516–8375 per month) than in the older child (11 yrs 11 mos at initiation, $55 per month). QOLCE markedly improved in 3 of 4 cases. The savings in medical costs by far exceeded the actual cost of STP (mean $135/mo, range $75–300).

Conclusions: STP initiation was associated with a reduction in medical costs for all 4 children with Dravet syndrome, but the reduction appeared most significant for younger patients. This medication is clearly cost-effective and should be initiated early on after the clinical diagnosis of Dravet syndrome is made. In a publically funded health-care system, funding should be obtained for families who are financially unable to afford STP.

2.236
NONLINEAR QUANTITATIVE EEG ANALYSIS DISTINGUISHES NORMAL FROM SEIZURE-PRONE NEWBORNS

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Rationale: Seizures occur more often in the newborn period than at any other time during childhood. Quantitative analysis of EEG activity may help to determine the degree of brain dysfunction which may provide some early clinical insight. In this study, we test the hypothesis that there exists dynamical difference in brain electrical activity that differentiates normal from epileptic conditions in newborns.

Methods: It has been shown that the nonlinear dynamical measure short-term maximum Lyapunov exponent (*STLmax*) is useful for distinguishing pre-seizure state from the interictal state in patients with temporal lobe epilepsy (TLE). In this study, we test our hypothesis by applying *STLmax* measures to EEG from: (1) normal newborns ($n = 23$), and (2) newborns at risk for seizures ($n = 12$). EEG recording consisted of 22-electrode montage based on the 10–20 international system was recorded (12-bit A/D conversion, 256 Hz sampling, 0.1–70 Hz signal bandwidth) for 30 ∼ 60 minutes from each newborn. *STLmax* values were estimated in each of the 11-channel bipolar EEG recordings iteratively for every non-overlapping 8-second epoch (sampling frequency

256 Hz). In each recording, the lower 25% *STLmax* values were sampled for the statistical comparison between two groups of newborns.

Results: *STLmax* values range from 4.14 to 5.40 in at risk newborns (mean value of 4.88). while values range from 3.79 to 6.48 (mean value of 5.34) in normal infants. A non-parametric two sample test (Wilcoxon rank-sum test) revealed that the mean *STLmax* values between the two groups were significantly different ($p = 0.0157$).

Conclusions: Results suggest that measurable differences in brain electrical activity exist between normal newborns and those prone to seizures. The long-term goal of this research will be to develop a real-time automated bedside monitoring system capable of differentiating normal from at risk infants. To accomplish this goal, it will be necessary to estimate the normal range of measures in a larger sample size that distinguish the category of newborn with seizures from the category of newborn without seizures by defining the optimal confidence interval as a function of conceptional age. (Supported by Epilepsy Foundation of America Partnership for Pediatric Epilepsy Research.)

2.237

EFFICACY OF ZONISAMIDE IN PROGRESSIVE MYOCLONIC EPILEPSY: LONG-TERM FOLLOW-UP

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Rationale: Progressive myoclonic epilepsy (PME) is a neurologic syndrome with myoclonic and mixed seizures and progressive neurologic decline (usually cerebellar symptoms and dementia). PME is caused by a variety of diseases and represents a heterogeneous group. The seizures in PME are notoriously refractory to treatment. In 2001 we reported the early efficacy of zonisamide in the treatment of seizures in 8 patients with PME[1]. With short term follow up, 6 had improved seizure control, 1 deteriorated, and 1 died. Five of the 6 responders had improved overall neurologic function. This study reports the longer term followup of the 7 surviving patients with PME.

Methods: Seven patients (4 males, 3 females, mean age at diagnosis 5.6 y) treated with ZNS were followed for a mean of 3.63 years (range 3.33–4 years). Seizure types included myoclonic (6/7), tonic/tonic-clonic (4/7), drop (5/7), partial (3/7), and absence (2/7). Medications were adjusted as clinically indicated. Seizure control and overall neurologic function were assessed serially.

Results: Overall improved seizure control was sustained in 4 of the 6 early responders. 4/6 had >90% decrease in myoclonic seizures; 2/4 had >90% decrease in tonic/tonic clonic seizures; 3/5 had >90% decrease in drop seizures; 0/3 had a dramatic change in partial seizures. 2/2 had a complete resolution of absence seizures. Ataxia was better in 3, stable in 1 and worse in 3 patients. Cognitive function, while normal in none, improved in 3, was stable in 1 and deteriorated in 3. All 4 of the patients who had a sustained improvement in seizure control also had an apparent stabilization in neurologic function. Two patients who initially had an improvement in seizure control gradually deteriorated. The mean dosage of ZNS with short term follow up was 5.6 mg/kg/d (range 2–10) and longer term was 5.9 mg/kg/d (range 0.5–11.6). Mean number of AED short term was 2.7 (range 2–3) and at most recent follow up was 2.7 (range 2–4).

Conclusions: ZNS was well tolerated and effective in treating seizures in 4 of 7 patients with PME. 4 of 6 early responders had a sustained response. The group of patients segregated into two groups: "responders" who had an apparent stabilization of neurologic function, and those who had deterioration in neurologic function in addition to poorly controlled seizures. Multiple different underlying defects caused the PME in this group of patients, and no "definitive" treatment of the underlying defect was given to any of the patients. This population suggests that stabilization of seizure control may be an important factor in the arrest of neurologic decline. Zonisamide appears to have an important role in the sustained control of seizures in some patients with PME.

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2.238

OXCARBAZEPINE-INDUCED HYPONATREMIA IN CHILDREN: IMPROVEMENT WHEN VALPROATE DOSAGE IS REDUCED

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Rationale: When seeking the best combination of antiepileptic drugs (AEDs), information regarding the most efficacious combination is often lacking. Most clinicians rely on their experience with seizure control and toxicity when deciding which combination to select. This may result in ill-advised biases against some combinations. To assess Oxcarbazepine tolerability as adjunctive therapy in children, we focused on the incidence of hyponatremia before and after reduction of the concomitant AED.

Methods: In this study we prospectively assessed 6 children less than 4 years of age (mean age of 17 months years) with inadequately-controlled partial seizures. Oxcarbazepine was added to other AED (3 with Valproate, 1 with Phenobarbital, 1 with Levetiracetam, 1 with Carbamazepine, 1 with Gabapentin). When hyponatremia (sodium less than 130 mEq/L) occurred, reduction of the concomitant AED was authorized.

Results: Hyponatremia occurred in 2 children and was associated with lethargy. Both children were receiving high doses (40 mg/kg/day) of Oxcarbazepine concomitantly with Valproate. Reduction or discontinuation of the Valproate resulted in a rapid correction of the hyponatremia.

Conclusions: Oxcarbazepine-induced hyponatremia improves when Valproate dosage is reduced. Further studies are needed to demonstrate if competition of Valproate with Oxcarbazepine for the hepatic glucuronidation is responsible for the increased Oxcarbazepine toxicity.

2.239

COMPLEX VISUAL AND AUDITORY HALLUCINATIONS IN A CHILD WITH FRONTAL LOBE EPILEPSY

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Rationale: Hallucinations are commonly believed to reflect temporal lobe dysfunction. In contrast, disturbances of the frontal lobe are associated with altered motor activity, behavior, planning and organization. We report a boy who presented in an acute psychotic state characterized by formed vivid visual and auditory hallucinations due to frontal lobe partial status epilepticus.

Methods: Case report.

Results: An 8 year old right handed boy presented with new onset hallucinations. He reported being scared by visions of people and animated characters. He initially saw familiar faces talking to him which later commanded him to kill his mother and himself. His sleeping was disturbed and he became impulsive and hyperactive. There was no history of prior psychiatric illness and he was on no medications. He had one generalized seizure at age nine months. There were no family members with psychiatric illness.

His physical and elementary neurological examinations were unremarkable. Neurology consultation was requested because of vague complaints of headaches. EEG revealed frequent electrographic discharges from the right frontal lobe. Video-EEG monitoring demonstrated stereotyped seizures characterized by motor restlessness and gestural automatisms. Electrographic seizures were characterized by rhythmical spike-wave activity maximal at the FP2 and F8 electrodes. MR imaging revealed loss of gray-white matter arborization in the right orbital frontal and inferior frontal gyrus consistent with cortical dysplasia. Ictal SPECT revealed hyperperfusion corresponding to the structural lesion. Resection of the lesion and its surround tailored to ECoG data led to secession of seizures; his impulsive behavior normalized and his psychotic state ameliorated. Histologic tissue examination revealed Taylor type cortical dysplasia without balloon cells.

Conclusions: This case demonstrates conclusively that seizures consisting exclusively of formed visual and auditory hallucinations can begin in the frontal lobes. We hypothesize that electrographic discharges originating from epileptogenic orbitofrontal regions propagated to temporolimbic structures via the uncinate fasiculus to trigger complex hallucinations. Alternatively, propagation pathways may have involved aberrant neural networks known to be associated with cortical malformation.

2.240

SEIZURE ORIGIN AND PROPAGATION IN HYPOTHALAMIC HAMARTOMA: EVIDENCE FROM SUBTRACTION ICTAL SPECT

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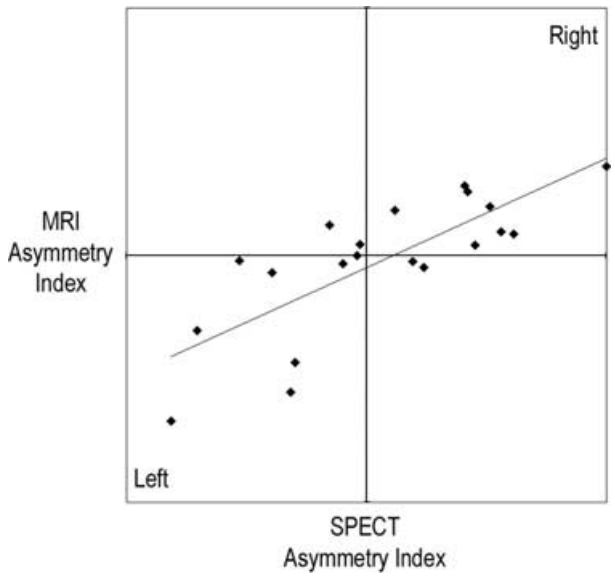
Rationale: Gelastic, partial and generalised seizures are characteristic of the progressive epilepsy syndrome associated with hypothalamic hamartoma (HH), yet the relationship between seizure origin, propagation and epileptogenesis is poorly understood.

Methods: We used subtraction peri-ictal ^{99m}Tc-HMPAO SPECT, co-registered with MRI in standard space, to study seizure origin and spread in 20 patients with HH and refractory seizures. HH hyperperfusion was analysed with respect to patient factors, timing of injection, seizure semiology and epilepsy characteristics. An index of the asymmetry of HH attachment to the hypothalamus was compared to a hemispheric hyperperfusion asymmetry index [(right − left)/(right + left)].

Results: Thirteen patients had HH hyperperfusion, including all 7 with ictal laughter or crying ($p = 0.045$). HH hyperperfusion was also significantly associated with true ictal injection ($p = 0.029$) and longer seizure duration ($p = 0.006$). Analysis of pooled subtraction studies revealed focal cortical hyperperfusion in common regions, including the orbitofontal, mesial frontal, anterior and posterior cingulate gyri, temporal pole, superior temporal gyrus, supramarginal gyrus and thalamus. Mesial temporal hyperperfusion was infrequent. No cortical regions of hyperperfusion were correlated with ictal laughter or tonic seizures. Cerebral hyperperfusion was asymmetric and linearly correlated with asymmetry of HH attachment to the hypothalamus ($r = 0.78$, $p < 0.001$) (Fig. 1).



Conclusions: Subtraction peri-ictal SPECT confirms a role for the HH in all seizure types in this syndrome. Gelastic seizures are associated with HH hyperperfusion, while asymmetric hemispheric hyperperfusion is correlated with HH attachment asymmetry. Cortical propagation appears more frontal than temporal and temporal propagation is more neocortical than mesial. Thalamic and cingulate hyperperfusion may be relevant to the evolution of symptomatic generalised epilepsy in some patients. [Supported by NHMRC Postgraduate, University of Melbourne and Murdoch Childrens Research Institute research scholarships (J.L.F.).]

2.241

HIGH-DOSE MELATONIN THERAPY FOR PEDIATRIC PATIENTS WITH EXTREMELY INTRACTABLE EPILEPSY

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Rationale: The anticonvulsive effect of melatonin has been reported clinically and experimentally. However, most of clinical reports are based on relatively low dose administration (3–10 mg/d) and small number of patients. We applied high dose melatonin therapy for treatment of extremely intractable epilepsy in childhood in order to evaluate clinical efficacy of high dose melatonin in treating those patients.

Methods: Among 13 patients (2 to 20 years old) enrolled in this study, 12 patients were classified into secondary generalized epilepsy. 9 of them had West syndrome in infancy and their seizures had not been controlled since then. 1 patient was classified into cryptogenic localization-related epilepsy. All patients had daily seizures in spite of intensive treatment with multiple drugs and moderate to severe mental retardation. After receiving an informed consent from the parents and an approval of local ethical committee, melatonin was added to the baseline anti-epileptic drugs with gradual increase to 1 mg/kg/day (15 mg to 45 mg/day), that was taken at every night. Seizure frequency and side effects were monitored.

Results: 5 patients showed significant decrease in seizure frequency in the course of melatonin administration. Among them, a patients who had infantile spasms showed complete disappearance of spasms and hypsarrhythmia. However, spasms re-appeared after 2.5 months later. The rest of patients showed continuous decrease in seizure frequency. None of patients studied showed side effects or sleepiness.

Conclusions: High dose melatonin therapy may be considered as one of choice for treatment of extremely intractable epilepsy, since 38% of such patients responded partially after administration of melatonin.

2.242

PROGRESSIVE MYOCLONUS EPILEPSY STILL REMAINS A GREAT THERAPEUTIC CHALLANGE

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Rationale: Progressive myoclonus epilepsies (PME) are a group of rare, severe, hereditary conditions, that includes many specific, mainly metabolic disorders. Pharmacoresistant myoclonus and generalized seizures, neurological deterioration, cognitive decline, overall unfavorable clinical course and poor prognosis are the main characteristics of PME.

Methods: A group of 19 patients, children and adolescents with PME was studied for the efficacy and safety of antiepileptic treatment. The specific diagnosis included neuronal ceroid lipofuscinosis-NCL (4), Lafora disease (8), Unverriht-Lundborg disease (1), MERRF (3) and sialidosis type I-cherry red spot–myoclonus (2). Underlying pathology remained unknown in one child. Clinical follow-up lasted from 11 to 68 months.

Results: Conventional AEDs were mainly ineffective for myoclonus and generalized seizures. Carbamazepine (10–18 mg/kg) and vigabatrin (20–30 mg/kg) aggravated myoclonias in early, still unrecognized stages of PME in four patients. Valproate was partially effective in PME seizure control (seizure reduction for $\leq$50%). Piracetam (7.2–14.4 g/daily) or L-tryptophan (0.5–2 g/daily) was given in patients with Lafora disease with no stable and long-term therapeutic effect. High-dose imunoglobulins i.v. administered in two boys with Jansky-Bielschowsky disease and one girl with syalidosis had no influence on myoclonus. Polyvitamine cocktail and diet with polyunsaturated fatty acids for patients with NCL were not helpful. No therapeutic response on N-acethylcistein (2g/daily) in two patients with Lafora disease was noted. Ketogenic diet was cancelled because of complications or inefficacy in two adolescents with Lafora disease in one boy with NCL. Pulses of methyl-prednosolon induced dramatic but short-term cessation of myoclonus in two PME adolescents. Lamotrigine, topiramate or zonisamide as new add-on AEDs were administered. All patients were comedicated with valproic acid and clonazepam/clobazame. Lamotrigine (4–8 mg/kg) was given in 9 patients. Five children (NCL-3, MERRF-2) experienced favorable control of GTCS and reduction of stimulus sensitivity, with no significant LTG

effect on myoclonus. Moderate efficacy for generalized seizures was noted in four (Lafora-3, sialidosis-1) of 8 patients treated with topiramate (8–11 mg/kg). Zonisamide given in a daily dose of 400 mg significantly reduced both myoclonias and generalized seizures in four of 8 patients with Lafora disease for >6 months. Two patients showed stable, long-term favorable seizure control for 18 months.

Conclusions: No actually effective antiepileptic treatment for seizures in PME was available. Neither conventional or new AEDs nor alternative therapy are recommended. The need for new treatment strategies in PME was imperative. It is hoped that new antiepileptic agents, other neuroactive molecules and molecular genetic approach will provide a rational therapy for both underlying pathology and seizures.

2.243

EFFICACY, SAFETY, AND PROGNOSIS OF KETOGENIC DIET FOR INTRACTABLE PEDIATRIC EPILEPSIES: KOREAN MULTICENTRIC EXPERIENCE

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Rationale: To evaluate efficacy, safety and prognosis of the ketogenic diet (KD) in infants, children and adolescents with refractory epilepsy.

Methods: We undertook a retrospective analysis of epilepsy patients referred and treated with the KD during 1998–2003 by Korean multicenters. The efficacy and safety of the classic 4:1 KD (87) or initial non-fasting KD (112) as add-on treatment in refractory partial or generalized epilepsies were evaluated. Ketogenic milk was introduced supplementarily in 55 patients and exclusively in five patients. Outcome measures included seizure frequency, EEG findings such as background and epileptiform discharges, and adverse effects during the KD. We also compared between favorable (a reduction of seizure frequency with over 50% and maintenance of KD for over 12 months) group (77) and unfavorable (with less than 50% and for less than 12 months) group (73) to the KD.

Results: Of the 199 patients enrolled in this study, male were 110 and female were 89 patients. The mean (±SD) age of the patients at the beginning of the KD were 57.9 (±45.7) months and the mean duration of the KD was 13.5 (±10.8) months. Outcomes for a reduction of seizure frequencies at 3, 6, 9 and 12 months after initiating the diet were as followings; 87.9% (175/199), 67.8% (135/199), 55.3% (110/119) and 45.7% (91/119) patients remained on the diet; 61.8% (123/199), 57.3% (114/199), 47.2% (94/199) and 41.2% (82/199) showed a reduction of seizure frequency with over 50% including 35.2% (70/199), 32.7% (65/199), 28.1% (56/199) and 25.1% (50/199) who showed seizure free state. Supplementarily introduced ketogenic milk was well tolerable to most patients. Of five patient who KD was tried exclusively by ketogenic milk, two patients could complete the KD with seizure free state. During the KD, 26.1% (52/199) patients should discontinue the diet due to various complications in 12.1% (24/199) and/or intolerance in 14.1% (28/199) in spite of effectiveness. Five patients died during the KD. The outcomes of seizure reduction between favorable and unfavorable groups were not statistically related to classifications of focal or generalized seizures ($p = 0.07$), age ($p = 0.62$), underlying etiologies ($p = 0.72$). Of 55 patients of favorable group, 76.4% (42/55) showed improvement of backgrounds as well as 68.8% (53/77) showed improvement of paroxysmal discharges. Forty-two patients who had completed the KD with a favorable seizure outcome were followed for mean 27.7 (±SD, 22.5) months after the KD and 35.7% (10/42) showed a relapse of seizures.

Conclusions: The ketogenic diet is a safe and effective therapies for intactable childhood epilepsies but life-threatening complications should be monitored closely during follow-up.

2.244

ABSENCE OF SEIZURES DESPITE HIGH PREVALENCE OF EPILEPTIFORM EEG ABNORMALITIES IN AUTISTIC CHILDREN MONITORED IN A TERTIARY CARE EPILEPSY MONITORING UNIT

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Rationale: Children with autistic spectrum disorder (ASD) are commonly referred for video-EEG monitoring to determine the precise nature of their seizure-like events.

Methods: We studied 29 autistic children using continuous video-EEG telemetry monitoring at a tertiary care referral center.

Results: Of the 29 total patients, 18 were primarily referred for seizure evaluation and 9 for 24-hour interictal EEG recording. Studies were prematurely terminated in 2 patients who could not tolerate the procedure; mean duration of monitoring in the remaining 27 was 3 days. Of 18 children referred for seizure evaluation, 11 had recorded events, but none were epileptic seizures (seven had no recorded events). Interictal epileptiform EEG abnormalities were detected in 14 of 27 patients. These abnormalities included: focal sharp waves (in 5 patients), multifocal sharp waves (in 6 patients) and generalized spike-wave complexes (in 8 patients). Focal/multifocal and generalized epileptiform abnormalities co-existed in five children. Notably, seven of the 11 patients with non-epileptic events had interictal epileptiform EEG abnormalities.

Conclusions: Video-EEG evaluation of children with ASD reveals epileptiform EEG abnormalities in the majority. However, most recorded seizure-like events are not epileptic, even in children with epileptiform EEG abnormalities.

2.245

TOPIRAMATE MONOTHERAPY IN INFANTILE SPASMS

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Rationale: Infantile spasm is an age-related refractory epilepsy. Topiramate (TPM) is a new anticonvulsant with multiple action mechanisms that may be effective in intractable epilepsies. We evaluate the efficacy and tolerability of first-line TPM treatment for newly diagnosed patients with infantile spasm.

Methods: TPM was given at a dose of 1 mg/kg per day, with a progressive titration of 1 mg/kg a week until spasms were controlled, the maximal tolerated dose was reached, or the maximal dose of 12 mg/kg/day was achieved. Effectiveness was evaluated by scalp EEG and by parental interview about count of seizure frequency.

Results: We administered TPM as monotherapy to twenty patients with newly diagnosed infantile spasms. This study included 17 boys and 3 girls, ranging in age from 3 to 24 months (mean age, 11 months). Regarding the etiology, cryptogenic group was 40%, and symptomatic 60%. Six (30%) patients became seizure free, eight (40%) patients achieved a seizure reduction of >50%, spasm frequency decreased from 10.6 ± 8.5 to 3.5 ± 1.4 spasms/day. Adverse effects during titration and stabilization included sleep disturbance, lethargy, irritability, rash, and oligohidrosis.

Conclusions: TPM is effective and tolerated in patients with infantile spasm. Our results suggest that TPM may be considered a new first-line drug in infantile spasm.

2.246

TEMPORAL LOBECTOMY IN CHILDREN WITH MEDICALLY INTRACTABLE EPILEPSY: NEUROPATHOLOGY, CLINICAL FEATURES, AND SEIZURE OUTCOME

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Rationale: Recent studies have suggested temporal lobe epilepsy (TLE) in children may constitute a different entity compared to TLE in adults, from both the clinical and neuropathologic perspectives. To confirm this hypothesis, a retrospective analysis of temporal lobectomy cases from our institution was performed to characterize the pathological findings, clinical features and surgical outcome in children with medically intractable TEL.

Methods: Charts of all children who underwent temporal lobectomy for refractory TLE from 1992–2003 were reviewed. Analysis of

pathological findings was performed to correlate with clinical features and surgical outcome.

Results: Thirty-nine children met inclusion criteria. Mean age of seizure onset was 5 years, 6 months (range 2 months to 14 years). Mean age at surgery was 12 years, 6 months (range 6 to 17 years). All patients had complex partial seizures and majority with secondary generalization. Post-resection follow-up averaged 5 years, 10 months (range 1 to 12 years).

Dual pathology characterized by mesial temporal sclerosis (MTS) with an extra-hipocampal lesion such as cortical dysplasia (CD), amygdale sclerosis (AS) or low grade tumor accounts for 33% (13/39) cases. Isolated MTS accounts for 21% (8/39) cases. Isolated low grade tumor, CD or AS account for 20% (8/39), 15% 6/39) and 10% (4/39) respectively. Total cases of MTS (isolated MTS and dual lesion pathology) occur in 54% (21/39) cases. Total cases of CD with and without MTS occur in 36% (14/39). History of febrile seizures was found in 75% (6/8) isolated MTS cases, 38% (5/13) dural pathology cases and only 5% (1/21) non-MTS cases. There is no significant difference in age of seizure onset in patients with isolated MTS (4.7 years), dural pathology (5.5 years), and non-MTS (7.3 years). Seizure-free was achieved in 84% of all patient with temporal lobectomy after 1 year follow up. The seizure free rate came down to 76% and 67% after 3 and 5 year follow up respectively.

Conclusions: Our result confirmed that high incidence of dual pathology and CD is the characteristic pathological findings in children with TLE. History of febrile seizures may play a role in MTS. This study demonstrates once again that temporal lobectomy is a safe and potentially curative treatment for children with refractory TLE.

2.247

RELATIONSHIP BETWEEN BRAIN GLUCOSE PET AND EEG IN CHILDREN WITH CONTINUOUS SPIKE AND WAVE DURING SLOW-WAVE SLEEP

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Rationale: The neurological substrates associated with continuous spike-wave activity during slow wave sleep (CSWS) are poorly understood, but can be studied with 2-deoxy-2-[18F]fluoro-D-glucose (FDG) positron emission tomography (PET).

Methods: Data were analyzed from six children with CSWS (ages: 4–8 years; 3 girls), all of whom had presented with intractable epilepsy and global neuropsychological and language decline upon the onset of seizures. Spike-wave discharges were present in more than 85% of slow-wave sleep EEG segments during PET scanning in all patients, which satisfied the original definition for the diagnosis of CSWS. FDG PET imaging was visually analyzed and focal brain areas showing increase of glucose metabolism compared to the homotopic area were documented. EEG during FDG PET scanning was quantitatively analyzed, and the frequency of interictal epileptic activity was measured. Subsequently, apparently generalized spike-wave discharges on EEG were averaged at least 50 times, and sequential voltage mapping of spike potential fields was applied to the averaged generalized spike-wave discharge. The relationship between brain glucose metabolism patterns on PET and EEG parameters such as origin of spike activity was analyzed.

Results: FDG PET imaging revealed focal brain regions showing increased glucose metabolism in five patients (Table 1). Focal brain regions showing increased glucose metabolism had a correlation with the presumed origin of averaged generalized spike-wave activity in all five patients (patients #1–5). A single patient (patient #2) had a cortical resection involving the areas of focal hypermetabolism on PET and has been seizure-free for two years. Another patient (patient #1) is scheduled for surgery. Conversely, no increase of focal glucose metabolism was seen on FDG PET in the remaining patient (patient #6). The origin of averaged spike-wave activity was not lateralized in this patient.

Conclusions: The areas of glucose hypermetabolism may be well correlated to the presumed origin of the generalized spike-wave activity in children with CSWS. This finding adds further support to the hypothesis that the generalized spike-wave in most cases of CSWS is the result of secondary bilateral synchrony. Resective surgery may be effective in selected patients with uncontrolled seizures and CSWS, if there is concordance of focal abnormalities on both PET and EEG.

2.248

THE UNITED KINGDOM INFANTILE SPASMS STUDY COMPARING VIGABATRIN WITH PREDNISOLONE OR TETRACOSACTIDE IN A RANDOMISED TRIAL: DEVELOPMENTAL OUTCOME AT 14 MONTHS

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Rationale: Infantile spasms is a severe epilepsy with a high risk of poor developmental outcome. Management is controversial with insufficient information on the best initial treatment. We undertook a randomised controlled trial of 107 infants, comparing hormonal treatments (prednisolone or tetracosactide) with vigabatrin. Minimum doses per day were: vigabatrin 100mg/kg, oral prednisolone 40mg, IM tetracosactide depot 0.5mg (40iu) alt days. Baseline characteristics were well matched. Control of spasms at 14 days was: hormonal treatments 40/55 (73%) vigabatrin 28/52 (54%) difference 19% (95% confidence interval 1% to 36% $p < 0.043$). We report developmental outcome.

Methods: Vineland adaptive behaviour scales (VABS) were administered by 1 researcher at 14 months. VABS composite scores were analysed without transformation by one-way analysis of variance with randomised treatment as the grouping factor. Individual (single degree of freedom) contrasts were extracted to compare (i) vigabatrin with the combined hormonal treatments, and (ii) the two hormonal treatments with each other. Analysis was by intention to treat and was conducted using the BMDP release 7, program 7D.

TABLE 1. *Results*

Age/Gender	FDG PET	Spike Frequency during PET	Spike origin
6y/M	Increase in Rt P-T-O	60 spikes/min	Rt Posterior
8y/M	Increase in Lt P-T-F	24 spikes/min	Lt Posterior
5y/F	Increase in Rt T-P-F	30 spikes/min	Bi-posterior (Propagated to Rt hemisphere)
4y/M	Increase in Rt T-P	39 spikes/min	Rt C-T (Propagated to Lt C-T)
5y/F	Increase in Rt P	22 spikes/min	Bi-posterior (Propagated to Rt Hemisphere)
4y/F	No Increase; Decrease in Bi-T-P	37 spikes/min	Bi-Posterior (No lateralized propagation)

Rt: Right; Lt: Left; F: Frontal; C: Central; P: Parietal; T: Temporal; O: Occipital.

TABLE 1. *Results*

	Prednisolone	Tetracosactide depot	Hormonal treatments combined	Vigabatrin
Number randomised	30	25	55	52
Died	2	0	2	3
VABS not done	1	0	1	0
Number VABS available (%)	27 (90%)	25 (100%)	52 (95%)	49 (94%)
VABS Composite score				
Mean (standard error)	78.0 (3.0)	78.8 (3.6)	78.4 (2.3)	77.5 (1.8)
Standard deviation	15.8	17.8	16.6	12.7

No significant differences were seen (Table 1). [vigabatrin v combined hormonal treatments $F = 0.09$, $df = 1,98$, $P = 0.76$; difference (95%CL): 0.9 (−5.0 to 6.8)] [prednisolone v tetracosactide $F = 0.04$, $df = 1,98$, $P = 0.84$; difference (95%CL): 0.8 (−7.4 to 9.1)].

Conclusions: No difference in developmental outcome was seen despite the difference in control of spasms at 14 days. It is possible that more prolonged or detailed follow up will detect a difference or there is no difference. It is not known if better control of spasms will improve developmental outcome in the longer term. [Supported by Bath Unit for Research in Paediatrics, Wellcome Trust (F.J.K.O.C.), Cow and Gate (E.H., A.L.)]

2.249

PEDIATRIC EXPERIENCE WITH SUDDEN UNEXPLAINED DEATH IN EPILEPSY AT A COMPREHENSIVE EPILEPSY CENTER

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Rationale: To describe the clinical characteristics of patients with childhood-onset epilepsy who died from sudden unexplained death in epilepsy (SUDEP) at a comprehensive epilepsy center.

Methods: The charts of all patients with onset of epilepsy less than age 18 years who suffered SUDEP between August 1992 and April 2004 were studied. The autopsy reports and circumstances of death were reviewed. Deaths were classified as possible, probable, or definite SUDEP based upon previously established criteria.

Results: Seventeen epilepsy patients (10 females and 7 males) suffered SUDEP. The average age of seizure onset was 4.3 ± 1.4 years (range 2 months to 17 7/12 years). Three patients presented with febrile seizures; all were less than or equal to 1 year of age. The average age of death was 12.6 ± 2.1 years (range 22 months to 27 years). The average duration of seizures was 9.2 ± 2.2 years (range 15 months to 26 years). There were 1 possible, 11 probable, and 5 definite cases of SUDEP. The results of 5 full autopsies were available; one child only had histopathological examination of the brain. All 5 patients with full autopsies were diagnosed with SUDEP. Seven patients (41%) had structural lesions by imaging or pathology. The lesions included a previously resected dysembryoplastic neuroepithelial tumor, prior repaired nasal encephalocele, hypoplastic optic nerves with a pericallosal lipoma, cortical dysplasia (2 patients), and right mesial temporal sclerosis. One patient had radiation necrosis and strokes in the right hemisphere following treatment for a left choroid plexus carcinoma. This case was classified as possible SUDEP due to other potential causes of death. Another patient had a prior right temporal lobectomy (pathology was not available); she had been seizure-free 2 years prior to her death. Another 5 patients (29%) had cognitive delay. Eleven children (65%) were found dead in bed. One patient was found pulseless and apneic 6 months prior to her death. All patients had generalized tonic-clonic (GTC) seizures (secondarily [10 patients], symptomatic [6 patients], or febrile seizures [1 patient]). Three patients had undergone a complete callosotomy for intractable generalized seizures. The average number of AEDs (antiepileptic drugs) given during the course of epilepsy was 5.5 ± 0.9 (range 1 to 13). At the time of death, patients were on an average of 1.6 ± 0.2 AEDs (range 0 to 3). Of the 3 autopsies with AED levels, all were subtherapeutic. Three patients had functioning vagus nerve stimulators.

Conclusions: Although most of the children began having seizures before age five years, age at death was evenly distributed in childhood. Most children died in their sleep. The majority of patients (71%) had structural lesions, cognitive delay, or both. All patients had GTC seizures (secondarily, symptomatic, or febrile seizures). Some had successful epilepsy surgery and still suffered SUDEP.

2.250

SUCCESSFUL RESECTION OF HYPOTHALAMIC HAMARTOMAS: PROSPECTIVE EPILEPSY OUTCOME STUDY IN 36 PATIENTS

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Rationale: Hypothalamic hamartomas (HHs) are rare developmental malformations of the hypothalamus that typically result in gelastic seizures followed by the development of other seizure types that are often refractory. Prior experience with surgical resection has shown limited efficacy and a significant rate of complications. We describe the successful resection of HHs in 36 patients with complete seizure control in 27.

Methods: Surgical: The patients had their HHs removed either by a transcallosal-intraforniceal approach, endoscopic resection or orbitozygomatic approach. Neurologic: The baseline seizure types and frequencies were recorded prospectively pre and post-operatively. Other changes and/or complications were also recorded.

Results: Twenty-five patients underwent transcallosal resection, nine patients endoscopic resection and two patients had their HHs resected via an orbito-zygomatic approach (their HHs were pedunculated/parahypothalamic i.e. low-lying in position, unable to be accessed from a superior approach). There were no mortalities or significant complications. The 36 patients were followed up for an average of 6.5 months (range 1 to 13 months). One patient was lost to follow-up. Their average age was 11.9 years (range 2 to 55 years) and consisted of 24 males. Pre-operatively, all patients had at least weekly seizures, most with multiple, daily mixed seizure types. Four patients had Pallister-Hall syndrome and one patient, Mohr syndrome. Twenty-seven patients (77.1%) are currently seizure-free, five patients have had >90% reduction, two patients >50% reduction in seizure frequency and one patient with only slightly improved seizure control. Overall 91.4% (32 of 35 patients) achieved excellent seizure control. Most patients also report a dramatic improvement in behavior and/or developmental/learning ability.

Conclusions: Neurosurgical resection of HH can be safe and effective treatment for patients with refractory epilepsy and should be considered in all HH patients with the often-devastating clinical scenario. The transcallosal approach and endoscopic resection appear to be superior to previously published surgical and other ablative techniques.

2.251

LEVETIRACETAM AS ADJUNCTIVE THERAPY IN CHILDREN WITH PARTIAL SEIZURES

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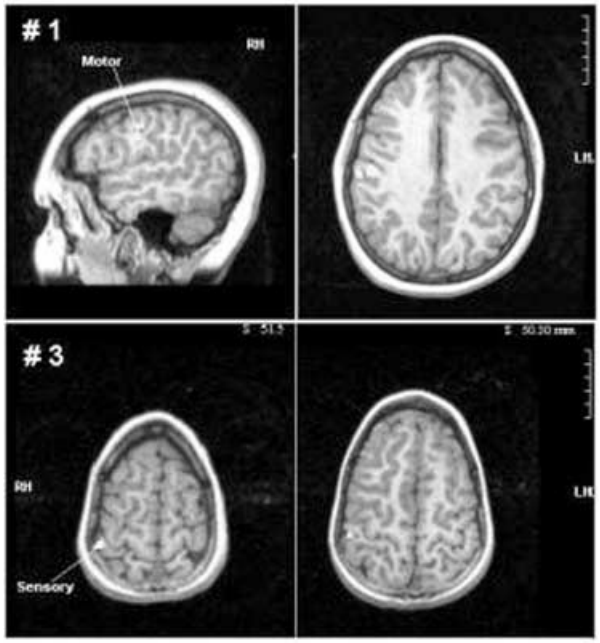
Rationale: Levetiracetam was approved in 1999 as adjunctive therapy in adults with partial seizures with or without secondary generalization. The precise mechanism by which levetiracetam exerts its effects is unknown but it does not appear to be related to the mechanisms of current drugs. The objective of this study is to assess the efficacy of levetiracetam in children ages 16 and under with partial seizures.

Methods: A retrospective chart review was performed for 16 patients ages 16 years and under with partial seizures who had received levetiracetam as adjunctive therapy over the past three years.

Results: The mean age of patients when levetiracetam was initiated was 10 (age ranged between 3 and 16 years old). 9 patients had partial seizures (PS), 4 had primary generalized seizures (GS), and 3 had Lennox Gastaut Syndrome (LGS). Of the 16 patients, 7 (43.75%) experienced ≥50% reduction in seizure frequency. The average starting dose was 11.44 mg/kg bid (doses ranged between 5.7mg/kg bid and 22.9mg/kg bid). The mean maintenance dose in the 7 patients who improved was 33.1 mg/kg daily. Levetiracetam was added to 2 antiepileptic drugs (AED) in 3 patients and 1 AED in two patients. Three patients with PS and one patient with LGS had their previous AEDs stopped due to side effects including rash and difficulty swallowing the other AEDs. The three patients with PS remain seizure free while the patient with LGS has had a ≥50% reduction in seizure frequency. Two patients had a vagal nerve stimulator. Seven patients discontinued the medication secondary to adverse side effects including increase in number of seizures (3), personality change (3), increased infections (1). One patient discontinued due to lack of efficacy and one was lost to follow up.

Conclusions: Levetiracetam is effective when used as adjunctive therapy in children ages 16 years and under with partial seizures.



2.252

BENIGN ROLANDIC EPILEPSY: NEUROPSYCHOLOGICAL TESTING AND MAGNETIC SOURCE IMAGING ANALYSIS

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Rationale: To evaluate children with Benign Rolandic Epilepsy (BRE), a childhood epilepsy characterized by centro-temporal/rolandic spike-wave discharges with infrequent partial seizures which may secondarily generalize. The term "benign" is incurred because cognitive development has generally been considered unaffected. Recently, some investigators have questioned whether BRE is "benign" or whether long-term cognitive outcome may be adversely affected. We attempt to better define specific inter-ictal neuropsychological deficits seen in these children and to better localize and lateralize their discharges using magnetoencephalography (MEG)/magnetic source imaging (MSI).

Methods: In our institution, we have initiated an ongoing study, identifying children with BRE. These children were all sent for evaluated to our Epilepsy Monitoring Unit (EMU). All children received continuous video-electroencephalography (VEEG) monitoring, brain magnetic resonance imaging (MRI), MEG/MSI and detailed neuropsychological testing.

Results: Seven children between the ages of 5 and 11 years have been thus far studied (Fig. 1). Varying degrees and patterns of neuropsychological deficit were identified in all subjects. Fine motor dysfunction was seen in the majority, 4/7 patients. Visuomotor integration deficits, dyscalculia and/or expressive language deficits were also identified, thus reaffirming that BRE is not necessarily a benign disorder. MRI was normal in all individuals. Scalp EEG using the International 10–20 System of electrode placement, localized discharges to a fairly wide region including the centro-temporal (perisylivian/perirolandic) areas. MSI derived localization, completed thus far in five patients revealed maximal involvement of the primary motor (M1) and/or primary sensory (S1) cortex.

MEG-derived localization: Case #1 showed frequent discharges arising from the M1 cortex; and case #3 revealed discharges arising from the S1 cortex.

Conclusions: Our study shows a high concordance of specific motor and/or cognitive deficits in BRE. Furthermore, magnetic source imaging shows a higher resolution of dipole localization in the primary motor and sensory areas, when compared with conventional EEG. MEG is a valuable diagnostic tool in the evaluation of children with BRE and may be a valuable tool in predicting deficits found.

2.253

A DISTINCT ASYMMETRICAL PATTERN OF CORTICAL MALFORMATION IN PEDIATRIC EPILEPSY: LARGE UNILATERAL CORTICAL DYSPLASIA WITH CONTRALATERAL PERIVENTRICULAR NODULAR HETEROTOPIA

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Rationale: Malformations of cortical development are a common cause of epilepsy. Focal cortical dysplasia (FCD) and periventricular nodular heterotopia (PNH) may occur either alone or together in the same patient. When together, both lesions are typically bilateral and diffuse but can also occur unilaterally. The presence of PNH with FCD in the immediately overlying cortex suggests an early clonal phenomenon affecting neuronal migration and organization in that region. We report two boys with a large unilateral FCD and PNH in the contralateral hemisphere. This asymmetric distribution of cortical malformation in both hemispheres has not been previously reported and represents a distinct pattern.

Methods: We identified two patients with focal-onset epilepsy at Children's Hospital Boston. Evaluation included 1.5 Tesla MRI with sagittal T1-weighted images, axial FLAIR and FSE T2-weighted images, and coronal high-resolution SPGR and FSEIR T2-weighted images.

Results: Patient 1, an 18-year-old right-handed boy, had mild mental retardation and focal seizures since age 14 years. EEG revealed seizure onset in the right frontal region. MRI revealed a large dysplastic right frontal lobe and a single left-sided PNH adjacent to the left frontal horn. Patient 2, a 10-year-old left-handed boy, had focal seizures since age 6 years. Interictal EEG revealed bilateral intermittent posterior slowing (left greater than right), without epileptiform activity. MRI revealed a large dysplasia involving the entire left temporal, parietal, and occipital lobes, and three foci of PNH on the right side.

In both, the areas of cortical malformation were grossly deformed and involved entire lobes; there was no obvious pachygyria or polymicrogyria; the pattern was clearly distinct from a tuber; and the regions of PNH were contralateral to the large malformations.

Conclusions: The novel pattern highlighted in these two children with epilepsy is unilateral FCD with contralateral PNH. We hypothesize that a combination of diffuse and local mechanisms, operating at different times during development, would be necessary to produce this asymmetric pattern. The strikingly asymmetric involvement of the two hemispheres suggests that the stage at which there is disruption of cortical development may differ between the hemispheres and that processes associated with lateralization or regional lobar differentiation may be involved. Further study into the basic mechanisms underlying such patterns of cortical malformation may ultimately enhance our understanding of cortical development, specifically lateralization, in the human brain.

2.254

VERY FEW CHILDREN WITH TYPICAL ABSENCE SEIZURES MEET THE RECENTLY PROPOSED DIAGNOSTIC CRITERIA FOR CHILDHOOD ABSENCE EPILEPSY (CAE)

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Rationale: Recently proposed diagnostic criteria for Childhood Absence Epilepsy (CAE) by Loiseau and Panayiotopoulos include additional features to those specified in the current ILAE classification (www.epilepsy.org/ctf/childhood_absence.html). To assess their diagnostic utility, these criteria were analyzed in a large unselected group of children with newly diagnosed CAE.

Methods: 70 consecutive untreated developmentally normal children presenting with typical absence seizures associated with generalized spike and wave on video-EEG were studied. The clinical and EEG features of all 509 seizures recorded, were analysed independently by two investigators. Using the ILAE classification, children were diagnosed with CAE if they were under 11 years of age, had frequent daily absence seizures and no other seizure type. The additional inclusion and exclusion criteria for CAE as suggested by Loiseau and Panayiotopoulos were applied to the group of children with CAE.

Results: Using the ILAE classification, 47 (67%) children had CAE. Applying the newly proposed diagnostic criteria to these 47 children, children were excluded from a diagnosis of CAE for the following criterion: photic stimulation precipitated a seizure (8); age younger than 4 years (4); a seizure lasting less than 4 seconds (15); partial awareness during a seizure (12); a seizure with more than 3 spikes per wave (3); a seizure which showed fragmentation (20); perioral myoclonia or single or arrhythmic myoclonic jerking of limb, head or trunk during a seizure (14). Thus the recently proposed diagnostic criteria eliminated 42 of 47 children with CAE, leaving only 5 (11%) children meeting the recently suggested classification criteria.

Conclusions: In a pure unselected group of children with newly diagnosed absence seizures, the proposed diagnostic criteria allow a diagnosis of CAE to be made in only a minority of children previously regarded as having CAE. This suggests that the proposed criteria are overly stringent and fragment the clinical syndrome of CAE. Diagnostic criterion should only be adopted if there is compelling evidence that they are useful clinically or for genetic studies.

2.255

LONG-TERM CLINICAL OUTCOME OF HEMISPHERECTOMY IN A SINGLE EPILEPSY SURGERY CENTER

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Rationale: Hemispherectomy has been performed for refractory epilepsy in association with unilateral hemispheric abnormalities and hemiplegia for over 60 years.The classic anatomic hemispherectomy is now rarely performed due to complications such as superficial hemosiderosis. The most recent procedure is functional hemispherectomy. Studies have shown general improvement and significant seizure control, however only a few studies have been done with mixed results regarding cognitive outcome. The purpose of this study is to evaluate long term outcome of children undergoing functional hemispherectomy in a single pediatric epilepsy surgery center over a 10 year period.

Methods: A retrospective chart review of the children undergoing functional hemispherectomy at The Hospital for Sick Children (Toronto, Canada), from 1993–2003 was done. A data abstraction sheet was used to collect information on etiology, seizure outcome, anticonvulsant medications use, pre and post surgical neuropsychology assessment.

Results: 14 children were identified. Follow-up post hemispherectomy ranged from 16 months to 9.5 years (mean 6 years). Age at surgery was 3.5 months- 16 years (median 6.5 years).The underlying pathology was developmental in 9 patients (6 hemimegalencephaly, 3 multifocal cortical dysplasia), acquired in 1 (1 post encephalitis) and progressive in 4 (3 Rasmussen's encephalitis, 1 Sturge-Weber syndrome). At follow-up, 12/14 were completely or nearly completely seizure free (Engel class I and II). Seizure freedom was better in patients with progressive and acquired pathology (4/6) compared to developmental pathology (1/9). 4/14 are no longer taking anticonvulsant medications. After surgery, seizure frequency was further improved in 3 patients by modifiying the anticonvulsants. The hemiplegia (but not fine motor movements) remained unchanged in 9, improved in 3 and deteriorated in 3 children.12/14 have normal ambulation. In 4/6 children who had left hemispherectomy, language development was regained or continued to develop normally. Presurgical behavioral problems remained unchanged or improved after hemispherectomy in all the patients. Neuropsychology outcome continues to be analyzed.

Conclusions: In this small retrospective long term outcome study, children benefited from hemispherectomy, especially with aquired or progressive etiology. The majority had an excellent outcome regarding seizure freedom. Motor disability was unchanged or improved in most children. Languge was preserved in the majority of left hemispherectomies. Post hemispherectomy seizure reduction can be further improved with pharmacological management.

2.256

PEDIATRIC EPILEPSY: PRIMARY CARE PROVIDER KNOWLEDGE, ATTITUDES, AND BEHAVIORS

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Rationale: Despite access to neurological treatment, children with epilepsy have unmet mental health needs (Ott et al., 2003). This discrepancy in care is significant because quality of life for these children is poor (Austin & Dunn, 2000; Sabaz et al., 2003) and psychopathology is frequent (Austin et al., 2001; Caplan et al., in press; Dunn et al., 1999). Prior findings on pediatric epilepsy and chronic illness suggest that differences in provider and parent perceptions about the mental health problems of these children underlie poor access to mental health care (Cadman et al., 1987; Coulter $\alpha\nu\delta$ Koester, 1985). This study examined provider knowledge, attitudes, and beliefs about co-morbid mental health problems, perceived barriers to mental health care, and parental concerns in pediatric epilepsy.

Methods: We examined potential barriers to mental health care in peditric epilepsy by comparing knowledge, attitudes, and management practices in two primary care provider groups. Pediatric neurologists ($n = 18$) and pediatricians ($n = 18$) completed a 39-item questionnaire before and after a lecture on psychopathology in pediatric epilepsy. Questions included psychosocial aspects, provider caseload, potential barriers to mental health assessment and treatment, parental concerns, and stigma of epilepsy.

Results: Knowledge of psychosocial aspects of epilepsy ($p < .0001$) and comfort prescribing stimulants ($p = .03$) increased significantly across groups after the talk. Before the lecture both groups rated seizure control as the most important parental concern but having no behavioral and learning difficulties after the lecture ($p < .0001$). At baseline although both groups felt they lacked training to do behavioral assessments, after the talk they felt more confident conducting these assessments ($p < .05$) and making mental health referrals ($p < .01$). Compared to pediatricians, pediatric neurologists were more aware of

cognitive effects of antiepileptic drugs ($p < .03$), felt adequately trained to assess and treat behavioral problems ($p < .03$), and benefited more from mental health practitioner feedback ($p = .05$). As predicted, the lecture provided no significant change in provider management practices.

Conclusions: Providers emphasize the relevance of seizures rather than psychosocial issues for quality of life in pediatric epilepsy. Knowledge about the impact of epilepsy on behavior and learning helps physicians understand parents' main concerns, importance of common comorbid mental health and learning problems, and the need for mental health referrals in these children. (Supported by Epilepsy Foundation of America: Shire Targeted Award.)

2.257

ASSESSMENT OF EPILEPSY SERVICE QUALITY IN ARMENIA

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Rationale: To assess epilepsy service quality in non-specialized hospitals.

Methods: The study included 687 patients with seizures. Male/Female ratio was 418/271. Age distribution was as follow: 304 (44, 2%) patients were in age group 0–7 years, whereas 383 (55, 7%) pts.—in 7–25 years. In 158 (23%) patients age of onset was by 0–1 years, 146 pts. (21,3%)—by 1–3 years, 113 pts. (16,4%)—by 3–5 years, 80 pts. (11,6%)—by 5–7 years, 157 pts. (22,9%) – by 7–14 years and 11 (1,6%)—by 14–25 years. The most common seizure type was GTCS (560 pts.—81,5%), which in 382 of cases (68,2%) was not associated with other seizure types, which may reflect low awareness of seizure types among physicians. CPS were recorded in 62 cases (9,02%), SPS—in 105 cases (15,3%), AS – in 75 cases (10,9%), M – in 26 cases (3,9%), tonic—3 cases (0,4%), akynetic—4 cases (0,6%), atonic—8 cases (1,2%), IS—in 6 cases (0,9%). Most frequently (155–22,3%) predominantly seizure type occurred 1–5 times per year, in 125 cases (18,2%) they occurred daily. The etiology was defined as idiopathic in 27 cases (3,9%), symptomatic—in 217 (31,6%) and cryptogenic – in 77 cases (11,2%). The seizures considered as febrile in 97 cases (14,2%). CT investigation was performed in 23 cases—3,3% (8 positive vs. 15 negative). 96 patients (14%) were on AEDs at the moment of receipt (62 {64,6%} monotherapy vs. 18 {18,75%} polytherapy), 246 (35,8%) did not receive any medication. 37 pts. (38,5%) had complete seizure control, 27 pts. (28,1%) experienced partial control, in 17 cases no control observed. In 29 cases (vs.14) we could define choice of AEDs as appropriate. Single EEG was performed in 615 cases {89,5%} (476 positive vs. 140 negative), in 70 cases {10,2%} it was not performed at all. High percentage of positive cases in single EEG performance expressed overinterpretation of the results obtained (namely non-specialized discharges considered as epileptiform). The anonymous term of seizure predictability had widespread distribution among neurophysiologists. The diagnosis of epilepsy was confirmed in 621 cases (90,4%). The classification of established diagnosis into focal and generalized syndromes was possible in 202 cases—29,4% (focal 150 vs. 70 generalized), in 378 cases (55%) it was hard to classify epilepsy in generalized or focal.

Results: This study allow us to find out low epilepsy service quality in children neurological hospitals in Armenia, which include inappropriate antiepileptic drug therapy, low qulity EEG examination, which fail to reveal epileptiform discharges, limitation and/or absence of visualization methods in diagnosis of epilepsy, absence of syndromal qualification of disease.

Conclusions: These results showed that there is a great diagnostic and treatment gap among neurologists. Our efforts are to optimize the knowledge and management of epilepsy.

2.258

EFFICACY AND ADVERSE EFFECTS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN CHILDREN AND ADOLESCENTS WITH DEPRESSION AND EPILEPSY

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Rationale: Studies on the risk of increased seizures secondary to antidepressants in people with epilepsy are scarce; especially in children. According to Schmitz (2002), risk of antidepressants provoking seizures is probably overestimated. In adults, selective serotonin reuptake inhibitors (SSRI) have shown a lower risk compared with tricyclic antidepressants (Kanner et al., 2000). We aimed to analyze SSRI in children and adolescents with epilepsy and depression as to efficacy, adverse effects and effect on epileptic seizures.

Methods: The multidisciplinary team of the Unit for Research and Diagnostic of Epilepsy and Psychiatric Disorders in Childhood of the University of Sao Paulo studied all patients with a standard questionnaire. Epileptic seizures and syndromes were classified according to ILAE guidelines (1981; 1989) by history, file revision and V-EEG, when necessary. Patients were evaluated by a child psychiatrist with a structured anamnesis and classified according to DSM IV, CID 10 and KIDDIE-SADS. We prospectively assessed the seizure frequency of consecutive children with depression and epilepsy treated with SSRI. We compared the monthly seizure frequency recorded with a calendar (6–12 months after SSRI) with those registered 6—12 months preceding the start of SSRI (baseline).

Results: Our group was made up by 69 patients (37 boys [53.6%]). Thirteen patients (18.8%) were under < 6 years, 27(39.1%) from 7 to 13, and 29 (42.1%) over 13 years. As to diagnosis of epilepsy, 55 children (79.7%) had partial epilepsy; 42 had symptomatic epilepsy (60.9%), 21 (30.4%) cryptogenic and 7 (10.1%) idiopathic. Twenty-five patients (36.23%) had diagnosis of depressive disorder and were treated with SSRI. Out of these, 16 were treated with sertraline and 9 with fluoxetine, with the following adverse effects: one (4%) had facial flushing with fluoxetine and one (4%) presented diarrhea with sertraline. Two (8%) had seizure worsening with sertraline. In three patients with adverse-effects, change of SSRI in use for another was warranted. Only one patient with seizure aggravation did not tolerate SSRI at all and parents did not allow AED increase.Therefore, 23/25 patients (92%) presented satisfactory therapeutic response with SSRI, without seizure worsening.

Conclusions: Although SSRI are considered as drugs of low epileptogenicity there are up to date no studies in children. In this series we were able to observe that SSRI may be a good therapeutic choice for children with epilepsy and depression, with excellent efficacy, few adverse effects, and maintenance of satisfactory seizure-control.

2.259

NOVEL PHENOTYPE IN A GROUP OF CHILDREN WITH CRYPTOGENIC EPILEPSY: IS THIS A NEW DYSMORPHIC SYNDROME?

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Rationale: A specific clinical phenotype was recognised in many children with cryptogenic epilepsy in a tertiary child neurology clinic in a large metropolitan city in India. A systematic study of such patients was therefore undertaken to verify whether this phenotype was significantly different from the general population.

Methods: Twenty children of cryptogenic epilepsy with the specific phenotype were selected by one of the authors (VPU). There were several features reminiscent of Cohen's syndrome a dysmorphic syndrome linked to 8q22. Seizures are however not described in this syndrome (1). We systematically looked for all features of Cohen's syndrome (1) in this group of patients i.e. facial physiognomy, head circumference, cubital angle, mid-truncal obesity (chest/abdominal ratio), narrow slender hands/feet, wide sandal gap, joint laxity, hypotonia, weakness, opthalmic abnormailities, mental retardation/learning difficulties and neutropenia.

Age, sex, height and weight matched 25 control children were recruited by one of the authors unfamiliar with the clinical phenotype (PM). The same clinical features were studied in this group. Each feature in the two groups was then compared and statistically analysed using the chi-square test/Fischer Exact test for categorical variables and the 't- test' for continuous variables. A p value of less then 0.05 was considered significant.

Results: There were 12 boys and 8 girls. The mean age was 10.9 years. There were 10 focal epilepsies, 7 generalised epilepsies (of which 3 were myoclonic – astatic), 2 had Dravet's syndrome and 1 had both generalised and focal seizures. Nine were refractory and 9 were

controlled for >6 months. Of 13 tested children 11 were mentally retarded and 2 had borderline intellect.

Significant differences between the cases and the controls was 1) presence of mid-truncal obesity ($p = .003$), 2) prominent incisors ($p = 0.00001$), open mouth ($p = 006$), hypotonia ($p < 0.001$), proximal lower limb weakness ($p < 0.001$), widened sandal gap ($p = 0.0002$). Differences tending to significance included a short philtrum and long & narrow hands/feet. The remaining findings were not statistically different. Importantly, pigmentary retinopathy was seen in none, myopia in only 3 and neutropenia in 1 patient. These features are considered of diagnostic significance in Cohen's syndrome.

Conclusions: In a subgroup of highly selected children with cryptogenic epilepsy certain dysmorphic features are seen more often than in the general population. Some of these features resemble those seen in Cohen's syndrome. and we are presently conducting linkage studies to the COH 1 locus. Further studies in unselected children with cryptogenic epilepsy are warranted.

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2.260

IDENTIFYING FACTORS ASSOCIATED WITH EPILEPSY IN CHILDREN WITH PVL

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Rationale: Recurrent unprovoked epileptic seizures are known to occur in children with cerebral palsy(CP) secondary to periventricular leukomalacia (PVL). However, it is not yet possible to accurately predict which PVL patients will develop epilepsy. Identifying demographic and clinical factors associated with presenting with epilepsy in this population is an important step toward developing an accurate predictive model.

Methods: Of 218 children having CP patterns known to be associated with PVL, seen at the regional CP treatment centre on or before September 2000, 157 had radiologically proven PVL, 130 had CT+/− MRI studies available for the scoring of PVL severity and 41/157 were diagnosed with epilepsy. A binary logistic regression analysis was performed on those cases with complete data ($n = 115$) to identify factors associated with epilepsy. Clinical factors in the regression model were chosen for their strong univariate associations with epilepsy and included: PVL severity, degrees of motor and mental disability, cortical visual impairment, level of ambulation and a history of neonatal seizures.

Results: A history of neonatal seizures was significantly associated with having epilepsy, with an adjusted odds ratio of 5.2, 95% C.I. (1.5, 17.8). All other investigated factors, both clinical and demographic, were not statistically significant.

Conclusions: Among patients with PVL, those who develop epilepsy are more likely to have experienced a neonatal seizure.

2.261

SLEEP DISTURBANCES IN CHILDREN WITH EPILEPSY COMPARED WITH THEIR NEAREST-AGED SIBLINGS

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Rationale: To determine if epileptic children have a greater incidence of sleep problems than their non-epileptic siblings and to identify which epilepsy-specific factors correlate with greatest risk.

Methods: Case-control study of children aged 6–18 years. Cases had at least a one year history of epilepsy and were followed in the Pediatric Neurology or Refractory Epilepsy clinics at the Alberta Childrens Hospital between 15/09/03 and 15/04/04. All cases had a non-epileptic sibling in the same age group who acted as a control. The parent or caregiver was asked to complete a Sleep Behavior Questionnaire (SBQ) and Child Behavior Checklist-6–18 (CBCL) for each child. Specific details regarding the cases epilepsy including seizure type and frequency, antiepileptic drug treatment, prior epilepsy surgery or ketogenic diet use, cognitive status, seizure timing (nocturnal vs. diurnal), etiology, family history of epilepsy and EEG findings (background, location of discharge, activation with sleep) were recorded from chart review. Total and subscale scores on the SBQ and CBCL were compared between cases and controls.

Results: Forty cases with sibling controls were recruited (20 M and 20 F in each group). Mean age for cases was 10.6 yrs (range 6–16) and for controls was 11.2 yrs (range 6–16). Epilepsy type was idiopathic generalized in 5, symptomatic generalized in 7 and partial in 28 (13 lesional). Twenty-two cases had mental handicap. Fourteen cases were refractory, having failed three or more AEDs and having seizures at least q3monthly. With the exception of the Bedtime Difficulties subscale, all other subscales and the total score on the SBQ were significantly higher in cases with epilepsy than non-epileptic controls (sleep latency, parent-child interaction during the night, sleep fragmentation, parasomnias, daytime drowsiness and total score, all $p < 0.004$). In cases, those with refractory epilepsy and cognitive delay had highest scores ($p < 0.02$ for both). Cases with epilepsy also had significantly higher scores than controls on most of the CBCL subscales (Withdrawn/Depressed, Somatic complaints, Social problems, Thought problems, Attention problems, Aggressive behavior, all $p < 0.02$) however higher total SBQ score did not correlate with problems on the CBCL. Cases with mental handicap scored significantly higher in the Withdrawn/Depressed, Social problems, Thought problems and Attention problems subscales than cases with normal IQ (all $p < 0.005$). Cases with refractory epilepsy had greater Attention problems than non-refractory cases.

Conclusions: Sleep difficulties are significantly more common in children with epilepsy than their non-epileptic siblings. Children with refractory epilepsy and those with cognitive delay appear at highest risk. Although cases also demonstrated greater problematic behavior on the CBCL, these difficulties did not appear to correlate with greater sleep disruption.

Clinical Epilepsy–All Ages 2

2.262

TONIC STATUS IN PATIENTS WITH IDIOPATHIC GENERALIZED EPILEPSY

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Rationale: Tonic status epilepticus (TSE) has been classically associated with secondary generalized epilepsy (SGE) and catastrophic epilepsies. Its occurrence in patients with idiopathic generalized epilepsy (IGE) is not well recognized. The objective of this study was to report episodes of TSE in patients with IGE.

Methods: We retrospectively reviewed the clinical and EEG evaluation of two patients with IGE who presented with episodes of TSE: both had childhood onset absence seizures and developed nocturnal tonic seizures in their teens.

Results: Patient 1 is a 24 year-old woman had typical childhood absences diagnosed at age five. She had no identifiable risk factors or family history of epilepsy. Neurological examination was normal and her EEGs showed three Hz generalized spike and slow wave (GSSW) discharges. Nocturnal tonic seizures, symmetrical and lasting 10 to 20 seconds, appeared during adolescence, mostly related to her periods. They increased in frequency and after age 15 she had several hospitalizations for clusters of such seizures. Her MRI was normal. Tonic seizures were characterized by elevation of both arms, flexion of the neck and trunk, upward eye deviation, and unresponsiveness lasting up to four seconds and ictal EEGs showed generalized polyspike activity. Patient 2 is a 21-year-old man who developed generalized tonic clonic and absence seizures at the age of eight years. The absences were not typical since he partially retained consciousness but was unable to answer. He had no cognitive deficits. His EEG showed irregular GSSW with some additional rhythmic discharges over the left frontal region. He then developed episodes

while falling asleep, characteristically related to fatigue and occurring in series or clusters. He was admitted for video-EEG monitoring and many seizures were recorded. They consisted of brief tonic asymmetric posturing of both arms, more evident on the right, upward eye deviation, and contraction of perioral muscles with some downward deviation of the labial commissures. These were associated with generalized polyspikes with fragmentation and irregular GSSW. He also had isolated bilateral myoclonus of the chin. He improved with treatment with lamotrigine and topiramate.

Conclusions: Although the pathophysiology of TSE in IGE patients is unknown, GABA mediated changes may disrupt the classical GSSW pattern associated with absence seizures. The perimenstrual progesterone reduction may explain the TSE in patient 1. The worse prognosis associated with perioral myoclonia with absences in patient 2 may relate to the development of TSE. Recognition of this seizure pattern highlights the presence of a continuum in some patients between IGE and SGE. (E.K. receives a Preston Robb fellowship from the Montreal Neurological Institute.)

2.263

SLEEP DISTURBANCES REPORTED BY PARTIAL-ONSET EPILEPSY PATIENTS RECEIVING POLYTHERAPY

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Rationale: Sleep disturbances are common in epilepsy, resulting from seizures, antiepileptic medications, and coexisting sleep disorders. This study reports sleep disturbances among patients (pts) taking stable regimens of at least two antiepileptic drugs (AEDs) and evaluates the impact of sleep problems on health-related quality of life (HRQOL).

Methods: We surveyed 201 partial-onset epilepsy adult pts receiving $\geq$ 2 AEDs for $\geq$ 60 days. Pts were recruited from community-based neurologists in the US. Neurologists recorded patient demographic and clinical information. Pts completed questionnaires including the Medical Outcomes Study (MOS) Sleep Scale, the Quality of Life in Epilepsy-10 survey (QOLIE -10), and the EuroQoL-5D survey (EQ-5D). The 9-item MOS Sleep Problems Index, derived from the MOS-Sleep Scale, provides a broad summary of sleep problems (e.g., getting to sleep, staying asleep, daytime sleepiness, feelings of being rested). Scores on the 9-item Index range from 0 to 100; higher scores indicate greater sleep problems. Conversely, higher QOLIE-10 (range: 0–100) and EQ-5D (range: -0.6–1.0) scale scores indicate better HRQOL. We correlated sleep outcomes with HRQOL and with clinical and demographic characteristics using correlation coefficients and analysis of variance models.

Results: The mean (sd) age of pts was 44.2 (12.5). 56% were female, and 86% were white. Neurologists reported that 34% of pts had been diagnosed with sleep disturbances, and 10% had been prescribed sleep medications, usually benzodiazepines. Pts diagnosed with a sleep disturbance reported poorer mean QOLIE-10 (55.2 vs 63.7; $p = 0.006$) and EQ-5D (0.5 vs 0.7; $p < 0.001$) scores relative to those without sleep disturbances. The mean (sd) MOS Sleep score in the overall sample was 36.2 (20.8), above the general population mean of 26. Women reported more sleep problems than men (42.3 vs 28.4; $p < 0.001$). Pts with physician-reported anxiety or depression had more sleep problems than those without these comorbidities (anxiety: 44.5 vs 33.1; $p < 0.001$; depression: 41.2 vs 32.8; $p = 0.005$). Higher MOS Sleep Problems scores were significantly correlated with poorer QOLIE-10 ($r = -0.49$; $p < 0.001$) and EQ-5D ($r = -0.56$; $p < 0.001$) scores. Pts experiencing a seizure within one week reported higher MOS Sleep Problem scores than those with a less recent seizure (41.5 vs 32.8; $p = 0.003$).

Conclusions: Pts with partial-onset epilepsy on stable polytherapy regimens experience more sleep problems than the general population, with women reporting more problems than men. Diagnosed and self-reported sleep disturbances are negatively associated with pts' daily functioning and well-being. The nature of these disturbances could not be determined by this study, however recognition and treatment of sleep problems clearly represent an opportunity to better the care of epilepsy pts. (Supported by Pfizer, Inc.)

2.264

MULTIPLE SUBPIAL TRANSECTION (MST) WITHOUT RESECTION: LONG-TERM OUTCOME IN PATIENTS WITH MEDICALLY INTRACTABLE EPILEPSY

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Rationale: Long-term outcome data from cases of focal onset intractable epilepsy treated with multiple subpial transection (MST) alone is very limited. Questions to be answered from this patient group include the efficacy of the procedure as a stand-alone procedure without resection, the duration of MST efficacy, and possible long-term side effects of MST.

Methods: From our epilepsy surgery database of over 700 cases, 9 cases were identified in which MST was the only procedure performed in the treatment of medically intractable epilepsy. A restrospective review and phone contacts were performed.

Results: Eight males and one female had an age range of 11–42 (median 16 years), and a preoperative seizure frequency between 2–450 (median 45) seizures/month. MRI or CT was normal in 7 of 9 patients. Metabolic imaging was performed in 5 patients and was localizing in only 2. Long-term follow up ranged from 2–15 years. At last follow-up, median 8 years, seizure outcome was as follows: Engel's class I-2, II-4, III-1, IV-2. At two years, outcome was I-3, II-3, III-2, IV-1. No patient developed a new seizure type. Permanent deficits were seen in 1 of 9 patients.

Conclusions: In this case series, we present the longest follow-up on MST in the literature. Long term follow up on cases of pure MST demonstrates efficacy as a stand-alone procedure in select patients. In long term follow up, this efficacy remained stable in most patients. In this series of pure MST, no unexpected late onset sequellae were noted.

2.265

ANALYZING STATUS EPILEPTICUS DATA WITH MULTIPLE ETIOLOGIES

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Rationale: Many patients with status epilepticus (SE) have more than one etiology associated with each SE episode. These etiologies are recorded in arbitrary order but are of equal importance. When analyzing data on outcomes such as mortality from SE, including multiple etiologies as covariates poses a challenge. It is often necessary to combine multiple etiologies into a single etiology category. In this study, different ways of assigning etiology by condensing information from multiple etiologies is addressed.

Methods: Since 1989, NIH Greater Richmond Metropolitan Area Data System on SE has been collecting data. The database, which consists of over 600 patients, is a comprehensive collection of laboratory, clinical and demographic data on every SE case. Several analyses have been performed in the past. The variables studied include mortality, etiology, race, sex, age, seizure duration, seizure type, time to treatment, etc. When more than one etiology was present, patients were assigned a single etiology using one of three different methods. In the first method, one etiology from the multiple etiologies reported was chosen based on consensus from clinicians (called ETCOM). The second and the third definitions were based on data alone. For these a table of mortality by etiology was constructed. Then the etiology that had the highest mortality was assigned to be the etiology of the patient (called ETMAX). For example, if CNS Acute and Withdrawal were observed and the mortality for CNS Acute and Withdrawal in the population were 24% and 6.4%, respectively, then the etiology assigned to that patient, ETMAX, was

CNS Acute. Similarly, ETMIN using the lowest mortality was also considered. Three logistic regression models were fitted for the mortality outcome with one of the three definitions of the etiology.

Results: The first method (ETCOM) led to 15 categories, which included combined etiologies. The second and the third methods led to 6 categories each. When included in the logistic regression model, in general the three different assignments were found to be comparable. The parameter estimates and the p-values turned out to be similar. Deatails of the analyses will be presented in the poster.

Conclusions: Data are being collected constantly in many fields of medical science. Often, in publications of the results from analyses of these data, the nuances applied in the analyses are not explained. To ensure consistency in the approaches in similar fields, it is important to disseminate the new methodology applied even if it is not directly relevant to the subject matter. In this poster, one such issue that relates to defining etiology in SE was addressed. It was found that the consensus based definition of etiology provided similar results to definitions that were purely data driven. It is concluded, to facilitate interpretation it is best to use consensus based definitions. (Supported by NIH P01 NS25630.)

2.266

THE FRONTAL LOBE EPILEPSY AND PARASOMNIAS (FLEP) SCALE: DEVELOPMENT AND PILOT VALIDATION STUDY OF A CLINICAL INSTRUMENT FOR THE DIAGNOSIS OF PAROXYSMAL NOCTURNAL EVENTS

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Rationale: Abnormal paroxysmal events in sleep may be parasomnias or epileptic seizures. In the case of nocturnal frontal lobe epilepsy (NFLE) the unusual seizure semiology often leads to an incorrect diagnosis of parasomnias. Despite this, the clinical presentation of these conditions is different, and it should usually be possible to differentiate them on the basis of the clinical history. We have developed the Frontal Lobe Epilepsy and Parasomnias (FLEP) scale as a clinical tool to distinguish these conditions based on relevant features of the patient's history.

Methods: 1) Scale development. The FLEP scale, consisting of specific questions reflecting the diagnostic features of NFLE and parasomnias, was developed by an expert panel following review of the literature. The scale weightings were adjusted by unblinded application to a sample of cases. 2) Pilot validation 11 subjects with NFLE and 6 with parasomnias were enrolled. All patients had been reviewed by at least two neurologists or sleep physicians, and 14 of the 17 subjects had undergone diagnostic video EEG monitoring. A 15 minute telephone interview was conducted by a blinded researcher in each case; this involved both the patient and a witness to the patient's events. A diagnosis was made on the basis of their FLEP score. 3) Validation study. Sixty subjects using the same methodology are currently being assessed.

Results: NFLE was correctly diagnosed from the FLEP score in 11 out of 11 patients giving a sensitivity of 1.0 (95% CI: 0.81, 1.0). The specificity of a diagnosis of NFLE was 0.8 (95% CI: 0.37, 0.8). The diagnosis of NFLE from the FLEP scale had a positive predictive value of 0.92 (95% CI 0.74, 0.92) and a negative predictive value of 1.0 (95% CI 0.47, 1.0).

Conclusions: The FLEP scale appears to be a sensitive, specific and easily administered clinical instrument for the differentiation of Nocturnal Frontal Lobe Epilepsy from parasomnias on the basis of the clinical history. (Supported by The Brockhoff Foundation, Australia.)

2.267

CORTICAL TRIGGERS IN GENERALIZED REFLEX SEIZURES

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Rationale: Some patients with reflex seizures have apparently generalized or bilateral ictal manifestations triggered by stimuli classically associated with specific cortical sensory territories, including flickering light or geometric pattern. Activation of less restricted brain areas by stimuli such as calculation or reading can also trigger generalized seizures. Many such patients appear clinically to have an idiopathic generalized epilepsy, especially JME.

Methods: We reviewed the clinical and experimental data regarding these different types of reflex seizures.

Results: Photosensitive patients present with seizures when exposed to environmental stimuli producing flickering light or arranged in geometric patterns with specific characteristics of luminance, colour and contrast. Seizures induced by thinking are triggered by non-verbal higher mental activity (e.g. calculation). Praxis-induced seizures are triggered by similar mental activities accompanying the use of the hands (e.g.writing). Language–induced seizures are usually triggered by verbal higher mental activity (e.g. reading). Functional imaging and other advanced methods have recently contributed to a further understanding of the cortical regions involved during these tasks and how seizures may be triggered.

Conclusions: It appears that patients with generalized reflex seizures present regions of cortical hyperexcitability overlapping the areas physiologically activated during specific sensory stimulations (flash and pattern), and cognitive (thinking, praxis and reading) or motor (praxis and reading) activities. In visual sensitivity the relevant system is occipital. For verbal and non-verbal cognitive tasks the system involves complex networks extending over multiple cortical areas in both hemispheres. When these areas receive appropriate afferent volleys and a critical mass of cortex is activated, an epileptic activity is produced that ultimately involves the cortico-reticular or cortico-cortical pathways, with the final result of a generalized or bilateral epileptic event. We believe that three major patterns of cortical activation of generalized or bilateral reflex seizures can be distinguished:

1. Sensitivity to visual stimuli, originating in the occipital cortex.
2. Sensitivity to non-verbal cognitive stimuli. This includes thinking-induced seizures involving predominantly the non-dominant or both parietal lobes, and praxis-induced epilepsy in which, in addition, the sensorimotor cortex is involved.
3. Sensitivity to verbal cognitive stimuli, involving both hemispheres with a major role played by the dominant lateral frontal cortex.

Although the underlying mechanisms are similar, as are the resulting seizure types, the triggering stimuli are different. All depend on cortical hyperexcitability which is diffuse but not necessarily uniform. This gives additional evidence that the cortical machanisms of IGE are complex and non-uniform.

2.268

ELEVATED BUN PREDICTS STATUS EPILEPTICUS MORTALITY

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Rationale: Status Epilepticus (SE) has a high morbidity and mortality. This study was conducted to identify common laboratory values that can be useful in predicting SE outcome.

Methods: The NIH Greater Richmond Metropolitan Area Status Epilepticus Data System was used; prospectively collected data on SE cases in Richmond, Virginia. Common chemistry laboratory results were examined, including sodium, potassium, chloride, CO2, glucose, BUN and creatinine. The time the specimen was obtained, either during or after SE, was also analyzed. Cases were divided into 3 age groups: pediatric (up to age 16), adult (16–59) and elderly (60 and above). Race, gender and SE etiology were also examined, as well as SE duration, location of SE onset (in the hospital or outside of the hospital) and SE type (nonconvulsive, partial, general and other).

Results: A total of 948 cases were available for this analysis: 275 pediatric, 327 adult and 346 elderly. Utilizing multivariate logistic regression analysis, the following variables were identified as significant in

predicting mortality: elevated BUN ($p < 0.05$), age ($p < 0.0001$), etiology ($p < 0.0001$), whether the specimen was obtained during or after SE ($p < 0.006$) and location of SE onset ($p < 0.02$). There were no significant differences in race, gender, SE type, SE duration, sodium, potassium, chloride, CO2, creatinine or glucose. Elevated BUN was more common in elderly cases (28%) versus adult (15%) and pediatric (5%) cases, and was seen in proportionately higher percentages in the nonCNS acute and Hypoxia/Anoxia etiology categories in all age groups. Mortality was significantly higher in cases with elevated BUN in all age groups. In pediatric cases with normal BUN, mortality was 5% versus 27% in cases with elevated BUN; for adults mortality was 12% in the normal BUN group and 36% in the elevated BUN group, and in elderly cases, mortality was 23% in the normal BUN group and 43% in the elevated BUN group. Elevated BUN values were more commonly seen when the laboratory sample was obtained during SE versus after SE. When examining location at SE onset, elevated BUN was seen in 33% of SE cases that began in the hospital versus 11% of cases that began outside of the hospital.

Conclusions: Blood chemistry tests are routinely obtained on patients, with results being available relatively quickly. This study shows that elevated BUN levels are highly predictive of SE mortality and may be useful in making decisions regarding patient management. (Supported by NIH P50NS25630.)

2.269

IS MONOTHERAPY PREFERRED BY PATIENTS WHOSE SEIZURES REMAIN WELL CONTROLLED?

Nicole C. Hank, Steve S. Chung, and David M. Treiman (Neurology, Barrow Neurological Institute, Phoenix, AZ)

Rationale: Monotherapy has become the "golden standard" of epilepsy treatment by physicians; however, patients who suffer from epilepsy are rarely asked their preference for monotherapy vs. polytherapy. This study explores the thoughts and concerns of patients who are currently seizure free on either mono- or polytherapy.

Methods: Clinical and demographic data was retrospectively reviewed from over 1200 medical records from patients treated at Barrow Neurological Institute, of which, 82 seizure- free patients were identified. Information was collected from patients aged 12–84 years, all whom had been seizure free for at least 3 months. Patients were then called to confirm their seizure status and were asked a series of questions pertaining to quality of life and treatment preference.

Results: Of the 82 patients, 46% were currently receiving monotherapy, at the time of the interview, of which 74% were previously treated with polytherapy. Since being off multiple AED's, 98% of these patients reported their health had improved considerably and they were experiencing few to no side effects. 54% were currently being treated with polytherapy, of which, 90% of these patients were willing to risk seizure free status by trying monotherapy. Nearly all patients reported they hoped to improve their cognitive capacity with monotherapy and that they experienced remarkable improvement in the quality of life as a whole while on monotherapy.

Conclusions: The majority of patients seem to prefer monotherapy when their seizures are well controlled. Patients who are on polytherapy also prefer monotherapy and often willing to chance their seizure freedom in order to achieve improved quality of life and overall well-being. This study confirms that monotherapy treatment is indeed the patient's choice of treatment as often recommended by neurologists.

2.270

STARTLE EPILEPSY: CLINICAL CHARACTERISTICS IN 8 PATIENTS

Ji-hyun Kim, Joong Koo Kang, and Sang-Ahm Lee (Neurology, Asan Medical Center, Seoul, Korea)

Rationale: To determine the clinical characteristics of startle epilepsy characterized by reflex partial seizure of sensorimotor cortex

Methods: Eight patients with startle epilepsy were evaluated for clinical seizure history, neurologic examination, MRI, routine EEG, video-EEG monitoring, and ictal SPECT

Results: Etiologies were perinatal injury(4 patients), kernicterus following hemorrhage during infancy(1 patient), near-drowning at age 4(1), and unknown(2). Age of sezure onset varied from several months to 16 years. All patients had spontaneous as well as reflex seizures. The effective triggers were several sensory modalities, typically proprioceptive and auditory. The stimuli should be sudden and unexpected. Their seizures usually occurred daily and were medically intractable. Neurologic examination was abnormal in 6 patients. Five had mental retardation, and 4 motor deficit. MRI was abnormal in 6 patients, generally large encephalomalatic changes involving cortical and subcortical structures. Five had bilateral lesions. The semiology was characterized by unilateral or generalized tonic posture. Scalp interictal and ictal EEGs had limited value to lateralize the epileptogenic focus. Intracranial EEG in one patient who underwent surgery showed ictal onset on lateral sensorimotor cortex.

Conclusions: Startle epilepsy is a rare but distinctive epileptic syndrome characterized by reflex seizure triggered by unexpected, sudden sensory stimuli. Some clinical findings including etiologic events(kernicterus following hemorrhage, near-drowning), high incidence of bilateral lesions, ictal onset on lateral sensorimotor cortex without involvement of medial cortex, and ictal SPECT findings are not reported or different from previous studies.

2.271

ELECTROGRAPHIC PATTERNS IN REFRACTORY STATUS EPILEPTICUS

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Rationale: Refractory Status Epilepticus (RSE) is a severe condition where seizures do not stop with first- and second-line antiepileptic drug (AED). The risk factors that predispose to it are still poorly defined. RSE ranges from 9% to 40% of SE in different series. Few studies have focused on clinical factors but detailed ictal EEG studies in RSE still lacks. If a stereotyped sequence of ictal patterns exist, then the most severe patterns should be found in RSE. It is also not yet clear whether ictal EEG predicts outcome of RSE. To address these points we reviewed all EEGs performed during RSE and classified them according to previously defined patterns.

Methods: RSE was defined as SE that had failed to first-and second-line AED therapy, and lasted a minimum of 60 minutes. All patients had serial EEGs performed and the recordings were usually prolonged (60–120 min), and 3 patients had continuous EEG. Clinical data was reviewed and correlated to ictal patterns. EEG patterns were classified in discrete seizure (DS), merging seizures (MS), continuous ictal discharges (CID), periodic epileptiform discharges lateralized or diffuse (PLEDs/PEDs), and combination of ictal patterns (more than one pattern in the same record). Electrographically SE was defined when the ictal pattern occupied a minimum of 80% of the recording time.

Results: Fifteen patients totaling 17 episodes of RSE were analysed (2 patients had more than one episode). Ages ranged from 18 months to 84 years, mean of 33.9 years. 6/15 (40%) patients were females and 9/15 (60%) males. Etiologies were: epilepsy in 3/17 (17.6%%), brain structural lesion (tumor, metastasis, trauma) in 2/17 (11.8%), non-structural lesions (metabolic, hypoxic-ischemic, infection) in 7/17 (41.2%), and miscellanea in 5/17 (29.4%). Ninety EEGs and 3 continuous EEGs were analyzed. Pattern of first EEG recording were classified as DS (23.5%), MS (35.3%), CID (17.6%), PLEDs/PEDs (5.9%), and combination of ictal patterns (17.6%). Regarding the progression of patterns, 7/17 RSE (41.2%) had variable pattern but 10/17 (58.8%) had invariable ictal patterns. The mortality rate was 6/17 (35.3%), but 2 patients were already out of the SE when died. The analysis of mortality and ictal pattern disclosed: 2/6 PLEDs and MS, 1/6 PLEDs, 1/6 DC, 1/6 CID and 1/6 DS. The analysis of mortality and age showed 47.7yrs and 24.8 years, respectively, for the groups death and survivors.

Conclusions: The repertoire of ictal EEG patterns in RSE includes all previously described EEG patterns. When dealing with prognosis initial as well as evolution of ictal patterns need to be carefully considered and correlated to mortality risks. Approximately half of the

patients that died had PLEDs as the initial EEG pattern, but other variables including etiology and age may also play an important role. (Supported by FAPESP.)

2.272
REFLEX SEIZURES: FOCAL OR GENERALIZED HYPEREXCITABILITY?
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Rationale: To report two cases of reflex seizures in two patients with focal seizures, one with probably symptomatic focal epilepsy and the other with generalized epileptiform EEG pattern.

Methods: Two patients with reflex seizures were analyzed, one with video EEG and SPECT, and the other with routine EEG.

Results: Patient 1: girl, 7 yrs., started having seizures at the age of two months characterized by elevation or the arms; EEG, brain CT, metabolic screen were all normal.

The seizures were controlled with CBZ but the patient presented a mild slowing of developmental milestones acquisition. At the age of 4 yrs. she stop CBZ, which was reinitiated at 6 yrs. when she started having generalized clonic movements, controlled with this AED. After six months she started having micturation seizures characterized by tremors in legs, arm elevation, generalized hypertonia and fall to the floor. Video-EEG showed micturation seizures and spontaneous seizures after AED reduction, accompanied by diffuse rhythmic slowing in anterior regions and interictal EEG, focal epileptiform activity in right median parietal area; brain MRI, normal; interictal SPECT revealed hypoperfusion in right parietal region and ictally, hyperperfusion in the same area. She received several AED and presented status epilepticus twice. Now the patient is receiving LTG, OCBZ, CLB and presents short seizures only during micturation. Patient 2: healthy woman, 29 yrs., had one convulsion at two yrs. of age and at age 10 yrs. focal complex seizures followed by hypertonic posture once a week, at times precipitated by hot water showering. All exams were normal (brain MRI, EEG, CSF). She received several AED, including PB, CBZ, and VPA. Recently she has been using CBZ and VPA, and when CBZ was increased (600–1200mg/d) and VPA reduced (1000–750mg/d), the frequency of the seizures increased and the EEG showed generalized irregular spike-wave discharges during hyperventilation. Now she is taking VPA 2gxd and LTG 25mgxd, and avoiding hot hater showers and she is seizure free.

Conclusions: Focal or generalized reflex seizures are precipitated often or even exclusively by specific stimuli. Seizures at micturation are rare, as well as precipitated by hot hater. The finding of focal seizures dos not preclude diagnosis of reflex seizures, that may reflect abnormal focal cortical activity superposed to generalized hyperexcitability. Hence, it is important to search for precipitating factors in patients with refractory seizures in order to improve diagnosis and treatment.

2.273
REPEAT AND INDIVIDUALIZED DOSING INSTRUCTIONS WITH DIAZEPAM RECTAL GEL
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Rationale: Diazepam rectal gel, the only antiepilepsy medication approved by the Food and Drug Administration for the at-home treatment of breakthrough seizures by medically trained as well as nonmedically trained caretakers, has demonstrated efficacy and safety. Dosing guidelines are based on patient age and weight; few adverse events have been reported even in cases where the recommended dosage was exceeded. Because underdosing may pose a greater health risk than overdosing, a higher dose may be the better option for some patients whose age and weight falls at the upper limit of a dosage category. In some instances seizures may not resolve with the first dose of diazepam rectal gel, and repeat dosing may be beneficial. Individualized and repeat dosing represent 2 important components for providing effective seizure management. We surveyed epilepsy specialists to determine how they instruct patients regarding repeat and individualized dosing of diazepam rectal gel.

Methods: Members of the International Epilepsy Consortium were surveyed to obtain information about their clinical experience with diazepam rectal gel. The survey was sent to 41 epilepsy centers and included questions about individualized and repeat dosing instructions for diazepam rectal gel.

Results: Fourteen centers responded, representing information from 34 epileptologists. Thirteen of 14 centers reported following the dosing recommendations in the diazepam rectal gel package insert, with 1 center consistently dosing higher. Of the centers that followed insert dosing recommendations, however, 43% also developed individualized dosing regimens for some patients. In total, 6 sites reported using higher doses and 5 sites lower ones, including 1 center that reported using lower doses for patients receiving chronic benzodiazepines. Fifty-eight per cent of responding centers instructed caregivers to administer a second dose of diazepam rectal gel if the first dose was ineffective; only 1 center specifically instructed caregivers not to give a repeat dose. The time period between administration of first and second doses of diazepam rectal gel varied among respondents. If seizure activity persisted, the time ranged from 10 to 30 minutes after the initial dose; the average recommended time was 15 minutes. If the first dose did not stop the seizure, 71% of centers advised seeking emergency medical attention regardless of whether a second dose was given. Four centers recommended that both a second dose be administered and that emergency medical treatment be sought as an additional precaution.

Conclusions: The results of this survey indicate that individualized dosing of diazepam rectal gel is practiced by epilepsy specialists. Together with repeat dosing, diazepam rectal gel can provide significant contributions to effective seizure management. (Supported by Xcel Pharmaceuticals.)

2.274
CHARACTERIZATION OF TUMOR-RELATED EPILEPSY
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Rationale: Patients with intractable epilepsy who undergo surgery have a 10–20% incidence of CNS neoplasms and the overall incidence of neoplastic lesions among all epilepsy patients has been reported at 4.1%. The purpose of this study is to evaluate tumor related epilepsy from the epileptologist's perspective and characterize patients with tumor related epilepsy.

Methods: The UVA Epilepsy Database was queried for patients with brain tumors. Tumor type and grade were identified by review of database information, clinic notes, radiology reports, discharge summaries, and pathology results.

Results: Out of 1674 patients in the database, 615 were categorized as symptomatic localization related epilepsy (SLRE) and 55 of these had brain tumors (3.3% of all patients in the database and 8.9% of SLRE). 26 of the 55 tumor patients had gliomas and 29 had non-glial tumors. For all tumor patients the average current age was 42.4 ± 14.2 years, age of seizure onset was 28.2 ± 17.3 years, duration of epilepsy was 14.5 ± 13.0 years, number of antiepileptic drugs (AEDs) tried was 4.1 ± 2.6, and current number of AEDs used was1.8 ± 1.3. Male to female ratio was 31:29. A history of status epilepticus was present in 7 (12.5%). A breakdown of patients by tumor type and grade is illustrated in Table 1. No statistical differences between glial and non-glial tumor patients were found. Tumor type or grade did not predict refractoriness to AEDs or risk of status epilepticus.

Conclusions: Among patients with SLRE close to 10% have brain tumors. Tumor type or grade did not predict the degree of refractoriness, although this may be due to the small sample size. Tumor patients of all types required multiple AED trials and often polypharmacy. Epileptologists are most familiar with the management of refractory epilepsy and this study suggests that their participation in the care of tumor patients may be of benefit and should routinely be considered. Seizures may significantly impair the quality of life of many of these patients and if the initial AED trial is ineffective a referral to an epilepsy center is warranted for aggressive medical and potentially surgical treatment of seizures.

TABLE 1. *Patient distribution and characteristics by tumor type and grade*

Gliomas	n	sex (M)	age	years of epilepsy	# AED's tried[1]	# AED's now	SE[2](%n)
Low grade*	14	10	38	10	3.1	1.9	2(14%)
High grade*	8	4	40	5	3.3	1.9	1 (14%)
Grade unknown	4	2	39	31	7.3	2.0	2 (33%)
Non-glial tumors							
Meningioma	7	1	52	6	4.0	2.0	0
PNET[3]	5	4	22	10	3.6	1	0
Pituitary	2	1	40	10	3.0	1.5	1 (50%)
Metastases	2	1	58	7	3.5	2.5	1 (50%)
Vascular	3	3	49	28	6.7	2.3	0
Other	4	1	33	15	5.8	1.5	0
Unknown	6	3	42	13	2.5	1.5	0
Total Gliomas	10	4	42	13	4.0	2.0	5 (19%)
Total Non-glial	29	14	43	16	4.0	2.0	2 (7%)

[1]AED = Anti-epileptic drug; [2]SE = Status epilepticus; [3] Primary neuroectodermal neoplasms; (Low grade = WHO grade 1 and 2, High grade = WHO grade 3 and 4.

2.275

REVIEW OF THE TREATMENT OF STATUS EPILEPTICUS WITHIN THE REGINA QU'APPELLE HEALTH REGION (RQHR), SASKATCHEWAN, CANADA

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Rationale: Generalized convulsive status epilepticus (GCSE) is a medical emergency associated with significant mortality. Seizure duration has been identified as an important contributor to mortality, prompting several publications on treatment algorithms in an effort to decrease the time from onset of GCSE to initiation of treatment. We sought to determine the need for developing guidelines and algorithms by assessing the current management of GCSE within the RQHR.

Methods: Medical records of patients with a diagnosis of GCSE between April 2001 and March 2002 were reviewed. Demographic data, as well as seizure classification, etiology, treatment (drug, dose, administration, monitoring) and location of treatment initiation were abstracted.

Results: Data on 15 patients, 7 males and 8 females, aged 1–88 years (mean, 32 years), who experienced 28 episodes of GCSE were available for analysis. Low antiepileptic drug concentration was determined to be the seizure etiology in 54% of the episodes, while GCSE occurred secondary to alcohol withdrawal, infections, trauma and hypoxia in 18% of the episodes. Etiology was indeterminate for 8 episodes. Treatment was initiated outside of a hospital in 17 episodes (61%), in the emergency room (ER) in 25% and in the hospital in 15% of the episodes. Diazepam (DZP) was the initial drug used in 24 episodes, lorazepam (LZP) in 3 episodes and midazolam (MDZ) in 1 episode. A second agent was required in 21 episodes, with phenytoin (PHT) being used in 10 episodes, DZP in 4, LZP in 3 and both MDZ and phenobarbital being used in 2 episodes each. A third agent was required in 13 episodes, with PHT being used in 8, MDZ in 4 and LZP used in one episode. Of those episodes of GCSE in pediatric patients where DZP was administered initially, doses ranged from 1–15 mg administered intravenously (i.v.), and repeated 2–4 times over a period of 28–70 minutes. In adults DZP doses of 5–30 mg i.v. were administered. LZP was used as initial therapy in 3 episodes, 2 of which were in a 10 year old child. Both times, parents initiated treatment at home with LZP 1 mg x 3 doses, and emergency medical services arrived to administer DZP. In the third episode, an adult received an initial dose of LZP 2mg (0.018 mg/kg) in the ambulance followed by 4 × 1 mg doses administered in the ER over 240 minutes (for a total dose of 0.05 mg/kg). PHT was used in 18 episodes of GCSE. A dose of $\geq$15 mg/kg was used in 33% of the episodes (range: 8–20 mg/kg). PHT was infused at a rate of 50 mg/min in 22% of the episodes, at rates of 20–50 mg/min in another 22% and at <20 mg/min in 33% of the episodes (range: 3–50 mg/min).

Conclusions: Standardization of the treatment of GCSE through guidelines and an algorithm is necessary to decrease the discrepancies in dosing, infusion rates and the response time to treatment.

2.276

CLINICAL EXPERIENCE WHEN SWITCHING FROM CARBAMAZEPINE TO OXCARBAZEPINE IN EPILEPSY PATIENTS

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Rationale: Patients who did not respond to carbamazepine (CBZ) or who developed side effects with CBZ were switched to oxcarbazepine (OXC), a newer antiepileptic drug (AED). This study looked at the effect of switching these patients to OXC.

Methods: A total of 424 charts of patients attending the outpatient clinic from January 2000 to September 2003 were reviewed retrospectively. Patients on CBZ, who were converted to OXC monotherapy or who had OXC added to their existing AED regimen were identified and the data collected and analyzed. Demographics, seizure severity, side effects, dose of AEDs, concomitant medications, failed AEDs, sodium levels, OXC plasma levels and EEG findings recorded at each visit were reviewed.

Results: A total of 154 patients had been switched from CBZ to OXC, 61 were on CBZ polytherapy and 93 were on CBZ monotherapy on their first visit. Ninety-three were female and 61 were male. The average age at onset of seizures was 19 yrs. In the whole group, 1 (1%) had worsening of seizures, 49 (32%) had decreased severity of seizures, 78 (51%) became seizure free, 20 (13%) showed no change and there was no information available for 6 (4%).

Among the 61 patients on CBZ polytherapy, 21 (34%) could be converted to OXC monotherapy while 40 (66%) had OXC added to their polytherapy regimen. Among the 93 patients on CBZ alone, 82 (88%) were converted to OXC monotherapy and 11 (12%) had OXC added on. Of the 103 patients converted to OXC monotherapy, 65 (63%) were seizure free, and 21 (20%) had decreased severity. Of the 51 patients for which OXC was added, 13 (25%) were seizure free and 25 (49%) had decreased severity.

Side effects developed in 78(51%) of the patients ranging from mild to severe, and 13 (8%) of these had to stop their treatment. Thirteen patients (8%) who were switched from CBZ to OXC, had to be switched back to CBZ due to side effects from OXC. Three of these developed rashes and the remaining developed side effects such as diplopia, dizziness and lethargy. A total of 12 (8%) patients developed hyponatrenia (sodium<125 mmol/L) however only 3 patients had to stop their treatment due to side effects related to the hyponatremia. Sodium levels ranged from 115–153.

Oxcarbazepine levels ranged from 9–63μg/ml. Patients with mild seizures appeared to require levels ranging from 10–20 μg/ml, patients with moderate seizure severity required levels in the range of 20–30 μg/ml and those with severe seizures levels above 30 μg/ml. Of the 54 patients who had OXC levels above 30, 20 (37%) were seizure free, 24 (44%) had decreased severity and 9 (17%) showed no change. However, 32 (59%) of these patients developed side effects which resolved over time in all but 1 patient who had to discontinue OXC.

Conclusions: OXC can be safely used for conversion to monotherapy or as add-on in patients already on CBZ. Plasma levels of OXC appear to

correlate with the severity of seizures. (Supported by Unrestricted grant from Novartis Pharmaceutical Corporation.)

2.277

EPILEPSY IN BAND HETEROTOPIA: ICTAL EEG PATTERNS

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Rationale: Band heterotopia (BH) is a severe form of migrational abnormality that presents with mental retardation and epilepsy. This condition may have a genetic basis. The associated epileptic syndrome, neuroimaging and interictal EEG findings have been described, but there are few reports about ictal EEG patterns.

The aim of this study is to describe the clinical, neuroradiological and EEG (interictal/ictal) features of patients with BH.

Methods: CCF MRI database (1999–2004) was searched to identify patients with diffuse bilateral BH who underwent Video-EEG evaluation. MRI findings were confirmed. Details about their clinical presentation, seizure semiology and interictal/ictal EEG findings were reviewed from the charts.

Results: Four patients were identified with diffuse bilateral BH. All of them had mental retardation and medically refractory seizures with multiple seizure types. One patient had positive history for epilepsy.

The most common seizure type was Generalized Tonic-Clonic Seizures (in all patients), followed by dialeptic seizures in 3 patients. 2 Patients had atonic, one each had myoclonic or complex motor seizures. Interictal epileptiform discharges were generalized or multiregional involving both hemispheres in three patients and one did not show interictal epileptiform activity. Ictal recording showed generalized EEG seizure pattern in two of the cases, while two patients showed either regional (1) or lateralized (1) EEG seizure patterns.

Conclusions: Band heterotopias with diffuse bilateral MRI abnormality may present with regional ictal patterns on EEG. Epilepsy surgery may be an option for this subgroup of patients with medically refractory seizures, however better tools (imaging, stereotactic EEG) would be needed to map the ictal onset zone. Genetic testing and counseling should be considered as part of the clinical management. (Supported by Department of Neurology, The Cleveland Clinic Foundation.)

2.278

ROLE OF OXCARBAZEPINE IN PRIMARY GENERALIZED EPILEPSY

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Rationale: Seizures may worsen in many patients with primary generalized epilepsies (PGE) when given traditional antiepileptic drugs (AEDs). We report on our experience with oxcarbazepine (OXC), a new AED in patients with PGE

Methods: We retrospectively reviewed outpatient charts of epilepsy patients from January 2000 to September 2003. Patients with PGE converted to OXC monotherapy or who had OXC added as part of their polytherapy regimen were identified and the data was analyzed. Available data for patient demographics, seizure severity, side effects, dose of AEDs, concomitant medications, failed AEDs, sodium levels, OXC plasma levels and EEG findings recorded at the time of first visit and each subsequent visit was reviewed.

Results: Out of 424 charts, 31 patients with PGE were identified, 20 females and 11 males (age range 14–71 years). The median age of onset of seizures was 12 years. Eleven patients had a positive family history of seizures, 13 had no family history and no data were available for 7. All patients showed EEG abnormality of generalized bursts of 3 Hz spike and wave which were predominant in the frontal regions.

Sixteen patients had generalized tonic-clonic (GTC) seizures, 7 had absence seizures and GTC seizures, and 8 had absence seizures, myoclonic jerks and GTC seizures. Most patients had failed at least 2–5 antiepileptic drugs. Therapeutic OXC doses ranged from 900–3000 mg/day.

Of the 16 patients with GTC seizures, 11 (69%) became seizure free, 1 (6%) had a decrease in seizure frequency and 4 (25%) had no change in seizure frequency. Of 7 patients with absence seizures and GTC seizures, 3 (43%) became seizure free, 2 (29%) had persistent absence seizures, 2 (29%) had no change in seizure frequency. Of 8 patients with absence seizures, myoclonic jerks and GTC seizures, 4 (50%) became seizure free, 2 (25%) had persistence of few absence seizures and 2 (25%) had persistence of some myoclonic jerks.

Of the 11 patients converted to OXC monotherapy, 8 (73%) patients became seizure free for $\geq$6 months, 2 (18%) experienced a decrease in seizure severity, and 1 (1%) had no change in seizure severity. Twenty patients received OXC as adjunctive therapy, with regimens including valproic acid, lamotrigine, zonisamide, gabapentin, topiramate and carbamazapine. Ten (50%) patients became seizure free after addition of OXC, 6 (30%) had a decrease in the severity of their seizures, and 4 (20%) with no change in seizure severity.

Twelve (39%) patients had no adverse effects and 19 (61%) patients who experienced adverse effects did not discontinue OXC treatment. The most common side effects(>15%) were fatigue, sedation and nausea.

Conclusions: Oxcarbazepine appears to have a role in patients PGE and should be considered as monotherapy or adjunctive therapy for patients with PGE who have failed to respond to other AEDs. In this small cohort of 31 patients with PGE, there was no precipitation of absence seizures or myoclonic jerks (Supported by unrestricted grant from Novartis Pharmaceutical Corporation.)

2.279

PREDICTABILITY OF THE INTERSEIZURE INTERVAL DEMONSTRATED BY USING A DISCRETE SEQUENCE OF AUTOMATED DETECTION TIMES

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Rationale: There is evidence in the literature that the occurrence of epileptic seizures may not be independent or uncorrelated in a statistical sense. Statistical approaches have been used to model seizure occurrence with some success. However, these relied on patient diaries, which are inherently inaccurate, and dealt almost exclusively with daily seizure frequency. Most current approaches to prediction analyze continuously sampled EEG data using nonlinear dynamic measures to identify putative preictal states and thereby anticipate seizures. Statistical evidence that the ictal states themselves may be serially correlated has been ignored. However, inspection of sequences of durations of the interseizure interval (ISI) derived from clinical ECoG records of subjects with intractable epilepsy suggested that the time of seizure occurrence might depend on past behavior. This hypothesis was tested formally using concepts from nonlinear time series analysis: specifically, the method of analogues was used to make one-step forecasts of ISI and the prediction error compared with suitable surrogate data to test for significance.

Methods: ECoGs from 60 subjects with intractable epilepsy were screened and those with at least 40 visually verified automated electrographic seizure detections ($n = 24$; median number of seizures = 84.5; median recording length = 5.6 days; median seizure index = 18.6 day) were analyzed. Detections occurring within 60 s of one another were clustered. The ISI sequence (time between successive seizure onsets) was computed, differenced, delay-embedded (unit lag) and the method of analogues used to determine the embedding dimension that minimized the root-mean-squared prediction error (in-sample error, excluding the current sample) relative to the standard deviation of the data. The error was compared with that of 100 surrogate sequences generated by random permutation of the ISI sequence to test for serial correlation. A second set of linear surrogates (identical power spectrum but randomized phase compared to original sequence) was used to test for the null hypothesis of a linear stochastic process. The first test determines whether there is any serial correlation, and the second if the correlation cannot be described adequately by a linear autoregressive model.

Results: The null hypothesis (seizures are uncorrelated) was rejected ($p < 0.01$) for 17/24 subjects. The linear hypothesis was rejected for 14 of these ($p < 0.01$): in addition, eight of the 14 had a relative error <0.9 and prediction correlation coefficient >0.5. In about half of all cases, prediction error increased with lead-time until saturation.

Conclusions: These findings provide a reasonable case for predictability of seizures based on discrete observations alone. Assessment of the practical utility of these results is under way. (Supported by NINDS/NIH grant NS046060–01.)

2.280
EPILEPTIC FEATURES OF PATIENTS WITH MALFORMATIONS OF CORTICAL ORGANIZATION
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Rationale: Malformations of cortical development may present different epileptic features according to the type of the malformation. The objective of this study was to investigate clinical features of epilepsy in patients with malformations of cortical organization comparing the performance of patients with schizencephaly with patients with polymicrogyria.

Methods: We studied all patients with schizencephaly and polymicrogyria diagnosed by MRI in our University Hospital. The following data were assessed: presence of epilepsy, treatment with AED (monotherapy x polytherapy), seizure control, EEG abnormalities, and diagnosis of epileptic encephalopathy (mental retardation + uncontrolled seizures). Statistical analysis was performed using the chi-square and t-Student test.

Results: Forty-four patients with schizencephaly (GI) and 23 patients with polymicrogyria (GII) were studied. Age ranged from 1 to 75 years. Epilepsy was present in 26 patients of GI and in 8 of GII ($p = 0.058$); polytherapy was required in 13 patients of GI and in 4 patients of GII ($p = 1$); 3 patients of GI and 1 of GII had seizures controlled with AED ($p = 0{,}941$); EEG abnormalities occurred in 20 patients in GI and in 6 of GII ($p = 0{,}056$); epileptic encephalopathy was diagnosed in 9 patients of GI and in 3 of GII ($p = 0{,}881$).

Conclusions: Schizencephaly and polymicrogyria present similar epileptic features. This may occur because both entities belong to the same spectrum of malformations of cortical organization.

2.281
FACTORS ASSOCIATED WITH MEDICALLY REFRACTORY EPILEPSY AND MENTAL RETARDATION IN THE TUBEROUS SCLEROSIS COMPLEX
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Rationale: Tuberous sclerosis complex (TSC) is an autossomal dominant multisystemic disease. Seizure and mental retardation are prominent neurologic features. Epilepsy usually presents in the first year as epileptic spasms. Seizures are often refractory to medical treatment. Correlation between mental retardation and seizures are less clear. We studied factors associated with medical intractability of seizures and mental retardation in a case series of TSC patients.

Methods: Retrospective chart review of clinical, EEG and neuroimaging data of 33 cases with the diagnosis of TSC. Data analyzed included occurrence of epilepsy, age at epilepsy onset, seizure types and response to antiepileptic drugs. Cognitive performance was evaluated by interview and neurological exam.

Results: Epilepsy occurred in 90,9% of the patients. In 19/33 (63,3%) patients, epilepsy started before 1 year of age (group 1) and after 1 year of age in 11/33 (33,3%) (group 2); 3 patients did not present epilepsy. In group 1, epileptic spasms occurred in 47,4% of cases and focal seizures in 63,1%. In group 2, all patients presented focal seizures. Medically refractory epilepsy was observed more commonly in group 1 (63,1%) than group 2 (18,2%) ($p = 0{,}12$), in patients with more than one type of seizure than in patients with a single seizure type (71,4% vs 25%, $p = 0{,}12$) and in patients with epileptic abnormalities than in patients without epileptiform abnormalities on EEG (52,4% vs. 22,2% $p =$ NS). Mental retardation was seen more frequently in patients with medically refractory epilepsy than in patients without cognitive impairment (92,8% vs. 25% $p = 0{,}04$) and in patients with epileptiform discharges on EEG. (77,3% vs. 36,3% $p =$ NS)

Conclusions: In this series, epilepsy started more frequently during the first year of age. Mental retardation was associated with refractory epilepsy. Association between medical refractoriness and epilepsy onset before age one or occurrence of more than one seizure type should be evaluated in larger series.

Human Imaging–Adult 2

2.282
SEVERE HIPPOCAMPAL ATROPHY WITH MEMORY IMPAIRMENT AFTER STATUS EPILEPTICUS
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Rationale: Status epilepticus has been associated with focal neurological deficits, cognitive impairment and transient MRI abnormalities including changes on diffusion weighted imaging (DWI).

Rapid development of sever hippocampal atrophy after status epilepticus is however rare. We report a case of status epilepticus that was associated with development of severe bilateral hippocampal atrophy with profound memory impairment.

Methods: A case of status epilepticus in a 45 year old woman is reviewed with clinical, EEG, neuropsychological and radiographic correlation.

Results: A 45 year old woman with a history of epilepsy was admitted with complex partial status epilepticus after a single prolonged generalized tonic clonic seizure. EEG monitoring showed right temporal electrographic seizures. She was initially given lorazepam and loaded with phenytoin without resolution of the ictal pattern. Propofol infusion resulted in resolution of the seizures with transient appearance of independant right and left temporal periodic epileptiform discharges. High resolution MRI performed initially after stabilization showed bilateral mesial temporal high signal abnormality on DWI and T2 weighted imaging with no evidence of hippocampal atrophy. There was no clinical or laboratory evidence of an underlying infection, hypoxia or other causes of temporal lobe dysfunction. CSF examination was normal with a negative Herpes Simplex Virus (HSV) PCR.

Profound visual and verbal memory impairment was noted both on bedside and formal neuropsychological testing.

Repeat high resolution MRI performed two months after hospitilization showed resolution of changes on DWI but severe bilateral hippocampal atrophy (right greater than left) was noted.

Conclusions: This case is important as it demonstrates evidence of hippocampal injury associated with status epilepticus. The early diffusion weighted imaging changes and EEG localized the seizure focus to the mesial temporal region. The acute and severe memory impairment documented by neuropsychological assessment and severe atrophy on repeat MRI also supports the hypothesis that this change was a result of status epilepticus. Previous MRI performed four years earlier and one at the time of status epilepticus did not show any loss of hippocampal volume further supporting our conclusions.

In summary status epilepticus can lead to irreversible hippocampal damage and profound short term memory impairment. This finding may also have implications in development of abnormalities such as mesial temporal sclerosis in patients with epilepsy.

2.283
CEREBELLAR ATROPHY IN TEMPORAL LOBE EPILEPSY AFFECTS PROCEDURAL MEMORY
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Rationale: Cerebellar atrophy is a recognized complication of chronic epilepsy, including temporal lobe epilepsy (TLE). It has been shown that the cerbellum contributes to a variety of higher cognitive abilities, including specific types of memory. The neural circuitry underlying classical conditioning, a form of procedural memory, has been shown to be dependent on the cerebellum. The purpose of the current study was to determine if classical eyeblink conditioning, a cerebellum-dependent learning task, was affected by cerebellar atrophy in chronic epilepsy.

Methods: 77 TLE subjects (26 males, 51 females) and 59 healthy controls (26 males, 33 females) underwent classical eyeblink conditioning. consisting of pairing a conditioned stimulus (CS, headphone delivered 75 dB 1-kHz tone), with an unconditioned stimulus (UCS, a 5 psi air puff to left eye), that elicited the unconditioned response (UCR, an eyeblink measured by infrared photobeam). Quantitative volumetric processing

of MRI scans with manual tracing of the cerebellum was performed for a consecutive series of 49 TLE and 57 control subjects.

Results: Corrected cerebellar volumes (ICV) were significantly (3.8%) smaller in the TLE group compared to the controls ($p = .028$). Epilepsy patients exhibited significantly fewer conditioned responses on the classical conditioning task (59%) compared to controls (67.5%, $p = .045$). Among controls, the partial correlation (ICV as covariate) of cerebellar volume with classical eyeblink conditioning was significant ($r = 0.49$, $p = .005$). There was no association of classical conditioning performance with volumes of segmented (gray or white matter) total brain or lobar (temporal, frontal, parietal, occipital) tissue or total CSF volume (all p's ns). Among epilepsy subjects, the relationship between classical conditioning and cerebellar volume was disrupted with a non-significant correlation ($r = -.10$, $p = .52$), and there were no significant associations between classical conditioning and segemented volumes of segmented whole brain or lobar tissue volumes or CSF volume (all p's ns).

Conclusions: Compared to healthy controls, TLE patients exhibited significantly smaller cerebellar volumes and poorer classical eyeblink conditioning, a form of procedural learning. Among the controls there was a specific association between classical conditioning performance and cerebellar volume. In contrast, this unique structure-function relationship was disrupted and non-significant in patients with TLE. Further research into the cognitive consequences of volumetric abnormalities distant to the site of seizure onset may help to elucidate the consequences of these volumetric abnormalities on circuitry-specific cognitive abilities, leading to a better understanding of the etiology of the overall cognitive burden associated with TLE. (Supported by NIH NS 2-RO1 37738 and MO1 RR03186.)

2.284

MRI VOLUMETRY OF THE THALAMUS IN PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY

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Rationale: The objective of this study was to examine the thalamic volume in a large group of patients with juvenile myoclonic epilepsy (JME) using high resolution magnetic resonance imaging (MRI) and compare the results with a control group of healthy normal subjects.

Methods: All patients had JME diagnosis supported by clinical and EEG features according to ILAE recommendations. MRI images were acquired in a 2.0T scanner and a 3D T1 gradient echo sequence with 1 mm isotropic voxels was used for volumetry. Images were previously processed for field non-homogeneity correction and linear stereotaxic transformation into a standard space to reduce interindividual variation. Volumetry was performed with manual segmentation of the right and left thalamus using the software Display (BIC, Montreal Neurological Institute) which permits simultaneous visualization of the images in three different planes facilitating the identification of anatomic boundaries. Right and left thalamic volumes achieved of each patient were compared with ipsilateral volumes of 35 normal control subjects using Student's *t*-test. The relation between thalamic volumes with patients' age and duration of epilepsy was assessed using Pearson correlation test.

Results: We performed volumetry of 64 patients with JME. Thalamic volumes of patients with JME (mean z-score $\pm$ SD, right thalamus 0.83 ± 1.16 and left thalamus 0.83 ± 1.19) were larger in comparison with controls ($p < 0.001$). There was no correlation between thalamic volumes with patients' age and duration of epilepsy.

Conclusions: Our study shows, for the first time, an increased thalamic volume in a large group of patients with JME in comparison with normal controls. This finding supports the importance of this structure in the physiopathology of JME. (Supported by CAPES, FAPESP.)

2.285

DIFFUSION MRI IN EARLY POSTICTAL PERIOD OF FOCAL SEIZURES: COMPARISON WITH ICTAL SPECT

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Rationale: Detection of abnormalities in neuroimaging studies greatly enhance the chances of surgical success in patients with refractory epilepsy. We evaluated the use of diffusion MRI (DW) performed in the early postictal period (defined as less then 2 hours) after a focal seizure and to compare the findings with ictal SPECT.

Methods: We studied a consecutive series of patients who had a focal seizure documented by video-EEG monitoring, during which a 99nTc-ECD was injected to obtain ictal SPECT images. Before SPECT imaging, patients were taken to the MRI scanner, where whole brain (24 five milimeter slices) rapid DW acquisitions were obtained on a 1,5T Ge scanner (GE Medical Systems), with single shot echo planar sequences, using a 128×128 matrix, a TE = 114 and fov 26 cm. The sequence was applied in the three orthogonal planes, with a b+ 1000s/mm^2 in each direction. DW-MRI results were interpreted by three independent neuroradiologists. Results were compared with those of ictal SPECT, ictal EEG and structural brain MRI.

Results: Six consecutive patients with focal epilepsy were studied (4 symptomatic: hippocampal sclerosis in 2, tuberous sclerosis in 1, focal cortical dysplasia in 1 and cryptogenic in 2: frontal and temporal), with ages ranging from 7 to 55 years. DW-MRI was performed in all cases less than two hours after the video-EEG documented focal seizure, during which 99nTc-ECD was injected to obtain ictal SPECT. No abnormalities were seen on DW images in any of the cases. On the contrary, ictal SPECT showed increased flow, concordant with neuroimaging or ictal EEG in 5 cases, and, in the remaining case, increased blood flow was noted in the cerebellum, in the opposite side of the lesion.

Conclusions: This preliminary study did not detect abnormalities on DW-MRI performed in the early postictal period (less than two hours) of focal seizures, while ictal SPECT showed increased flow in all cases (regionalizing in 5 and lateralizing in the remaining case).

2.286

QUANTITATIVE MRI PROFILING OF FOCAL CORTICAL DYSPLASIA

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Rationale: On T1-weighted MRI, Taylor's focal cortical dysplasia (FCD) is characterized by a combination of increased cortical thickness, hyperintense signal within the dysplastic lesion relative to normal cortex and blurred transition between grey and white matter (GM/WM). The visual identification of these abnormal characteristics is difficult and it is unclear to which degree these features occur among different FCD lesions. Our purpose was to investigate the pattern of occurrence of abnormal MRI characteristics in FCD using a set of computational models.

Methods: We studied 32 patients with known FCD lesions and 39 sex- and age-matched healthy control subjects. A set of voxel-wise operators were applied to high-resolution 3-D T1-weighted MRI for each subject using our previous methods (Antel et al., 2002), creating maps of cortical thickness, a relative intensity operator (designed to emphasize areas with hyperintense signal) and gradient magnitude (modeling the GM/WM transition). FCD lesions were segmented manually on the MRI by an expert observer. For each patient, we computed the mean thickness and relative intensity in the GM component of the FCD lesion. The gradient was computed along the edges of the lesion at the GM/WM interface. For the controls, the computation of each feature was performed in brain areas corresponding to the distribution of FCD lesions. In controls, mean, inter-subject standard deviation (SD) and ranges were calculated for each feature. Values were also calculated in FCD patients, and a given feature was considered abnormal if its value fell outside the range mean $\pm$ 2SD.

Results: For each feature, mean, standard deviation and ranges are presented in the Table. In healthy controls, inter-subject variation was low for all three features (cortical thickness: 13%; relative intensity: 2%; gradient: 5%), indicating the high reliability of our measurements. Twenty-seven (84%) patients exhibited an increased cortical thickness, 27 (84%) an abnormal relative intensity and 30 (94%) a blurring of the GM/WM interface. All three features were abnormal in 22 (69%) patients, 8 (25%) had two abnormal features, and 2 (6%) had only one.

		Cortical Thickness (mm)	Relative Intensity (arbitrary units)	Gradient (arbitrary units)
Controls	Mean (±SD)	3.2 (±0.4)	79.4 (±1.3)	112.9 (±5.8)
	Range	2.3–4.1	76.7–82	101.4–124.5
Patients	Range	2.7–10.2	76.1–90.2	36.7–115.5

Conclusions: The majority of FCD lesions are characterized by increased cortical thickness, a hyperintense signal and a blurring of the GM/WM transition. However, there is considerable variability in the pattern of these abnormalities across patients, some FCD lesions being characterized only by one or two of these features. FCD lesion profiling may assist the development of strategies for their visual and automatic detection on MRI.

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2.287

PET WITH AN NK1-RECEPTOR ANTAGONIST IN TLE

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Rationale: Substance P (SP) is a neuropeptide that exerts its biological effect through binding to the neurokinin 1 (NK1) receptor. Substance P has been shown to facilitate glutaminergic excitatory synaptic transmission. In animal models, intrahippocampal injections of SP induce status epilepticus and histopathological damage resembling hippocampal sclerosis in man. This suggests that the activation of NK1- receptors could play a part in the generation of limbic seizures and related pathology.

The high affinity and selective NK1-receptor antagonist ^{11}C-GR205171 has been shown to be suitable for in vivo characterisation of NK1-receptor binding using positron emission tomography.

The aim of this study was to explore whether there is altered NK1 receptor distribution in patients with TLE using PET with ^{11}C-GR 205171.

Methods: We performed positron emission tomography (PET) with ^{11}C-GR205171 in five patients, all female, with TLE undergoing evaluation for epilepsy surgery. All patients had mesiotemporal sclerosis defined by MRI and seizure onset zone was confirmed with ictal video-EEG.

Summation images were obtained by adding together images acquired in the time interval 20–55 min after injection. In these images, regions of interest were manually generated to represent 15 different areas of the brain. All regions delineated sufficiently small to be representative for radioactivity concentration for respective region. Cerebellum was used as a reference region utilizing the Patlak graphical method. With this method, linear graphs were made suggesting slow dissociation from the binding site.

Transaxial and coronal images were made and analysed by visual inspection and manually drawn regions of interest. Contralateral homologous regions served as control and asymmetry index were calculated with the formula: $(R - L) * 200/(R + L)$.

Results: A substantial reduction of the binding of ^{11}C-GR 205171 was seen in the affected temporal lobe in two patients and in two patients there was an increased tracer uptake. In the fifth patient the result were ambiguous.

Conclusions: In this pilot study with PET with ^{11}C-GR 205171, an NK-receptor antagonist, no uniform uptake pattern of the tracer was seen. Further evaluation with a more refined methodology, including voxel-based statistical analysis may improve the accuracy of the method.

2.288

HIPPOCAMPAL ATROPHY IN PATIENTS WITH TEMPORAL LOBE EPILEPSY IS CORRELATED WITH VOLUME LOSS IN THE EXTENDED LIMBIC SYSTEM

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Rationale: To study to what extent hippocampal volume loss in patients with temporal lobe epilepsy (TLE) is associated with correlated loss in cortical gray matter amount throughout the entire brain.

Methods: In 16 patients with TLE and unilateral hippocampal sclerosis on T2-weighted images, hippocampal volumes were measured using manual segmentation. Furthermore, cortical 'local gray matter amount' (LGM) throughout the brain was estimated in each patient using voxel-based morphometry. Then, hippocampal volumes were correlated with whole-brain LGM of each patient. In order to improve statistical power, the LGM data of each patient were flipped such that hippocampal sclerosis was on the left in all patients.

Results: Hippocampal volumes correlated with LGM of the parahippocampal region, anterior and posterior cingulate, ventral striatum, basal and medial forebrain, anterior and mediodorsal thalamus and insula.

Conclusions: The degree of atrophy in the sclerotic hippocampus is not regionally limited but is accompanied by correlated loss of gray matter volume in the extended limbic system. Therefore, dysfunction of the sclerotic hippocampus can be expected to be accompanied by more widespread limbic system dysfunction. (Supported by Volkswagen foundation.)

2.289

MAGNETIZATION TRANSFER IMAGING IN PATIENTS WITH TEMPORAL LOBE EPILEPSY AND INTERICTAL PSYCHOSIS: EVIDENCE FOR INVOLVEMENT OF THE LEFT TEMPORAL LOBE

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Rationale: Interictal psychosis can be observed in about 4–10% of patients with epilepsy and is more commonly associated with temporal lobe epilepsy (TLE). Pathophysiological mechansisms of interictal psychosis are poorly understood. We aimed to examine neuropathological abnormalities in vivo in patients with interictal psychosis using Magnetization Transfer Imaging (MTI), a technique known to be more sensitive than conventional MRI in detecting subtle neuropathological changes.

Methods: MTI was performed in 20 TLE patients and interictal psychosis with either unilateral hippocampal sclerosis (HS—left HS: 6; right HS: 4) or no focal lesions on conventional MRI (normal MRI—10 patients). Twenty age-matched patients without psychosis (6 left HS, 4 right HS, 10 normal MRI) were investigated for comparisons. Magnetization Transfer Ratio (MTR) maps were created for each subject. These maps were then stereotactically normalised using a MTR template and compared as groups using SPM 2. In addition, each subject was tested neuropsychologically and test-scores were used for correlational analysis with MTR maps.

Results: Group analysis of the MTR maps revealed no significant differences comparing psychotic and non psychotic patients. We found significant reductions of MTR in the left middle temporal gyrus when comparing psychotic and non-psychotic patients with normal MRI. These abnormalities could not be attributed to volume reductions.Neuropsychological testing revealed significant differences in executive functions and semantic memory functions between the psychotic and the non psychotic patient groups. Correlation of test-scores with MTR in the psychotic group showed decreases of MTR in the left temporal lobe correlating with semantic memory functions.

Conclusions: Our findings suggest that there may be subtle neuropathological abnormalities in the left temporal cortex of patients with interictal psychosis that are undetectable on conventional MRI. These abnormalities appear to be functionally relevant as they are associated with impaired semantic memory functions (Supported by National Lottery, National Society for Epilepsy.)

2.290

ANALYSIS OF THE EEG-*f*MRI RESPONSE TO PROLONGED BURSTS OF INTERICTAL EPILEPTIFORM ACTIVITY

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Rationale: The measurement of EEG and fMRI is increasingly being used in the study of epilepsy, but the haemodynamic response to epileptiform activity remains incompletely characterised. In particular, it is not known whether the haemodynamic consequences of prolonged bursts of interictal spikes are equivalent to those of short bursts and to those provoked by normal brain function, or to what extent the assumptions of the general linear model (GLM), commonly used in fMRI studies, are upheld.

Methods: Fourteen patients were selected from a database of ninety-one patients on the basis that bursts of focal or generalised interictal epileptiform activity of different durations were observed on the scalp EEG recorded during fMRI scanning. Echo-planar fMRI images were acquired in one of two 1.5T MR scanners (Vision and Sonata, Siemens, Germany; voxels $5 \times 5 \times 5$ mm, 25 slices, TE = 50 ms, TR = 3 s, flip angle 90°). EEG data were recorded with an EMR32 amplifier (Schwarzer, Germany) and 21 Ag/AgCl electrodes.

Nineteen data sets underwent statistical analysis, as 5 patients had more than one type of spikes. To determine whether inclusion of the event durations in the model resulted in higher statistical values, two maps were created by either including or ignoring the event durations.

To test the assumptions of the GLM, a region of interest of five voxels was defined for each data set around the voxel with the highest t value from either of the two maps. The haemodynamic response functions (HRFs) for bursts of different durations (i.e. 0–1 seconds, 2–3 seconds etc) were estimated and their amplitudes and latencies compared with the expected values from the GLM.

Results: In fifteen data sets at least one cluster was significant in both maps and in thirteen there was a mean increase in t value when durations were included. The mean increase across all data sets was 14.5% in peak t value and 29.5% in volume when including the duration of the events.

There were some consistent differences between the amplitudes of the measured HRFs and the GLM. In eight data sets the HRF for events of 0–1 seconds could be reliably estimated and the measured response was always larger than predicted. In the two data sets with the widest range of event durations, the measured amplitude increased with event duration without the plateau that was expected from the GLM.

Conclusions: In the majority of data sets, the statistical significance of areas of activation increased when burst durations were included in the model. Analysing the fitted HRFs leads to some evidence of non-linearity, but is generally consistent with the observation that including the duration of the bursts leads to a more accurate model than considering each burst as an instantaneous event. (Supported by CIHR grant MOP 38079. C.G.B. was funded by a CIHR doctoral research award. E.K. was funded by a Preston Robb Fellowship from the MNI.)

2.291
LATERALIZATION OF THE AFFECTED HEMISPHERE BY SINGLE-VOXEL ^{1}H-MR SPECTROSCOPY IN MRI-NEGATIVE PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: We investigated the sensitivity of short echo time hippocampal ^{1}H-MR Spectroscopy in lateralization of the affected hemisphere in 15 MRI negative patients with temporal lobe epilepsy (TLE).

Methods: Patients without pathologic findings in high resolution MRI were consecutively scheduled for focus evaluation by intensive video EEG monitoring. In all patients with a temporal focus localization (n = 15) short term single voxel spectroscopy of temporomesial structures were carried out. Spectral analysis and metabolite quantitation of N-acetylaspartate (tNAA), Cholin (Cho), Creatin (Cr), total glutamate plus glutamine (Glu+Gln) and myo-Inosidol (Ins) in the hippocampus were carried out using LC-Model, using water as an internal reference. Normal ranges were established by the 95% confidence interval of age matched controls. The significance of the difference of metabolite means between the affected hemisphere of patients and normal values of controls were measured by unpaired students t-test. The correlation between the degree of metabolitealteration (z-scores) and the degree of seizure activity in EEG findings was estimated by Pearson coefficient.

Results: 6 patients were classified as unilateral by EEG investigations 4 of them with unilateral left hemiospheric focus and 2 of them unilateral right hemispheric focus. 9 patients showed a bilateral focus localization. 7 of 11 (9 bitemporal + 2 unilateral) patients with an EEG focus located in the right temporal lobe demonstrated significant NAA reduction in the right hippocampus while 10 of 13 (9 bitemporal + 4 unilateral) patients with an EEG focus located in the left temporal lobe demonstrated significant metabolite alterations in the left hippocampus. Additionally the degree of spectroscopic metabolite alterations was correlated to the degree of pathologic findings in interictual EEG activity. (Pearson coefficient: -0.709^{**} for absolute tNAA in the right hemisphere and -0.45 for absolute tNAA in the left hemisphere).

Conclusions: Our results show that, if optimized and standardized techniques are used, ^{1}H-MRS provides lateralizing information in MRI negative TLE patients which can be added to EEG findings in focus localization. Metabolite alterations correlated at high level of concordance between the degree of EEG abnormalities in the right hemisphere and at a moderate level in the left hemisphere. (Supported by Wilhelm Sander Foundation.)

2.292
LONGITUDINAL MRI VOLUMETRIC CHANGE IN TEMPORAL LOBE EPILEPSY

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Rationale: Among patients with temporal lobe epilepsy (TLE), volumetric abnormalities have been reported in a variety of extrahippocampal structures including the thalamus, basal ganglia and cerebellum. The degree to which these abnormalities represent progressive losses over time versus fixed and static anomalies remains to be determined. This 4-year prospective investigation followed a cohort of patients with temporal lobe epilepsy along with age and gender matched controls. The question of interest here is whether patients with TLE exhibit greater declines over time in volumes of the basal ganglia, thalamus, and cerebellum compared to contrrols.

Methods: To date, a total of 27 patients with TLE (mean age = 32.2 yrs) and 23 healthy controls (mean age = 33.4 yrs) have completed the follow-up procedures, including a follow-up MRI scan 4 years after their baseline evaluation. The TLE group suffered from chronic epilepsy (mean duration = 22.4 years). Quantitative MRI volumetrics were obtained for each subject. Measurement of the various regions of interest was performed using segmented image sets. These image sets were generated by sampling a large number of voxels from realigned and co-registered T1, T2 and PD images and were used as the basis for brain structure delineation.

Results: At baseline there were significant group differences in adjusted volumes (age, gender) of thalamus ($p = 0.03$) and cerebellum ($p = 0.002$), with a trend of reduced total basal ganglia volume ($p = 0.09$). Prospectively, there was no differential loss between groups in the volumes of the thalamus ($p = .57$) or basal ganglia ($p = .97$). In contrast, there was a different trajectory between the TLE and control groups in regard to change in cerebellar volume, with significantly greater volume reduction in the TLE group ($p = .02$).

Conclusions: TLE patients exhibited significant volumetric reductions in both the cerebellum and thalamus (with a similar trend for total basal ganglia volume) at baseline. These findings are consistent with previous reports indicating that that extra-temporal structures can be adversely affected in chronic TLE. Analyses of volumetric changes over time demonstrated significantly greater decline in cerebellar volume in chronic TLE patients over the 4-year interval. This differential change suggests that the cerebellum may be one structure that is adversely affected in a progressive fashion by chronic and unremitting TLE. [Supported by NIH NS RO1–37738 and MO1 RR03186 (GCRC).]

2.293
THE EFFECTS OF LAMOTRIGINE AND TOPIRAMATE ON CEREBRAL GLUCOSE METABOLISM

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Rationale: Antiepileptic drugs (AEDs) are known to have inhibitory effects on brain. To investigate the effects of lamotrigine and topiramate on cerebral metabolism, we performed 18F-fluorodeoxy glucose positron emission tomography (FDG-PET) in patients with new-onset epilepsy.

Methods: FDG-PET were performed two times (before and after AED medication) in 13 patients (Topiramate group, M/F = 9/4, 28.2±11.4 years) and 11 patients (Lamotrigine group, M/F = 5/6, 29.1±10.4 years). For SPM analysis, all PET images were spatially normalized to the standard PET template, then smoothed with 12-mm full width at half maximum gaussian kernel. The *paired t*-test was performed for comparison between pre- and post-AED PET images. The height threshold was set to false discoveryrate (FDR) corrected $P < 0.05$, and extent threshold was set to $K_E > 100$.

Results: SPM analysis between post- and pre-AED FDG-PETs in lamotrigine group showed hypometabolism in both inferior temporal gyri, left superior frontal gyrus, both superior parietal lobules, right hippocampus, left para hippocampal gyrus, left lingual gyrus, both putamens, both caudate nuclei, left thalamus, both hypothalamus, left midbrain (corrected $p < 0.05$)(Fig. 1) whereas that in topiramate group showed hypometabolism in both parietal lobules, left inferior posterior temporal gyrus, both superior anterior frontal gyri, left middle frontal gyrus, both midbrains, both caudate nuclei, both thalami, right cingulate gyrus, corpus callosum, and the white matters of both parietal lobes and right temporal lobe (corrected $p < 0.05$)(Fig. 2). There was no brain regions showing post-AED hypermetabolism.

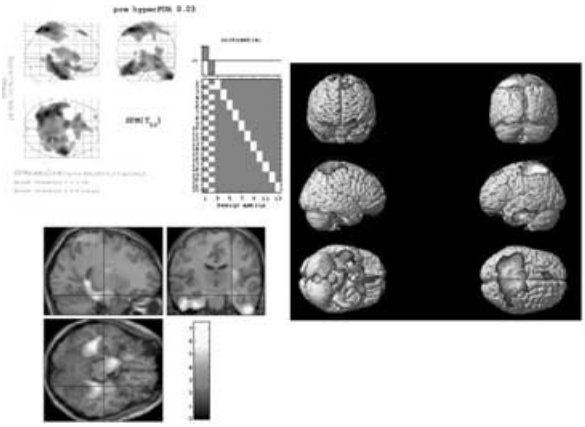

FIG. 1. Brain regions showing post-AED hypometabolism in lamotrigine group.

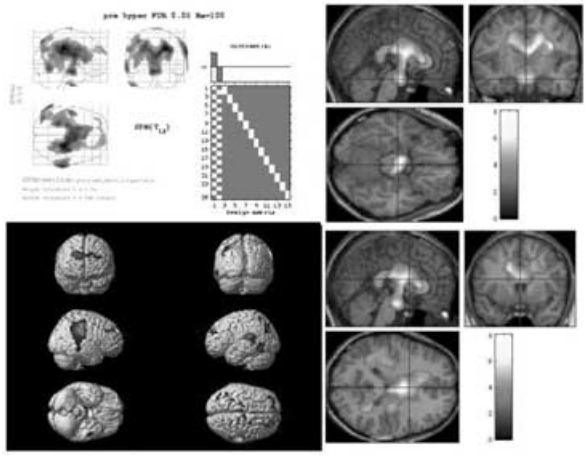

FIG. 2. Brain regions showing post-AED hypometabolism in topiramate group.

Conclusions: Lamotrigine decreased glucose metabolism more in cerebral cortex (both inferior temporal and parietal lobes), less in deep gray and white matters while topiramte decreased glucose metablism more in corpus callosum, thalamus, white matters and midbrain, less in cerebral cortex. (Supported by The NRL grant 2000-N-NC-01-C-163(2003) by the Korean Ministry of Science and Technology, and the grant A18-01-00 from the next-generation new technology development program of the Korean Ministry of Commerce, Industry and Energy.)

2.294
CLINICAL USEFULNESS OF SUBTRACTION IMAGES OF ICTAL-INTERICTAL SPECT USING STATISTICAL COUNT NORMALIZATION IN TEMPORAL LOBE EPILEPSY

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Rationale: For the subtraction of interictal from ictal SPECT coregistered to MRI (SISCOM), count normalization is an essential procedure and may affect the outcome of SISCOM. Although whole-brain activity is widely used to normalize the count of ictal and interictal SPCET, the statistical normalization method has been reported to be shown good results on various simulate images. We compared the sensitivity and usefulness of whole brain activity normalization (WN) SISCOM, statistical normalization (SN) SISCOM, and visual assessment of ictal and interictal SPECT images in the patients with unilateral temporal lobe epilepsy (TLE) to determine whether SN SISCOM method is more useful than WN SISCOM and visual analysis.

Methods: Twenty TLE patients (M/F = 10/10, age = 32 ± 7.7, right = 8, left = 12) with successful outcome after surgery were included in the study. Ictal and interictal SPECT was performed using Tc-99m ECD and triple head gamma camera. For SISCOM, the count normalization of ictal and interictal SPECT images was performed by both methods (WN and SN). While the count scaling factor of WN was obtained by the linear regression between ictal and interictal counts in the whole brain, that of SN was obtained by the linear regression of ictal and interictal voxels within one standard deviation of mean value in whole brain. Two reviewers, who were blinded to clinical data, assessed these three image sets (WN SISCOM, SN SISCOM, and ictal/interictal SPECT images) using three grading scale: good (possible localization); fair (possible lateralization); and bad (non-lateralization).

Results: SN SISCOM had good (45%) or fair (38%) in 16.5 (83%) of 20 patients, whereas WN SISCOM had good (35%) or fair (38%) in 14.5 (73%) patients and visual analysis showed good (50%) or fair (25%) in 15 (75%) patients. The concordance rates of two reviewers in SN SISCOM, WN SISCOM, and visual analysis were 85%, 85% and 45%, respectively. Diagnostic sensitivities of SN SISCOM, WN SISCOM, and visual analysis for the correct local/lateralization were 75% (15/20), 60% (12/20), and 40% (8/20), respectively. There were 2 (10%) false positives for the local/lateralization in all methods.

Conclusions: This study suggested that SISCOM is more sensitive and objective method than visual analysis of ictal/interictal SPECT to localize the epileptogenic area in TLE patients. SN method may improve the diagnostic sensitivity of SISCOM and make interpretation easier than WN method.

2.295
UTILITY OF MRI IN ADULT FIRST SEIZURE PATIENTS: DEVELOPMENT AND VALIDATION OF A CLINICAL ALGORITHM

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Rationale: Unlike in chronic epilepsy, the role of MRI in management of adult patients presenting with a first seizure is uncertain. No evidence is available to determine which patients should receive an MRI following a first epileptic seizure.

Methods: A clinical algorithm to determine which patients may gain benefit from MRI following a first seizure was developed based on findings in 105 consecutive adult patients from a hospital-based First Seizure Clinic. Data from a second First Seizure Clinic cohort, of 100 patients from a different hospital, was used to validate the predictive value of the algorithm.

Results: In the development cohort, MRI provided useful information additional to CT in 16.2% (17/105) of patients, identifying six lesions missed by CT, and clarifying the nature of the CT lesion in 11, including three CT lesions which were shown to be artifactual. Predictors of added value from MRI were (i) a CT showing a lesion that required clarification ($p < 0.001$), (ii) a partial or unclassifiable seizure type ($p = 0.001$), and (iii) a history of head-injury ($p = 0.011$). Based on these findings a clinical algorithm was proposed where MRI was only offered to patients with a CT lesion needing clarification, a partial or unclassifiable seizure type, or a history of head-injury. In the development cohort the algorithm had a sensitivity of 100%, and a specificity of 79.6%.

In the validation cohort, 9% (9/100) of patients gained additional value from MRI. When the algorithm was applied to the validation cohort, no patient not offered a MRI, would have gained value from this test. The algorithm had a sensitivity of 100%, and a specificity of 47.25%.

Conclusions: The results of this study identify subgroups of patients presenting following a first seizure in whom MRI has a high yield for adding value to CT and a group in whom the yield is low. This algorithm may be useful in clinical practice to guide selection of which patients should be referred for MRI.

2.296

EEG-*f*MRI RESPONSES IN PATIENTS WITH PERIVENTRICULAR NODULAR HETEROTOPIA

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Rationale: Periventricular nodular heterotopia (PNH) is a malformation of cortical development characterized by abnormal migration of neurons, which remain grouped in nodules around the ventricles. Scalp EEG findings in PNH patients are frequently related to the location of the nodules, which often show epileptogenicity, as demonstrated by recordings with depth electrodes. We investigated whether interictal scalp EEG abnormalities are associated with functional magnetic resonance imaging (fMRI) responses in the nodules or close cortical regions, using continuous EEG-fMRI.

Methods: Seven PNH patients underwent two-hours continuous EEG-fMRI monitoring with 21 MRI compatible scalp electrodes and amplifier. BOLD-EPI fMRI data were collected in runs of six minutes with the patient in the resting state. EEGs were filtered offline and spikes were marked according to spatial distribution and morphology. Maps of the t statistic (t-maps) were created using the timing of the spikes as events for fMRI analysis. At each voxel, the maximum t value was taken from t-maps created using four haemodynamic response functions with peaks at 3, 5, 7 and 9 seconds. BOLD-fMRI responses were defined as positive (activation) and negative (deactivation) for voxels which exceeded a corrected $p = 0.01$. We determined if the maximum t-value for activation and deactivation occurred in the nodules or in the cortical area corresponding to the region of the nodules.

Results: All patients showed spikes during EEG-fMRI, but one patient had only one spike, and was not analysed further. One patient had four types of spikes and therefore a total of nine studies were analysed. In 7/9 studies, the spike spatial distribution on the scalp was concordant with nodule location. Four studies showed fMRI activations and deactivations, one only activation and three only deactivations. Activation was found in 5/9 (55%) studies, and did not involve the nodules. Maximum activation was in the cortical area corresponding to the nodule in two patients and in a remote area in the other three. Deactivation was found in 7/9 (78%) studies and was also always outside the nodules. Maximum deactivation was in the cortical area corresponding to the nodule in three patients, in a remote cortical area in three studies and in the thalamus in one study.

Conclusions: EEG-fMRI responses in PNH patients were predominantly negative and not in the nodules. This may be due to the fact that we did not acquire fMRI data related to EEG abnormalities from inside the nodules. (Supported by grant MOP 38079 of the Canadian Institutes of Health Research. E.K. receives a Preston Robb fellowship from the Montreal Neurological Institute.)

2.297

AROMATASE INHIBITORS AS ADD-ON TREATMENT FOR MEN WITH EPILEPSY

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Rationale: Aromatase inhibition has been used to treat men with epilepsy who have decreased libido and sexual dysfunction, since it decreases circulating estradiol and increases testosterone. Estrogen in the brain is generally proconvulsant in animal models and testosterone is anticonvulsant when its' physiologic conversion to estradiol via aromatase is blocked. Therefore, we explored the possibility that aromatase inhibition could improve seizures in men with epilepsy as well.

Methods: In this pilot study, anastrazole was used in an open-label, add-on manner in men with intractable partial epilepsy after a 4 week prospective baseline. Two seizures per month was the minimum baseline rate to enroll in the study. Subjects meeting criteria then started the FDA-approved dose of 1 mg per day. The main outcome variable was seizure frequency over a 12 week treatment period compared to the 4 week baseline. Androgenic adverse effects, sexual functioning and libido were monitored using subject interview and the ASEX scale.

Results: Results are available for seven out of ten enrolled subjects. Six men have completed the study; four completed 12 weeks of treatment. Two of the six chose to discontinue prior to 12 weeks of treatment due to no seizure improvement, but not due to side effects.

The subjects' ages range from 26–51 years (median 40 years). Subjects took 1–3 standard AEDs throughout the study; one subject also had the VNS on during the study. Details of the seven subjects including seizure localization, initial monthly seizure count, and seizure and hormone changes on treatment are in the Table.

No subject had low baseline testosterone levels; initial testosterone levels ranged from 338–831 ng/dL (median = 414, mean = 506 ng/L) and tended to increase throughout the study (see Table 1 for percent increase). The greatest increases in FSH occurred in subjects with the greatest seizure reduction.

No change in AED levels or libido was found during anastrazole treatment compared to baseline. No CNS side effects were reported.

Conclusions: Add-on anastrazole in this open-label pilot study in men with intractable partial epilepsy produced seizure frequency decrease of clinically important magnitude in some subjects. Few side effects occurred and AED levels were not altered. Increases in FSH levels may be a marker for seizure improvement, indicating a favorable effect of aromatase-inhibition on CNS reproductive hormone levels. (Supported by AstraZeneca International.)

TABLE 1. *Effect of Anastrazole on Seizures and Hormones*

Pt #	Sz site	Baseline Sz Rate	% Sz Change	% TST increase	E2 Change	% FSH Increase	% LH Increase
1	R Frontal	59	decreased 34%	2%	3–27	63%	41%
2	R Ttemp	5	decreased 35%	35%	0–11	469%	14%
3	R+L Temp	2	decreased 100%	31%	8–25	119%	96%
4	L temp	7	decreased 47%	37%	4–26	71%	97%
5	Multifocal	32	increased 96%		1–5	35%	31%
6	L Parietal	2	increased 150%	65%	0–8	39%	−32%
7	L Frontal	7	decreased 14%	32%	4–32	11%	11%

E2 = estradiol in ng/dl.

2.298

GRAY-MATTER DEFICITS CORRELATE WITH SEIZURE DURATION IN MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

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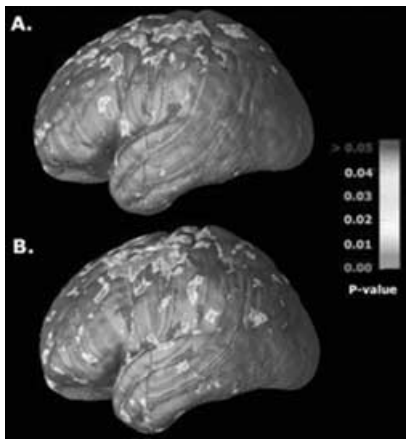
Rationale: There is emerging evidence that patients with mesial temporal lobe epilepsy (MTLE) and hippocampal sclerosis (HS) have structural abnormalities that extend beyond the hippocampus. We report on a quantitative volumetric MRI study of patients with pathologically confirmed HS. Gray and white matter deficits were correlated with clinical variables.

Methods: Quantitative volumetric analyses were performed on preoperative MRI brain scans of 15 left and 15 right MTLE (LMTLE/RMTLE) patients who underwent anteromesial temporal resection and have been seizure free for at least 2 years, and 20 age matched normal controls. MRI images were linearly registered to the International Consortium for Brain Mapping (ICBM) space. Tissue were classified into gray matter, white matter and cerebrospinal fluid. Lobar and whole hemisphere gray and white matter volumes were compared to normal controls. Regression analyses were performed to correlate tissue volumes with age, seizure duration, and history of febrile seizures.

Results: In LMTLE patients, a 35.6% average gray matter deficit was found in the left and a 34.6% average deficit in the right hemisphere (both $P < .0001$). In the RMTLE patients, a 39.4% gray matter deficit was found in the left and 40.4% in the right hemisphere (both $P < .0001$). There also was significant white matter loss in both MTLE groups with maximal deficit in the frontal and temporal lobes. Regression analysis showed that the age of the patient and duration of seizures were negatively correlated with gray matter volume ipsilateral ($P < .04$) and contralateral ($P < .05$) to the side of seizure onset. A history of febrile seizures did not correlate with tissue volumes. When data from the affected hemispheres of both MTLE groups were pooled, cortical gray matter deficits in superior frontal regions correlated significantly with seizure duration ($P < .05$, permutation test) (Fig. 1).

Conclusions: Quantitative volumetric analysis of MTLE with HS showed widespread deficits in gray and white matter. Gray matter loss in superior frontal regions correlated with age and duration of seizures. This suggests MTLE may be a progressive disease involving multiple specific brain regions outside of the temporal lobe.



(Supported by Epilepsy Foundation and National Epifellows Foundation.)

FIG. 1. Superior frontal gray matter deflict correlates with duration of illness (N = 30). (A: Ipsilateral Map, B: Contralateral Map)

2.299

STATISTICAL PARAMETRIC MAPPING OF 5-HT_{1A} RECEPTOR BINDING IN MESIAL TEMPORAL LOBE EPILEPSY (MTLE)

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Rationale: Experimental data in animals show that 5-HT_{1A} receptors are predominantly located in limbic areas and suggest that serotonin, via these receptors, mediates an antiepileptic and anticonvulsant effect. In this PET study we used an antagonist of the 5-HT_{1A} receptor, [18F]MPPF, to assess the extent of 5-HT_{1A} receptors binding changes in a group of seven temporal lobe epilepsy (TLE) patients with hippocampal ictal onset demonstrated by intracerebral EEG recording.

Methods: On the basis of MRI-measured hippocampal volumes (HV) patients were classified into "normal HV" or "hippocampal atrophy" (HA). Voxel-based analyses (SPM99) were performed to objectively assess the differences in [18F]MPPF binding potential (BP) between patients (taken as a group or as individuals) and a database of 48 controls subjects.

Results: In the full group of patients, a significant decreased BP was detected ipsilateral to the epileptogenic zone in the hippocampus, temporal pole, insula and temporal neocortex. This result was confirmed in the subgroup of patients with HA. In patients with normal HV, the BP decrease was restricted to the temporal pole. TLE patients also demonstrated an increased BP in various regions contralateral to the epileptogenic zone.

Conclusions: These data suggest that in TLE patients with hippocampal seizure onset, the decrease in 5-HT_{1A} receptor binding partly reflects hippocampal neuronal loss, but is also observed in various regions involved in temporo-limbic epileptogenic networks which appeared normal on MRI. Further studies are warranted to evaluate the clinical usefulness of [18F]MPPF-PET, as compared to other established PET tracers in drug resistant TLE. [Supported by Claude Bernard University of Lyon (BQR, 2001).]

2.300

^{1}H MRSI SHOWS DIFFERENT PATTERNS OF METABOLIC HIPPOCAMPAL DAMAGE IN TEMPORAL LOBE AND NEOCORTICAL EPILEPSY

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Rationale: Hippocampal metabolic abnormalities (HMA) as detected by MR spectroscopic imaging (MRSI) not only can be found in different forms of temporal lobe epilepsy (TLE), i.e., with and without hippocampal sclerosis, but also in neocortical epilepsies (NE). The aim of this study was to learn more about the specific characteristics of HMA in TLE and NE by determining differences regarding severity, frequency of bilateral damage, concordance with EEG lateralization, and extent of HMA between these 3 patient groups.

Methods: 41 patients with partial epilepsy (16 with NE, 15 with TLE with medial temporal sclerosis (TLE-MTS), and 10 with TLE and normal MRI (TLE-No)) and 16 controls were studied with hippocampal 2D MRSI (TR/TE: 1800/135 ms). In the control and patient groups 12 voxels were uniformly chosen in each hippocampus. Voxels with NAA/(Cr+Cho)$\leq$(Meancontrols–2SDcontrols) were defined as pathological voxels (PV). HMA were classified according to severity (number of PV in both hippocampi), bilaterality (presence of PV in both hippocampi), concordance with EEG (higher number of PV in ipsilateral hippocampus) and extent (restricted: PV adjacent; diffuse: PV non adjacent). Statistical analysis was done by U-tests.

Results: HMA were found in 73% of TLE-MTS, 50% of TLE-no and 63% of NE. In TLE-MTS, HMA was significantly more restricted ($p = 0.007$) and concordant with EEG lateralization ($p = 0.016$) than in TLE-no in whom it was often bilateral and non-concordant. HMA in NE differed from TLE-MTS by being more often diffuse ($p = 0.036$) and from TLE-no by being more often unilateral ($p = 0.038$) and concordant with EEG lateralization ($p = 0.046$).

Conclusions: HMA had distinct characteristics in each of the 3 groups which very likely reflect differences of hippocampal neuronal

loss/dysfunction in these groups. In patients with TLE-MTS the pattern is consistent with the hippocampus being the seizure origin. The fact that HMA in TLE-no and NE in comparison to TLE-MTS were more often diffuse, i.e., not restricted, bilateral or not concordant with EEG lateralization, might either indicate a secondary involvement of the hippocampal formation (NE) or a seizure onset zone not restricted to the hippocampus (TLE-no). (Supported by NIH grant ROI-NS31966 to K.D.L.)

2.301
MRI FINDINGS IN PARTIAL STATUS EPILEPTICUS
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Rationale: MRI changes in partial status epilepticus (PSE) have been previously reported and include increased signal changes in the hippocampus or the neocortex on T2 weighted imaging.

Human and animal studies of PSE indicated that these changes are related to increased local cerebral blood flow and cytotoxic edema.

We studied acute MRI changes following partial status epilepticus and late follow-up MRI findings.

Methods: Six consecutive patients with simple partial and complex partial status epilepticus documented by EEG were identified

Brain MRI using a 1.5 T Seimens or GE consisting of fluid attenuated inversion recovery (FLAIR); T1 weighted SPGR and T2 spin echo images were obtained within 24–48 hours of status epilepticus. A follow-up MRI was available in 4/6 patients.

Results: Two patients had increased signal changes on FLAIR MRI involving the grey matter in a gyriform pattern without involvement of the white matter (superior frontal gyrus and peri-central gyri). Four patients had increased signal within the hippocampus without involvement of adjacent peri-hippocampal structures. In 3/4 of the patients without hippocampal MRI signal changes, seizure onset was extra-temporal with secondary temporal propagation. On follow-up MRI 2/2 patients had resolution of neocortical signal changes without atrophy. In 2/2 patients with follow-up MRI had resolution of hippocampal increased signal. However, one patient developed hippocampal atrophy.

Conclusions: MRI findings following partial status epilepticus consist of gyriform increased signal intensity or hippocampal increased signal intensity that resolves on follow-up MRI.

Furthermore, hippocampal increased signal occurs with partial status epilepticus of extra-temporal origin with secondary temporal propagation, and can lead to hippocampal atrophy in some cases.

2.302
REORGANISATION OF VERBAL AND NONVERBAL MEMORY IN UNILATERAL TEMPORAL LOBE EPILEPSY: AN EVENT-RELATED STUDY
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Rationale: Mesial temporal lobe (MTL) structures are important for episodic memory. Lesional studies have suggested a dissociation in function between left hippocampus subserving verbal memory, and right hippocampus subserving non-verbal memory.

Lateralization and localisation of both verbal and non-verbal memory function would be useful for the prediction of memory deficits following anterior temporal lobe resection. We describe here the findings from a memory encoding experiment in patients with both left and right mesial temporal lobe epilepsy (MTLE) due to unilateral hippocampal sclerosis, compared to controls.

Methods: We studied 10 right-handed healthy volunteers, 7 patients with left MTLE and 7 patients with right MTLE using a novel event-related memory encoding paradigm.

A total of 210 stimuli of three different types (pictures (P), words (W) and faces(F)) were presented during a single scanning session. Subjects were instructed to decide whether they found each stimulus pleasant or unpleasant.

Recognition tests were performed 60 min after scanning for each of the stimulus types. 210 stimuli presented during scanning were randomly mixed with 105 foils. Subjects were instructed to indicate whether they could remember seeing each word during scanning (R response) or whether it was new (N response).

Data was analysed using SPM2. An event-related design was employed and contrasts of parameter estimates were calculated to produce 3 contrast images for each subject (PR-minus-PN, WR-minus-WN and FR-minus-WN). A second level random effects analysis was used to look at the group effects ($p < 0.001$ uncorrected unless stated otherwise).

Results: The control group showed activations in the left MTL associated with memory for words, bilateral MTL for pictures, and right MTL for faces.

Patients with left MTLE showed decreased left sided MTL activation associated with memory for words compared to the control group and right MTLE patients($p < 0.01$ uncorrected). Compared to controls, left MTLE patients showed increased activation in the right MTL ($p < 0.05$ uncorrected).

Patients with right mTLE showed decreased activation in the right MTL in association with memory for faces compared to left mTLE patients ($p < 0.01$ uncorrected). Compared to controls, patients with right mTLE showed reduced activations in the right fusiform gyrus associated with memory for faces ($p < 0.01$ uncorrected).

Conclusions: We demonstrated that the normal pattern of material-specific lateralization of encoding activation in the MTL is affected by unilateral hippocampal pathology with reorganisation of encoding processes to the contralateral MTL.

We hypothesize that the lateralized activation patterns demonstrated here could be used in the prediction of memory deficits seen following anterior temporal lobe resection. (Supported by Wellcome Trust, National Society for Epilepsy.)

2.303
THE EFFECTS OF PREEXPOSURE TO PROBE ITEMS DURING AUTOBIOGRAPHIC MEMORY RETRIEVAL: AN *f*MRI STUDY OF THE HIPPOCAMPAL RESPONSE
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Rationale: Traditional memory theory argues that the role of the hippocampus in the processing of autobiographic information is time-limited. That is to say, the retrieval of personal events becomes independent of the structure once memories have been integrated into neocortical stores. However, the fMRI evidence pertaining to this effect is inconsistent. The prevalent use of pre-scan interviews might be to blame, which are typically used to procure autobiographic information from each participant prior to scanning. As a consequence, memories are refreshed during this process and could alter subsequent brain activity during in-magnet retrieval. To explore this issue, we constructed an autobiographic memory recall test that did not require a pre-scan interview, but relied on a list of common life experiences (e.g., a job held in high school). Subjects were scanned twice, one-month apart, with the same set of memory probes, in order to evaluate the effect of prior reflection on retrieval activation.

Methods: Twelve, right-handed participants (18–29 years of age) were recruited from the Yale University campus and scanned at 3 Tesla using gradient-echo planar imaging. The images were acquired on the coronal-oblique plane perpendicular to the hippocampus.

Results: Behavioral testing revealed that the quality of recall (i.e., vividness, level of detail) did not significantly differ across test sessions. The overall pattern of neural activity was also very similar across sessions, although the magnitude of the response was significantly more pronounced for the initial scan. Subtractions between sessions showed significantly more positive activation for scan one, relative to scan two, within the prefrontal cortex, inferior temporal gyrus, inferior parietal lobule, thalamus, and cerebellum ($p < .02$). Although this subtraction did not show a significant difference in BOLD intensity within the hippocampus proper, the strength of hippocampal activation relative to baseline was considerably more robust for scan one than scan two.

Conclusions: The study demonstrates that recent consideration of autobiographic events weakens the strength of the neural response during subsequent retrieval. While the reason for this effect is unclear, it is possible that participants may not engage in a new memory search during scanning, but rely on their previous (pre-scan interview) recollections of these events. These findings should discourage the use of pre-scan

interviews as they complicate the interpretation of the data and can provide false support for traditional consolidation theory. (Supported by NIH: NS38467 NS40497.)

2.304
[^{11}C]-METHIONINE PET HELPS DISTINGUISH DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMORS FROM OTHER EPILEPTOGENIC BRAIN TUMORS

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Rationale: Brain tumors responsible for long standing partial epilepsy are characterized by a high prevalence of dysembryoplastic neuroepithelial tumor (DNT), which natural evolution is much more benign than that of gliomas. The pre-operative diagnosis of DNT, which is not yet feasible based on available clinical and imaging data, would help optimizing the therapeutic strategy in this type of tumor. In this study, we have tested whether [^{11}C]-Methionine Positron Emission Tomography (MET-PET) could distinguish DNTs from other epileptogenic brain tumors.

Methods: MET-PET examination was performed in 27 patients with a partial epilepsy of at least six months duration related to a non rapidly progressing brain tumor on MRI. Pathological data were 11 DNTs (41%), 5 gangliogliomas (18%) and 11 gliomas (41%) including 7 low grade (1 pilocytic astrocytoma, 1 pleomorphic xanthoastrocytoma, 3 oligodendrogliomas grade II, 2 oligoastrocytomas grade II) and 4 high grade gliomas (1 astrocytoma grade III, 3 oligodendrogliomas grade III). Visual comparison of methionine uptake between DNT, Gangliogliomas and Gliomas were performed using a chi-2 test. In 25 patients, we also calculated the ratios between 5 mm diameter ROIs placed on the tumor portion dysplaying the highest [^{11}C]-Methionine uptake activity and the controlateral homotopic cortical region (Max AR = Maximal Asymetry Ratio) or the controlateral occipital cortex (OR = Occipital Ratio). Statistical analysis of these semi-quantitative data used a one factor ANOVA.

Results: MET-PET visual findings significantly differ between the various tumor types ($p < 0.0002$), regardless of gadolinium enhancement on MRI, and were confirmed by semi-quantitative analysis ($p < 0.001$ for all calculated ratios). Visually, all gliomas and gangliogliomas were associated with moderate or marked increased tumor methionine uptake, whereas 63% of DNT had a normal methionine uptake, including 100% of those located in the mesio-temporal structures ($n = 6$). No DNT presented with a marked MET-PET abnormality. On semi-quantitative analysis, post-hoc tests showed that DNTs methionine uptake remained significantly different than gangliogliomas (Max AR: $p < 0.005$) and gliomas, even after excluding the four high grade gliomas (Max AR: $p < 0.0001$; OR: $p < 0.0001$).

Conclusions: A normal MET-PET in patient with an epileptogenic and non-rapidly progressing brain tumor is highly suggestive of DNT, whereas a marked increased tumor methionine uptake makes this diagnosis very unlikely. MET-PET appears to be clinically useful in the management of epileptogenic brain tumors.

2.305
ADVANCED MAGNETIC RESONANCE IMAGING TECHNIQUES DEMONSTRATE OCCULT ABNORMALITIES IN FOCAL EPILEPSY

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Rationale: Visual assessment of conventional magnetic resonance imaging (MRI) fails to reveal structural abnormality in 20% of patients with intractable focal epilepsy. Surgical management of these MRI negative patients is often associated with poor outcome. Magnetization transfer imaging (MTR), fast flair T2 (FFT2) and double inversion recovery (DIR) are new imaging techniques that detect developmental and acquired cerebral lesions in epilepsy patients. We investigated whether MTR, FFT2 and DIR can identify abnormalities in patients with focal epilepsy and normal conventional MRI.

Methods: One hundred and two patients with focal epilepsy and normal conventional MRI were scanned with MTR, FFT2 and DIR using a 1.5T scanner. All patients had scalp ictal video-EEG telemetry recordings to localize the onset of epileptiform activity. Statistical parametric mapping was used to compare the images of each individual patient to a template created from the images of 30 controls.

Results: Altogether 40% of the patients had MTR signal abnormalities. T2 and DIR showed signal changes in 58% of the patients. FFT2 and MTR signal abnormalities co-localized in 48%. MTR and DIR findings were concordant in 58%, and DIR and FFT2 in 67% of the patients.

In temporal lobe epilepsy patients FFT2 was abnormal in the temporal lobe (TL) in 36%, DIR in 23% and MTR in 9%, and was confined to the TL ipsilateral to the EEG focus in 19% (FFT2), 13% (DIR) and 2% (MTR).

In frontal lobe epilepsy patients FFT2 was abnormal in the frontal lobe (FL) in 40%, DIR in 43% and MTR in 8%, and was confined to the FL ipsilateral to the EEG focus in 8% (FFT2), 15% (DIR) and 8% (MTR).

Signal changes outside of the presumed lobe of onset were also found in 34% (FFT2), 41% (DIR) and 22% (MTR) of all patients.

Conclusions: Advanced MRI with MTR, FFT2 and DIR reveals areas of signal change suggesting underlying structural damage in patients with focal epilepsy and normal conventional MRI. The successful identification of a focus aids the assessment of possible surgical treatment in these patients. (Supported by Academy of Finland, Action Medical Research.)

2.306
INTERICTAL EPILEPTIFORM DISCHARGES AND ICTAL HYPERPERFUSION: ICTAL-INTERICTAL SPECT SUBTRACTION

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Rationale: Severeal studies reported that there are some differences of ictal EEG, clinical semiology, and lateralization of ictal SPECT between patients with unilateral vs. bilateral interictal spikes in mesial temporal lobe epilepsy (TLE). To investigate the relationship between interictal epileptiform discharges (IED) vs. patterns of ictal hyperperfusion, we performed ictal-interictal SPECT subtraction in 54 patients with mesial TLE.

Methods: The patients were divided into three groups: 1. patients with no IEDs during a long-term EEG monitoring (NIED group), 2. patients with $\geq$90% of IEDs occurring in one side of temporal lobes (UIED groups), 3. patients with $\leq$ 90% of IEDs occurring in one side of temporal lobes (BIED group).

Results: All patients showed ictal hyperperfusion in ipsilateral temporal lobe to the seizure origin. In NIED group ($N = 7$), all patients showed ictal hyperperfusion in anterior and mesial regions of the ipsilateral temporal lobe, and four had ipsilateral insular hyperperfusion. In UIED group ($N = 27$), 12 patients (44.4%) showed small and subtle hyperperfusion in contralateral mesial temporal area, 14 (51.9%) had insular hyperperfusion of epileptic side and 12 (44.4%) showed ipsilateral basal ganglia hyperperfusion. In BIED group ($N = 21$), 18 patients (85.7%) showed bilateral temporal hyperperfusion with ipsilateral predominance and there were multiple hyperperfusion areas in ipsilateral and contralateral frontal lobes and basal ganglia.

Conclusions: The patterns of ictal hyperperfusion suggests that seizures of NIED or UIED groups are more localized while seizures of BIED group are more likely to spread to basal ganglia and frontal lobes, and contralateral temporal lobe.

2.307
LOCALIZING VALUE OF MRI AND SPECT IN POSTTRAUMATIC EPILEPSY

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Rationale: Surgical outcome for patients with refractory partial epilepsy secondary to head trauma has been previously reported to be less favorable when compared to other risk factors. Localization of an epileptogenic zone for focal resection in this population has been postulated to be difficult because of the diffuse nature of the initial brain injury and the potential for multiple sites of epileptogenicity. This study analyzes the localizing value of MRI and SPECT when determining surgical candidacy in this population.

Methods: All patients in whom head injury (HI) was the sole risk factor for refractory partial epilepsy and who underwent epilepsy surgery at Henry Ford Hospital between 6/93 and 12/02 were identified. Patients were stratified into two subgroups: mild/moderate head injury (<30 minutes alteration in consciousness), and severe head trauma (>30 minutes alteration in consciousness). To determine accuracy of MRI, ictal SPECT, and interictal SPECT, only patients with well localized intracranial ictal patterns and Class I or Class II surgical outcomes were included in the final analysis. Localizing accuracy of imaging studies was based on determining concordance of imaging abnormalities with either the focal ictal onset identified by intracranial recording, and/or the focal resection.

Results: MRI abnormalities (gliosis, obvious atrophy, or encephalomalacia) either matched or overlapped the epileptogenic zone in 13/25 (52%) of patients. Accuracy of MRI was 46% in patients with mild/moderate head injury, and 60% in patients with severe head injury. Ictal SPECT showed an area of hyperperfusion in the region of the epileptogenic zone when compared to the interictal SPECT in 14/16 (87.5%) patients. Both incorrect studies were in patients with severe head injury. Interictal SPECT demonstrated a region of hypoperfusion matching the epileptogenic zone in 14/23 (61%) of subjects. Accuracy of interictal SPECT was 87% in severe HI, and 38% in mild/moderate HI.

Conclusions: Although MRI and interictal SPECT studies in refractory posttraumatic epilepsy patients may show abnormalities concordant with the epileptogenic zone, localizing value may be limited or incorrect in some cases due to the multiplicity of the abnormalities. The maximum area of brain unjury determined by neuroimaging, or by reported neurologic deficits at the time of injury, may not correlate with the epileptogenic zone.

2.308

LONG-TERM SEIZURE FREEDOM IN PATIENTS WITH PARTIAL SEIZURES TREATED WITH ADD-ON PREGABALIN: AN ANALYSIS OF FOUR, LONG-TERM, OPEN-LABEL TRIALS

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Rationale: Pregabalin has anticonvulsant, analgesic, and anxiolytic effects. It is a potent ligand for the $alpha_2$-delta subunit of voltage-gated calcium channels. Results from clinical trials demonstrate robust efficacy for pregabalin used as add-on therapy for partial seizures.

Methods: 1480 patients entered four, long-term, open-label, add-on trials, 968 from double-blind, randomized, placebo-controlled trials and 512 *de novo* patients. Pregabalin, up to 600 mg/day, was taken BID or TID. Daily seizure frequency was recorded in patient diaries.

Results: At the data cut-off, 77.2% and 59.4% of patients were exposed to pregabalin for at least 24 and 52 weeks, respectively, with a maximum of 1989 days. 68.9% of pregabalin exposure was at doses of 450 mg/day or greater. Approximately 69% of patients were taking at least two other AEDs at screening. At the data cut-off, the mean number of seizure-free days per 28 days of treatment was 21.5 days, representing a mean 41.3% improvement compared with baseline. In total, 7.9% (88/1119) of patients were seizure-free over their last 6 months of pregabalin treatment, and 5.9% (52/877) were seizure-free over the last year. Across the four studies, the proportions of patients who were seizure free ranged from 7.4% to 24.2% and from 4.5% to 18.4% over the last 6 months and 1 year, respectively. Examined by quarter over the first four years of the studies, the weighted mean dose remained in the range of approximately 450–500 mg/day. At the data cut-off, 13% had discontinued the study due to adverse events. Pregabalin was well tolerated, and no new concerns were identified with long-term treatment.

Conclusions: The proportions of patients free of seizures with long-term treatment further supports the robust and sustained efficacy of pregabalin in patients who had very poor control of seizures before initiating pregabalin treatment. (Supported by Pfizer, Inc.)

2.309

VOXEL-BASED MORPHOMETRY (VBM) WITH HIGH-CONTRAST MRI COMPARED WITH NORMAL MRI: A METHODICAL STUDY

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Rationale: Voxel based morphometry (VBM) is a statistical automated approach to evaluate brain pathology in group comparisons. In epilepsy, it has detected various brain pathologies exceeding the visual detected pathology. The aim was to evaluate a high contrast MRI sequence (hcontMRI) with an increased signal to noise ratio compared to conventional MRI (convMRI) in VBM.

Methods: 6 patients with histologically proofed Ammon's Horn Sclerosis (AHS) and temporal lobe epilepsy (TLE) and 12 age matched normal controls. HcontMRI sequence included a four-fold average. All patients and controls were scanned with both sequences. VBM was performed with an individual created template separately for both MRI sequences. We compared different smoothing kernels as well as different significance levels, with respect to voxel threshold and cluster size. Conditions for significance and specificity to detect AHS were defined.

Results: HcontMRI VBM showed with smoothing kernels of 3 to 5 mm results, which met both criteria sensitivity and specificity. All significant voxels were within the ipsilateral hippocampus. ConvMRI VBM showed significant voxels in various smoothing steps, mostly between 6 and 9 mm smoothing but never met both criteria sensitivity and specificity.

Conclusions: HcontMRI enhances the statistical significance of VBM and increases spatial resolution as smoothing of 3 to 5 mm showed best significant results.

2.310

FUNCTIONAL MRI PREDICTS MEMORY PERFORMANCE AFTER EPILEPSY SURGERY

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Rationale: The validation and clinical usefulness of fMRI will depend on the method's ability to predict postoperative outcome, i.e. morbidity. We aimed to investigate whether presurgical memory-fMRI is able to predict postoperative memory loss after anterior temporal lobectomy (ATL) in right sided mesial temporal lobe epilepsy (MTLE).

Methods: We included 16 medically intractable MTLE patients, who had a presurgical evaluation including continuous video-EEG monitoring, an epileptogenic lesion in the right hippocampal formation proven by high-resolution MRI, and consecutive ATL. The activation condition during the memory-fMRI (1.5 T, coronal EPI, voxel dimensions 3.0x3.0x5.0 mm3) consisted of covert retrieval from long-term memory induced by self-paced performance of Roland's Hometown Walking task, an imaginative walk through the patient's hometown (Jokeit et al. *Neurology* 2001; 57:1786–93). To perform group data analysis, two investigators blinded to clinical data counted the voxels in a predefined region of interest over both mesiotemporal areas. Outside the scanner, we evaluated visual memory retention using Rey Visual Design Learning Test preoperatively and 6 months postoperatively.

Results: We found a correlation between the preoperative asymmetry index on memory-fMRI and the change between pre- and postsurgical measures of memory retention by using the Spearman rank correlation test ($R = 0.71$, $p = 0.002$). Reduced activation of the mesiotemporal region ipsilateral to the epileptogenic region correlated with a favourable memory outcome after right-sided ATL.

Conclusions: Reduced activation of the mesiotemporal region ipsilateral to the epileptogenic region correlated with favourable non-verbal memory outcome after right sided ATL. Conclusively, memory-fMRI was found to be sensitive to material-specific memory decline after right sided ATL in which the Wada test is usually inconclusive. We suggest

that memory-fMRI might replace the invasive Wada test in right sided MTLE using a simple fMRI paradigm.

Human Imaging–Pediatric

2.311
THALAMIC AND HIPPOCAMPAL DIFFUSION TENSOR IMAGING (DTI) ABNORMALITIES IN CHILDREN WITH TEMPORAL LOBE EPILEPSY

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Rationale: Subcortical structures, especially thalamus, are considered important for the regulation of cortical excitability and seizure propagation in human epilepsy. Previous studies in temporal lobe epilepsy showed abnormalities of water diffusion in the hippocampus. The purpose of this study was to analyze diffusion tensor imaging (DTI) abnormalities in subcortical structures and hippocampus of children with partial epilepsy of temporal lobe origin with (N = 7) and without (N = 7) secondary generalization.

Methods: Fourteen children with unilateral temporal lobe epilepsy underwent MRI including DTI and EEG monitoring. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were obtained in thalamus, lentiform nucleus, and hippocampus. In addition, 10 of the patients had glucose PET scans and nine patients had volumetric MR images performed. For these patients, glucose metabolism and volumes were also analyzed in these three structures.

Results: ADC and FA in the thalamus ipsilateral to the epileptic focus showed significantly higher values than on the contralateral side in patients with secondary generalized seizures ($p = 0.015$ and 0.006, respectively; paired t-test), but not in those with partial seizures only ($p = 0.06$ and $p = 0.26$, respectively). Increased ADC and decreased FA values were observed in the hippocampus ipsilateral to the seizure focus when the entire group (N = 14) was analyzed ($p = 0.03$ and $p = 0.02$, respectively). No significant side differences of ADC or FA were found in the lentiform nuclei. In glucose metabolism measurements, only thalamus showed lower glucose metabolism on the side of epileptic focus. No significant group asymmetries were found in volumetric measurements.

Conclusions: These results demonstrate differential changes of ADC in the hippocampus and thalamus ipsilateral to the seizure focus of children with temporal lobe epilepsy. Increased ADC and decreased FA in hippocampus ipsilateral to the seizure focus have been described previously in adults with temporal lobe epilepsy. Increased thalamic ADC and FA ipsilateral to the focus in patients with secondary generalized seizures is a new finding suggesting secondary involvement of the thalamus, perhaps due to recruitment of this structure into the epileptic network, as shown in animal studies. DTI is a sensitive method to detect such remote abnormalities even in cases in which no structural changes are apparent on conventional MRI.

2.312
THE ROLE OF ICTAL SPECT IN NON-LESIONAL EPILEPSY SURGERY IN CHILDREN

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Rationale: Excisional surgery is challenging in children with medically refractory partial epilepsy and normal neuroimaging studies. We assessed the utility of ictal SPECT to define the epileptogenic zone and assist surgical planning in this population.

Methods: We retrospectively reviewed records of 31 children (ages 9 mo-17 yrs; mean, 8.8 yrs) who underwent surgery for medically refractory partial epilepsy and who had normal or non-specific neuroimaging. All patients underwent ictal SPECT (three headed Multispect Siemens' Medical System) performed following injection of HMPAO (300 microcuries/kilogram) within 16–30 sec of ictal onset. The SPECT images were classified as focal or non-localizing. Focal areas of hyperperfusion were compared for convergence with localization of the epileptogenic zone defined on scalp EEG/ECoG (n = 4) or chronic intracranial EEG (n = 27).

Results: Resections were temporal (n = 6), extratemporal (n = 20) and multilobar (n = 5). Ictal SPECT revealed focal hyperperfusion in 26/31 patients (84%) and was non-localizing in 5. In the focal group, 23 out of 26 (88%) were convergent with EEG localization. At follow up, 12/23 convergent patients (52%) are seizure-free, 1 has > 90% reduction, 3 had >50% reduction, and 7 were unchanged. 3/8 patients with non-convergent/non-localizing SPECT are seizure free, 1 >90% reduction, 1 > 50% reduction, and 3 unchanged.

Conclusions: When performed early after seizure onset ictal SPECT reliably defines focal hyperperfusion in a large majority of pediatric epilepsy surgical candidates with normal or non-specific neuroimaging studies. Used in conjunction with EEG data, ictal SPECT permits accurate characterization of the epileptogenic zone and facilitates surgical planning.

2.313
SUBTRACTION ICTAL SPECT COREGISTERED TO MRI IN CHILDREN WITH TUBEROUS SCLEROSIS COMPLEX: CORRELATION WITH INTRACRANIAL EEG

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Rationale: Tuberous sclerosis complex (TSC) is characterized by multiple cortical tubers and intractable epilepsy. Epilepsy surgery is considered if seizures originate from a single lesion in a non-eloquent area of the brain. However, patients with TSC are not optimal candidates for surgery because of multiple cortical tubers and multifocal epileptogenic foci. Recent development of multi-modality functional neuroimaging (i.e. interictal [^{11}C]AMT PET, FLAIR MRI) have been reported to improve localization of epileptogenic tuber(s), and thus the outcome of surgery in TSC. We studied correlation between intracranial EEG recording and subtraction ictal SPECT co-registered to magnetic resonance images (SISCOM) in this group.

Methods: Eight children with TSC and drug resistant epilepsy, ages 14 months to 18 years (mean 6.2 years) were identified out of 154 children who underwent resective surgery since 1992 in Medical College of Georgia. Six out of 8 patients had SISCOM due to unlocalizing scalp-video EEG. All 8 patients underwent chronic implanted subdural EEG recording. Ictal SPECT was not performed in two children who had localized ictal scalp EEG.

Results: Bilateral multiple tubers by MRI were present in all eight children. The SISCOM findings successfully guided the placement of intracranial electrode implantation in all 6 patients. All but one patient was required multilobar cortical resection based upon intracranial ictal EEG findings. SISCOM localizations were concordant with intracranial EEG localization in five out of six and included in cortical resection. Five children have had more than12 months of postoperative follow-up. Seizure-free outcome was achieved in 5 (12–33 months).

Conclusions: While the SISCOM lesion provided excellent guidance in terms of intracranial electrode placement, epileptic zones were often multiple including the SISCOM lesion. Our data suggest that more extensive subdural grid or strip coverage is required in children with TSC and intractable epilepsy not to miss the presence of multiple epileptic foci.

2.314
MAGNETIC RESONANCE IMAGING IN CHILDREN WITH NEWLY DIAGNOSED EPILEPSY

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Rationale: To evaluate the need for magnetic resonance imaging (MRI) in children with newly diagnosed epilepsy.

Methods: All children with newly diagnosed epilepsy who came from the primary catchment area of our hospital were prospectively recruited from 1998–2002. The epilepsy was defined as at least 2 unprovoked seizures occurring = 1 day apart. MRI was performed in all children at

the onset of epilepsy (n = 81) with the exception of idiopathic epilepsies [childhood and juvenile absence epilepsy (n = 5), Rolandic epilepsy (n = 2), juvenile myoclonic epilepsy (n = 1), Panayiotopoulos epilepsy (n = 1)], in one child with focal epilepsy and Down syndrome, and in one child with focal epilepsy who had been examined with MRI just prior to the onset of epilepsy in the routine follow-up of his leukemia. MRI findings were compared to EEG findings and to the clinical presentation. The etiologically significant MRI finding was defined as an abnormality that is associated with an increased risk of epilepsy and which is presumed to be relevant to the child's epilepsy.

Results: Of the 70 MRIs, 52 (74.3%) were normal, 7 (10.0%) had etiologically insignificant findings (2 Chiari I malformations, 2 arachnoideal cysts, one pineal cyst, one hypophyseal cyst, and one enlarged cisterna magna). In 5 children (7.1%) MRI had been performed earlier for other reasons (2 hydrocephalus, one intrauterine insult, one encephalitis, and one achondroplasia) and the repeated MRI at the onset of epilepsy showed no new findings. Six children (8.6%) had new etiologically significant findings: one frontal glioma (1,4%), 3 large cortical dysplasias, one hippocampal dysplasia, and one hemimegalencephaly. The child with frontal glioma had repeated daily myoclonic jerks of the head, trunk, and the extremities, but his neurological examination and the routine EEG were normal. Video EEG revealed ictal spike-and-slow wave discharges arising from the right frontal area. The other 5 children with etiologically significant MRI findings had abnormalities in the neurological examination and/or in the routine EEG.

Conclusions: It seems not reasonable to perform an MRI in all children at the onset of epilepsy. However, if the neurological examination is abnormal or if the routine EEG or video EEG show focal features, an MRI should be performed. One frontal brain tumor was found in this series (1,4%). The rest of the etiologically significant MRI findings did not influence the primary treatment of epilepsy but may be important in planning surgical procedures if the epilepsy turns out to be medically intractable.

2.315
ASYMMETRICAL WHITE MATTER VOLUMES AND MEASUREMENT OF CORTICAL THICKNESS IN FOCAL EPILEPSY

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Rationale: Children with clinically focal seizures from cortical dysplasia (CD) can still have relatively generalized EEG epileptiform discharges (ED). CD can be detected on MRI as altered cortical thickness. Gyral foldings in the plane of MRI sections can appear thick, limiting visual detection of actual altered thickeness. We hypothesize: 1. Segmentation of 3D reconstruction into gray and white matter (WM), and subsequent quantitation, can improve detection. 2. Lateralized differences in WM volumes indicate regions of prior neuronal loss or abnormal development that may be regions where seizures start. 3. Measurement of cortex perpendicular to mantle surface can increase detection of altered cortical thickness.

Methods: 14 patients 3.5 to 20 y old with intractable clinically focal onset epilepsy had EEG and thin slice SPGR isotropic voxel studies with 1.5T GE scanner. 3D MRI were reconstructed with Curry software. Reconstructions were placed in Tailarach orientation, then segmented into gray and white matter after transition pixel intensity was optimized. WM volumes were calculated for whole brain and for each hemisphere. White matter hemisphere volumes (WMHV) were considered significantly different only when difference was >10% of total WM volume. Measurement points for cortical thickness were established on both external (cortex-CSF) and internal (cortex-white matter) surface of the 3D cortical mantle for completeness (40–50K points). Cortical thickness was measured perpendicular to the surface at each point and color-coded. All 3D surfaces were visually reviewed for thinner and thicker regions.

Results: Five patients had bilateral ED. Three had no ED recorded. Three had left and 4 had right hemisphere ED. MRI scans were formally read as normal in 4 with bilateral ED and in one each with left hemisphere, right hemisphere, or no recorded ED. The MRIs of the remaining 7 were formally read as focal cortical dysplasia. For patients with bilateral ED, no ED, and/or MRI scans formally read normal, WMHV were more often symmetric or left smaller than right. For patients with right ED, WMHV were symmetric. At certain regions (major fissures, operculum, and at tentortium), the proximity of two contiguous folded gyral surfaces was measured as correspondingly thicker. Three of 7 abnormal MRIs were identified; 3 of normal MRIs had focal regions specified as thicker by the algorithm.

Conclusions: White matter hemispheric volume asymmetries did not directly reflect side of epileptiform discharges. In this limited population, WMHV were symmetric or more often left smaller than right. Measurements perpendicular to the cortical surface identified some regions of abnormal mantle thickness. Improvements in the algorithm to evaluate two contiguous cortical surfaces are required to improve detection.

2.316
α-[^{11}C]METHYL-L-TRYPTOPHAN (AMT) PET CAN LOCALIZE EPILEPTOGENIC TUBERS WHEN SCALP EEG IS POORLY LOCALIZING IN CHILDREN WITH TUBEROUS SCLEROSIS

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Rationale: Tuberous sclerosis complex (TSC) is often associated with medically intractable seizures. Surgical resection of epileptogenic tubers may result in seizure-freedom. However, scalp EEG is commonly poorly localizing and, without any other localizing information, such patients are often rejected from epilepsy surgery. Previous studies have demonstrated that alpha-[^{11}C]methyl-L-tryptophan (AMT) PET can show selectively increased uptake in epileptogenic tubers, and may be a useful imaging method to localize epileptogenic brain regions in children with TSC. In the present study, we evaluated the additive localizing value of AMT PET in TSC patients whose scalp EEGs did not provide sufficient information to proceed with surgery.

Methods: From a sample of 51 children with TSC and intractable epilepsy who underwent AMT PET scanning in our center, 15 children with non-lateralizing (generalized seizure onset) and/or localizing (seizure onset lateralized but not localized) EEG were selected for this study. AMT uptake values were measured in all tubers visualized on MRI, and those patients with at least one tuber showing AMT uptake higher than the normal cortical uptake were selected and compared to scalp EEG, ictal intracranial EEG findings, as well as surgical outcome data.

Results: Eight of 15 children (53%) with poorly lateralizing/localizing scalp ictal EEG had at least one tuber with increased AMT uptake. In these 8 children, scalp ictal EEG was non-lateralizing in two, while it was lateralizing but showed extensive hemispheric seizure onset in the other 6 cases. In this subgroup, AMT PET showed increased uptake in a single tuber in 6 children, in 2 adjacent tubers in 1 child, and in 2 tubers in two opposite hemispheres in another patient. Intracranial EEG with subdural electrodes was performed in 5 cases, and demonstrated that tubers with increased AMT uptake were epileptogenic. Four of 6 children who underwent resective surgery (including the tuber with increased AMT uptake) became seizure-free; the remaining two showed >75% improvement in seizure frequency. In one child who has not yet been operated, scalp ictal EEG showed bi-frontal onset, while increased AMT uptake was found at a right frontal tuber close to the mid-line. Seizure semiology was consistent with a right hemispheric focus.

Conclusions: In TSC patients with intractable epilepsy but poorly lateralizing and/or localizing scalp EEG findings, AMT PET can identify epileptogenic tubers and can guide subdural grid placement to assist in the identification of epileptogenic brain regions to be resected. Thus, following AMT PET, some patients with TSC and intractable epilepsy,

not otherwise considered for surgery, may indeed be suitable candidates. (Supported by NIH grant NS 38324.)

Human Imaging–All Ages

2.317
MESIAL TEMPORAL SCLEROSIS: APPLICATION OF DIFFUSION TECHNIQUES AND COMPARISON WITH MRI SPECTROSCOPY

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Rationale: Diffusion analysis can be useful to detect ultrastructural brain changes. This technique has been used to study hippocampal sclerosis, and its utility has been compared with MR spectroscopy (MRS). It is considered that diffusion can give an independent measure of hippocampal abnormalities. Comparison of lateralizing abnormalities using diffusion with high b-values and with multivoxel spectroscopy may be of clinican relevance, in order to identify situations for which each technique provide more acurate information. Our work describes the technique of hippocampal analysis with diffusion, analyzes different diffusion patterns in healthy subjects and patients with mesial temporal sclerosis (MTS) using different b-values, and correlates findings in diffusion with multivoxel MRS.

Methods: Thirty healthy volunteers were compared with 30 patients with clinical, electroencephalography, and MR imaging consistent with MTS using a 3 T MR unit. Values of diffusion studies were obtained using a b-value of 1000 and 3000 at the head and body of the hippocampus. Multivoxel MRS was performed and NAA/Cr values obtained in the same locations were correlated with diffusion values.

Results: No technical difficulties were found during the procedure of diffusion studies. Concerning apparent diffusion coefficients (ADC), there was mild intersubject variability, and less than 3% difference between each side in healthy subjects. In MTS side to side differences in ADC were above 10%, and were more pronounced when higher b-values were used. The head of the hippocampus had higher differences in diffusion studies than the body. MR spectroscopy had higher technical difficulties, due to poor shimming, most notably at the head of the hippocampus, where MRS could not be interpreted, both in healthy volunteers as well as in patients. There was adequate correlation between diffusion and MRS.

Conclusions: There is adequate concordance between diffusion and MR imaging in patients with distinct signs of MTS. However, the correlation in patients with less clear signs of MTS should be investigated. There is also good correlation between diffusion and MRS, but the sensibility of diffusion is superior to MRS at the head of the hippocampus, where pathology is more common in MTS. Considering this difference, diffusion may be a complementary tool to MRS.

2.318
ABNORMAL ACTIVATION OF LANGUAGE CORTEX IN PATIENTS WITH CHRONIC SEIZURES AND ACADEMIC ACHIEVEMENT DEFICIT

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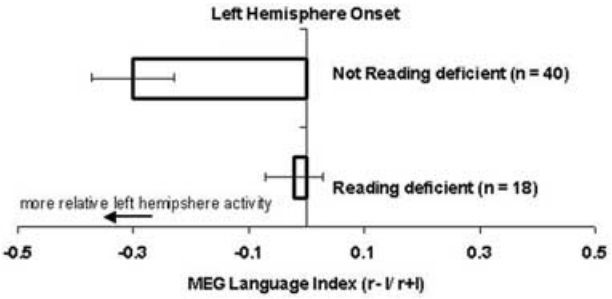
Rationale: Patients with chronic seizure disorder are at increased risk for academic achievement deficits; however, the relation of neurophysiological abnormality to these deficits is not well known. We used magnetoencephalography (MEG) to examine the functional status of brain mechanisms for language in patients with chronic epilepsy and reading achievement deficits, and the manner in which seizure variables affect this status.

Methods: MEG data was collected while 83 patients (IQ > 69; age 9–56 yrs.) performed a continuous recognition memory task for concrete nouns presented auditorily. Patients raised either the right or left index finger (counterbalanced across patients) for a repeated stimulus. Sources of late (post N1m resolution) MEG activity were modeled as equivalent current dipoles at 4 ms intervals; MEG scans were co-registered with structural MRI scans using fiducial markers. An index of interhemispheric asymmetry of activation in perisylvian language areas in the left hemisphere and homologous areas of the right hemisphere was formed as: $r - l/l + r$. All patients underwent pre-surgical evaluation, including 24-hour VEEG, MRI, and neuropsychological testing. Patients were identified as reading deficient if the reading score on the Wide Range Achievement Test was <25% ile.

Results: Among patients with left hemisphere seizure onset ($n = 58$) those with reading achevement deficits ($n = 18$) exhibited a greater degree of bilateral activation during the MEG task than the non-impaired group, $F(3,54) = 11, p < .002$, (see Fig. 1). Results were unchanged when Full Scale IQ was used as a covariate to control for global intellectual disability.



Within the left hemisphere group with seziures of cryptogenic etiology ($n = 33$) the degree of atypical (bilateral) language representation was independently related to age at onset (partial $r = .50, p < .003$) and age at MEG scan (partial $r = .53, p < .002$), with earlier onset and increasing age associated with a greater degree of right hemisphere engagement during the MEG language task.

Conclusions: Reading achievement deficit in chronic epilepsy of left hemipshere origin is associated with abnormal activation of left hemipshere areas during a task previously shown to be valid for localizing language cortex. In a subgroup of these patients with cryptogenic etiology this abnormality is greater with earlier onset and longer duration of the disorder. (Supported by NINDS grant NS37941 to A.C. Papanicolaou.)

2.319
IS LINGUISTIC FUNCTION STILL THERE AFTER MULTIPLE SUBPIAL TRANSECTIONS OVER WERNICKE'S AREA?

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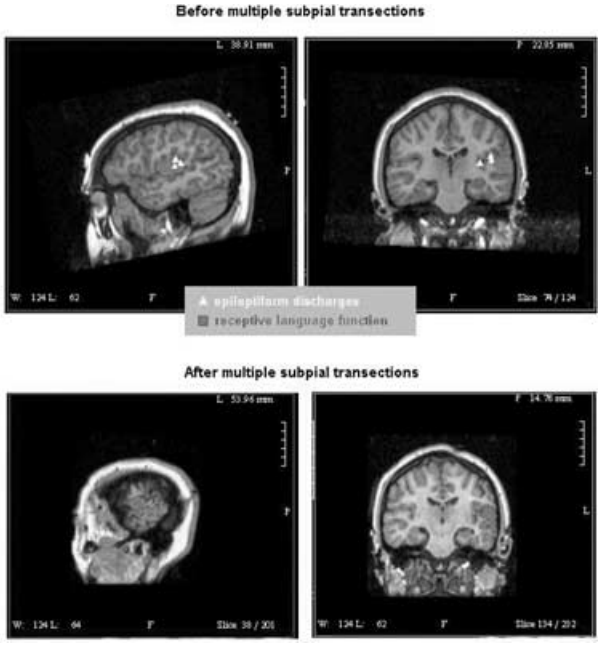
Rationale: Multiple subpial transection (MST) is the procedure of choice when the affected brain area includes regions known or expected to mediate a sensory, motor, or higher cognitive function. In such cases MST minimizes the risk of morbidity when compared to other, more aggressive, surgical procedures. The fact that functional outcome after MST in language-specific cortex has been reported to be positive (although some transient deficits are in some cases evident) has been used to support the concept that the cortical representation of the underlying function is not altered. The truth is that little is known about the changes in the representation of function that MST can trigger.

Methods: In this report we describe the pre- and post-operative maps of receptive language activation obtained using an externally validated MEG procedure in a patient diagnosed with the Landau-Kleffner

syndrome. Seizure control was achieved with MST over the left temporo-parietal junction.

Results: The linguistic deficits present pre-surgically worsened for approximately 6 months following MST. Three years later, the patient was re-evaluated. His linguistic skills, especially those involving receptive language functions, were found, at that time, to have improved beyond their pre-surgically levels. When compared, the MEG-derived maps of receptive language were similar pre- and post-surgically, showing the "typical" profile of activation involving the posterior superior temporal gyrus of the left hemisphere (the area where the MTS was carried out) (Fig. 1).



Conclusions: In this case, the spatial overlap between pre- and post-surgical MEG-derived maps suggest that the cortical substrates of receptive language function are not reorganized after MST even in those cases were an initial transient linguistic regression is present. [Supported by NINDS grant (NS 37941) to Andrew C. Papanicolaou.]

2.320
HIPPOCAMPAL ^{1}H MRS FINDINGS IN PATIENTS FAMILIAL MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Familial mesial temporal lobe epilepsy (FMTLE) is highly associated with hippocampal atrophy (HA), which can be found not only in patients with refractory seizures, but also in family members with good outcome and even asymptomatics. Our objective was to investigate metabolic changes in patients with FMTLE, using ^{1}H magnetic resonance spectroscopy (MRS), and correlate these findings with seizure control and hippocampal volumetry.

Methods: MRI and ^{1}H MRS were acquired in an Elscint 2T scanner (Prestige, Haifa, Israel), after signed informed consent. Anatomical MRI included coronal T2 and T1-IR 3mm slices, perpendicular to hippocampal long axis and T1–3D volumetric acquisition. HA was determined by visual and quantitative studies, using a standard protocol: volumes were corrected by the variation in total intracranial volumes and an asymmetry index (AI) was defined as the ratio smaller/larger hippocampus for each subject. Volumes or AI below two standard deviations from the mean of the control group were considered abnormal. We used PRESS sequence for single voxel ^{1}H MRS (TR = 1500 ms, TE = 135ms, NEX = 200), over the head of hippocampal formation bilaterally. The spectra were post-processed using software supplied by the MRI machine manufacturer. After zero-filling and baseline correction we determined peak areas by integration of the corresponding signals from from *N*-acetyl compounds, mainly the neuronal marker N-acetylaspartate (NAA) at 2.01 ppm, choline-based compounds (Cho) at 3.2 ppm and creatine and phosphocreatine contained compounds (Cr) at 3.0 ppm and determined NAA/Cr ratios. Spectra with broad peaks and poor separation of individual peaks were excluded from analysis. Values below two standard deviations from controls were considered abnormal.

Results: We studied 30 FMTLE individuals: ten with good seizure control, five with refractory seizures, and 13 asymptomatics. HA determined by volumetry was found in 23 individuals: 11 bilateral, five right and seven left. Abnormal NAA/Cr ratios were found only in three asymptomatic individuals: one had bilateral HA and left NAA/Cr reduction, one had left HA and NAA/Cr reduction on the left and the third had normal hippocampal volumes and bilateral NAA/Cr reduction.

Conclusions: This preliminary study in patients with FMTLE showed that relative NAA reduction was less frequent than the reported figures in series of patients with refractory TLE. Whether this is related to better seizure control in this group of FMTLE or to other differences between FMTLE and sporadic refractory TLE remains to be determined. [Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), São Paulo, Brazil (grants 95/9659-5, 97/07584-3 and 99/10702-3).]

2.321
STEREOLOGIC ESTIMATION OF CORTICAL SURFACE AREA IN TUBEROUS SCLEROSIS COMPLEX: AN MRI-BASED IMAGING STUDY

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Rationale: Tuberous Sclerosis Complex (TSC) is an autosomal dominant condition in which the most significant neurological features of the disease are directly attributable to lesions of the cerebral cortex (tubers), which are known to distort both the internal and external cortical surface. The geometry of the cortical surface has a direct influence on the degree to which the surface is inter-connected, how fast a signal can travel across the surface, and how much of the grey matter can be affected by that signal. It is postulated that the area of the cortex is directly related to its intrinsic properties. Stereological estimates of the surface area may be determined from *in-vivo* volumetric MRI data. The aim of this study was to measure cortical surface geometry from MRI data in a cohort of TSC brains and to correlate these measures with other quantitative radiological data (tuber count and volume) and clinical features (seizure control and cognitive status).

Methods: Using a 3 Tesla MR scanner, 3D MPRAGE contiguous fine cut sequences were acquired for five TSC patients and five normal controls. A semi-automated, computer based stereological software programme (MEASURE) was used to estimate cortical surface area.

Results: When corrected for cortical volume, three of the five TSC patients had increased surface areas above the 95% confidence limit as determined by the normal control group. The mean and standard deviation of surface areas measured for the control group was 1595 cm^2 (32.14), and for the TSC patient group was 1907.12cm^2 (305.92). It was found that increasing surface areas correlated with increasing tuber load, poorer seizure outcome and cognitive decline.

Conclusions: The findings in this study of increased surface area to volume ratio in the more clinically affected brains of TSC suggests a process of arrested cortical development. It is envisaged that surface area measurements may act as a reliable surrogate of external cortical deformation caused by the pathological lesions of TSC. Further studies will be required to confirm the initial findings of this study. (Supported by Tuberous Sclerosis Alliance.)

2.322

METHOD FOR AUTOMATIC GENERATION OF CLINICAL REPORT FOR SEIZURE FOCUS LOCALIZATION AFTER IMAGING WITH MEG, EEG, AND MRI

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Rationale: Candidates for epilepsy surgery are routinuely worked up using a variety of imaging modalities, including MEG and EEG. Experts are needed to examine large amounts of data to search for spikes. Once spikes are successfully identified, an inverse solution must be obtained to locate the spike on an anatomical image of the brain. The clinical reports are written based on these localizations. The above process is time consuming and error-prone. By automating these tasks, fatigue and human error are removed from the equation, and clinical reports can be produced in much less time.

Methods: Five surgical candidates for epilepsy were evaluated using EEG and MEG for one hour. Anatomical MRI images were subsequently obtained. Trained experts visually inspected the raw data and wrote clinical reports for each patient. The same data was then re-evaluated using automated software. Data was filtered to 0.1–30Hz. Equivalent dipoles were obtained at increments of 10ms. Dipoles which had a goodness-of-fit $> 80\%$, and whose current $*$ length values were between 200 and 400 nA$*$m were considered potential spikes. Artifacts from eye movements and QRS complexes were excluded. MRIs were mapped using Freesurfer to obtain inflated brain surfaces. The software generated images of potential spikes, as well as a written report of named regions of the brain. For example, a named area could be "left hemisphere inferior temporal sulcus." The written report included an appendix with the time of each potential spike.

Results: All five images generated by the automatic spike detector included the areas identified by the human reports. The detector found, on average, 157 candidate spikes per patient. The automatically generated text report correctly identified areas which the human reports had indicated. There was an average of 6 such named areas per patient. Both the image and written report included additional areas which either were not actual spikes, or were not identified as such by the original human report.

Conclusions: The automatic spike detector software was able to narrow down potential seizure generation sites to a short list, as well as identify times when possible spikes occurred. Because this list was relatively small, a skilled expert (human or computer) could then quickly narrow down the list to identify true spikes. This more focused search could take the place of the more exhaustive search now commonly done by clinicians. The automatic spike detector and report generation software represent a tool which has high sensitivity and low specificity. The ideal way to take advantage of this would be to use the software as a screening tool prior to final examination by a trained expert. The end result would be a faster, more reliable clinical reporting mechanism for clinical workup of epilepsy surgical candidates using EEG and MEG. (Supported by The MIND Institute.)

2.323

CAN dSPM BASED ON MEG BE A NEW METHOD TO SHOW PRIMARY AREA AND PROPAGATION FOR BILATERAL PARTIAL EPILEPSY?

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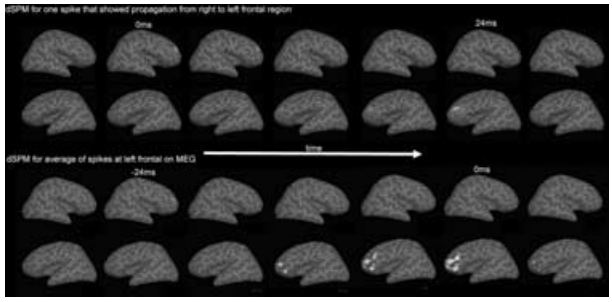
Rationale: Patients (pats) with partial epilepsies (PE) may candidates for surgery. In pats whose EEGs show bilateral interictal spikes (IIS), it is necessary to precisely localize their primary epileptogenic area before surgery. We report a use of dynamic statistical parametric modeling (dSPM) and Magnetoencephalography (MEG) to investigate primary area and propagation in PE showing bilateral IIS on electroencephalograly (EEG).

Methods: Pats with refractory PE with bilateral EEG IIS were studied using 306-channel MEG (Neuromag) and 70-channel EEG for (60mins including sleep. Equivalent current dipoles (ECD) were calculated for MEG IIS. Only ECDs with Goodness of Fit $>80\%$ and $100 <$ Qvalue <400nAm were accepted. The MEG dSPM were calculated.

Results: There are 7 pats who showed bilateral independent EEG IIS. 3 of 7 showed 3–8 IIS propagated from one to another region over short durations on MEG (15ms(382ms). There were no propagations in the opposite direction. We suspected the first region prior to propagation showed the primary area. To confirm this, we calculated average dSPM for a pat.

Sample; An11 year old girl. EEG showed independent left and right IIS (more spikes at left F3 than right) on EEG using 2 kinds of bipolar montage and a monopolar montage. Some MEG IIS were not accompanied by EEG IIS, and some right MEG IIS appeared at left on EEG. MEG showed 3 types IIS, 8 IIS clustered at right frontal (Clu R), 16 IIS at left frontal (Clu L) and 3 IIS propagated from right frontal to left frontal region (Clu RL). We suspected that all left frontal IIS were propagated from the right frontal area. To support our assumption, we calculated the dSPM of the averaged spikes for each spike cluster. The dSPM of the average spikes in Clu RL and even dSPM for each 3 IIS in Clu RL showed clear propagation from right to left frontal lobe. (Fig. 1, Upper pictures) In Clu L, the dSPM of each spike did not showed clear propagation. However the dSPM of the average spikes in Clu L showed the right frontal activity proceeding to left frontal lobe activity (Fig. 1, Lower pictures) The duration between right and left frontal activity (24ms) and locations in the left and right frontal lobe were same as each and average dSPM of Clu RL. The dSPM of average for Clu R did not show proceeding activity. This result supports our assumption that the left frontal activity is propagated from a right frontal focus.



Conclusions: In cases with bilateral independent IIS on EEG, the MEG and dSPM is useful delineate the primary region and the existence of propagation from one to anther region. MEG with dSPM may be useful for presurgical evaluation. (Supported by The MIND Institute.)

2.324

COINCIDENTAL MRI CHANGES IN TEMPORAL PARIETAL OCCIPITAL CORTEX AND THE IPSILATERAL PULVINAR ASSOCIATED WITH PARTIAL STATUS EPILEPTICUS

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Rationale: Reversible diffusion-weighted MR imaging (DWI) hyperintensities have been reported in the setting of status epilepticus, and likely represent seizure-induced cytotoxic edema. We describe a neuroanatomically distinct pattern of cortical and thalamic DWI changes among six patients with partial status epilepticus.

Methods: The history, EEG findings and serial neuroimaging results of six patients with partial status epilepticus and focal, reversible DWI hyperintensities on MRI were reviewed and compared.

Results: While DWI abnormalities were present in all six patients in the series, two of three patients with predominantly posterior temporal, parietal and occipital involvement had concomitant reversible DWI hyperintensities in the ipsilateral pulvinar (Fig. 1). No thalamic DWI abnormalities were found in patients whose MRI changes involved primarily frontal cortex.

Conclusions: The pattern of MRI findings in this series suggests involvement of the pulvinar with seizures that emanate primarily from posterior temporal, parietal or occipital cortices. A similar coincidence of cortical and thalamic MRI abnormalities is reflected in previous reports, though not specifically identified. Anatomically, the pulvinar receives

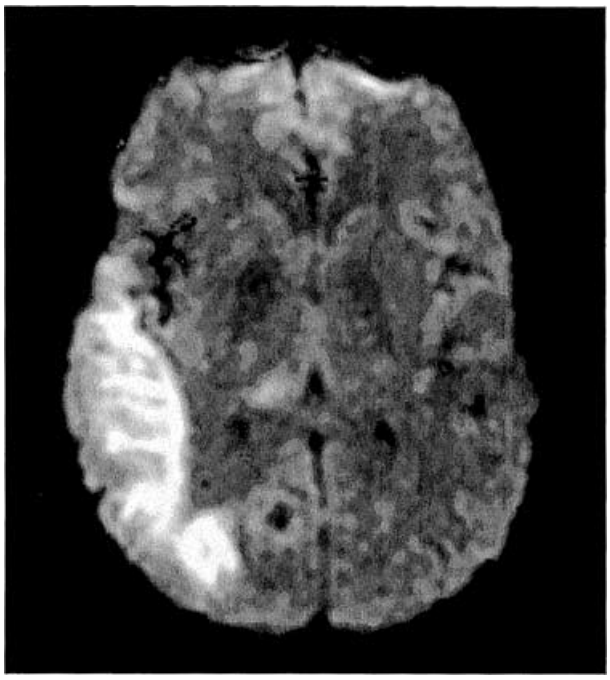

FIG. 1. Hyperintense DWI pattern after status epilepticus (right temporoparietal and pulvinar hyperintensities)

afferents from the superior and inferior parietal lobules, posterior temporal region, and peristriate occipital cortex. Our neuroimaging findings reinforce the functional significance of these connections, and comprise a distinct MRI pattern in temporal-parietal-occipital partial status epilepticus.

2.325
LOCATING SUBDURAL ELECTRODES IN CT IMAGES USING 3-D SURFACE RECONSTRUCTION

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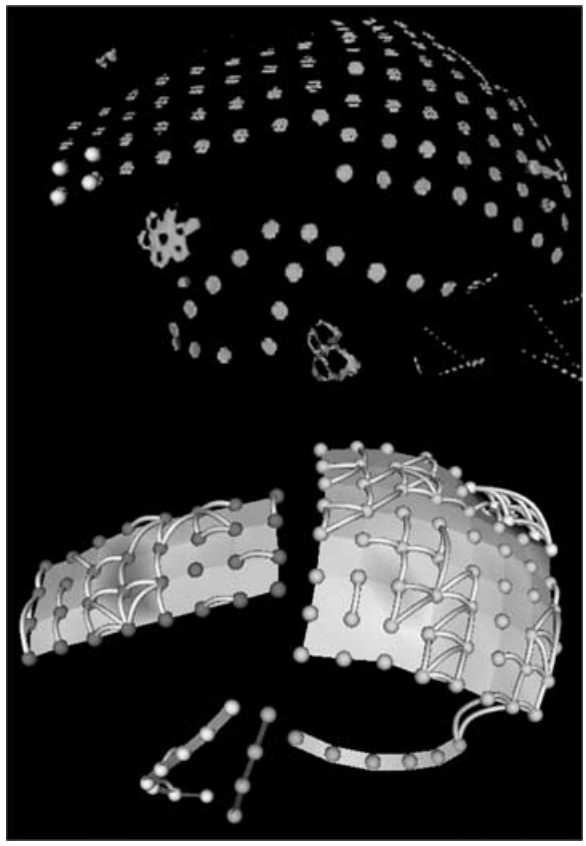
Rationale: Chronically implanted subdural electrodes are increasingly being used in invasive epilepsy evaluations as a means to locate intractable epileptic foci. In difficult multifocal cases, often more than 100 electrodes are implanted. Accurately determining the location of the electrodes in 3-D space in a timely manner is a critical first step in interpreting the electrocorticographic (ECoG) findings for planning seizure focus resections. Accurate localization and identification has traditionally been ignored, or at best is a tedious process, taking a trained technologist up to five hours per patient.

Methods: Previously, we developed an interactive application in which the electrodes could be marked in image plane slices from the CT (Fig. 1). We present an extension of this method in which surface rendering techniques are used to reconstruct the electrode surfaces automatically from high resolution CT scans (1 mm slices). After identifying the intensity of the electrodes in the scan, the rendering algorithm parameters are set to eliminate everything but the electrodes from the rendered image. The resulting objects are then filtered and segmented to eliminate other metallic artifacts and viewed in a 3-D window. A ray casting technique is used to define the spatial coordinates of the rendered electrodes interactively. The application runs across operating systems platforms and is developed solely with open source tools free for non-commercial use.

Results: The new procedure produces accurate results (less than half the width of an electrode) validated against visual localization and intraoperative photographs in a small fraction of the time. The localization of electrodes allows for the control of distance effects on coherence. Using this information, we present findings from an analysis of the spatial distribution of coherence and spectral power in 15 surgery candidates with intractable epilepsy.



Conclusions: This technique dramatically reduces the time required to accurately identify subdural electrodes locations, increasing their value for both clinical evaluations and research applications, such as source localization. (Supported by NIH NS40514-02.)

2.326
FUNCTIONAL CONNECTIVITY IDENTIFIES AN EPILEPTOGENIC NETWORK IN IDIOPATHIC GENERALIZED EPILEPSY

Graeme D. Jackson, Anthony B. Waites, Regula S. Briellmann, Angelo Labate, Richard Masterton, and David F. Abbott (Brain Research Institute, Austin Health, Heidelberg West, Victoria, Australia)

Rationale: Analysis of simultaneous EEG and functional MRI has given insight into the brain regions involved in seizure generation. The first purpose of this study was to analyse spikes that appeared different on the EEG to determine if the underlying brain activation was different. The second aim was to use other analysis approaches, including connectivity analysis and temporal clustering analysis (TCA), to further probe the epileptic circuits that underlie abnormal brain activity.

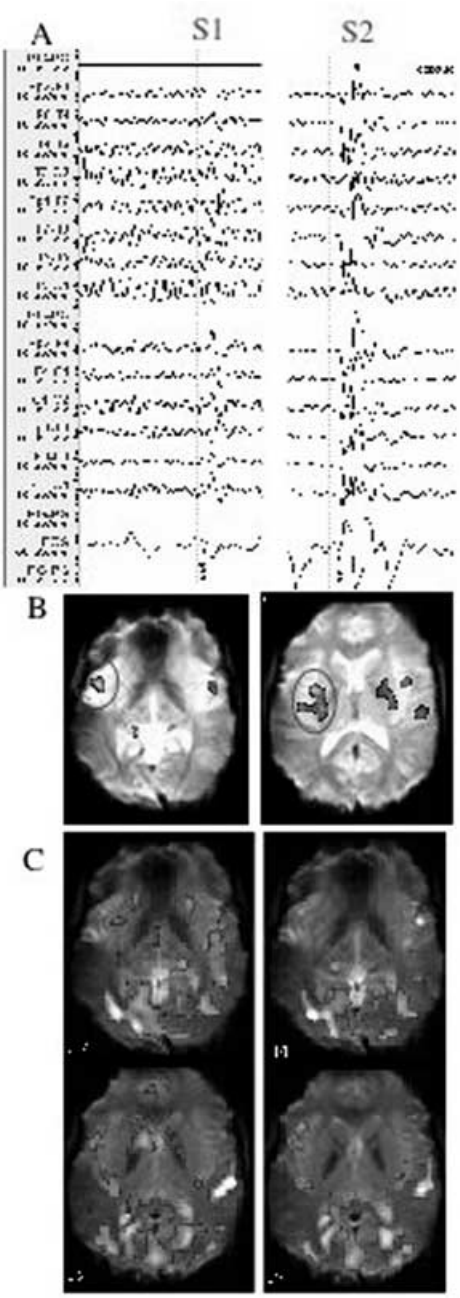
Methods: fMRI studies used a 3 tesla GE Signa LX scanner (GE, Milwaukee, WI). Functional images were acquired as a series of gradient-recalled echo planar imaging (GR-EPI) volumes (TR/TE = 3600/40ms, flip angle = 60 degrees, 25 oblique slices 4mm thick+1mm gap, 24cm FOV, 128x128 matrix), over a period of one hour (1200 volumes).

We assessed a patient with idiopathic generalized epilepsy, her EEG analysis identified two types of spikes, called S1 and S2 (Fig. 1A). Simultaneous fMRI/EEG was analysed using SPM99 (www.fil.ion.ucl.ac.uk/spm). Event-related analysis was performed to obtain maps of involved brain voxels for S1 and S2. The points of maximum statistic from each map were used as seeds in a functional connectivity analysis. The timecourse of each region (filtered to remove high frequency

noise >0.08Hz) was correlated against all brain voxel timecourses. Connectivity maps were then contrasted statistically against control maps, obtained by seeding these regions in four healthy controls. TCA analysis detected times when many voxels reach their maximal signal, and used these timepoints in an event-related analysis.

Results: Panel 1B shows the BOLD activation from the EEG/fMRI study (S1 on the left, S2 on the right). The S1 spikes showed primarily deactivation in the insular cortex. The S2 spikes showed activation in subcortical nuclei, primarily the basal ganglia.

Panel 1C shows the increased connectivity above normal (control) levels measured statistically, based on the seed areas circled in panel B. Note that the areas involved in the connectivity pattern are virtually identical for each spike type, despite the seed point and the BOLD activation pattern being different. The TCA results show a pattern very similar to the network identified using connectivity analysis, together with some other brain regions.



Conclusions: These data support the idea that interictal epileptiform events are an expression of activity in an epileptogenic network and the different EEG pattern may merely reflect peak activity in different parts of this network. (Supported by Neurosciences Victoria and National Health and Medical Research Council.)

2.327

SENSORIMOTOR ORGANIZATION IN DOUBLE-CORTEX SYNDROME

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Rationale: The function and connectivity of the subcortical heterotopic band in double cortex syndrome (DCS) is only partially understood. Tracers studies that examined the thalamo-cortical connections in the somatosensory system of the tish mutant rat model of double cortex have shown that both neurons in the normotopic cortex and those in the heterotopic band establish topographically-organized bidirectional connections with the thalamus (Schottler et al., 1998), suggesting that primary sensorimotor information is represented in a parallel manner in both cortices. However, it is unclear whether sensorimotor organization of the normotopic cortex in DCS involves only primary areas or a more widespread network. The aim of this study was to investigate the motor and somatosensory function in patients with DCS using functional magnetic resonance imaging (fMRI).

Methods: We studied six DCS patients (five females and one male; mean age 23 years) with intractable epilepsy, except for one patient whose seizures were controlled with medication. High-resolution anatomical MRI showed bilateral diffuse subcortical band heterotopia with varying degrees of asymmetry in all patients. Blood oxygen level dependent (BOLD) fMRI images were obtained on a 1.5 T scanner using a T2∗-weighted gradient EPI sequence. The motor task consisted of acoustically cued fingers-to-thumb opposition. The sensory stimulus consisted of light manual brushing using a soft brush over the skin of the palm and fingers. Two runs of 100 volumes each were obtained sequentially for right and left motor task and sensory stimulus using a block design. Image processing and statistical analysis was done using fMRISTAT-MULTISTAT software (Worsley et al., 2002).

Results: Simple motor task elicited a contralateral activation of both the primary motor cortex and the underlying heterotopic band in all patients. Ipsilateral motor activation was seen in 4/6 DCS patients. Furthermore, there were additional areas of activation of non-primary normotopic cortical areas (supplementary motor area and premotor area). Sensory stimuli resulted in activation of the contralateral primary sensory cortex in all patients and secondary somatosensory areas in 5/6. The underlying band beneath the primary sensory area became activated in 3/6 patients. Activations were also seen in subcortical structures for both paradigms.

Conclusions: The activation patterns found in our patients suggest that in DCS the heterotopic band may participate to the processing of simple motor and sensory tasks. To perform these tasks, patients with DCS recruit a widespread network involving bilateral primary areas and higher order association normotopic cortices, suggesting an increased attentional demand and motor programming. (Supported by Canadian Institutes for Health Research.)

2.328

TEMPORAL LOBE DEVELOPMENTAL TUMORS: AN *f*MRI STUDY FOR LANGUAGE LATERALIZATION

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Rationale: Most healthy people have left hemispheric language dominance. Atypical language lateralization may occur naturally, but is more

frequent in epilepsy patients. Atypical language may be induced by an early disturbance of the left hemisphere. Dysembryoblastic neuroepithelial tumours (DNET) and ganglioglioma (GG) are developmental tumors, and are an important cause of refractory partial epilepsies. They tend to occur in the temporal lobe. Here, we aim to assess language activation in patients with temporal lobe DNET or GG.

Methods: We recruited 14 patients (9 DNET, 4 GG, 1 DNET+GG). They all had histological or MRI diagnosis of the tumour. MR imaging was performed on a 3-tesla GE scanner. Functional MRI (fMRI) was performed using a whole brain (22 slides) gradient echo-planar imaging (EPI) technique. The task was a natural language task, where a noun was presented and a corresponding verb had to be generated (Noun-Verb Generation task, NV). Laterality indices (LI) of activated voxels in language related areas were calculated using the formula (Left-Right)/(Left+Right). Left-sided lateralization was diagnosed if the LI was greater than 0.2, atypical lateralization if LI was smaller than 0.2. The analysis was done with SPM99 and iBrain®.

Results: Three subjects were left-handed and 11 subjects were right-handed. Two right-handed patients had a right-hemispheric tumor. The tumor was in language related areas in three subjects, and in other temporal lobe regions, not typically involved in language functions, in the remaining 11 patients.

Atypical language was found in thee patients; one had a right-sided tumor (LI 0.04), one had a left posterior middle temporal gyrus (LI-0.4) and one a left insular tumor (LI-0.0). Left-lateralized language was found in the remaining 11 patients, including two patients with a tumor in the superior temporal gyrus (LI 0.4; and 0.7). The two left-handed subjects both had clearly left-lateralized language. The average LI (0.3 ± 0.3) was not different from our control group (LI 0.5 ± 0.5, $p = 0.187$).

Conclusions: These results indicate that a developmental tumour in the left temporal lobe does not generally induce atypical language lateralization. This may suggest that an early developmental tumor is not interfering with language organization.

2.329
MAGNETIC SOURCE LOCALIZATION OF RECEPTIVE LANGUAGE FUNCTION AMONG EPILEPSY PATIENTS: A RELIABILITY STUDY

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Rationale: The external validity of non-invasive language mapping has been examined in studies where MEG localization was confirmed by either intracarotid amobarbital procedure and/or intraoperative cortical stimulation during epilepsy surgery. A previous study using normal subjects indicates that MEG estimates of cerebral dominance for language and localization of temporal lobe language area are reliable on two different occasions for the same subjects. However, in order for MEG language mapping to be used clinically, it is important to establish its ability to produce reliable measurements for individual subjects from different raters as well as on different occasions. This study examined the reliability of MEG language mapping through two different raters over two different occasions for the same epilepsy surgery candidates.

Methods: Nine epilepsy surgery candidates preformed an auditory recognition task for words. The task was repeated during two different sessions on the same day. Three lists of forty words were presented in each session. Thirty of the words were used as targets and ten words as distractors. Target words were presented for study before each MEG recording session. Subjects were instructed to raise their index finger to indicate that they recognized target words. Focal neurophysiological activity producing detectable magnetic fields at the surface of the head was modeled at each 4-ms time slice using the single equivalent current dipole model. Two raters (R1 and R2) analyzed data independently, and results of each rater were summarized in four parameters.

Results:

1. Inter-rater reliability
   a. Asymmetry Index [AI = (left hemisphere − right hemisphere)/(left hemisphere + right hemisphere)] for magnetic sources showed agreement between two raters (Pearson correlation coefficient $r = .984$).
   b. Average distance of localized magnetic sources between two raters was .86cm (SD = .48cm).
   c. Average root mean square magnetic value (RMS) from R1 was 87fT, and 116fT from R2.
   d. Average spatial volume that encompasses 95% probability of source localization from two raters was .66 (SD = .73) and .40cm^3 (SD = .57) respectively.
2. Intra-rater reliability
   a. Each rater's AI over two sessions for the same patient showed a high degree of agreement with $r = .99$ and .95 respectively.
   b. R1's average distance of magnetic sources between two separate sessions was .85 cm, and R2's average distance between two sessions was 1.0 cm.
   c. Average RMS over two sessions was 85 and 92fT for R1, and 115 and 127fT for R2.
   d. Confidence volumes for each rater over two sessions were .61 and .67cm^3 for R1, and .20 and .54 cm^3 for R2

Conclusions: In all four parameters of magnetic sources associated with receptive language function, there was a high degree of agreement between raters as well as within raters. These results suggest that MEG is a promising tool for determination of the localization of temporal lobe language areas for epilepsy surgery candidates.

2.330
PROGNOSTIC IMPLICATION OF SECONDARY HYPERPERFUSION IN THE TEMPORAL LOBE CONTRALATERAL TO THE SEIZURE FOCUS IN PATIENTS WITH TEMPORAL LOBE EPILEPSY: SUBTRACTION SPECT STUDY

[1]Ki Hyeong Lee, [1]Yong D. Park, [1]Anthony M. Murro, [1]Jeffrey M. Politzky, [2]Mark R. Lee, and [2]Joseph R. Smith ([1]Neurology and [2]Neurosurgery, Medical College of Georgia, Augusta, GA)

Rationale: The usefulness and prognostic value of Subtraction Ictal SPECT Co-registered to MRI (SISCOM) for presurgical evaluation in intractable partial onset epilepsy has been well established. However, the prognostic significance of bitemporal hyperperfusion on SISCOM has not been studied in patients with intractable temporal lobe epielpsy. Our previous study with smaller number of patients did not show significant difference in surgical outcome between unilateral vs. bilateral temporal hyperperfusion group.

Methods: We included patients who met the following criteria: 1) patient underwent presurgical evaluation including video-EEG monitoring, brain MRI, ictal/interictal SPECT, formal neuropsyhcologic testing and Wada test; 2) SISCOM result was concordant with the epileptogenic foci determined by scalp EEG-Video monitoring and brain MRI; 3) patient subsequently underwent unilateral temporal lobectomy; 4) patient was followed at least 1 year post-operatively. Surgical outcome using Engel's classification, clinical and electrophysiologic data was compared with regard to the presence of bitemporal hyperperfusion on SISCOM.

Results: Forty-one patients (M 20, F 21; age range 10–61, mean 34.4 yrs) were included in our study. Twenty-seven patient showed unilateral temporal hyperperfusion on SISCOM while 14 patients had bitemporal hyperperfusion. Patients' age, sex, duration of seizures were comparable between two groups. History of complex febrile seizure was more frequent in unilateral temporal group (10/27 (37%) vs. 1/14 (7%)). Ictal EEG was more often unlocalizing in bitemporal group (12/14, 86%) than unilateral group (12/27, 44%). Surgical outcome was significantly worse in patients with bitemporal hyperperfusion than unilateral (seizure free at 1 year, 6/14 (43%) vs. 21/27 (78%); $p = 0.03$, Fisher's Exact Test).

Conclusions: Our data suggest that bitemporal hyperperfusion on SISCOM may be a signficant prognostic factor for surgical outcome in temporal lobe epilepsy patients. More careful presurgical evaluation including intracranial EEG may be required for this group of patients.
(Supported by National Epifellows Foundation.)

2.331
ICTAL SPECT IN SECONDARILY GENERALIZED TONIC–CLONIC SEIZURES

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Rationale: Cerebral blood flow (CBF) changes measured with single photon emission computed tomography (SPECT) can be helpful for localizing partial seizures. However, CBF changes during partial seizures with secondary generalization have not been thoroughly investigated. We sought to determine whether the whole brain is homogeneously involved in generalized tonic-clonic seizures (GTCS), or whether focal networks may be crucial. Investigation of brain regions involved may provide insight into the mechanisms of behavioral changes during GTCS.

Methods: We identified 30 GTCS injected with Tc-99m HMPAO SPECT either during or immediately after seizures. Images were analyzed in SPM2 in comparison to interictal scans from the same patients. Also, in order to correlate the SPECT changes with behavioral changes, videos of each seizure were reviewed by 2 readers blinded to the imaging results, to classify and describe the different phases of the GTCS.

Results: We found that GTCS caused focal network activation on SPECT imaging, rather than involvement of the entire brain. Specifically, group analysis of all patients revealed that GTCS were associated with significant CBF increases in the cerebellum and decreases in the cingulate gyrus and orbitofrontal cortex. Interestingly, the changes in the cerebellum were time dependent during the posticta period: in patients injected during the early post-ictal period (0–60s after seizure end, mean injection time = 34.5s) cerebellar increases were confined to the superior vermis, whereas patients injected later (>60s after seizure end, mean injection time = 135.9s) showed bilateral increases in the inferolateral cerebellar hemispheres. We found that the perfusion increases in the cerebellum may be related to the extent of the tonic phase. 8 of the 10 (80%) seizures with motionless tonic contraction were associated with significant cerebral blood flow increases in the cerebellum, whereas only 5 of the 20 (25%) seizures with less dramatic tonic motor activity had significant changes in the cerebellum. Cortical changes in other regions varied widely among patients, and did not correspond to the seizure localization identified by other data (EEG, MRI, and clinical information).

Conclusions: GTCS are not truly generalized, rather specific networks are involved while others are relatively spared. These networks may explain some of the behavioral manifestations of GTCS. Cerebral blood flow increases in the cerebellum may be related to tonic activity. The functional significance of CBF decreases in the cingulate and orbitofrontal cortex during and following GTCS is not known. However, given the known role of these regions in attention, further investigations should determine whether these CBF decreases are related to impaired consciousness in GTCS. (Supported by Dana Foundation.)

2.332
A COMBINED EEG (ELECTROENCEPHALOGRAPHY) REFERENCE METHOD FOR SIMULTANEOUS EEG-*f*MRI (FUNCTIONAL MAGNETIC RESONANCE IMAGING) RECORDING OF EPILEPSY

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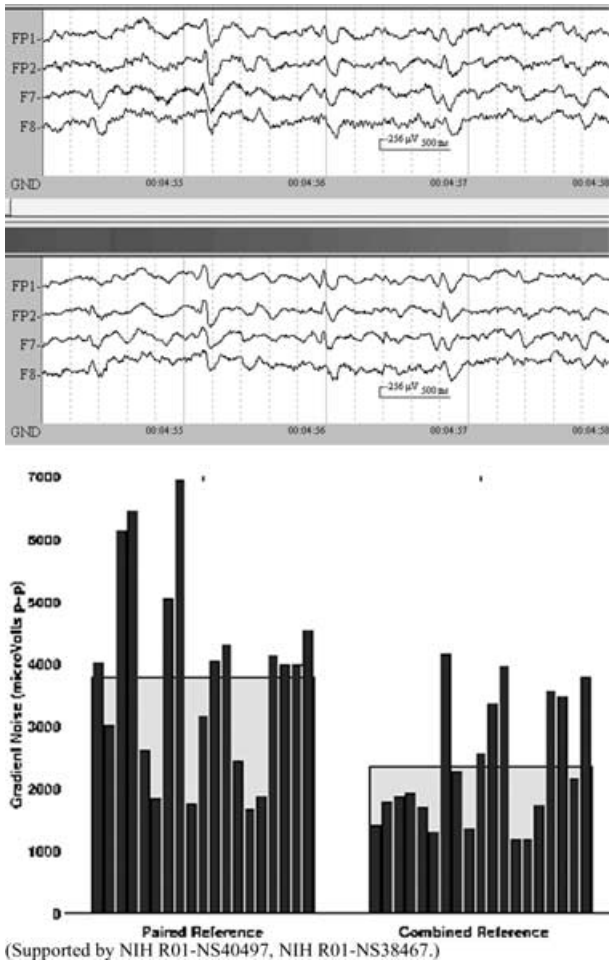
Rationale: Simultaneous electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) recording is a promising tool for non-invasive epileptiform localization (*Magn Reson Med* 2000; 44:791–8). Selection of EEG referencing scheme greatly affects the level of gradient noise in such recordings. We developed a new referencing method that uses weighted sum of multiple reference leads to reduce the gradient noise.

Methods: We made an electrode cap each of whose 19 measurement leads was twisted with a linked ear reference. Because all reference leads branches out from the same source, any linear combination of reference leads is a correct reference as long as the sum of the weights is one. We used a constrained optimization to compute optimal combined reference to minimize the gradient noise. Here we show an example of the application of this method to a data obtained from an epileptic patient who participated in the study after written consent. The patient lay still during four six-minutes runs of simultaneous EEG-fMRI acquisition.

Results: Fig. 1 shows the average peak-to-peak voltage after paired (twisted pair) reference (left) and combined reference (right). Average voltages of all electrodes were 3.8 and 2.6 millivolts, respectively. Fig. 2 shows EEG data showing interictal spikes (left: paired reference, right: combined reference) after PCA-based gradient noise removal (*Clin Neurophysiol*, in press). FMRI parametric map using detected spikes as regressors showed significant activations at the left inferior frontal gyrus and the left parietal lobe.

Conclusions: Use of combined reference significantly reduced the gradient noise before gradient artifact reduction. Spike waveforms after gradient noise removal were visibly cleaner when combined reference was used.



(Supported by NIH R01-NS40497, NIH R01-NS38467.)

2.333
FACTORS INFLUENCING SISCOM YIELD IN EXTRATEMPORAL EPILEPSY SURGERY CANDIDATES

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Rationale: Subtraction Ictal SPECT Co-registered to MRI (SISCOM) has proven valuable in localizing the epileptogenic focus in extratemporal epilepsy surgery candidates. However, little is known about the factors tht predict a positive study in these patients. We assessed the

effect of various factors on SISCOM result in extratemporal epilespy surgery candidates.

Methods: Pateints in this study had extratemporal seizure semiology by history and video recording. Exclusion criteria were the presence of exclusively temporal interictal epileptiform discharges or potentially epileptogenic MRI lesion in the temporal lobe. The following factors were evaluated: age at first unprovoked seizure, age at SISCOM study, MRI lesion presence and location, dominant interictal EEG focus, generalized interictal discharges, lateralizing seizure semiology, clinical secondary generalization, lateralizing ictal EEG onset, ictal EEG spread to contralateral hemisphere or generalization, location of ictal EEG focus, duration of injected seizure, SPECT injection latency, time from injection to seizure offset, and ratio of injection latency and seizure duration.

Results: Two hundred and four SISCOM studies performed from 1997 to 2003 met the study criteria. Median age at SISCOM was 20.5 years (range 1–62 years). Median seizure duration was 56 seconds (range 5–4140 seconds). Median injection latency was 24 seconds (range 2–840 seconds). The median ratio between injection latency and total seizure duration was 0.5 (i.e. half-way into the seizure). SISCOM was localizing in 74%. 89% of the studies were concordant with localization by scalp EEG. Factors which contributed significantly to a non-localizing study were clinical secondary generalization ($p < 0.01$) and generalized discharges on inctal EEG ($p < 0.05$).

Conclusions: Generalized seizure activity, either clinical secondary generalization or ictal generalized EEG activity, is the single most important factor influencing the yield of SISCOM studies in extratemporal epilepsy surgery candidates. Strategies to enhance the yield of SISCOM in these patients must emphasize prompt injection of the radioligand prior to seizure generalization, or the avoidance of secondary generalization of seizures. (Supported by Mayo Foundation for Clinical Education and Research.)

2.334

IMPORTANTCE OF TRUE ICTAL SPECT IN LOCALIZING TEMPORAL AND EXTRATEMPORAL EPILEPSY

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Rationale: Single-photon emission computed tomography (SPECT) is a valuable tool in the localization of focal onset epilepsy. However, radiotracer injection latency is a difficult to control variable which may dramatically affect the interpretability of these images. We have investigated the effect of radiotracer injection latency on the localizing and lateralizing sensitivity of ictal-interictal SPECT images.

Methods: Scans obtained from patients injected during seizures, based on video/EEG review, were defined as ictal, while those obtained after seizures were post-ictal. We used SPM2 to analyze ictal-interictal SPECT image pairs from 28 consecutive temporal lobe, and 16 extra-temporal epilepsy patients. Seizure localization was based on concordance of EEG, MRI and clinical data. For each patient, ictal-interictal SPECT differences were compared to scan pairs obtained from 14 healthy normal subjects using SPM2. We investigated the localizing value of increased perfusion based on the lobe containing the largest number of voxels with significant hyperperfusion. Our investigation of hypoperfusion found that it was not helpful for localizing the lobe of seizure onset, so we instead focused our studies on its sensitivity in lateralizing the hemisphere of seizure onset.

Results: In 28 patients with mesial temporal lobe epilepsy, we obtained 7 ictal and 21 post-ictal injections; in 16 patients with extra-temporal epilepsy we obtained 7 ictal and 9 post-ictal injections. With true ictal SPECT injections, perfusion increases correctly localized the lobe of seizure onset in 6 of 7 temporal lobe epilepsy patients (86%), and in 6 of 7 extra-temporal lobe patients (86%). Considering only scans obtained at post-ictal injection times, perfusion increases correctly localized only 5 of 21 (24%) temporal lobe patients, and 1 of 9 (11%) in extra-temporal patients. For post-ictal injections, we found that the hemisphere with greater hypoperfusion correctly lateralized the side of seizure onset in 17 of 21 temporal lobe patients (81%) and 7 of 9 extra-temporal patients (78%).

Conclusions: These results demonstrate that ictal-interictal SPECT analysis is highly sensitive for localizing both temporal and extra-temporal epilepsy. However, post-ictal injections have very poor localizing value based on conventional image interpretation. Nevertheless, when total hypoperfusion is compared between the two hemispheres, more extensive hypoperfusion can be helpful for lateralizing the side of seizure onset even with late post-ictal injections. (Supported by Epilepsy Foundation of America Merritt-Putnam Clinical Research Fellowship.)

2.335

EVALUATION OF MR COMPATIBILITY FOR EEG ELECTRODES

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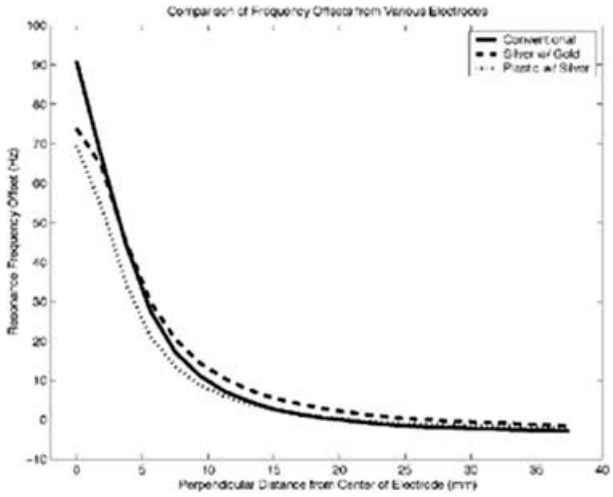
Rationale: Simultaneous electroencephalography (EEG) and magnetic resonance (MR) research has shown vast potential for investigating partial epilepsy disorders. However, with the increasing trend towards the use of high static magnetic field strenghs and power-intensive pulse sequences, greater magnetic susceptability artifacts and the potential for electrode heating must be considered. The purpose of this study was to evaluate the MR-compatibility of three electrodes based on a quantitative comparison of induced magnetic susceptibility artifacts and electrode heating.

Methods: To quantify magnetic susceptibility, resonance frequency maps were produced for a spherical saline phantom with a single electrode and lead wire attached using an optimized magnetic field mapping pulse sequence (*Magn Reson Med* 2004; 51:881–7) at a static field strength of 4 Tesla. Temperature measurements of the electrodes were acquired using a fiber-optic sensor during the application of research protocol MR experiments, including anatomical and functional gradient echo sequences and a single voxel spectroscopy sequence (all powers calibrated for a human head). Three types of EEG electrodes were sequentially tested: conventional copper (Type 1), pure silver with a gold flash (Type 2), and conductive-plastic coated with a layer of silver epoxy (Type 3).

Results: Resonance frequency offsets were plotted as a function of the perpendicular distance from the center of the electrode plane for all three types of electrodes (Fig. 1). The maximum frequency offsets for the Type 1, 2 and 3 electrodes were 91 Hz, 74 Hz and 69 Hz, respectively. No significant temperature changes were detected in any of the electrodes for any of the applied pulse sequences (maximum 5 minute power delivered to the RF coil $\sim$ 9.4 W).



Conclusions: As expected, the maximum frequency offset for the conventional copper electrode was greater than the offsets for the two silver-containing electrodes. Magnetic field mapping is a promising technique for quantitatively evaluating the severity of susceptibility artifacts induced by EEG electrodes. The spatially dependent frequency information combined with pulse sequence timing parameters can be used to predict the amount of signal loss created by the electrodes for any given MR experiment. [Supported by Natural Science and Engineering Research Council of Canada (NSERC) and Robarts Research Institute.])

Antiepileptic Drugs–Adult 2

2.336
COST SAVINGS ASSOCIATED WITH ALTERNATIVE TREATMENTS FOR REFRACTORY PATIENTS WITH PARTIAL SEIZURE DISORDER

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Rationale: Partial epilepsy is typically managed initially by monotherapy with anti-epileptic drugs (AEDs). Patients refractory to AED monotherapy may be switched to monotherapy with another AED or another AED may be added to the current AED. This retrospective study was designed to assess the economic costs of switching patients refractory to initial non-oxcarbazepine AED monotherapy to oxcarbazepine (OXC) monotherapy (Cohort A), compared with the costs of add-on therapy (Cohort B).

Methods: Data from the PharMetrics integrated medical and pharmacy claims database, which includes 57 managed care plans, were collected for adult patients who were receiving treatment with AEDs between January 1, 2000 and March 30, 2002. Patient data were analyzed over 6 months prior to treatment failure with either carbamazepine, phenytoin, or valproic acid, and post-failure defined as 12 months after switching to OXC monotherapy (Cohort A) or add-on therapy (Cohort B). Total treatment costs were compared within each cohort pre- and post-failure and between cohorts, with statistical differences tested using Wilcoxon rank sum tests. Multivariate econometric analyses of cost examined the impact of cohort, controlling for age, gender, geographic location, Charlson comorbidity score, and specific comorbidities.

Results: Data from a total of 169 and 380 patients were reviewed in cohorts A and B, respectively. Demographic and clinical characteristics were statistically similar between cohorts. Annual treatment costs rose for both groups during the post-failure period ($p < 0.01$). Pre-failure costs were not different between cohorts, however post-failure costs for cohort B were higher than for cohort A ($p < 0.10$). The mean increase in the cost of overall care was lower for Cohort A at $1,248 (SD $15,174) compared with Cohort B at $1,806 (SD $17,827). Although not statistically significant, a switch to OXC monotherapy was associated with an average annual savings of $558, compared to add-on therapy. Pharmacy cost constituted 31.2% and 42.9% of the total costs during the post-failure period for Cohort A and Cohort B, respectively. Additionally, Cohort B was nearly twice as likely as Cohort A to have an emergency room (ER) visit during the post-index period ($OR = 1.89$, $p = 0.08$).

Conclusions: These analyses suggest that, for patients refractory to initial standard AED monotherapy, e.g. carbamazepine, phenytoin, or valproic acid, switching to OXC monotherapy may provide a less costly alternative for managed care organizations than add-on therapy. Switching to OXC monotherapy also may be associated with fewer ER visits as well as lower pharmacy costs. (Supported by Novartis Pharmaceuticals Corporation.)

2.337
NO DOSE ADJUSTMENTS OF OXCARBAZEPINE REQUIRED IN MILD OR MODERATE HEPATICALLY IMPAIRED PATIENTS

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Rationale: To evaluate the pharmacokinetics of a single dose of oxcarbazepine in healthy volunteers and subjects with mild and moderate hepatic impairment.

Methods: Healthy volunteers and hepatically impaired subjects (45 to 65 years of age) were stratified using the Child-Pugh Impairment Classification System to one of the following groups: mild hepatic impairment, Child-Pugh Classification A; and moderate hepatic impairment, Child-Pugh Classification B. All subjects received a single dose of 900 mg of oxcarbazepine. Blood samples were collected pre-dose and at 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post-dose for the determination of levels of the active monohydroxy derivative, MHD. The following PK parameters for MHD were determined using model independent methods: C_{max}, t_{max}, $t_{1/2}$, AUC (0–96 h), and AUC (0-∞). An analysis of covariance (ANCOVA) model with baseline hepatic function as the covariate was used to determine the influence of any hepatic effects on MHD pharmacokinetics.

Results: A total of 26 subjects entered the study and samples were obtained from 19 subjects (healthy volunteers $n = 6$; mild hepatic impairment $n = 7$; moderate hepatic impairment $n = 6$) for analysis. All three groups were well matched with respect to race and age. No major differences in baseline medical history/concomitant diagnosis data between the three groups were noted, except for expected liver function-related findings separating the Child-Pugh A and B groups. There were no statistically significant differences in any pharmacokinetic parameters, in particular C_{max} and AUC values, between the healthy volunteers and the subjects with mild or moderate hepatic impairment. None of the hepatically impaired subjects reported adverse events. Three healthy volunteers reported the following mild adverse events: dry mouth, dizziness, and somnolence. Decreased creatinine clearance was noted for one healthy volunteer 5 and 15 days post-dose (13% and 59% decrease, respectively). Creatinine clearance returned to normal by 21 and 30 days post-dose. This volunteer was asymptomatic throughout the study and no action was required.

Conclusions: Mild and moderate hepatic impairment does not seem to affect plasma levels of MHD after a single dose of oxcarbazepine. The data presented suggest that oxcarbazepine doses may not have to be altered in subjects with mild to moderate hepatic impairment. (Supported by Novartis Pharmaceuticals.)

2.338
LEVETIRACETAM IN MONOTHERAPY

J. M. Bird and Z. Joseph (Neuropsychiatry, The Burden Centre for Neuropsychiatry, Bristol, United Kingdom)

Rationale: Antiepileptic drug (AED) monotherapy is increasingly preferred to combination therapy as seizure control can be achieved with fewer risks of adverse effects and drug interactions. Levetiracetam, well established as add-on therapy for refractory partial seizures, has been shown to be effective as monotherapy for up to 12 weeks in patients responding to it use initially as add-on therapy (Ben-Menachem et al. *Epilepsia* 2000; 41:1276–83).This study aimed to review the long-term efficacy of levetiracetam in patients with refractory epilepsy successfully converted from levetiracetam add-on therapy to monotherapy following the withdrawal of baseline AEDs.

Methods: This is a retrospective (and still ongoing) analysis of our epilepsy clinic patient database. Data were reviewed from 352 patients who had received levetiracetam initially as add-on therapy. Our study population consisted of those patients who successfully converted to levetiracetam monotherapy and remain on monotherapy.

Results: In our clinic of 538 patients with chronic intractable epilepsy, 352 have been commenced on levetiracetam over a 3 year period. Of these, 52 are currently receiving levetiracetam monotherapy, having withdrawn from all other AEDs. Of these 52 patients, 24 (46%) have been entirely seizure-free for over 12 months and a further 8 (15%) seizure-free for 6 to 12 months. Of the 52 patients, 19 (36.5%), 21 (40.4%) and 12 (23%) were withdrawn from 3, 2 and one other AED(s) respectively.

Of the 20 patients still having seizures on levetiracetam monotherapy, all report reduced seizure frequency of more than 75% and 13 report reduced seizure severity.

This paper will also present three typical case histories of patients receiving levetiracetam monotherapy.

Conclusions: Levetiracetam, on the basis of this open series, appears to be effective and safe when used as monotherapy for epilepsy. (Supported by Research Grant from UCB.)

2.339

LEVETIRACETAM FOR THE TREATMENT OF TRIGEMINAL NEURALGIA

Keith R. Edwards, Judy T. O'Connor, and Judy Button (Neurology, Neurological Research Center, Bennington, VT)

Rationale: Trigeminal neuralgia (TN) is one of the most excruciating neuropathic pain syndromes known. Although the course of TN is typically that of spontaneous exacerbations and remissions that occurs over months and years, TN can become refractory to medical treatment and so may require invasive measures including ablative and surgical techniques. More effective and safer treatments are needed. Since the mainstay of medical treatment for TN are the antiepileptic drugs (AEDs), it is a rational consideration to try levetiracetam (LEV), a new AED for the treatment of TN. Since neuropathic pain involves mechanisms similar to that of epileptic mechanisms but in a different location in the nervous system, the use of AEDs for neuropathic pain is rational.

Methods: We treated 9 consecutive, unselected patients who were suffering from TN with LEV. Five were female, 4 male with a mean age of 62 years (range 34 to 78 years). Causes of their TN were idiopathic in 5, multiple sclerosis (MS) in 3 and Arnold-Chiari Syndrome in one patient. The mean duration of symptoms was 6.8 years (range 0.3 to 23 years). In 5 patients LEV was begun with a gradual titration. LEV was begun at an initial dose of 500 mg twice daily in 4 patients and at 250 mg twice daily in one patient. In 4 patients who presented with severe suffering at the time of initial evaluation, an initial dose of 2000 mg was given in the office and a maintenance dose of 1000 mg twice daily was immediately begun. Three of the TN patients had not previously been treated with any specific agent such as an AED. The others had been treated with carbamazepine (CBZ), oxcarbamazepine (OXC), gabapentin (GBP), baclofen, amitriptyline and various analgesics, usually opioid. Patients were titrated rapidly up to a dose that controlled their pain to a maximum of 2000 mg twice daily if needed.

Results: All 3 of the new TN patients experienced complete relief of pain within 48 hours and they had no recurrence of pain during the observation period of 6 months. One severely disabled MS patient who was in pain despite a 3 month treatment trial of CBZ developed complete relief of pain within 3 weeks on 500 mg bid LEV. The CBZ was tapered and discontinued over the next 3 weeks without return of pain. In the 5 patients with severe, long-standing and refractory TN, all 5 had good relief of pain but in 2 relief was temporary. One had recurrence of refractory pain after one year and the other had recurrence of refractory pain after one month. Those 2 patients required microvascular decompression for pain relief.

Conclusions: LEV appears effective in treating the neuropathic pain associated with TN. LEV may have a unique ability for rapid and total relief of the pain of newly occurring or recurrent TN since LEV can be rapidly increased or even 'loaded' to achieve effective CNS levels without debilitating side effects. In refractory patients, LEV appears to add significant relief and may eliminate in need for invasive procedures in some patients. (Supported by UCB.)

2.340

LAMOTRIGINE AS INITIAL MONOTHERAPY FOR EPILEPSY: A META-ANALYSIS OF 5 DOUBLE-BLIND COMPARATIVE STUDIES

Paul T. Caldwell, Clay R. Warnock, and John A. Messenheimer (Neurosciences, GlaxoSmithKline, Research Triangle Park, NC)

Rationale: We have reviewed aggregated data to determine the comparative risk of seizure during the initial 8 weeks of treatment using LTG and comparator anti-epileptic drugs (AEDs) for initial monotherapy.

Methods: A meta-analysis was conducted using data from 5 double-blind, randomized, active comparator studies comparing LTG with standard AEDs for initial epilepsy monotherapy. The goal of this analysis is to assess the efficacy of LTG relative to standard AEDs during the titration period. The studies were of similar design, duration (26–50 weeks), and patient population. The primary comparison in this analysis is the seizure-free rate during the first 8 weeks for pooled LTG data versus pooled comparator AED data using survival estimates of the proportion seizure-free at each week to assess therapeutic equivalence. Therapeutic equivalence is characterized as $>/= 50\%$ of the 'treatment effect' of standard therapy. For this analysis, treatment effect is defined as the difference in seizure-free rate between an active comparator and an estimated placebo response rate of 35%. LTG was considered therapeutically equivalent to the pooled comparator AEDs if the lower limit (LL) of the 95% confidence interval (CI) was more positive than the 50% of the treatment effect.

Results: Over the 5 studies, 383 patients were treated with LTG. Three studies used carbamazepine (CBZ, $n = 176$) as a comparator, and one study each used valproic acid (VPA, $n = 68$) and phenytoin (PHT, $n = 95$). Study completion rates were similar and ranged from 47% for PHT to 64% LTG.

Analysis of the primary comparison showed that LTG retained >50% of the comparator treatment effect in each of the first 8 weeks. The difference between the LTG and the pooled comparator AED response rate was never more than 8% (LTG seizure-free, 56–77%) and the difference decreased during the 8 weeks. For all therapies, seizure occurrence was greatest during the first week. Subsequently, first seizures occurred at a much lower frequency in all groups throughout the remaining 7 weeks of treatment. The results are similar when the analysis is limited to partial seizures.

In some of the studies, the dose escalation period was extended for CBZ (1 week) or PHT (2 weeks). Data were reanalyzed to exclude all first seizures during these times in patients randomized to these drugs. In this analysis, LTG maintained at least 50% of the comparator treatment effect for the first 3 weeks and was only marginally less for weeks 4–8.

Conclusions: During the first 8 weeks of therapy, LTG was therapeutically equivalent to the pooled active comparator AEDs using an estimated placebo seizure-free rate of 35%. The difference in response between LTG and the pooled AEDs was never greater than 8%. This analysis supports the position that the risk of seizure during dose escalation of LTG does not exceed the risk with other AEDs commonly used as initial monotherapy. (Supported by GlaxoSmithKline.)

2.341

COSMETIC SIDE EFFECTS OF THE ANTIEPILEPTIC DRUGS

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Rationale: Cosmetic side effects (CSEs) occur in a significant number of patients taking antiepileptic drugs (AEDs). Although this type of side effect has been well described for the older AEDs, the relative prevalence of these side effects among the newer AEDs is not known.

Methods: As part of the Columbia AED Database Project, we reviewed patient background, medical history, AED use, efficacy, and side effects for 1291 patients. CSEs included gingival hyperplasia, hair loss, hirsutism, weight gain, and acne; there were no reports of coarsening of facial features due to AEDs. We compared the overall rate of cosmetic side effects attributed to a particular AED. We repeated this analysis for monotherapy. Additionally, we examined the rate of cosmetic side effects in patients while taking, but not necessarily attributed to, a particular AED.

Results: Overall, CSEs were medication specific, occurred in 290/1291 (22%) patients, and led to dosage change or discontinuation in 155/1291 (12%) patients. Of the 753 patients receiving phenytoin (PHT), 45 (6%) developed gingival hyperplasia and 11 (1.5%) developed hirsutism attributed to PHT. Of the 560 patients on valproic acid (VPA), 37 (6.6%) experienced hair loss, and 80 (14.3%) experienced weight gain attributed to VPA. (All $p < 0.001$.) Of the 411 patients receiving gabapentin (GBP), 14 (3.4%) experienced weight gain attributed to GBP (NS). No other cosmetic side effect was attributed to any AED at a rate >1.2%. Results were similar whether on mono- or polytherapy, and were unchanged when including cosmetic side effects that occurred while taking, but not necessarily attributed to, a particular AED.

Conclusions: PHT and VPA were associated with cosmetic side effects. PHT was associated with gingival hyperplasia and rarely hirsutism, whereas VPA was associated with weight gain and hair loss. Cosmetic side effects were rarely associated with the newer AEDs. (Supported by Elan, GlaxoSmithKline, Ortho-McNeill, Pfizer, and UCB Pharma.)

2.342
FOOD DOES NOT AFFECT THE PHARMACOKINETICS OF SPM 927

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Rationale: SPM 927 is a new drug developed for the treatment of epilepsy and neuropathic pain. Essential clinical pharmacologic data have been established in a series of phase 1 trials. Clinical development requires information about a possible influence of concomitant food intake on the pharmacokinetics of SPM 927.

Methods: In a single-center, open-label, two-fold crossover trial 24 healthy male subjects (age: 30.5 ± 6.5 ys., weight: 74.7 ± 7.9 kg) received a single oral dose of 300 mg SPM 927 in the fasted state (treatment A) and 30 minutes after a standard high-fat and high-calorie breakfast (treatment B) in accordance with the FDA guidelines. There was a washout phase of one week between the two periods. In each period, 15 blood samples were taken from predose until 72 hours after administration of SPM 927. SPM 927 plasma concentrations were detected with a highly sensitive and selective LC-MS/MS method. The following pharmacokinetic parameters were determined using non-compartmental methods: maximum plasma concentration (C_{max}), area under the concentration time curve from zero up to the last measurable plasma concentration ($AUC_{0\text{-}tz}$) and up to infinity ($AUC_{0\text{-}inf}$), time to reach C_{max} (t_{max}), terminal half-life ($t_{1/2}$). Log transformed data of C_{max}, $AUC_{0\text{-}tz}$, $AUC_{0\text{-}inf}$ and untransformed data of t_{max} in the fasted and fed state were analyzed using analysis of variance (ANOVA). Based on these analyses point estimates and 90% confidence intervals (CI) for the ratio (for C_{max}, $AUC_{0\text{-}tz}$ and $AUC_{0\text{-}inf}$) "fed" versus "fasted" and for the difference (t_{max}) "fed" minus "fasted" were calculated.

Results: All 24 subjects completed both periods of the trial and were included in the analysis. C_{max} was 7.4 [16.9] μg/mL (geom. mean [geom. CV%]) and 7.7 [15.3] μg/mL, $AUC_{0\text{-}tz}$ was 138.0 [13.2] h*μg/mL and 140.8 [13.1] h*μg/mL, $AUC_{0\text{-}inf}$ was 141.9 [13.5] h*μg/mL and 144.3 [13.3] h*μg/mL after the administration of 300mg SPM 927 under "fed" and "fasted" conditions, respectively. t_{max} under "fed" as well as under "fasted" conditions was between 0.5 h and 4.0 h. Geom. mean of $t_{1/2}$ was nearly identical with 13.4 h and 13.3 h under "fed" and "fasted" conditions, respectively.

The ratios "fed" versus "fasted" (90% CI) for C_{max}, $AUC_{0\text{-}tz}$ and $AUC_{0\text{-}inf}$ were 97% (91–103%), 98% (96–100%), and 98% (97–100%), respectively. The difference "fed" minus "fasted" (90% CI) for t_{max} was 0.5h (0.0–1.0h].

Conclusions: The 90% confidence intervals of the $AUC_{0\text{-}tz}$, $AUC_{0\text{-}inf}$ and C_{max} point estimates were within the generally accepted bioequivalence ranges of 80–125%. Thus, it was demonstrated that administration with food does not alter the rate or extent of gastrointestinal absorption of SPM 927. Based on these results, it can be concluded that SPM 927 can be taken without regard to meals. (Supported by Schwarz Biosciences GmbH, Alfred-Nobel-Straße 10, 40789 Monheim, Germany.)

2.343
SIMULTANEOUS MEASUREMENT OF MHD AND CARBAMAZEPINE LEVELS IN PATIENTS TAKING OXCARBAZEPINE OR CARBAMAZEPINE

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Rationale: It has been suggested that patients taking higher doses of oxcarbazepine (OXC) may have measureable levels of carbamazepine (CBZ). This is a important clinical issue when patients taking OXC present to the emergency room with breakthough seizures. Since many emergency room physicians are still not familiar with OXC, this may lead to the erroneous overdosing of OXC as "compensation" for the observed low, but measureable CBZ level. We sought to make concurrent measurements of OXC and CBZ in patients taking either drug in an attempt to determine how likely such cross reactivity might be.

Methods: A retrospective review of adult epilepsy and trigeminal neuralgia patients (2001–2004) was performed to identify those taking OXC or CBZ in monotherapy. From this list, we noted simultaneous steady state measurements of the mono-hydroxy deriviative (MHD) of OXC and CBZ in 15 different patients (12 epilepsy; 3 trigeminal neuralgia). Some had more than one concurrent level performed; there were a total of 19 concurrent levels. CBZ levels were performed locally in the hospital lab. MHD levels were sent out to a commercial lab (Quest). With two exceptions (1- MHD, 1- CBZ), levels represented troughs. Due to the relatively small sample, data were analyzed descriptively.

Results: No obvious differences in doses or levels between the epilepsy and trigeminal neuralgia patients were noted, so these data were collapsed. The median age of OXC patients was 42 (27–69). The median dose was 1200mg/day (525–2550mg, n = 14). The median MHD level was 19.5 μg/ml (8.2–65). The concomitant median CBZ in these same patients was < 0.6 μg/ml (<0.2–<2.0).

The median age of CBZ patients was 31(27–69). The median dose was 1100 mg/day (600–1500mg; n = 5). The median CBZ level was 8.9 μg/ml (7.3–17.7). The concomitant median MHD level in these same patients was 0 μg/ml (0–0).

Conclusions: Simultaneous measurement of MHD and CBZ levels in OXC treated patients, and in CBZ treated patients, did not reveal evidence of cross reactivity at doses typically used in clinical practice. Although the sample sizes were small, they did include a number of patients treated with high doses of OXC (>1200 mg/day) and CBZ (>1000mg/day); those in which assay cross reactivity might be expected to occur. While confusion between the two drugs might still exist on the basis of similarities of both the trade and generic names; at least on the basis of this series, cross measurement by their respective assays is probably not common.

2.344
IMPROVED SEIZURE CONTROL WHEN OXCARBAZEPINE IS ADDED TO SODIUM CHANNEL BLOCKERS OR OTHER ANTIEPILEPTIC DRUGS

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Rationale: Oxcarbazepine (OXC), carbamazepine (CBZ) and phenytoin (PHT) are first-line antiepileptic drugs (AEDs) as monotherapy and are widely used in the treatment of epilepsy. Although all are sodium channel blockers, different mechanisms on the sodium channel may result in improved seizure control when they are combined or added to AEDs with different mechanisms of action.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of OXC 600, 1200 and 2400 mg/day as adjunctive therapy for 28 weeks in patients with refractory partial seizures (Barcs et al. *Epilepsia* 2000; 41:1597–607). This study consisted of an 8-week baseline, 2-week titration, 24-week maintenance, and a 2-week down titration. Eligible patients were 15–65 years old with simple or complex partial seizures (with or without secondarily generalized seizures) who were currently receiving treatment with 1–3 AEDs and were poorly controlled (≥4 seizures/month during baseline). OXC was initiated at 300 mg/day, increased to 600 mg on day 2, titrated up 300 mg every 2 days over 2 weeks, and maintained on patients' final fixed dose. Efficacy assessments included: percentage of patients who experienced seizure reductions of >50%, >75% and 100%. We performed a subanalysis of these data for the 4 most common concomitant AEDs: CBZ, valproate (VPA), PHT and lamotrigine (LTG). Adverse events were recorded.

Results: A total of 692 (n = 519 OXC, n = 173 placebo) were randomized and received treatment. Of the OXC-treated patients, 52.6% completed the double-blind treatment phase and 38.5% discontinued due to adverse events. A >50% reduction in mean seizure frequency was observed in 33% to 40.5% of patients and 100% reduction was observed in 11.9% to 14.5% of patients whether CBZ, VPA, PHT or LTG were part of their AED regimen. The response rates as observed by concomitant AED for all OXC-treated patients are shown (Table 1).

A similar response was observed when patients' data were analyzed by OXC dose level, with a trend showing improved seizure reduction with increased OXC dose. The most common adverse events involved the CNS or gastrointestinal systems and occurred at similar frequency regardless of concomitant AED.

TABLE 1. *Seizure reduction from baseline*

		>50%		>75%		100%	
	N	n	%	n	%	n	%
OXC + CBZ	387	146	37.7	86	22.2	47	12.1
Placebo + CBZ	123	13	10.6	5	4.1	1	0.8
OXC + VPA	131	53	40.5	32	24.4	16	12.2
Placebo + VPA	46	5	10.9	1	2.2	0	0
OXC + PHT	109	40	36.7	23	21.1	13	11.9
Placebo + PHT	38	6	15.8	2	5.3	0	0
OXC + LTG	69	33	33.0	12	17.4	10	14.5
Placebo + LTG	23	3	13.0	0	0	0	0

Conclusions: In this subanalysis, OXC was shown to reduce seizure frequency whether added to CBZ, PHT or other AEDs in patients with refractory seizures. Improved seizure control when OXC is added to the standard sodium channel blockers CBZ or PHT suggests that its mode of action may involve distinct mechanisms. (Supported by Novartis Pharmaceuticals.)

2.345

DETERMINANTS ASSOCIATED WITH POOR COMPLIANCE IN NEWLY DIAGNOSED EPILEPSY PATIENTS

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Rationale: Compliance is known to be a major issue in the management of epilepsy. Thus, the identification of factors associated with poor compliance should lead to improved seizure control.

Methods: In a French, multi-centric, open, prospective study, neurologists were asked to include newly diagnosed epileptic patients and to ask them to fill out auto-questionnaires assessing: compliance (P Loiseau and C Marchal compliance questionnaire, 1988), knowledge of epilepsy (adapted from Jarvie questionnaire, 1993), impact of epilepsy (Jacoby, 1993), quality of life (QOLIE 31) and stigmatization (from Jacoby stigmatization of epilepsy scale, 1994). Compliance were also assessed using pills count and blood levels of valproic acid. Regression analysis was performed in order to identify determinants associated with compliance.

Results: A total of 356 patients (mean age: 38.5 years, sd: 15.78; male: 50%) were included by 124 neurologists and treated with valproate for 26 weeks.

According to the Loiseau questionnaire item 1, at week 26, compliance was globally high. Among patients who have taken the treatment at least once, only 53 patients (21.3%) notified to have forgotten their medication sometimes (n = 47) or often (n = 6), versus 121 never and 75 exceptionally (missing data: n = 81).

Under Loiseau questionnaire item 2, patients who reported having forgotten to take their pills for at least one day, had more seizures than others (11.5% vs 32.0%, Exact Fisher test, p = 0,028).

By regression analysis:

- According to Loiseau questionnaire item 1three determinants appeared related to high compliance:
  - Being a female (p = 0.012, male versus female odds ratio: 0.531, 95%CI: [0.324–0.872])
  - Being older (p < 0.0001, odds ratio: 1.036, 95%CI: [1.019–1.053]),
- According to pills count, two determinants (only statistical trends) were associated to poor compliance:
  - Having a high score at D0 to the QOLIE 31 (p = 0.0893).
  - Antecedent of anxiety disorder (p = 0.0543).

Neither the nature of the epileptic syndrome, nor the impact of epilepsy, nor the stigmatization nor the knowledge about epilepsy influenced compliance.

Conclusions: These data emphasize the heavy consequences of poor compliance in epilepsy and plead for developing therapeutic alliance. They also underline that factors related with compliance are highly dependent on the criteria used for assessing compliance. (Supported by Sanofi~synthelabo.)

2.346

IS MULTIPLE DAILY DOSE ENTERIC-COATED DIVALPROEX MORE PROTECTIVE THAN EXTENDED-RELEASE DOSED ONCE DAILY WHEN A DOSE IS MISSED?

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Rationale: Missing and replacing at a later time [m/r], enteric-coated divalproex [dvp] dose given twice daily compared to m/r once-daily extended-release divalproex [dvp-ER] may have different effects on the ability of these formulations to sustain steady-state total plasma valproate concentrations [VPA]. Computer-simulated changes in [VPA] when a patient m/r their dose(s) of multiple-daily dose dvp were compared to a m/r once-daily dvp-ER dose to determine which formulation is better able to sustain [VPA], and therefore is "more protective" clinically.

Methods: Various scenarios include virtual adult epilepsy patients, taking dvp 562.5mg q12h, compared to dvp-ER 1250mg qam (higher dvp-ER dose compensates for lower dvp-ER bioavailability) chronically as monotherapy (uninduced); likewise in polytherapy (hepatic enzyme-induced) patients, taking 1125 mg dvp q12 h vs 2500 mg dvp-ER qam. [VPA] was analyzed when dvp or dvp-ER dose(s) were missed, then replaced at 12, 18 or 24 hours, while resuming scheduled therapy with the next dvp or dvp-ER dose(s) at 24 hrs. [VPA]-time profiles were simulated for 1000 hypothetical patients for each scenario using a 1-compartment population kinetic model with nonlinear protein binding (Monte Carlo stochastic simulations, ADAPT II software) and incorporated 20% inter-patient variability and 10% residual error.

Results: In induced patients, steady-state baseline (no m/r dose) mean [VPA] Cmin and Cmax values for dvp were 67 and 98 mg/L, and for dvp-ER were 81 and 88 mg/L, respectively. When dvp dose(s) were m/r, mean [VPA] Cmin values fell to 37, 28 and 20 mg/L upon replacement at 12, 18 and 24 hrs, respectively. Replacing, then resuming dvp increased the mean [VPA] Cmax values to 113, 117 and 129 mg/L upon replacement at 12, 18 and 24 hrs; maximum mean increase of 31 mg/L above the baseline Cmax. When a dvp-ER dose was m/r, mean [VPA] Cmin values fell to 46, 34 and 25 mg/L upon replacement at 12, 18 and 24 hrs, respectively. Replacing, then resuming dvp-ER bumped the mean [VPA] Cmax values up to 107, 111, 114 mg/L upon replacement at 12, 18, 24 hrs; maximum mean increase of only 26 mg/L above the baseline Cmax. For these simulations,%CVs ranged from 22% to 61%. When dvp doses or a dvp-ER dose is m/r at 24 h, 90% of patients would have a [VPA] Cmax increment of <43 or <33 mg/L, for dvp or dvp-ER, respectively. In uninduced patients, [VPA] changes were similar, but less pronounced.

Conclusions: The fall in [VPA] after missing the dvp or dvp-ER dose(s) is pronounced in the induced patient, especially at 24 hours; replacing the missed dvp or dvp-ER dose(s) while resuming therapy produces a large, but not unexpected rise in [VPA]. Our simulations predict multiple-daily dvp is not more protective than daily dvp-ER in the case of m/r dose(s) with respect to maintenance of [VPA]. (Supported by Abbott Laboratories.)

2.347

WILLINGNESS TO PAY FOR A NEW ANTIEPILEPTIC DRUG TREATMENT (LEVETIRACETAM): ANALYSIS AND RESULTS OF A SURVEY OF QUEBEC

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Rationale: Evaluate the value of a new anti-epileptic add-on drug, namely levetiracetam (LEV) and compare the theoretical point of

consumption estimate obtained through the willingness to pay (WTP) method to the actual LEV wholesaler price in Quebec. The WTP approach measures the resources that individuals are willing and able to give up for a reduction in the probability of encountering a hazard that will compromise their health. The WTP methodology might be useful in economic analysis of new specific treatment for epilepsy like levetiracetam. Consumers' willingness to pay can be expressed as a point of consumption context and an optimal pricing policy can be scheduled and validated.

Methods: The data originate from a survey of 1484 randomly selected households. The study area of this research was the province of Quebec (Canada). The survey yielded 727 (52%) usable interviews about WTP for a new anti-epileptic treatment. Respondents were assigned randomly to four subgroups, with members of each sub-groups being asked to respond to a different set of bids (in Canadian Dollars - CAD). The designed questionnaire and the set of bids used were derived from expert opinion and based on LEV characteristics and profile. A recent methodological development within the dichotomous choice (DC) method - called Double-Bounded Dichotomous Choice Contingent Valuation (DBDC-CV) model - was used for analysis. A variety of models was fit by maximum likelihood, using different cumulative distribution functions, with one or more covariates (age, gender, occupation, education and income). Goodness-of-fit measures were estimated to assess how well the models fitted the observed data. By considering only the range of feasible values, normalized truncated measures for the WTP were calculated from the estimated models.

Results: From the 727 usable interviews, 669 respondents answered to the four possible response pairs. The odds-change log-logistic model for the true WTP provided a good fit to the data. The estimates and the width of confidence intervals indicated a normalized truncated mean of 10.76 CAD (Bootstrap 95% CI: 9.97, 11.59) for the point of consumption estimate. The socio-demographic characteristics appeared non-significant on the basis of likelihood ratio tests. After model checking and examination of the impact of socio-demographic variables, it was concluded that a value of 10.76 CAD can be considered as the daily amount that an individual is willing to pay for a new antiepileptic drug having LEV characteristics.

Conclusions: The main result indicates that the value for the normalized truncated mean of the willingness to pay is much higher than the average wholesaler price for LEV (estimated 5.46 CAD for 1500 mg daily) suggesting that the actual market price requested for levetiracetam is valid in the context of Quebec. (Supported by UCB Pharma SA.)

2.348

LEVETIRACETAM IN DRUG-RESISTANT FOCAL AND GENERALIZED EPILEPSY

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Rationale: Levetiracetam (LEV) had demonstrated its efficacy in pivotal clinical trials of adjunctive therapy in focal (FE) and generalized (GE) drug-resistant epilepsy. There are few post-marketed studies about the long-term efficacy and safety of LVT. We report our experience with LEV in FE and GE.

Methods: This prospective observational, add-on, open study explored the efficacy (number of seizures/month) and tolerability (adverse events) of LEV in a prospective series of 43 patients with drug-resistant focal and generalized epilepsy attending a single epilepsy unit between February 2002 and April 2004

Results: 43 patients (21 women and 22 men), 39 with FE and 4 with GE. Mean age: 37.7 years. Mean time with epilepsy: 22.1 years (FE: 36.52, GE: 27.5). Mean duration of treatment 12 months (range 1 week-23 months). Mean doses of LEV 1,900 mg/day (range 500–3,000 mg/day). FE group: seizure-free 5 patients (13%), frequency of seizures was reduced by more than 50% in 15 patients (38%), less than 50% in 5 patients (13%), did not vary in 8 (21%) and 6 patients (15%) showed an increase in seizure frequency. In the GE group: one patient with Lennox-Gastaut Syndrome suffered a generalized status, two patients (one with absence with eyelid myoclonia and another with Lafora disease) did not vary their frequency of seizures and another patient with Lennox-Gastaut Syndrome showed less than a 50% decrease in seizure frequency. Early tolerance (lees than 2 months) appeared in one patient and late in another two. Adverse effects of LEV, (lethargy, dizziness, irritability, depression and anorexia) appeared in 39% of patients, all of them at the FE group. Treatment cessation with LEV was necessary in 14 FE patients (tolerance, adverse effects and seizure increase) and 3 GE patients (inefficacy).

Conclusions: LEV reduced the frequency of seizures by more than 50% in half of patients (13% seizure-free). In our few cases of GE, LEV was less effective. LEV appears to be well-tolerated in most cases.

2.349

PROOF OF PRINCIPLE IN THE NEW AED UCB 34714: USE OF THE PHOTOSENSITIVITY MODEL

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Rationale: To assess the pharmacodynamics and the tolerability of single doses of the new AED ucb 34714, a 2-pyrrolidinone derivative, in photosensitive subjects. This new drug exhibits a high, selective interaction with the brain-specific levetiracetam (LEV) binding site. LEV has shown to be effective in this POP model before.

Methods: A placebo-controlled, single blind, single period study was conducted in 19 photosensitive subjects (15 females) between 18- 60 yrs of age, taking one or two concomitant AEDs (VPA, LTG, PHT, GBP and LEV) or none (3). During a three day period, subjects underwent standardized intermittent photic stimulation (IPS) to define the Standard Photosensitive Range (SPR) per patient at fixed time points. After the first day with placebo, single oral dosages of ucb 34714 were given, starting with 80 mg and subsequent lowering of the dose per 4 patients. The SPR was the main parameter to identify the lowest single oral dose of ucb 34714 producing maximal diminution or suppression of the IPS evoked photoparoxysmal EEG response (PPR) comparing the SPRs before and after intake of ucb 34714. Pharmacokinetic parameters of ucb 34714 were computed from the blood samples collected up to 72 hours post-dose.

Profile Of Mood State (POMS) and Addiction Research Center Inventory short form questionnaire (ARCI-49) were administered to investigate possible effects on mood.Descriptive statistics were used.

Results: A total of 18 patients were evaluable: important SPR changes (100%) or complete abolishment (14/18, 78%) of the PPRs were observed after ucb 34714 intake (doses tested and effective: 80, 40, 20 and 10 mg). No relationship between the pharmacodynamics of the drug (expressed as SPR change and duration of response) and the dose or the exposure to the drug (expressed as AUC or Cmax) was found. The 80 mg dose appeared more efficient (time to maximal response and duration of response). The pharmacokinetic and side-effect profile was similar to that in healthy volunteers. Twelve subjects reported 20 mild to moderate AEs (4/20 after placebo). Dizziness (5), dry mouth (1) and nausea (1) were reported exclusively in the verum period. A small increase in sedation (ARCI-49) was noticed 3 hrs after administration of 80 mg of ucb 34714. The POMS did not show any change.

Conclusions: All the single doses (10, 20, 40, and 80 mg) of ucb 34714 were effective in reducing or even abolishing (78%) the photoparoxysmal EEG response in photosensitive subjects. Eighty mg of ucb 34714 was however the most efficient dosage. Compared to levetiracetam, the efficacy of ucb 34714 in this model is more potent. (Supported by UCB Pharma BV.)

2.350

THE CHANGE OF CLEARENCE OF VALPROATE IN TRAUMATIC BRAIN INJURY PATIENTS

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Rationale: Traumatic brain injuries induce plasma clearance of several compounds. Phenytoin is usually used prevention of posttraumatic

seizure, and it is known that its clearance is increased in traumatic brain injury patients. Valproate is another important anti-epileptic drug for prevention of posttraumatic seizure. We evaluated the metabolism of valproate in acute traumatic brain injury patients.

Methods: Twenty-five acute traumatic brain injury patients were selected. They were received loading dosage (15–20 mg/kg) and maintain with valproate. Trough serum valproate level was obtained between 7–20 days after acute brain injury. We calculated clearence level of valproate of each patients and compared with the clearence rate of chronically valproate use patients.

Results: The total clearance rate of valproate was increased in acute traumatic brain injury patients than chronically valproate use patients (6.71 ± 1.58 ml/kg/hr vs. 9.13 ± 2.18 ml/kg/hr, $p < 0.05$).

Conclusions: Acute traumatic brain injury results in induction of valproate metabolism during acute 7–20 days and it is related to enhance of multiple metabolism pathway.

2.351

A RETROSPECTIVE STUDY OF THE EFFICACY AND TOLERABILITY OF ZONISAMIDE IN THE TREATMENT OF EPILEPSY IN PATIENTS WITH MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES

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Rationale: Epilepsy is common in developmental disabled (DD) or mentally retarded (MR) patients, yet few studies specifically address the experience with antiepileptic medications (AEDs) in this special patient population. This study is to assess the response to Zonisamide (ZNS) in patients with DD/MR.

Methods: A retrospective review was made of all DD/MR patients treated with ZNS as adjunctive therapy from July 2000 to March 2004 at the Long Island Jewish Comprehensive Epilepsy Center.

Results: Eighteen patients (8 male, 10 female) have been identified so far. The median age was 40.5 years (range, 21–62 years). Median ZNS dose was 350 mg/day (range, 100–600 mg/day). Patients' duration of ZNS exposure ranges from 1.8 months to 33.6 months (median, 13.8 months). These patients had either a single or a combination of a different seizure types, including generalized tonic-clonic, complex partial, absence, atonic, tonic and myoclonic seizures. The median seizure frequencies in the 6-month periods immediately before and after ZNS treatment are 1.98/month (range, 0.62–82/month) and 1.23/month (range, 0–12.9/month), respectively. 12 patients (66.7%) demonstrated a reduction in overall seizure frequency after ZNS treatment (median daily dose 300 mg; range 100–600 mg). Out of these 12 patients, eight experienced >50% reduction and four experienced <50% reduction in seizure frequency. Five patients (27.8%) reported increased seizures, and the seizure frequency change in one patient (5.6%) is unknown. The overall improvement in seizure control in patients while taking ZNS is statistically significant ($p < 0.05$). Adverse reactions were reported in nine patients while taking ZNS (median daily dose 300 mg, range 100–400 mg). Two patients demonstrated behavioral or mood symptoms. One of them had a history of behavioral disorder, and symptom abated spontaneously in the other patient. Other adverse reactions reported included 3 patients with tremors (one of them has Alzheimer's disease), 3 patients with fatigue or drowsiness, 2 patients with gastrointestinal (GI) upset, 1 patient with dizziness.

Conclusions: Similar to the experience in the general epilepsy population, Zonisamide is an efficacious and generally well-tolerated treatment for epilepsy patients with developmentally disabilities or mental retardation. (Supported by Elan Pharmaceuticals, Inc.)

2.352

SEIZURE EFFICACY AND QUALITY-OF-LIFE IMPROVEMENT WITH THE USE OF LAMOTRIGINE

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Rationale: Assessment of anti-epileptic medication effects are commonly performed in somewhat artificial experimental conditions. This study evaluates seizure efficacy and mood and quality-of-life effects of lamotrigine (LTG) in a real-world clinical setting.

Methods: This ongoing prospective observational study recruited adult patients at the outpatient centers of the Long Island Jewish Comprehensive Epilepsy Center who were identified as appropriate candidates for LTG treatment by their epileptologists. Patients completed the Quality of Life in Epilepsy-31 inventory (QOLIE-31), the Profile of Mood States (POMS), and a seizure severity scale at baseline, 2 months, 6 months, and one year after beginning LTG, with the dosage titrated according to concomitant antiepileptic medications.

Results: Of 61 patients enrolled, 23 have completed the baseline evaluation and one year assessment after LTG initiation. There are 10 males and 13 females. The mean age is 39, and the mean duration of epilepsy is 13.5 years. Fourteen patients (61%) had greater than 50% reduction in seizures, and 9 patients (39%) had no change in seizures. Significant improvement was found on the QOLIE-31 in the overall score ($p < 0.009$) and in subsets assessing cognition ($p < 0.43$) and medication effects ($p < 0.035$). Trends of improvement were found in subsets of emotional well-being ($p < 0.057$) increased energy ($p < 0.072$). POMS scores found significant improvement in the subset assessing increased vigor ($p < 0.009$). There were no significant differences on all scores between the groups who had improvement in seizure control and those who did not.

Conclusions: Improvement in quality of life and mood occurs with the use of LTG. While most patients had better seizure control with LTG, these quality of life effects were independent of seizure efficacy, suggesting an independent medication effect. (Supported by GlaxoSmithKline.)

2.353

EFFECTS OF LEVETIRACETAM ON STROKE-RELATED SEIZURES: AN OPEN-LABEL TRIAL: PRELIMINARY REPORT

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Rationale: In the elderly, stroke is the most common cause of seizures that occur in about 5–10% of cases either as early or late seizures (cut point: two weeks). Most early onset seizures occur within the first 48 hours after stroke. Early seizures are a risk factor for occurrence of late seizures which in turn carry a high risk for epilepsy developing in 35% of early seizures and in 90% of late seizures. The size of regional metabolic dysfunction may be relevant in causing early seizures, whereas permanent lesion can explain higher frequency of epilepsy in patients with late than early seizures. We tested levetiracetam to evaluate its effects on early and late seizures, to verify its effects on avoiding patients to become epileptic and to assess its tolerability.

Methods: In 2003 we treated 29 patients with stroke-related seizures (first ever seizure or late seizures not treated with antiepileptic drugs in the last three months). Patients were given 1,000–2,000 mg of drug in mono therapy for six months. Follow-up is about six months (study in progress).

Results: Demographics: 15 men, 14 women, mean age 74 years (range 57–80); 25 had ischaemic stroke (in more than half of cases, hemispheric parieto-temporal and with a multiinfarct condition) and 4 had cerebral haemorrhage (10% out of 250 and 39, respectively). Early seizures were 10 (9 in ischaemic and 1 in haemorrhagic stroke); late seizures were 19 (16 in ischaemic and 3 in haemorrhagic stroke). In 16 cases, seizures were initially focal with or without secondary generalisation and in 13 they were apparently generalised "d'emblee." Among the patients with ischaemic stroke, 7 had atrial fibrillation, 11 had hypertension, 3 were diabetic. Among the haemorrhagic patients, 3 were hypertensive. Recurrence of seizures occurred in only 3 patients (10%),all with ischaemic stroke and late, focal seizures. Despite low titration, in 2 cases patients complained of somnolence that was not so severe to induce the withdrawal of drug.

Conclusions: On the basis of these preliminary results, levetiracetam proves to be an effective and safe drug in the treatment of stroke-related seizures.

2.354

TREATING SEIZURES DUE TO BRAIN NEOPLASMS: RATIONAL NEW CHOICES

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Rationale: CNS neoplasms are frequently the cause of new adult onset seizures. Treatment involves treatment of the neoplasm as well as adjuvant antiepileptic drug therapy (AED). Phenytoin has historically been used as the AED of choice. As a P450 3A4 metabolized AED, it may alter chemotherapy drug (CD) efficacy. Efficacy of new AEDs and CD efficacy needs to be evaluated in treatment of patients with CNS neoplasms.

Methods: Retrospective review of patients referred for brain mapping or new onset seizures due to tumors from Jan 1999 to April 2004 was performed noting: tumor type, location, presenting symptoms, presence of seizures at onset, result of AED treatment, tumor treatment and functional status at last visit. Forty patients ages 18–77 were reviewed (26 males, 15 females). Tumors were: 5 glioblastomas, 10 astrocytomas, 7 oligoastrocytoma, 10 oligodendrogliomas, 1 meningioma, 1 ganglioglioma, 2 DNET, 5 unknown. All received AEDs; 81.6% had resection; 45% had CD; 55% had radiation; 10% cyberknife therapy. AEDs used: gabapentin (GBP) monotherapy (MT) 3; levetiracetam (LEV) MT 22 and polytherapy (PT) 5; oxcarbazepine (OXC) 3 MT and 3 PT; phenytoin MT 2 and 1 PT; topiramate (TPM) MT 1. CD utilized were temozolomide 72.2%; BCNU/CCNU 10%; and 5% each cisplatin, procarbazine, thalidomide, etoposide and imatinib.

Results: There were 5 deaths (12.5%) and 7 lost to follow-up. 87.5% presented with seizures. 77.8% of LEV patients were seizure free or only SPS. 71.4% OXC were seizure free or SPS only. The 1 TPM patient was seizure free. No phenytoin patients were seizure free. Tumor treatment resulted in survival and good functional outcome in 84.8%.

Conclusions: AEDs with no or minimal hepatic metabolism include GBP, LEV, TPM. OXC is reduced by a noninducible ketoreductase. CD metabolic pathways vary: temozolomide is conjugated; etoposide, BCNU and CCNU are hydroxylated; procarbazine, imatinib and vincristine are oxidized and inducible. Dexamethasone, frequently utilized initially, induces P450 AED metabolism. Choice of CD regimen is not often know at time of initial diagnosis. Choice of GBP, LEV, OXC or TPM would potentially avoid drug interactions and allow maximum CD effectiveness. All 4 AEDs showed excellent seizure outcome whereas phenytoin did not, although numbers are small. Patients with CNS neoplasms should be given maximum opportunity for successful outcome both for seizure control and survival. Treatment of seizures in these patients is effective utilizing GBP, LEV, OXC, and TPM with low risk of interfering with chemotherapy.

2.355

ANTIEPILEPTIC DRUG USERS HAVE AN INCREASED RELATIVE PROPORTION OF ABDOMINAL FAT, AS DETERMINED BY DUAL-ENERGY X-RAY ABSORPTIOMETRY (DEXA): A USAGE-DISCORDANT FEMALE TWIN AND MATCHED-SISTER PAIR STUDY

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Rationale: Antiepileptic medication (AED) usage is well established to be associated with a change in total body weight. Valproate (VPA) users in particular are prone to weight gain. Other AEDs, such as topiramate, are associated with weight loss while lamotrigine is weight-neutral. The mechanisms for AED-associated weight changes are unknown. It is now recognized that changes in the distribution of body fat have important health implications independent of total body weight, specifically the association of increased relative abdominal fat as a risk factor for cardiovascular disease. Dual energy x-ray absorptiometry (DEXA) has proven a valuable tool in the assessment of body fat distribution, but has not been applied to the study of the effects of AED use on the distribution of body fat. The aim of this study was to utilize an AED usage-discordant twin and matched sister approach to examine this issue.

Methods: 16 twin (9 monozygous,7 dizygous) and 3 sister pairs discordant for >12 months of any AED use with a mean(SD) age of 37.8(16.0) were included. Body composition including fat distribution was acquired using DEXA scanning (Hologic 4500A/1000W). The abdominal region was defined as the area extending from the superior surface of the 2nd lumbar vertebra to the inferior surface of the 4th lumbar vertebra and laterally to the inner aspect of the ribcage. Conventional whole body analysis was used to determine total body and trunk fat. Abdominal fat was expressed as a percentage: of the abdominal region (Afat%); of total trunk fat (AfatTT%); of total body fat (AfatTB%). Height and weight were measured. Paired t-tests (two-tailed) were used to test for within-pair differences.

Results: There was no significant within-pair difference in height, weight, total body fat and lean mass. There was a within-pair difference (AED user vs. non-user) in AfatTB% (6.6% vs. 5.6%, $p = 0.038$) and in Afat% (25.1% vs. 20.0%, $p = 0.079$). Pairs discordant for >2 years of AED use ($n = 16$) had a within-pair difference in AfatTT% (18.5% vs. 16.3%, $p = 0.038$), AfatTB% (6.7% vs. 5.5%, $p = 0.030$) and within-pair difference in Afat% (23.8% vs. 18.3%, $p = 0.057$). The within-pair difference in current valproate users ($n = 7$) was similar to that of non-valproate AED users ($n = 12$) for weight, height and the fat distribution.

Conclusions: AED users have altered body fat distribution compared to non-users, with an increase in the relative proportion of abdominal fat, independent of differences in body weight. There was no relationship to the type of AED used, with valproate users showing similar changes to non-valproate AED users. This novel finding demands further investigation and may have important health implications particularly for risk of cardiovascular disease in this population.

2.356

EFFICACY, SAFETY, AND TOLERABILITY OF RETIGABINE AS ADJUNCTIVE THERAPY IN PATIENTS WITH REFRACTORY PARTIAL-ONSET SEIZURES IN AN OPEN-LABEL STUDY

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Rationale: Retigabine (RGB) has a novel mode of action and exhibits potent anticonvulsant activity in broad range of animal models of epilepsy. It potentiates GABA-evoked currents and enhances K^+ current mediated by human KCNQ2 and KCNQ3 potassium channels. This study evaluated the efficacy and safety of RGB administered as adjunctive therapy to patients with refractory partial-onset seizures.

Methods: All patients who participated and completed a double blind placebo controlled study were invited to participate in an open label long-term extension study. During the double blind portion of the study, patients received placebo, 200 mg, 300 mg or 400 mg of RGB three times daily (tid). At the end of the study, all patients were converted to receive 300 mg tid of RGB. Following this, each patient's daily dose of RGB or concomitant AEDs could be either reduced or increased. The maximum daily dose of RGB allowed was 1,200 mg. Each patient maintained a daily seizure diary. Patients were followed-up at regular intervals and efficacy and safety parameters (AEs, ECG, hematology, biochemistry and urinalysis) were assessed.

Results: Of the 399 patients enrolled in the double blind study, 279 completed the study and 222 enrolled in the open label study. Of these, 18 (8%) discontinued within the first three months and 41 (18%) discontinued within six-months. The most common daily dose of RGB was 900 mg (105 patients; 47.3%) and only a minority of the patients titrated the dose to 1,200 mg (53; 23.4%). The median decrease in monthly total partial seizure frequency from baseline was 48.3%. 103 patients (46.4%) showed a reduction in monthly total partial seizure frequency of $\geq$50%. The most common cause for discontinuation from the study was adverse events related to CNS. There were no clinically significant changes in ECGs or laboratory parameters.

Conclusions: RGB appears to be safe, efficacious and well tolerated. RGB has demonstrated a meaningful reduction in total partial seizure frequency. The Phase III clinical development program for RGB will further evaluate the efficacy and tolerability of this novel AED.

2.357

THE OPTIMAL BLOOD SAMPLING TIME AFTER ONCE-DAILY DIVALPROEX EXTENDED-RELEASE DOSED IN THE MORNING SEEMS CLEAR, BUT WHEN DOES ONE SAMPLE AFTER EVENING DAILY DOSING?: RECOMMENDATIONS TO CLINICIANS

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Rationale: Therapeutic monitoring (TM) of plasma valproate concentrations [VPA] is routine; the lowest concentration (trough) during a dosing interval is often used. While clinicians have experience using TM for conventional formulations, their TM experience with divalproex extended-release [ER], a novel formulation intended for once daily administration (*Clin Drug Invest* 2003;23:661–70), may be limited. Questions have risen concerning the optimal time for obtaining a blood sample in relation to the dose, considering daily ER can be administered either in the morning or evening (*Epilepsia* 2003;44 [suppl 9];96). Predose or trough sampling is easily achieved just prior to morning daily dosing of ER, but the best time to sample after an evening daily dose is unclear. This investigation provides information and practical guidance regarding blood sample timing.

Methods: Steady state [VPA]-time profiles from 5 published ER studies (*Clin Drug Invest* 2004, in press) in healthy subjects and epilepsy patients on enzyme-inducing antiepileptic drugs were analyzed. The [VPA] profile for each subject was expressed as a percentage of that subjects trough concentration and summary statistics computed. A pooled estimate of the standard deviation across time was computed.

Results: For the typical patient, plasma valproate concentrations are 35, 35, 27, 25, 18, 13 and 3 percent higher than trough (i.e., 24-hour) concentrations at 3, 6, 9, 12, 15, 18 and 21 hrs after the last ER once-daily dose, respectively. For the typical patient taking ER once-daily in the morning, e.g., 8 AM, blood samples collected 21 to 24 hrs after the last ER dose is expected to have concentrations within 3% of the trough value. Conversely, for the typical patient taking ER once-daily in the evening, e.g., 8 PM, collecting blood samples 21 to 24 hrs after the last ER dose may be limited by the operational hrs of the laboratory. For typical patients dosed in the evening, a blood draw 12 to 15 hrs after the dose (i.e., 8 to 11 AM) will give plasma valproate concentration values that are 18 to 25% higher than trough values. However, waiting longer, e.g., 18 to 21 hrs (i.e., 2 to 5 PM), will result in concentration values that are merely 3 to 13% higher than trough values. The pooled standard deviation around the reported percentage change for the typical patient was 26%. It should be recognized that because of intra and intersubject variability, individual patients might have wider range than the typical patient.

Conclusions: The greatest deviation from the trough concentration occurs around Cmax, i.e., 3 to 9 hrs after a once-daily ER dose; sampling during this time period is not recommended. For patients taking daily ER in the evening, a blood sample obtained at least 18 hrs post-dose may be acceptable. (Supported by Abbott Labs.)

2.358

TOPIRAMATE IN ELDERLY PATIENTS WITH EPILEPSY

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Rationale: To evaluate the efficacy and tolerability of topiramate (Topamax®, TPM) in mono- or combination therapy in elderly patients with epilepsy.

Methods: Prospective multicenter observational study. Patients = 60 years of age were evaluated at baseline and after 12 and 24 weeks. Doses of TPM and concomitant AEDs could be adjusted individually. Seizure frequency and adverse events (AEs) were assessed at every visit.

Results: 108 patients (47.2% male, mean age 71 ± 8 years, mean time since epilepsy diagnosis 12 years, 79.6% partial epilepsy) were prospectively followed for 24 weeks. Etiology was symptomatic in 67.6%, kryptogenic in 9.3% and idiopathic in 22.2%. The most frequent seizure types were generalized tonic-clonic seizures (72.2%), complex partial (25.0%), simple partial (19.4%) and absence seizures (12.0%). 58 patients were treated with TPM in monotherapy (mean dose at endpoint 93 ± 10 mg/day), 50 patients in combination therapy with one or two other antiepileptic drugs (mean TPM dose at endpoint 93 ± 8 mg/day). Mean baseline seizure frequency was 7 ± 10.4 in the 12-week retrospective baseline and decreased to 1.6 ± 3.2 at endpoint ($p < 0.0001$). The responder rate (seizure reduction = 50%) was 87.6%, and 56.5% of the patients remained seizure-free for at least the last three months of the trial. 83.3% of the patients completed the study. Main reasons for drop-out were lack of tolerability (8.3%) and loss to follow-up (4.6%). Overall, 21 patients (19.4%) had at least one AE. The most frequently reported AEs were somnolence (3.7%), dizziness (3.7%) and decreased appetite (2.8%). Psychomotor slowing was reported in two and memory difficulties in one patient. Mean weight change from baseline to endpoint was −0.9 kg.

Conclusions: In elderly patients with epilepsy, TPM was associated with a significant decrease in seizure frequency both in mono- and combination therapy. Monotherapy doses used for elderly patients were slightly below the recommended target dose of 100 mg/day, while in combination therapy a considerably lower dose was used compared to the recommended target dose of 200 mg/day for adults. (Supported by Janssen-Cilag Germany.)

2.359

INFLUENCE OF INITIAL SEIZURE FREQUENCY ON PROGNOSIS FOR SEIZURE CONTROL IN THE ELDERLY

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Rationale: The recently completed VA Cooperative study, Treatment of Seizures in the Elderly Population, studied 593 older patients with newly diagnosed seizures in a three arm clinical trial comparing carbamazepine, gabapentin and lamotrigine. The primary outcome measure was retention in the trial for 12 months, a measure of efficacy and tolerability. Differences among the groups were significant, with gabapentin and lamotrigine demonstrating better retention than carbamazepine. The principle factor accounting for this result was tolerability. A secondary outcome measure, proportion of patients remaining seizure-free during the trial, showed no significant differences. We sought to determine whether seizure frequency before enrollment was a determinant of the liklihood of seizure freedom.

Methods: We divided the patient cohort into two groups: those with 0–1 seizure during the 3 months preceding enrollment in the trial, and those with > 1 seizure during the same period. For each of the two groups we determined the percentage of patients in each arm who were seizure free at 3, 6 and 12 months.

Results: In the 0–1 seizure group before enrollment, 80.43% were seizure free at 3 months, 80.36% at 6 months, and 73.74% at 12 months. There were no significant differences among the 3 treatment arms. In the > 1 seizure group 54.17% were seizure free at 3 months, 47.51% at 6 months, and 41.81% at 12 months. Again, there were no significant differences among the 3 arms.

Conclusions: Seizure frequency when seizures are newly diagnosed in the elderly appears to be a predictor of the probability of becoming and remaining seizure-free after treatment has been started. If a patient with lower seizure frequency is seizure-free at 3 months after being treated, it is likely that he/she will remain so for one year. Those with higher seizure frequencies are less likely to remain seizure-free for one year, and this becomes evident at 3 months. The particular antiepileptic drugs in this trial have little bearing on the liklihood of achieving seizure-freedom. (Supported by Department of Veterans Affairs. Antiepileptic drugs and their placebos were provided by Pfizer and Glaxo.)

2.360

PREVALENCE OF ECG PATHOLOGY IN NEWLY DIAGNOSED ELDERLY EPILEPSY PATIENTS: PRELIMINARY OBSERVATIONS

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Rationale: Carbamazepine, phenytoin and possibly oxcarbamazepine can induce or strengthen cardiac arrhytmias. Experience with lamotrigine on cardiac function is limited so far. The primary objective was (1) to detect the prevalence and character of cardiac function changes in elderly people with epilepsy, as these can be seen electrophysiologically by ECG, and (2) to examine and evaluate similar or different ECG abnormalities taking place during modern AED treatment. We present the data obtained from the first 21 patients.

Methods: The patients were included in the Norwegian branch of the European double-blind randomised comparative study of lamotrigine and slow-release carbamazepine in newly diagnosed epilepsy patients (LAM 40089 trial). Good quality 12 leads 50 millimeters/sec ECG recordings took place at inclusion and at the end of treatment (36 week visit). In the present group of patients, 13 were male. Since all these subjects completed the study, 42 single ECG recordings were analysed. Every subject was above the age of 65 years.

Results: 12 patients had a normal baseline ECG.

The prevalence of ECG abnormalities prior to treatment, and during AED therapy, respectively, are shown in Table 1.

TABLE 1. ECG characteristics before and during antiepileptic treatment (n = 21)

ECG parameter	Prior to treatment	During treatment
Heart frequency (mean range) *(1/sec)*	74,1 (53–104)	69,8 (52–112)
Sinus rhythm *(subjects)*	21	21
1st degree AV block *(subjects)*	0/21	1/21
Left anterior branch block *(subjects)*	1/21	2/21
PQ time (mean range) *(ms)*	180.0/140–220)	187,9 (140–240)
Myocardial infraction, old *(subjects)*	8/21	7/21
Left ventricular hypertrophy *(subjects)*	1/21	1/21
QRS time *(ms)*	87,3 (70–110)	85.7 (70–110)
QT time *(ms)*	378.0	388,6
QT dispersion	44,0	39,0
Noral ECG *(subjects)*	12/21	10/21

Conclusions: The preliminary data from a number of elderly epilepsy patients show a releatively high prevalence of ECG morphological changes. AED treatment seem to worsen this tendency.

2.361

PHARMACOKINETICS OF THE NEW ANTIEPILEPTIC DRUG SPM 927 IN HUMAN SUBJECTS WITH DIFFERENT AGE AND GENDER

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Rationale: SPM 927 is being developed for the treatment of epilepsy and neuropathic pain. The aim of the present analysis was to characterize possible gender and age differences in the pharmacokinetics (PK) of SPM 927 in healthy elderly subjects (>65 ys.) in comparison to young healthy subjects (18–45 ys.) based on PK data collected in two phase 1 trials: In trial 1, the PK and tolerability of SPM 927 in subjects of different age and gender was evaluated. In trial 2, a potential interaction between SPM 927 and an oral contraceptive was analyzed in female subjects.

Methods: Trial 1: Analysis of SPM 927 plasma levels was done in 11 elderly males, 12 elderly females and 12 young males. 100 mg SPM 927 od was administered on day 1, 100 mg SPM 927 bid on days 4 to 7, followed by 100 mg od on day 8. Trial 2: Analysis of SPM 927 plasma levels was done in 31 young females. 200 mg SPM 927 was administered bid on days 3–11, followed by 200 mg od on day 12. The PK parameters (AUC and C_{max}) of the two trials were dose-normalized and pooled for analysis.

Results: Plasma concentrations of SPM 927 in females were slightly increased compared to males. The AUC ratio of elderly females vs. elderly males was 114% with a 90% confidence interval (CI) of 102–128%. The corresponding C_{max} ratio was 119% with a 90% CI of 107–132%. The AUC ratio of young females vs. young males was 134% with a 90% CI of 122 to 147%. The C_{max} ratio was 142% with a 90% CI of 130 to 154%. Almost all of the differences can be explained by the different body weight. When the parameters are adjusted to body weight, there are no differences between females and males.

Elderly subjects exhibited higher values of C_{max} and AUC than young subjects. The AUC ratio of elderly males vs. young males was 131% with a 90% CI of 117 to 148%. The C_{max} ratio was 129% with a 90% CI of 116 to 143%. The AUC ratio of elderly females vs. young females was 112% with a 90% CI of 102 to 123%. The C_{max} ratio was 108% with a 90% CI of 99 to 117%. The higher values of C_{max} and AUC in elderly subjects can not be explained by differences in body weight. After adjusting of these parameters to body weight, the differences between elderly and young subjects still remain.

Conclusions: In summary, there is no effect of gender on the PK of SPM 927 in young and elderly subjects. The higher AUC and C_{max} values in young and elderly females compared to young and elderly males are most likely explained by a lower body weight. As SPM 927 is highly soluble in water, the differences between elderly and young subjects are mainly due to the reduced total body water in elderly subjects which results in higher drug concentrations in this age group. Due to the fact that there is only a slight increase of SPM 927 plasma concentration in elderly and the drug was well tolerated in all groups, the observed differences are considered to be without clinical relevance.

2.362

ANTIEPILEPTIC DRUG TREATMENT IN NURSING HOME RESIDENTS OF NORTHERN MANHATTAN AND CENTRAL HARLEM

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Rationale: Approximately 10% of nursing home residents are prescribed antiepileptic drugs (AEDs). In one cross-sectional study of nursing home residents, the primary factors associated with AED use were epilepsy/seizure, peripheral vascular disease and bipolar depression; however, the analysis determining the indication for AED treatment relied on multivariate analysis of International of Classification of Diseases, Ninth revision (ICD-9) coding and the minimum data set (MDS), rather than on direct chart abstraction. ICD-9 coding is often unreliable and MDS has been rarely used in studies of epilepsy or AED treatment. In this preliminary study, the indications for AED treatment were determined by direct review of the medical chart.

Methods: In a population-based study of nursing homes in Northern Manhattan and Central Harlem, we used pharmacy databases to identify nursing home residents taking AEDs. Chart reviews were performed to identify the medications prescribed and the indications for AED treatment. If an AED was used to treat a convulsive disorder, an attempt was made to further classify the seizure diagnosis using International League Against Epilepsy (ILAE) guidelines.

Results: Of the 73 patients reviewed thus far, 54 (74%) patients were prescribed AEDs because of a history of seizures. Twenty-six patients (36%) met definite criteria for the diagnosis of epilepsy or single-unprovoked seizure. An additional 25 patients (34%) had a

diagnosis of seizure disorder but could not be further classified. Three patients (4%) had acute symptomatic seizures or were being treated with AEDs for seizure prophylaxis. Nineteen (26%) patients who were receiving AEDs did not have a history of seizures. They were prescribed AEDs because of pain and/or psychiatric illness.

The most commonly prescribed AEDs were phenytoin (37/73 or 51%), gabapentin (18/73 or 25%) and valproic acid (14/73 or 19%). Thirteen out of 18 patients were prescribed gabapentin for pain and 10/14 patients were prescribed valproic acid for psychiatric reasons. All patients taking phenytoin were being treated for seizures or epilepsy. Fifteen patients (21%) were receiving two or more AEDs.

Conclusions: Among nursing home residents, phenytoin continues to be the most prevalent AED prescribed for the treatment of seizures/epilepsy. The second and third most commonly prescribed AEDs, gabapentin and valproic acid, are largely being used for the treatment of pain and psychiatric reasons. (Supported by AAMC grant MM0323.)

2.363

TOLERABILITY AND SUSTAINED EFFICACY OF SODIUM DIVALPROEX AS SECOND MONOTHERAPY IN ELDERLY PATIENTS WITH NEW-ONSET PARTIAL EPILEPSY

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Rationale: Incidence of new onset partial epilepsy is highest in elderly patients. Choice of anti-epileptic drug (AED) is limited due to multiple comorbidities, concomitant medications and scarce published clinical experience in this population, especially after an AED failure. Sodium divalproex (SDV) was chosen as alternative monotherapy, because it was available and approved for the intended use in our patients.

Methods: Medical charts of 13 male patients taking SDV monotherapy after failure (lack of efficacy n = 2, toxicity n = 11) of gabapentin, lamotrigine, or carbamazepine monotherapy were reviewed after obtaining IRB exemption of informed consent. Data regarding seizure frequency, side effects, comorbidities, hematology, chemistry, serum SDV levels, and demographics were collected from each visit note and compared longitudinally for each patient. SDV starting dose was 250 mg b.i.d. with weekly increments of 250 mg per day to reach a target maintenance dose of 500 mg b.i.d. Dose adjustments were performed to achieve or maintain seizure freedom, or minimize side effects.

Results: Age at onset and duration of SDV treatment averaged 74 years (62–86 years) and 13.9 months (0.2–28.0 months), respectively. SDV maintenance doses were 250 mg b.i.d. (n = 4), 500 mg b.i.d (n = 7), 500 mg t.i.d. (n = 1), and 750 mg b.i.d (n = 1). Serum SDV levels averaged 51.8 microgram/ml (n = 5), 55.0 microgram/ml (n = 6), and 63.5 microgram/ml (n = 7) at 3, 6, and 12 months, respectively. Comedications averaged 9 (2–16) per patient; the most common 5 were acetyl-salycilic acid (n = 9), albuterol (n = 5), lisinopril (n = 5), furosemide (n = 4), and KCl (n = 4). Seizure types included simple partial seizures only (n = 5), complex partial seizures (CPS) only (n = 3), secondarily generalized seizures (2GTC) only (n = 4) and CPS with 2GTC (n = 1). Nine patients continued to be seizure free from the first AED monotherapy, and four became seizure free at 6 months after starting SDV. Three patients discontinued within the first 3 months: due to rash (n = 1); myoclonic jerks, tremor, and unsteady gait with fear of falling (n = 1); and dizziness, tremor and impotence (n = 1). Of the remaining 10 patients only 2 reported side effects; namely, tremor of moderate severity. No clinically important changes in platelet count or liver function tests were observed. Four patients reported weight gain and three reported weight loss of >5 pounds. Patients' average weight was 192 pounds at the last visit.

Conclusions: SDV monotherapy was efficacious and well tolerated in the majority of our study population of elderly patients with new onset seizures. The use of SDV as first or second choice in elderly patients with new onset partial epilepsy is a reasonable option. (Supported by Malcom Randall VA Medical Center and the University of Florida, Gainesville, Florida.)

2.364

TOLERABILITY AND SAFETY OF TOPIRAMATE IN JUVENILE MYOCLONIC EPILEPSY

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Rationale: It has been suggested that valproate (VPA), considered the drug of choice in the treatment of Juvenile Myoclonic Epilepsy (JME), may affect reproductive function in women with epilepsy. Topiramate (TPM) may represent a therapeutic alternative since it has an equally broad profile. Some studies have suggested the effectiveness of TPM in the control of generalized tonic-clonic seizures (GTCS), although a few have demonstrated its efficacy in the control of absences and myoclonic seizures. This is the preliminary report of the results of an ongoing two-year prospective study for evaluation of TPM in a series of patients with JME.

Methods: TPM was administered as a first drug or as a substitute drug in the treatment of 22 patients (13–53 yr.; mean 23.2) with a confirmed diagnosis of JME. These were divided into three groups. Groups 1 and 2 included patients already being treated with other AED and were constituted by: (1) patients with seizure control but presenting side effects; (2) patients with non-controlled seizures and (3) patients with newly diagnosed JME. TPM was titrated according to patients' response over 12–14 weeks and maintained for an additional 32 weeks. Target TPM dose was 100–200 mg/day. The patients were evaluated in the 2^{nd}, 4^{th}, 6^{th}, 8^{th} and 12^{th} weeks and then in the 6^{th}, 9^{th} and 12^{th} months as therapeutic effect and adverse events.

Results: 22 patients (18 females) were enrolled, 16 of which completed the first year of the follow-up. 14/22 patients in this series were already being treated with other AED without seizure control. Discontinuations were due to inadequate seizure control and adverse events (N = 3), low compliance and loss of follow-up (N = 3). Mean dosage was 106.25± 55.43 mg/day. More specifically, in Group 1, 3 out of 5 patients remained seizure free, 1 presented an only seizure due to non-compliance and 1, seizure aggravation. In Group 2, 9 out of 14 patients showed > 50% seizure reduction, 4 presented seizure aggravation, and the seizure frequency persisted unaltered in one patient. Lastly, in Group 3, 2 out of 3 patients remained seizure-free and one presented persisting myoclonias when exposed to precipitant factors. Myoclonias also persisted in 10 patients of Groups 1 and 2. In this series, 5 patients also presented absences. Regarding this seizure type, it disappeared in one, there was >50% seizure reduction in 2 and aggravation in the other 2 patients. The most common side effects observed were thirsty/dry mouth, paraesthesia, weight loss, appetite decrease, somnolence, headache, facial rubor, humor instability and language problems.

Conclusions: TPM reduced the frequency of seizures in approximately 2/3 of patients with JME in the first year of follow-up seeming more effective in the control of GCTS. [Supported by JANSSEN-CILAG FARMACÊUTICA DO BRASIL, FAPESP (Fundação de Amparo a Pesquisa do Estado de São Paulo), CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior).]

2.365

UCB 34714: SINGLE AND MULTIPLE RISING DOSE SAFETY, TOLERABILITY, AND PHARMACOKINETICS IN HEALTHY SUBJECTS

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Rationale: Ucb 34714 is an investigational new drug structurally related to levetiracetam (LEV) with a higher affinity and similar high selectivity towards the brain-specific LEV binding site. The anticipated pharmacologically active dose in humans is around 150 mg based on animal models of epilepsy.

Methods: Single and repeated oral administration of ucb 34714 were performed in a Randomized, double-blind, placebo controlled manner. Healthy male volunteers were enrolled. For the single administration, 3 alternating panels of 9 subjects received the following doses: 10, 20, 40, 80, 150, 300, 600, 1000, and 1400 mg (6 active: 3 placebo). For the multiple dose administration, 3 different panels of 12 subjects (9 active:

3 placebo) received 200, 400 and 800 mg/day in 2 daily doses during 2 weeks. CNS effects were explored with psychomotor tests and rating scales. The food effect was also assessed after single administration of 150 mg to 8 subjects in a 2-way cross-over design.

Results: During single and repeated administrations, there was a dose-related increase in the frequency of CNS adverse events of which the commonest were dizziness, somnolence and euphoria. Adverse events were mild or moderate and resolved within the first day of treatment.

After single intake of ucb 34714, 25 of 27 subjects reported 56 adverse events. None were serious. The most frequent adverse events were dizziness (12/27), somnolence (9/27) and euphoric mood (3/27). One subject had severe somnolence after intake of 1400 mg. 1000 mg was then set as the maximal tolerated dose (MTD) in this population.

During multiple administrations, the adverse events reported in more than one patient were dizziness (17/27), somnolence (7/27), headache (7/27), euphoric mood (5/27), throat irritation (4/27), fatigue and nausea (3/27), blurred vision, feeling drunk, agitation and hypotension (2/27). There were no serious adverse events. There were no clinically significant abnormalities reported from neurological examinations, psychomotor tests or rating scales, clinical laboratory, vital signs, ECGs and physical examination. The MTD was not reached after 14 days at 800 mg/day.

Ucb 34714 was rapidly absorbed and followed first-order single compartment kinetics over a wide range of doses. The half life was 7 hours on average. The steady state was reached within 1 week. Ucb 34714 was rapidly excreted in the urine. When administered with food, Cmax was reduced by 28% while AUC was not altered.

Conclusions: The MTD of ucb 34714 is 1000 mg after single dose and more than 800 mg/day after 2 weeks of repeated dosing. The main adverse events are dizziness and somnolence. The pharmacokinetic steady state is reached within one week. (Supported by UCB Pharma SA.)

2.366

LEVETIRACETAM (Keppra) IN PATIENTS WITH CORTICAL MYOCLONUS: A CLINICAL AND ELECTROPHYSIOLOGICAL STUDY

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Rationale: Chronic myoclonus is often associated with severe functional disability and it frequently results intractable to currently used antiepileptic drugs (AEDs). Levetiracetam (Keppra, LEV) is a new AED with broad-spectrum activity including strong efficacy against myoclonus. We present data from an open-labeled treatment trial of LEV aimed to evaluate the clinical effect and the tolerability of orally administrated LEV in patients with chronic cortical myoclonus of various etiology. In addition, we attempted to determine if treatment with LEV modifies electrophysiological findings in these patients.

Methods: Patients affected with refractory chronic (i.e., present without remission for at least one year) myoclonus of cortical origin were enrolled. Each subject underwent a detailed electrophysiological study jerk-locked averaging, median nerve SEP and Long Latency Reflex I. Only patients showing myoclonus of cortical origin entered the study. Unified Myoclonus Rating Scale (UMRS) was used to assess severity of myoclonus. LEV was orally administered at a starting dose of 500 mg bid for one week followed by increments of 500 mg bid each week. In all patients, daily doses were increased up to 1500–2000 mg bid. Dosage of concomitant AEDs remained unchanged. Each subject was either clinically and electrophysiologically re-evaluated 4–5 weeks after having achieved the target dose.

Results: Sixteen patients (10 M, 6 F), aged 19 to 72 years, and affected with chronic myoclonus were enrolled. Five had the diagnosis of Unverricht-Lundborg disease; 2 had Lafora disease; nine patients received diagnosis of Benign Adult Familial Myoclonic Epilepsy. Enhanced SEP were found before LVT trial in 9 cases. All patients but one completed the trial. Add-on with LEV to the baseline therapy clinically improved myoclonus in 12/16 cases, as showed by lower UMRS scores after treatment. Follow-up electrophysiological study showed reduction of SEP amplitude in 4/9 patients.

Conclusions: This study confirms the antimyoclonic properties of LEV when added to existing treatment. LEV was very well tolerated. electrophysiological study showed that LEV tended to decrease N20-P25 as well as P25-N30 SEP amplitudes but not latencies in four cases. These results suggest that the electrophysiological approach may supply quantifiable data of the drug effect as well as help to understand the LEV mechanism of action.

2.367

LEVETIRACETAM IN THE TREATMENT OF PRIMARY GENERALIZED SEIZURES

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Rationale: Levetiracetam (LEV), a novel antiepileptic drug (AED), and piracetam (with a structure similar to that of LEV and proven to be effective in myoclonus) are pyrrolidone derivatives, a class of drugs not previously used in epilepsy. LEV, approved in the USA and Europe as add-on therapy for the treatment of patients with refractory partial seizures (Cereghino *et al.* 2000; Shorvon *et al* 2000; Ben Menachem and Falter, 2000), has been widely shown as effective and well tolerated. Motamedy *et al*. (2003) has reported that of 21 patients operated on unsuccessfully for refractory epilepsy 47.6% became seizure-free after at least 3 months of treatment with 1000–3000 mg of LEV and 28.5% showed a reduction in seizure frequency of more than 50%.

We evaluated the efficacy of LEV treatment in patients with generalised seizures.

Methods: Eight (8) patients (5 female, 3 male, aged 16–62 years) were include in our study. Three (3) patients had absence epilepsy, 3 primary generalised tonic-clonic seizures and 2 had juvenile myoclonic seizures. Doses of LEV varied between 1500 and 4000 mg/day. In all patients LEV was used as add-on therapy. The goal of our study is to treat all patients on LEV monotherapy so we are gradually reducing (and hoping to cease) their other AED therapy to achieve this goal.

Results: All patients improved both clinically and electroencephalographically after commencing LEV therapy with a reduction in seizure frequency of at least 50%. In 2 of them (1 with absence epilepsy and 1 with myoclonic seizures) their previous AED therapy (valproate), to which LEV had been added, was gradually reduced and then stopped leaving them on LEV monotherapy. Both these patients were seizure-free.

Conclusions: Our study has shown that patients with primary generalised epilepsy can be treated successfully with LEV initially used as add-on therapy, then withdrawn to monotherapy. Further studies are required to support our findings.

2.368

VALPROIC ACID DOES NOT CAUSE WEIGHT GAIN IN THE ELDERLY

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Rationale: Change in body weight is a common consequence of therapy with certain antiepileptic drugs. Weight gain is one of the most commonly reported adverse effects of therapy with valproic acid (VPA) occurring in about 50% of VPA-treated patients. Increases in body weight associated with VPA treatment pose considerable, well-documented health risks such as insulin resistance, hypertension, diabetes mellitus, and coronary artery disease which might be especially relevant in elderly patients. So far it was said that there are no predictive factors for weight gain such as age, gender, pretreatment body weight, or valproate dosage. But in most studies the mean age of investigated patients was in the younger age group.

Methods: We studied all patients newly treated with VPA for the diagnosis of epilepsy in the time period between May 2000 and May 2003 at the Department of Neurology, Kantonsspital St. Gallen, Switzerland. Investigated parameters included age, gender, body weight, and body mass index (BMI) at beginning of therapy and at the end of therapy or in August 2003, respectively.

Results: Included were 23 consecutive patients, 22 of them on VPA monotherapy, one patient with add-on CBZ and LTG. There were 15 women and 8 men with a mean age of 61.7 years ranging from 35 to

81 years. Mean body weight was 67.0 kg (range 45–88 kg) and mean BMI 24.4 (range 18–37) at beginning of therapy. After a mean observational period of 10.5 months the mean body weight was 67.4 kg and the mean BMI 24.5, respectively. Only 4 patients gained weight with an increase of BMI between 1 and 4.

All these 4 patients including 3 women and one man were younger than 55 years (mean age 49 years, range 45–52). In the overall study group there were only 9 patients with increase of body weight within the age group <55 years. In contrast, none of the patients aged 55 or above had a weight gain, 6 patients in this age group even lost some weight.

Considering age effects, the mean BMI before therapy was 25.3 for patients <55 years of age and 23.9 for patients ≥55 years. On VPA therapy these values were 26.1 and 23.6, respectively.

Conclusions: Contrary to previously reported side effects of VPA with an incidence of weight gain in about 50% of patients we did not find any increase of body weight in patients newly treated with with VPA at age 55 or above. So far, only Isojarvi (*Ann Neurol* 1996;39:579–84) reported a slightly lower percentage of women above age 20 with weight gain on VPA as compared to the younger age group.The metabolic causes of valproate-induced weight gain remain still unclear. Several mechanisms have been postulated including increased appetite and food intake, decreased beta oxidation of fatty acids, and hyperinsulinemia. Previously no predictive factor for weight gain was desribed. Considering our results age is a predictive factor for weight gain with no increase of body weight in elderly patients newly treated with VPA. This is of major importance considering the negative impact of weight gain on general health.

2.369

GAIT-INITIATION FAILURE IN TOPIRAMATE GOOD RESPONDERS WITH CENTRAL SEIZURES

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Rationale: To report Gait Initiation Failure (GIF) occurring in four patients successfully treated with topiramate for refractory partial epilepsy.

Methods: Retrospective medical charts analysis

Results: Four patients (three males) aged 21 to 65, with refractory partial epilepsy developed Gait Initiation Failure (GIF) when topiramate was added to their antiepileptic drug regimen. Three of them suffered from central epilepsy caused by ancient brain lesion responsible for hemiplegia (poststroke and posttraumatic epilepsy), whereas the last patient was treated since childhood for cryptogenic frontocentral epilepsy. Topiramate was used in all patients as add-on therapy, with dose ranging from 100 to 800 mg/bid. All patients showed an excellent response to topiramate, as two became seizure-free and two exhibited a strong reduction in seizure frequency. Subsequently, GIF was reported as a selective difficulty in starting the walk after rest. Noteworthy, once the walk was initiate, no further difficulty was experienced. Other motor functions, except for ancient hemiparesis in three patients, including standing up before initiating walking, were normal. Fluorodopa PET and BetaCIT SPECT were performed in two patients, respectively. In one patient, a decrease in the BetaCIT uptake was shown controlaterally to the hemiparesis. A Transcranial Magnetic Stimulation study performed in one patient showed a selective loss of intracortical inhibition associated with GIF, both reversed by acute treatment with apomorphine. Except for one patient, who was successfully treated with apomorphine, GIF improved in all patients after reduction in topiramate dosage. However, in two patients, the decrease in topiramate dosage was associated with an increase in seizure frequency.

Conclusions: An unpreviously reported motor side effect of topiramate is presented in four patients. Although the pharmacological action of topiramate remains almost obscure, a link can be speculated between the observed clinical efficacy on central seizures and Gait Initiation Failure reported by our patients.

2.370

FELBAMATE: CLINICAL AND LABORATORY CHARACTERISTICS IN LONG-TERM USERS

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Rationale: Felbamate (FBM) is an antiepileptic drug with proven efficacy in the treatment of partial and generalized seizures. Idiosyncratic aplastic anemia and hepatoxicity have significantly limited its use. The aim of this study was to describe the clinical characteristics and to evaluate changes in weight, hematological parameters and liver function in long-term FBM users.

Methods: During 1991, a computerized prospective database of all patients attending MINCEP® Epilepsy Care (Minneapolis, MN) was established, and informed consent for use of clinical information was obtained from each patient. This database was initiated for an NIH funded study of SUDEP. Age, gender, epilepsy syndrome, and antiepileptic drugs used for each clinic visit were prospectively recorded. This database was utilized to identify all patients taking FBM at the time of this study. Weight, WBC, platelet, lymphocyte, granulocyte counts and AST were recorded for each patient at three time intervals: 1) prior to starting FBM; 2) one year after initiating FBM; and 3) most recent data (Table 1). Data was obtained through chart review. Repeated measures ANOVA was used for statistical analysis.

Results: One hundred eleven patients were identified as being current FBM users. At the time of the writing of this abstract, data has been analyzed on 39 (35%) patients (15 male/24 female, average age 32.5 years old). Patients were on FBM an average of 83.2 months (range 1.4–215.4) totaling 270.4 person years of follow-up. Patient's epilepsy syndrome included: 28 (72%) localization related; 9 (23%) symptomatic generalized; 2 (5%) primary generalized. Twelve (31%) were developmentally delayed. Etiologies included: 21 (54%) unknown; 6 (15%) infection; 4 (10%) vascular; 8 (21%) other. Ten (26%) patients had a history of hypersensitivity reaction; 1 (3%) patient had systemic lupus erythematosous. Differences across time for weight, hematological parameters and AST were not significant.

TABLE 1. *Latest available laboratory data while on FBM*

	Mean	minimum	maximum	stdev
WBC	5.5	2.9	11.4	1.8
platelet	274.5	147.0	371.0	48.7
lymphocyte	2.1	1.0	5.9	1.0
granulocyte	3.2	1.1	8.1	1.5
AST	22.6	12	33	22.6

Conclusions: In this selected population of long-term FBM users, weight, liver function and hematological parameters appear to remain stable. Although this study does not identify predictive variables for the development of hepatotoxicity or aplastic anemia, the data supports the relative safety of the long-term use of FBM in selected patients. (Supported by MINCEP Epilepsy Care.)

Antiepileptic Drugs–Pediatric

2.371

LONG-TERM SAFETY OF LAMOTRIGINE IN PEDIATRIC SUBJECTS WITH PARTIAL SEIZURES: PRELIMINARY RESULTS

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Rationale: There is little information concerning the safety and efficacy of lamotrigine (LTG) in children younger than 2 years of age. We are evaluating the long-term safety of LTG in children with partial seizures

in an ongoing, open-label, multicenter, international, continuation study (LAM20007). We report the preliminary safety results from this study.

Methods: Subjects entering this study had completed either the open-label (OLP) or double-blind phases (DBP) of the primary study (LAM20006). In the primary study, subjects (age 1–24 months) with recurrent partial seizures receiving 1–2 anti-epileptic drugs (AEDs) were first entered into an OLP (≤27 weeks) where LTG was given as adjunctive therapy and was titrated, consistent with product labelling, to an individually optimized dose. Subjects with a ≥40% reduction in seizure frequency from historical baseline were randomized into an 8-week DBP to either continue or gradually withdraw LTG with background AEDs continued. In this continuation study, LTG doses are titrated to optimal benefit with the option of withdrawal to LTG monotherapy. Subjects are treated for 48 weeks or until their second birthday, whichever occurs later.

Results: Demographic and safety data were available for 96 subjects (52% male; mean age, 16.8 months; mean weight, 10.5 kg). Sixty-eight percent of subjects received enzyme-inducing AEDs (EIAEDs). Sixty-seven (70%) subjects were exposed to LTG for ≥48 weeks. The median of the modal total daily dose was 11.8mg/kg/day (range 0.9–30.7) for the EIAED group and 4.8 mg/kg/day (range 0.2–15.4) for the non-EIAED group. The most common adverse events (AEs) (≥20% of subjects) were mostly mild to moderate in intensity and consisted of pyrexia (43%), upper respiratory tract infection (26%), cough (26%), ear infection (25%), and vomiting (21%). AEs caused 11 subjects to discontinue the study. Rash was reported for 15 subjects (16%), caused one subject to discontinue study drug, and occurred more frequently in the EIAED group (25%) than in the non-EIAED group (4%). Rash was considered to be a serious AE (SAE) for one subject but was not considered to be LTG-related and did not require discontinuation of LTG. The most frequent (≥5% of subjects) SAEs were convulsion (13%), status epilepticus (7%), pneumonia (6%), and pyrexia (5%). Six subjects died during the study; none of the deaths was considered to be LTG-related.

Conclusions: This preliminary analysis indicates that LTG is a well-tolerated long-term treatment in infants with recurrent partial seizures. (Supported by GlaxoSmithKline.)

2.372

CLINICAL EXPERIENCE WITH LEVETIRACETAM IN CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: Levetiracetam (LEV, Keppra®) is an antiepileptic drug (AED) approved as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy. The purpose of this study was to evaluate the use of LEV in pediatric epilepsy patients referred to an academic medical center.

Methods: Patients in this study were children with intractable seizures despite appropriate treatment with AEDs other than LEV.

The study enrolled 22 patients ranging in age from 2 to 16 years, all of whom took Keppra for a minimum of 4 months.

Of these, 6 had partial-onset seizures, and 16 had primary generalized seizures. The majority of patients were taking 3 (95%) concomitant AEDs when LEV therapy was initiated. Associated conditions included malformations of cortical development, perinatal or post-traumatic sequela lesion, hemiatrophy and agenesis of the corpus callosum. One patient had vagus nerve stimulators which was turn off when LEV was initiated. The average therapeutic dose was 31 mg/kg (range 15–60 mg/kg).

Results: Of the 22 patients, 21 tolerated LEV at doses higher than the initial dose and were included in the efficacy analysis. Two patients became seizure free (9.5%). Thirteen (62%) achieved 50% or greater seizure reduction. Of these 21 patients, 17 were taking concomitant AEDs and 2 of 17 were on more than 3 drugs.

Conclusions: 71.5% of patients who tolerated LEV therapy had a significant decrease in seizure frequency.

This study supported LEV's efficacy in partial-onset epilepsy (83%) and a good improvement in generalized epilepsy (66%).

LEV was well tolerated in the majority of patients (95%) in this population of children with intractable partial-onset or generalized epilepsy.

In addition, a number of patients with behavior disorders showed a significant improvement with this behavior, as noted by parents.

2.373

A RETROSPECTIVE COMPARISON OF TWO TREATMENTS FOR INFANTILE SPASMS: ACTH VS. TOPIRAMATE, PYRIDOXINE, AND HYDROCORTISONE

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Rationale: Because the exact mechanism for infantile spasms is yet unknown, there is no treatment deemed most effective. The current standard is adrenocorticotropic hormone (ACTH). The optimal ACTH regimen, dose and duration, is unknown. A clinic visit or hospital admission is usually required to initiate ACTH and home nursing visits are common due to the risk of serious adverse drug reactions (ADRs). It is administered as an intramuscular injection, making it a comparatively expensive drug. The ADRs of ACTH can be severe and even life-threatening. Some examples are edema, hypertension, diabetes, electrolyte disturbances, osteoporosis, muscle wasting, and gastrointestinal ulcers. Because of the high costs and risk of serious ADRs, clinicians have tried other therapies. Conventional anti-epileptic drugs have been used with little or no success. In this retrospective chart review, the combination of Topiramate, Pyridoxine, and Hydrocortisone (TPH), chosen for its efficacy, safety profile, and low cost, will be compared to ACTH.

Methods: A retrospective chart review of the last five cases of infantile spasms was conducted at both Hennepin County Medical Center (HCMC) and Fairview University Medical Center (FUMC) in Minneapolis, Minnesota. Patients at HCMC used TPH. Patients at FUMC used ACTH. It was an IRB-approved, non-blinded, non-randomized, controlled case series. Birth history, symptoms and age at diagnosis, neurological or causative disease, seizure control, hospitalizations, ADRs, developmental progress, and EEG changes were collected from each group.

Results: All patients experienced a decrease in seizure severity. 2 out of 5 ACTH patients acheived temporary cessation, but had seizure recurrence. 4 out of 5 TPH patients acheived seizure cessation and 3 of those had seizure recurrence. The average number and duration of hospitalizations were 1.8 times and 4.7 days for the ACTH group and 1.4 times and 3 days for the TPH group. ADRs were experienced in 3 of the 5 ACTH patients and 1 of the 5 TPH patients. Ambulatory, social, and verbal development, and EEG results were quite similar between the groups.

Conclusions: TPH seems to have better outcomes concerning seizure reduction and ADRs. The number of patients studied was too small for statistical analysis, so the differences may not be statistically significant. When convenience, specifically the cost, is examined, TPH seems to be the less expensive alternative with a lower drug cost, decreased observed number of hospitalization admissions and shorter hospital durations. No in-patient admission is required for the initiation of the TPH combination treatment, nor did the side effects require a hospital stay. Since TPH performed better in efficacy, safety, and cost, it seems that TPH may be the more favorable choice.

2.374

LEVETIRACETAM DURING 1-YEAR FOLLOW-UP IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH REFRACTORY EPILEPSY

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Rationale: To evaluate the efficacy and safety of levetiracetam (LEV) in refractory crypto/symptomatic, partial or generalised epilepsy in children, adolescents and young adults.

Methods: we performed a prospective open label add-on study in 99 patients (age 12 months-32 years, mean 14 years) with partial or generalised, crypto/symtpomatic seizures. Levetiracetam was added to no more than two baseline AEDs and the efficacy was rated according to seizure type and frequency.After an observation period of 6 months (if seizure frequency was one or more per day, baseline period could be shortened to 3 months) during which antiepileptic treatment was generally not changed in most cases except for particular reasons such as the occurrence of status epilepticus, LEV was added to the baseline therapy at the starting dose of 10 mg/kg/day with 5-day increments up to 60 mg/kg/day, unless it was not tolerated. Concomitant therapy was generally not modified throughout the study.

Results: after a mean follow-up period of 6.7 months (range 3 weeks-29 months), 11 patients (11.1%) were free of seizures (cryptogenic partial epilepsy, 5; symptomatic partial epilepsy, 6). A more than 75% seizure decrease was found in 14 pts (14.1%) and $> 50\%$ in 8 (8.1%). Seizures were unchanged in 38 (38.4%), and worsened in 23 (23.2%). Overall, the drug appeared to be more effective, though not significantly, in partial (40.6%) than in generalized epilepsy (20%) ($\chi^2 = 1.676$; $p = .195$). Levetiracetam was equally effective in both cryptogenic and symptomatic partial ($p = 0.971$) or generalized ($p = 0.407$) epilepsies.Seizure frequency increased with levetiracetam in 23 patients (23.2%). Almost all seizure types worsened with a mild prevalence in secondarily generalised seizures. Seizure worsening manifested generally during the first weeks of treatment at daily doses less than 20 mg/kg. In three patients seizures became very frequent, and promptly stopped after LEV withdrawal. Mean age in this group was 12.7 years and seizure frequency was daily or weekly in all patients.Mild and transient adverse side effects were found in 17 patients (17.2%), mostly represented by irritability and drowsiness.

Conclusions: LEV appears to be well tolerated in children and adolescents with severe epilepsy and seems to be a broad spectrum AED, though in our experience, it was more effective against partial seizures with or without secondarily generalisation.

2.375

A MULTICENTER, RATER-BLIND, RANDOMIZED, AGE-STRATIFIED, PARALLEL-GROUP STUDY COMPARING HIGH- VERSUS LOW-DOSE OXCARBAZEPINE MONOTHERAPY IN PEDIATRIC PATIENTS WITH INADEQUATELY CONTROLLED PARTIAL SEIZURES

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Rationale: This study evaluated the efficacy and safety of low- vs. high-dose oxcarbazepine (OXC) monotherapy in patients 1 month to <17 years with inadequately controlled partial seizures.

Methods: Hospitalized patients were randomized in a 1:1 ratio to receive either 10 or 40–60 mg/kg/day of OXC monotherapy for 5 days. Patients were stratified by age as follows: 1−<6, 6−<12, 12−<24, 24−<48 months, or 4−<8 and 8−<17 years. Patients were either newly diagnosed or had inadequately controlled seizures on another monotherapy antiepileptic drug (AED) treatment. Patients had experienced 2–30 partial seizures 7 days prior to randomization (clinical seizures as reported by caregivers). For patients receiving monotherapy with another AED at entry, the AED dose was reduced by 50% on Day 2 and discontinued on Day 3. Patients completed the study by either completing the OXC treatment phase or by meeting one of two exit criteria based upon seizure frequency/severity. Seizures were measured by continuous video-EEG monitoring beginning with the first OXC dose on Day 3. Seizure records were assessed by a central reader blinded to study treatment.

Results: Of 92 patients randomized, 46 received high- and 46 received low-dose OXC. Results showed no significant difference ($p = 0.904$) in exit rates between the two treatment groups. The majority of patients in both groups completed the 5-day treatment. The exit rates of the high- and low-dose groups were 19.6% and 21.7% respectively, both better than the assumed rate of 35% of high-dose- and 70% of low-dose-treated patients as found in an adult presurgical study (Schachter, *Neurology*, 1999). Adverse events were reported for 21 (45.7%) low-dose- and 28 (60.9%) high-dose-treated patients. The most frequent AEs (>10% in either group) were somnolence, dizziness, nausea and vomiting.

Conclusions: This is the first reported controlled study of OXC monotherapy in infants as young as 1 month of age. The non-separation between the groups (due to a low exit rate in both groups) may have been caused by various factors e.g., efficacy of the 10 mg/kg dose and/or absence of a clear diagnosis of partial seizures in a very young patient population. The drug was well-tolerated with a safety profile in line with previous findings in adults and older children. (Supported by Novartis Pharmaceuticals.)

2.376

CLEARANCE OF TOPIRAMATE IN THE SPRINKLE AND TABLET FORMULATIONS IN SMALL CHILDREN WITH EPILEPSY

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Rationale: A sprinkle formulation is now available as an alternative to topiramate (TPM) tablets for the pediatric population. Our aim was to examine the plasma clearance of TPM in the sprinkle and the tablet formulations in a cohort of small (<5years old) children with epilepsy.

Methods: In an open study, 18 children with epilepsy with a mean age of 2.4 (range 0.3–4.9) years participated. All were on treatment with TPM, nine with the sprinkle and nine with the tablet formulation. In the sprinkle formulation group, TPM was given as monotherapy ($n = 2$) with comedication with nonenzyme inducers ($n = 4$) or enzyme inducers ($n = 3$) and, in the tablet group, TPM was given as monotherapy ($n = 1$) with comedication with nonenzyme inducers ($n = 5$) or enzyme inducers ($n = 3$). A large majority of the children had a generalized epilepsy and the most common seizure types were infantile spasms and tonic seizures. To determine the plasma levels of TPM, serial blood samples were drawn in the morning of the examination day before the intake of TPM as well as after 0.5, 1, 1.5, 2, 4, and 8 h after dosing. All TPM blood sampling was carried out in steady state. The TPM levels were determined by fluorescence polarization immunoassay method (FPIA) and the clearance was calculated by using the software WinNonlin. The clearance of TPM was related to type of formulation, type of comedication and age. The children were divided into age groups; <2 and 2–4.9 years.

Results: The TPM doses (mean ±SD) were 5.5 ± 2.4 mg/kg/day and 4.8 ± 1.8 mg/kg/day during treatment with the sprinkle and tablet formulation respectively. The treatment groups did not differ regarding the TPM dosage or age at time of investigation. The plasma clearances (CL/F; mean ± SD) of TPM were 66.7 ± 44 mL/h/kg with the sprinkle formulation treatment and 62.1 ± 33 mL/h/kg with the tablets and the difference was not significant. The children on comedication with nonenzyme inducers had a clearance of 41.9 ± 10 mL/h/kg and those on enzyme inducers 101.9 ± 36 mL/h/kg and the comparison showed highly significant differences ($P = 0.002$). Children <2 years of age had a clearance of 62.6 ± 35 mL/h/kg and those >2 years 68.0 ± 43 mL/h/kg and the difference was not significant.

Conclusions: In children under five years of age, the clearance of TPM sprinkle and tablet formulation did not differ. Within this age group the clearance of TPM was not affected by age but was markedly increased by enzyme-inducing comedication. (Supported by The Margaretahemmet Association.)

2.377

EFFICACY OF LEVETIRACETAM IN STIMULUS-SENSITIVE (REFLEX) EPILEPSY

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Rationale: Levetiracetam (LEV) is a novel anti-epileptic drug with efficacy against stimulus-sensitive epilepsy in animal models. It has been

reported to be effective in the treatment of photosensitive epilepsy. These findings prompted a trial of levetiracetam in patients with stimulus-sensitive (reflex) epilepsy.

Methods: Six patients, ranging from 3 to 18 years, were evaluated for stimulus-sensitive seizures. Clinical seizures were provoked by auditory stimuli in one patient, tactile stimuli in four patients, and photic stimulation in one patient. In two patients with acute symptomatic seizures, ictal epileptic activity was confirmed during continuous EEG monitoring. In the other four patients with remote symptomatic CNS injury, interictal epileptiform abnormalities were noted on EEG, and clinical seizures consistent with previously reported features, were provoked following patient-specific stimuli. These seizures interfered with care-giving and nursing tasks, as well as activities of daily living.

Results: Following the initiation of LEV, at doses ranging from 20–60 mg/kg/day, all patients showed a marked and sustained response to therapy (minimal or no seizure activity following stimuli). Two patients with acute symptomatic seizures were weaned off LEV in a few weeks, without recurrence of seizures. Four patients with remote symptomatic seizures, remain on LEV with significant attenuation of seizure severity in occasional break-through seizures. Reduction of provoked seizures resulted in improved quality of care in acutely ill patients; caregivers and school personnel reported improvement in activities of daily living in the other patients.

Conclusions: Levetiracetam has a rapid, marked and sustained clinical response effective in stimulus-sensitive (reflex) seizures. Clinical efficacy is noted in patients with acute as well as remote symptomatic etiology of reflex seizures, and is associated with increased ease of caregiving and improvement of social functioning.

2.378

TOPIRAMATE MONOTHERAPY IN CHILDREN WITH NEWLY/RECENTLY DIAGNOSED EPILEPSY: AN IN-PRACTICE FLEXIBLE DOSING STUDY

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Rationale: Double-blind, randomized controlled trials of topiramate included children ≥6 yrs of age, although most pediatric patients were adolescents. Patients were randomized to 50, 100, 200, 400, or 500 mg/day. Although these studies identified 100 mg/day as an effective, initial target dose, they were not designed to identify a maintenance dose. This open-label study allowed topiramate dosages to be adjusted according to clinical response in order to determine an optimal maintenance dose. We report on findings from the subset of children with newly/recently diagnosed epilepsy enrolled in this in-practice study.

Methods: An open-label, multicenter prospective study conducted in Europe and the Middle East followed children and adults treated with topiramate monotherapy for 7–13 mos. Children 2–16 yrs old were eligible if epilepsy was diagnosed <5 yrs previously and they were treatment-naive or had failed one antiepileptic drug. All epilepsy types were eligible. Study procedures allowed flexible topiramate dosing. Initial target dose: adolescents (13–16 yrs), 100 mg/day; younger children (2–12 yrs), 3 mg/kg/day.

Results: Of 690 patients with evaluable data, 66 were adolescents; 122 were children. 70% had focal epilepsy; 58% were treatment-naive. Most common reason for failing previous treatment was ineffectiveness. Mean topiramate maintenance dose at 7 mos: adolescents, 156 mg/day; younger children, 3.9 mg/kg/day. Seizure-free rates (≥7 mos): overall, 44%; treatment-naïve, 54%; previously treated, 37%. Most common (≥5% incidence) treatment-emergent events (other than childhood-related illnesses) were headache and appetite decrease in younger children and adolescents; somnolence, paresthesia, weight loss and dizziness in adolescents. 21% of patients discontinued: side effects, 2%; side effects and inadequate seizure control, 6%; inadequate seizure control, 11%; other reasons (eg, lost to follow-up), 6%.

Conclusions: Topiramate monotherapy appears to be effective and well-tolerated in adolescents and children with newly/recently diagnosed focal and generalized epilepsy. From these data, recommended initial target dose: adolescents, 100 mg/day; younger children, 3 mg/kg/day. (Supported by Janssen-Cilag.)

2.379

OXCARBAZEPINE AS MONOTHERAPY OR ADJUNCTIVE THERAPY OVER 6 MONTHS IN INFANTS AND VERY YOUNG CHILDREN WITH PARTIAL SEIZURES IS SAFE AND WELL TOLERATED

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Rationale: The safety and tolerability of oxcarbazepine as monotherapy and adjunctive therapy in infants and children 1 month to <4 years of age was assessed in two open-label pilot studies [Duchowny et al. *Eur J Neurol* 2003; 10:148 (P2082); Hernandez et al. *Neurology* 2003; 60(suppl 1):A145]. Safety and tolerability data from the 6-month extension phases of both studies are reported here.

Methods: Pediatric patients completing the treatment phases of the two pilot studies were included in the 6-month open-label extension phases. During the treatment phases, patients had received oxcarbazepine oral suspension as either monotherapy or adjunctive therapy. During the extension phases, patients could receive oxcarbazepine dosages of up to 60 mg/kg/day, adjusted to individual efficacy and tolerability. Concomitant use of antiepileptic drugs (AEDs) was allowed. Safety assessments for adverse events (AEs), vital signs, ECG, and laboratory tests were performed at 2, 6, 10, 18, and 26 weeks after entry into the extension phases.

Results: A total of 24 children (13 male, 11 female) were included in the 6-month extension phases of the two studies. The median (range) age, weight, and height were 17 (2–42) months, 11.3 (4.7–16.7) kg, and 82 (55–99) cm, respectively. A total of 15 (62.5%) patients completed the extension phases. The median (range) treatment duration during the extension phases was 182 (15–231) days. The median (range) oxcarbazepine dose was 49.3 (5.3–60.9) mg/kg/day. Seven (29%) patients remained on oxcarbazepine monotherapy during the treatment and extension phases; 17 (71%) patients received oxcarbazepine adjunctive therapy during the extension phases. Three (12.5%) patients discontinued because they no longer required AED therapy. One (4.2%) patient receiving adjunctive therapy discontinued due to AEs (fatigue, irritability, and ataxia). The most frequent AEs (≥20%), regardless of relationship to oxcarbazepine, were pyrexia, ear infection, irritability, nasal congestion, upper respiratory tract infection, lethargy, and nasopharyngitis. There were no new safety findings identified by laboratory tests, vital signs, ECG, or physical examination during this study.

Conclusions: Oxcarbazepine was safe and well tolerated as monotherapy and adjunctive therapy in infants and very young children (<4 years of age) over a 6-month period. (Supported by Novartis Pharmaceuticals.)

2.380

GAMMA GLUTAMYL TRANSFERASE IN THE ERA OF NEW ANTIEPILEPTIC MEDICATIONS

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Rationale: Multiple studies from the 1970s to the 1990s report elevated serum concentrations of gamma glutamyl transferase (GGT) in 50 to 80% of patients treated with antiepileptic drugs (AEDs). To a great extent, it has become standard practice to attribute elevated GGT to AED enzyme induction and not to hepatotoxicity. However, these studies were performed on patients predominantly treated with phenobarbital, phenytoin, and primidone, medications now infrequently used to treat children. We intermittently receive inquiries regarding elevated GGT from primary care physicians who have obtained a "liver panel" on patients taking AEDs. Many of the newer AEDs are not enzyme inducers,

and there is little information regarding their effect on GGT. The current study reexamines the frequency of elevated GGT to determine how it has changed over the last 10 years.

Methods: It is our standard practice to obtain a metabolic panel, which includes liver functions tests (LFTs), on all admissions to the pediatric inpatient epilepsy unit. We requested that GGT be included in this evaluation. Serum concentrations of GGT, ALT, AST were obtained prospectively on 50 consecutive admissions. These were evaluated with respect to age, sex, number and type of AEDs.

Results: There were 20 boys, 30 girls, age 1 to 18 (mean 7.9) years, 20 were on monotherapy, 30 polytherapy, 7 ketogenic diet + AED. AEDs included CBZ(4), CZP(1), FBM(16), GBP(3), LEV(18), LTG(10), OXC(5),PB(3),PHT(3), TPM(7), VPA(11), ZNS(7). There were 6 (12%) patients with elevated GGT, all on polytherapy, including 2/3 on phenobarbital, 1/3 on phenytoin, and 3/16 on felbamate. Only 2/6 had other elevated LFTs, both on felbamate. Patients on PB and PHT had 2–3 times the normal GGT. 2 of the patients on FBM had 1.2 and 1.5 times the normal GGT. The third patient, a 6 y.o. male on FBM, had 12.5 times the normal GGT with 1.5 and 2 times normal AST and ALT. This patient had been referred specifically for a GGT 125 times normal (>11,000), which had occurred following the addition of VPA to his treatment. The VPA had been stopped, and the GGT was decreasing.

Conclusions: With changes in AED treatment over the last 10 years, there has been a change in the frequency of elevated GGT. We found 12% as opposed to the 50–80% previously reported. Our 6 patients on PB and PHT had a 50% frequency of 2–3 X normal GGT, consistent with past reports. These were isolated, with AST and ALT normal, suggesting enzyme induction as the cause. Only 3/44 (6.8%) of the patients on the other AEDs had an elevated GGT, all associated with FBM, and 2 with other LFT elevations. The greatest elevation in GGT was with FBM, although VPA appeared to contribute in this case. These are more suggestive of hepatotoxicity. Elevations of GGT need to be evaluated carefully.

2.381

NEUROPROTECTIVE EFFECT OF LAMOTRIGINE ON HYPOXIC-ISCHEMIC BRAIN INJURY IN NEONATAL RATS

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Rationale: Lamotrigine (LTG) is a new antiepileptic drug indicated in all kinds of partial and generalised seizures, both in monotherapy and polytherapy. It is a presynaptic sodium channel blocker, thereby inhibits glutamate release. We tested whether it would protect against hypoxic-ischemic (HI) brain injury by LTG in postnatal day 7 Sprague-Dawley rats.

Methods: Right common carotid artery of the rat was coagulated and then the rat was exposed to 8% oxygen for 2 hrs. LTG (20, 50, 100, 200 mg/kg, every 12 hrs for 5 days) administered by nasogastric tube in pre- (n = 35) and post-treatment (n = 35) regimens, and controls (n = 60) received normal saline. Severity of injury was assessed 5 days later by visual evaluation of ipsilateral hemispheric infarction, and by measurement of bilateral hemispheric cross sectional areas.

Results: LTG pretreatment resulted in a decreased incidence of liquefactive cerebral infarction ($P < 0.05$). Quantitation of hemispheric areas in rats receiving TPM and control littermates confirmed the results of initial inspection ($P < 0.01$).

Conclusions: Pretreatment with LTG decreases the incidence and severity of ischemic brain damage in this animal model of perinatal cerebral hypoxia-ischemia. These data indicate that LTG plays a role in the evolution of HI injury to the developing brain, and that LTG pretreatment may offer an effective means to decrease the incidence and severity of perinatal HI brain injury. (Supported by Health Technology Planning and Evaluation Board Project-grant 02-PJ1-PG1-CH06-0001.)

2.382

CHILDHOOD ABSENCE SEIZURES: ONSET OF TREATMENT EFFICACY WITH LAMOTRIGINE

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Rationale: Lamotrigine (LTG) was shown in a double-blind, randomized trial to be an effective treatment for children newly diagnosed with typical absence seizures (TAS; *Epilepsia* 1999; 40(7):973–9). Since an escalation period is required to reach an effective mean maintenance dose, a post-hoc analysis was conducted to determine the onset of efficacy during the LTG dose escalation phase.

Methods: Patients were 2–16 years, with newly diagnosed TAS by clinical/EEG features on 1 of 2 3-min hyperventilation (HV) tests. The trial included a screen, an open-label escalation phase (OLEP, 4–18 weeks) with LTG (LAMICTAL®), a double-blind treatment phase (DBTP, ≤ 4 weeks), a treatment transition phase (1 week), and an exit visit. Patients who became seizure-free (SF) during the OLEP entered the DBTP and were randomized (1:1) to taper off the LTG and receive placebo, or to continue taking LTG at the effective dose achieved during the OLEP. The primary endpoint was the percent of patients who remained SF on HV-EEG during the DBTP.

Results: Demographics: Intent-to-Treat population n = 45, efficacy population n = 42, male = 36%, mean age (SD) = 7.4 kg (2.6). Seventy-one (71%, 30/42) of patients became SF during the OLEP with LTG. The median LTG dose providing complete SF was 5 mg/kg/day. The earliest onset of complete control of TAS occurred at a LTG dose of 2 mg/kg/day in 2 of 30 (6.7%) of patients who became SF and in 2 of 42 (4.8%) of all patients treated. The percent of patients becoming SF increases with further LTG dose increases, reaching 12 of 30 (40%) patients and 18 of 30 (60%) patients who became SF at LTG doses of 4 and 5 mg/kg/day, respectively. In the 30 patients who became SF, 17% sustained at least 25% reduction in clinical manifestations (e.g., blinking, staring) at a LTG dose of 0.5 mg/kg/day and 30% sustained at least 25% reduction at a LTG dose of 1 mg/Kg/day. *Note: LTG dosing schedule in this trial exceeds the current dosing schedule recommended in the product label.*

Conclusions: This study shows that LTG monotherapy is effective for the control of TAS in children with the initial onset of complete control at a LTG dose of 2mg/kg/day. (Supported by GlaxoSmithKline.)

2.383

USE OF ZONISAMIDE IN 50 PEDIATRIC PATIENTS WITH MEDICALLY REFRACTORY EPILEPSY: A RETROSPECTIVE CHART REVIEW

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Rationale: Zonisamide (ZNS) is a broad-spectrum antiepileptic drug (AED) with multiple mechanisms of action. The drug has been available in Japan since 1989 and has been used to treat a variety of seizure types. In the USA, ZNS has been approved for add-on-therapy in adult patients with partial epilepsy since 2000. Few data are available regarding the effects of ZNS in pediatric patients with medically refractory epilepsy. This chart review study investigates the efficacy of ZNS in 50 pediatric patients of this category.

Methods: This study includes pediatric patients with medically refractory epilepsy treated with ZNS between October 2001 and April 2004. Patients in whom adequate trials of two or more first-line AEDs had failed were defined as medically refractory. We included patients with generalized and partial epilepsy. The efficacy was assessed by caregiver reports and by seizure diaries. Safety and tolerability were assessed by reports of adverse effects.

Results: The charts of 50 patients (30 boys, 20 girls) were reviewed. Mean age by epilepsy debut was 2.2 years (range < 1 month to 9 years). Forty-two patients had generalized epilepsy, 8 had partial seizures. Mean age when ZNS-therapy was started was 7.2 years (range 3 months to 17 years). Forty-nine patients received ZNS as add-on therapy, one as monotherapy. Mean dosage was 5.4 mg/kg/d (range 2–12 mg/kg/d). A

reduction in seizure frequency of at least 50% was seen in 22 patients, but the efficacy diminished in 10 patients 2 to 6 months after onset of ZNS-therapy. Eight had a significant reduction of one seizure type (5 with myoclonic seizures, 3 with tonic-clonic seizures). Twelve of the patients had no effect of ZNS. Eight patients got a higher seizure frequency at a dosage of 2 mg/kg/d. After withdrawal of ZNS, the previous seizure frequency was restored. In most cases, the tolerability was good. Twenty-three patients had no negative adverse effects. Weight loss because of decreased appetite and vomiting was observed in 4 patients. Others had intermittent drowsiness (n = 7), restlessness (n = 4), decreased appetite without significant weight loss (n = 2), rash (n = 1).

Conclusions: Data from this cohort suggest that ZNS can be useful in patients with medically refractory epilepsy, especially in patients with generalized epilepsy, in contrast to the approved medical use. Generally, the tolerability was good. Onset of adverse effects was seen already at low-dose-ZNS (2 mg/kg/d). About 25% had no reduction in seizure frequency on ZNS-therapy. Controlled studies of the use of ZNS in pediatric patients are needed.

2.384

EFFICACY AND TOLERABILITY OF LEVETIRACETAM AS ADJUNCTIVE AND MONOTHERAPY IN PEDIATRIC EPILEPSY

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Rationale: Levetiracetam (LEV) is a novel antiepileptic drug (AED) approved for treatment of partial seizures in adults. The experience in children is limited. We sought to determine the efficacy of LEV as add-on and monotherapy in a cohort of pediatric epilepsy patients treated at our institution with LEV during 2001–2003.

Methods: A retrospective analysis of medical records identified 47 children. There were thirty males and 17 females. Ages ranged from 0.5 to 20 years.

Results: Dose range was 10–70 mg/kg/day. Follow-up range was 6–34 months. LEV was used as adjunctive therapy in 37 children. Their seizure types were partial in 18(48%), mixed in 17(46%), and generalized in 2(4%)**.** In this group, 50–100% seizure reduction was seen in 13(72%) children with partial, 5(31%) with mixed and 2(100%) with generalized epilepsy. 12/37 children (32%) became seizure free; 4 of them decreased concomitant AEDs from 2–3 to 1, while 4 others converted to LEV monotherapy. LEV was used as initial monotherapy in 10 patients due to side effects or lack of efficacy of first line AEDs. Nine had partial and 1 generalized epilepsy. Five children (50%) were seizure free at median follow up of 15 months. Adverse effects were noted in 7 children (15%): lethargy in 2, and behavior/cognitive changes in 5. LEV was discontinued in 12 patients (25%) for adverse effects or poor seizure control

Conclusions: LEV was well tolerated and effective (>50% seizure reduction) as both adjunctive and monotherapy in 53% of our patients. LEV is a therapeutic alternative for a variety of childhood epilepsies

2.385

SEVERE SIDE EFFECTS OF VALPROIC ACID: THE GERMAN EXPERIENCE OF THE PAST 10 YEARS

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Rationale: Valproic acid (VPA) is an excellent antiepileptic drug both against generalized and partial seizures. A number of severe adverse effects have been associated to VPA-treatment. 238 patients have died related to VPA worldwide, due to hepatotoxicity, pancreatitis and very rarely to bleeding complications.

Methods: We conducted a nation-wide survey asking members of the German Section of ILAE to report all patients with severe side effects related to VPA within the last 10 years.

Results: Pancreatitis: 46 unpublished patients were reported, all with a reversible outcome and lipase >500 U/l. This number approaches the number of all published patients in the literature, which shows that pancreatitis is by far under-reported but generally has a good outcome.

Bleeding complications: Pathological findings of coagulation parameters, especially of v.Willebrand-factor, Ristocitin-Co-factor and Factor XIII occurred frequently, but clinical complications were rare and reversible. (Only two patients had died directly due to impaired coagulation before 1994).

Hepatotoxcity: The pattern of liver complications changed very much during the past 10 years. By far most episodes of severe hepatotoxicity were reversible, VPA was withdrawn early and i.v.carnitine was substituted in most patients. An equal number of adult patients and children died related to VPA during the past 10 years in Germany: 4 children and 4 adults, most with polytherapy and additional risk factors.

Conclusions: Severe complications related to VPA continue to occur, but the increasing awareness of the problem greatly improved the chance for a reversible outcome. Considering the increasing number of patients treated with VPA and the decreasing number of fatalities, the frequency of the latter can be estimated to be below 1: 100000 overall. VPA remains an indispensable drug of first choice for both pediatric and adult patients.

2.386

OXCARBAZEPINE: CLINICAL EXPERIENCES IN 30 CHILDREN YOUNGER THAN 3 YEARS

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Rationale: Oxcarbazepine (OXC) was approved as adjunctive therapy for the treatment of focal epilepsies in patients older than 4 years.

Methods: 30 patients (14 male, 16 female) younger than 3 years (mean age 20 months) has been placed on OXC from April 2001 until February 2004. Most of them had focal epilepsies (26 symptomatic, 2 cryptogenic). They have beeen treated with 3,5 (mean) AEDs before without effect. Mean age at first seizure was 8,8 months. 4 patients received OXC-monotherapy. There was no prefered comedication.

Results: 2 patients became seizure free for longer than one year, 4 were seizure free from 4 weeks to 11 months, 1 for 4 weeks only. 5 had seizure reduction 75–99%, 10 showed a 50–75% seizure reduction. 4 patients had no effect, 4 had a provocation of seizures. Mean OXC-dose was 58,6 mg/kg BW (maximum 106 mg/kg BW) in effective treated patients with mean 10-OH-Carbazepine serum levels of 26 mg/l. We have seen no severe unwanted side effects. Hyponatremia was transient only in one child.

Conclusions: Oxcarbazepine is as well effective and as well tolerated in children younger than3 years compared to older patients. In relation to bodyweight younger children need a higher OXC-dose to reach the same bloodserumlevels. It is also well tolerated as monotherapy.

2.387

EFFICACY OF ZONISAMIDE IN JUVENILE MYOCLONIC EPILEPSY

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Rationale: Juvenile myoclonic epilepsy (JME) is a hereditary idiopathic generalized epilepsy syndrome found in 5–11% of patients with epilepsy. The recommended drug of choice in the treatment of JME is valproate (VPA), although recently topiramate and lamotrigine have demonstrated to be an effective therapeutic alternative. Zonisamide (ZNS) is a new anti-epileptic drug (AED), with multiple mechanisms of action, including its effect upon voltage- dependent T-type Ca channels. In the Japanese literature, there are data showing that zonisamide is efficacious in primary generalized epilepsy. The objective of this study was to assess the efficacy of ZNS in the treatment of JME.

Methods: We retrospectively analyzed the records of patients with the diagnosis of JME between seen at our institution between the years the years of 2001 and 2003, and further separated those who were on zonisamide in monotherapy or polytherapy. The diagnosis of JME was based on the criteria of the International Classification of Epilepsies, with EEG findings supporting the diagnosis. The response of generalized tonic clonic (GTC), myoclonic and absence seizures was separately evaluated.

Results: Fifteen patients with the diagnosis of JME and treated with ZNS were identified. Their age varied from 11 to 20 years; 12 were girls and 3 were boys. ZNS dose ranged from 200 to 500 mg/day (2–8.5 mg/k/d). Dose escalation was 100 to 200 mg every two weeks. Two patients were on polytherapy with ZNS and valproate, while the other 13 were on zonisamide monotherapy. Follow-up ranged from 2 months to 2 years with a mean of 12 months. One patient had to stop ZNS and was switched to VPA because of poor seizure control. There were no other side effects reported. The degree of seizure reduction of the 13 patients on ZNS monotherapy were as follows: 100% in 6 (46.2%), 75% in 3 (23.1%), 50% in 1 (7.7%), and less than 25% in 3 (23%). Overall, 80% of JME patients treated with ZNS showed good control ($\geq$ 50% seizure reduction). Sixty-two and 69% of the patients were free of myoclonic and GTC seizures respectively, compared to 37.5% of absence seizures. Adequate seizure control group was achieved within 4 to 8 weeks of attaining average maintenance dose of zonisamide. Of the 2 patients on polytherapy (ZNS and VPA), one of them experienced 75% reduction in seizure frequency and the other one had no change in seizures. None had signs of drug interaction.

Conclusions: ZNS demonstrated to be an effective and well-tolerated drug in the treatment of our patients with JME. ZNS appeared to be more efficacious treating myoclonic and GTC seizures. The ease of titration, good safety profile, once a day dosing, lack of significant drug interaction, and short latency for onset of efficacy makes zonisamide an attractive alternative choice in the treatment of JME.

2.388

EPILEPSY IN CHILDREN: MAY PARENTS EVALUATE ADEQUATELY THEIR CHILDREN'S PERCEPTION OF THE DISEASE AND THEIR QUALITY OF LIFE?

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Rationale: Quality of life in epilepsy (QOLIE) is a term that, according to some authors, aims to define certain features of human experience, in which the main factor is a subjective feeling of well-being. Most questionnaires on QOLIE in children are applied to parents, leading to an indirect measure of the effects of a disease that is in fact lived and experienced by the child in question. This study (1) evaluates QOLIE in children and adolescents with epilepsy using an auto-applicable questionnaire that enables an estimation of the child's own perception of his/her disease and (2) compares the child's with the parent's awareness.

Methods: We applied the *Children's Global Assessment Scale* (CGAS) and *Vineland Adaptive Behavior Scale* (VINELAND), with communicational, daily activity and sociability subscores, as well as total score (TOTAL VIN) to parents. *Autoquestionnaire qualite de vie enfant image* (AUQEI), validated for the Brazilian population by Assumpcao Jr. et al.(2000), was applied on 28 children with epilepsy, aged from 4 years to12 years and 11 months, and compared to 28 paired healthy, age-matched school children (controls). Independent t test was used, with a significance level of 5%.

Results: No significant differences as to CGAS results were observed between both groups. In children with epilepsy TOTAL VIN, and all of its subscales, showed significantly worse results than in controls. Likewise, as to total scores of AUQEI, children with epilepsy had significantly lower scores than controls.

Conclusions: In our study, children with epilepsy presented lower scores than controls as to their perception in QOLIE and in adaptative behavior. However, as observed by CGAS results, parents were unaware of a worsened state. Therefore, development of research instruments capable of pointing out the patient's own perception of his/her condition and treatment are crucial.

2.389

EFFICACY AND TOLERABILITY OF TOPIRAMATE AS MONOTHERAPY IN EPILEPSY: A PEDIATRIC EXPERIENCE

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Rationale: Topiramate (TPM) is a newer antiepileptic drug (AED) approved for use in patients above 2 years as add-on for partial (PE) and generalized epilepsy (GE). The objective of this study was to evaluate the efficacy and tolerability of TPM monotherapy.

Methods: We retrospectively reviewed the records of epileptic children seen at our institution during 2001–2003, and who were on TPM monotherapy

Results: Forty-two patients (21M, 21F), ages 0.5–23 years (mean 9.7 years) were identified. Fifty-five percent had developmental delay/mental retardation. Type of epilepsy was PE in 71%, idiopathic GE (IGE) in 17%, and symptomatic GE (SGE) in 12%. Range of TPM dose was 1–19 mg/kg/day (mean 6.0 mg/kg/day). Follow-up range was 0.5–5 years (mean 2.2 years). TPM was started as first-line monotherapy in 10 patients (24%), and as adjunctive therapy in 32 (76%), due to ineffectiveness (22) or side effects (10) of other AEDs. Mean number of previous AEDs was 1.2 (range 0–5). Global seizure reduction was as follows: 100% in 26 (62%), 75–99% in 2 (5%), 50–74% in 4 (9.5%), and $<$25% in 10 (24%). Overall, 32 (76%) patients showed $>$50% reduction in seizure frequency. According to epilepsy type, seizure reduction was as follows: PE: $>$50% in 73%, 60% seizure-free, and $<$25% in 27%. IGE: $>$50% in 86%, 71% seizure-free, and $<$25% in 14%. SGE: $>$50% in 80%, 60% seizure-free, $<$25% in 20%. Three patients (7%) had side effects: weight loss, memory difficulties, and lethargy.

Conclusions: TPM proved to be effective and safe as monotherapy in various types of pediatric epilepsy.

2.390

LOW-DOSE TOPIRAMATE COMPARED WITH CARBAMAZEPINE IN TREATING BENIGN ROLANDIC EPILEPSY

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Rationale: To evaluate the efficacy and tolerability of low dose topiramate (TPM) as compared with carbamazepine (CBZ) especially in neuro-psychological side effects including cognitive function in children with benign rolandic epilepsy (BRE).

Methods: Open-label, multi-center, randomized clinical trial was done in 71 children (36 males and 35 females) with BRE, aged 5–15 years, for 28 weeks of treatment with TPM($n = 40$) with low dose (1–2 mg/Kg/day) or CBZ($n = 31$) in usual doses (10–20 mg/Kg/day). All patients were categorized in BRE with acceptable indication for medication, having frequent, daytime, prolonged, and/or major secondary generalized convulsive seizures. The study included a baseline phase followed by titration and maintenance phases. Psychological testing was performed before the titration, and repeated at the end of maintenance phase. Seizure outcome, neuro-cognitive side effects were compared between low dose TPM and CBZ groups, using a 95% confidence interval approach.

Results: Analyses of variances showed no significant difference between TPM and CBZ (Table 1).

TABLE 1. *Comparison efficacy and safety between TPM and CBZ*

	TPM	CBZ
Patients	40	31
Mean AED dose (mg/Kg/day)	81/31.24	524/34.93
Seizure free rate (%)	71	63
Seizure relapse rate (%)	29	37
Dominant adverse events	Memory dysfunction, anorexia	Somnolence, fatigue, weight gain
Baseline IQ/endpoint IQ (mean/SD)	105.33(22.8)/ 109.71(21.31)	104.98(20.97)/ 104.72(21.34)
Baseline behavioral problems/endpoint behavioral problems rate (%)	8/3.1	6.72/2. 8

N.S.

Conclusions: There was no significant difference between low dose TPM and CBZ in seizure control, outcome of psychological tests and global assessment. Low dose TPM monotherapy can be substituted in treating BRE with expecting high efficacy and tolerability. (Supported by Janssen Korea Co.)

2.391

EFFICACY AND TOLERABILTY OF OXCARBAZEPINE MONOTHERAPY IN NEWLY TREATED PEDIATRIC PATIENTS WITH PARTIAL SEIZURES WITH OR WITHOUT SECONDARY GENERALIZATION

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Rationale: Oxcarbazepine, a "second generation" antiepileptic drug, was introduced to the United States in 2000, with FDA approval in monotherapy as well as adjunctive therapy in both children over the age of 3 and adults, with partial seizures, with or without secondary generalization. The purpose of this abstract is to report the efficacy and tolerability of oxcarbazepine monotherapy collected prospectively in pediatric patients under the age of 16.

Methods: Data was collected prospectively in patients with partial seizures with or without secondary generalization. Data was recorded on a standard database beginning at oxcarbazepine initiation and at 3 month intervals. Oxcarbazepine blood levels were recorded as part of routine visit in most cases. Serum sodium levels were routinely checked at three monthly intervals. Seizure frequency changes were recorded at each visit, as well as assessment of adverse effects.

Results: Eighteen patients (8 females, 10 males) ages 3–16 years were identified as treated with oxcarbazepine monotherapy. Two patients were lost to follow up and one additional patient demonstrated poor compliance. These three patients are therefore not reflected in the data analyses. Patients with less than 3 month exposure (n = 2) to oxcarbazepine were also not included. Ten patients were newly diagnosed and naïve to medication. Two patients had experienced seizures in the past but had been off medication for, 2 and 5 years respectively. Three patients were converted from carbamazepine to oxcarbazepine. In terms of tolerability, only one patient (8%) with previous drug exposure, discontinued oxcarbazepine secondary to an adverse effect (drowsiness). There was no recorded incidence of hyponatremia. Three patients had a 3 month exposure, five had 6 month exposure, one with 9 month exposure, two with 1 year exposure, and one with 4 year exposure (N = 12). Two patients (16%) experienced 75–99% reduction in seizures (3 and 6 months exposure respectively). The remaining patients (84%) are seizure free. The mean oxcarbazepine dose used was 18.3 mg/kg/day (range 9.6–42 mg/kg/day). Plasma levels were obtained and ranged from 9.3–20 μg/ml.

Conclusions: Oxcarbazepine as monotherapy, has shown outstanding efficacy and tolerability in this cohort of patients aged 3–16 years with partial seizures, with or without secondary generalization. 84% were seizure free on monotherapy. 16% demonstrated 75–99% reduction in seizure frequency at initial dosing. The incidence of adverse effects was low and there was no recorded incidence of hyponatremia. Data collection continues and will be added to the database.

2.392

URINARY REACTIVE OXYGEN SPECIES LEVELS IN PEDIATRIC PATIENTS RECEIVING VALPROIC ACID, CARBAMAZEPINE, OR CLOBAZAM

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Rationale: Animal studies have demonstrated that valproic acid (VPA) increases the hepatic and plasma levels of 15-F_{2t}-isoprostane (15-F_{2t}-IsoP), which is used as an in vivo marker of oxidative stress. It has been postulated that increased levels of reactive oxygen species may play a role in the pathogenesis of idiosyncratic VPA hepatotoxicity.

The objective of the study was to compare urinary 15-F_{2t}-IsoP levels in children receiving VPA with those in children receiving carbamazepine (CBZ) or clobazam.

Methods: A morning urine sample was collected from patients younger than 16 years of age, receiving monotherapy with VPA (n = 15), carbamazepine (CBZ) (n = 13) or clobazam (n = 6) for $\geq$ 4 weeks and from age-matched controls not receiving medications (n = 31). Urine 15-F_{2t}-IsoP levels were determined by ELISA.

Results: The mean ($\pm$ SD) urine 15-F_{2t}-IsoP levels (nmol/mmol Cr) were: VPA (0.36 $\pm$ 0.17); CBZ (0.24 $\pm$ 0.10); clobazam (0.18 $\pm$ 0.01); control group (0.19 $\pm$ 0.09). Using one-way ANOVA with a Bonferonni's pairwise multiple comparison test, patients treated with VPA had significantly elevated 15-F_{2t}-IsoP levels when compared to the control, CBZ and clobazam groups ($p < 0.05$). There was no difference in 15-F_{2t}-IsoP levels between CBZ, clobazam and control groups.

Conclusions: These data demonstrate that treatment of children with VPA is associated with increased urinary 15-F_{2t}-IsoP levels. The role of reactive oxygen species in the pathogenesis of VPA hepatotoxicity should be explored further. (Supported by Canadian Institutes of Health Research.)

2.393

LEVETIRACETAM (*KEPPRA*) IN CHILDREN WITH INTRACTABLE EPILEPSY: A MULTICENTRE CLINICAL AUDIT

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Rationale: Levetiracetam (LEV) is licensed for treatment of focal seizures in adults and has been reported to be effective in childhood epilepsy. We describe our experience of LEV in children with intractable epilepsy in the Midlands, UK.

Methods: Children prescribed LEV from 2001 to 2003 were systematically ascertained from the pharmacy records and departmental databases of 4 tertiary pediatric neurology centers. A retrospective chart review of patients using a standard proforma to assess seizure type, seizure frequency, prior and concomitant anti-epileptic drugs (AEDs) and adverse events was undertaken.

Results: So far data on 132 children (76 males) aged 1–18 years (mean 9 years 2 months), and 104.5 person years of exposure, has been collected. Mean age of onset of epilepsy was 3.4 years (2 days–14.9 years). Sixty five (49%) had focal seizures, 61 (47%) had generalised seizures and 6 (4%) had mixed seizure types. Forty seven (36%) children had received more than 5 AEDs, 43 (32%) 4 AEDs, 22 (17%) 3 AEDs, and 20 (15%) 2 AEDs prior to LEV. LEV dose ranged from 10–100 mg/kg/day. Follow up ranged from 6–28 months, duration of treatment ranged from 1–28 months (mean 9.5 months). Fourteen (11%) achieved LEV monotherapy.

More than 50% reduction in seizure frequency was obtained in 37 (57%) with focal seizures, 30 (49%) with generalised seizures and 2 (33%) with mixed seizure types. Seizure freedom for 6 months or more was achieved in 7 (11%) with focal epilepsy, 5 (8%) with generalised epilepsy and 1 (16%) with mixed seizure types. 20 (31%) with focal seizures, 24 (39%) with generalised seizures and 3 (50%) with mixed seizure types showed no improvement. 8 (12%) with focal seizures and 7 (11%) with generalised seizures had increased seizures.

21 (16%) children reported adverse events leading to withdrawal in 17 (13%). There were no serious adverse events.

Conclusions: LEV appears to be effective and well tolerated in a variety of intractable childhood epilepsies. We aim to have 12 month follow-up data on 150 children by the end of 2004.

2.394

TIAGABINE AS INITIAL TREATMENT FOR INFANTILE SPASMS: A PILOT STUDY

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Rationale: Infantile spasms is a catastrophic epilepsy of the young child associated with a hypsarrthymic EEG and poor long-term outcome. Current conventional treatments include ACTH and valproate which show limited efficacy and are associated with high morbidity and mortality in this population. Vigabatrin has demonstrated efficacy in infantile spasms but is not available in the United States. The purported mechanism of action is through elevation of whole brain GABA.Tiagabine raises brain GABA levels by blocking reuptake. We performed a pilot study of tiagabine for treatment of infantile spasms.

Methods: Patients age 1–36 months with infantile spasms experiencing at least one cluster of spasms per day for three days prior to enrollment with an EEG containing hypsarrthymia or modified hypsarrthymia were recruited for a prospective open label study of tiagabine as first line therapy. Dosing started at 0.2 mg/kg/day and increased every 3 days by 0.2 mg/kg/day until resolution of seizures, intolerability or a maximum dosage of 5 mg/kg/day.MRI's of the brain were obtained prior to enrollment to confirm the absence of a progressive lesion. Patients were evaluated weekly during titration and every 2 weeks during stabilization. Patients were recruited between 10/00 and 11/01.

Results: 5 patients were enrolled (3 female, 2 male) ages 6–10 months. At baseline patients experienced 3–7 spasm clusters/day. 2 patients had been diagnosed previously with a seizure disorder prior to development of spasms. All had symptomatic spasms (2 with trisomy 21, 1 traumatic brain injury, 1 tuberous sclerosis, 1 with porencephaly). 3 patients experienced resolution of hypsarrthymia and cessation of spasms. 2/3 developed other seizure types, 1 focal tonic,1 generalized tonic with development of a slow spike wave EEG. 2 demonstrated no efficacy with one withdrawing at low dose due to intolerability (sedation). Hematology and chemisrty labs including liver function tests were monitored during the study. No clinically significant changes in lab values occurred.

Conclusions: In this pilot study, tiagabine demonstrated efficacy in infantile spasms with 3/5 showing resolution of hypsarrthymia and control of spasms.No life threatening reactions were noted and compared to current therapies were well tolerated.

Tiagabine demonstrates potential as treatment for infantile spasms.Tiagabine has a superior safety profile compared to treatments available in the United States. Further studies are warranted to determine its exact role. (Abbott Laboratories supplied drug at no cost.)

2.395
IS RAPID TITRATION OF LEVETIRACETAM EFFECTIVE AND WELL TOLERATED IN CHILDREN?

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Rationale: Levetiracetam (LEV) is an antiepileptic drug (AED) approved for adjunctive therapy of partial onset seizures in adults and children over 16 years of age. Current prescribing information recommends gradual titration at a rate of advancing 1000 mg every two weeks in adults (target dose 3000 mg/day) and by 20mg/kg every two weeks in children (target dose 60 mg/kg/day). LEV is well tolerated, effective AED with wide margin of safety. There are some reports of rapid titration in adults (1), reaching therapeutic dose in 3 days and inconsistent data on medium quick titration in children, advancing every 4 days (2, 3). The purpose of this analysis is to examine efficacy and safety of rapid titration in the certain circumstances that require rapid control of seizures due to ineffectiveness or unacceptable side effects of other AEDs. We report 8 pediatric patients who had an improvement or full control of seizures with the rapid titration.

Methods: Retrospective chart review was performed on patients seen at Children's Hospital of Pittsburgh with childhood epilepsy treated with Levetiracetam that was titrated to full dose in 2 weeks or less. Data regarding demographics, seizure type, epilepsy syndrome, MRI and EEG findings, treatment duration, AED's use were collected and analyzed.

Results: 8 children (7 females and 1 male) ages 19 months-17 years (mean age 8.6) with complex partial seizures (75%), mixed seizures (12.5%), generalized seizures (12.5%) were started on Levetiracetam and titrated up over 2 to 14 days (mean 10 days). All had improvement in seizure activity and 6(75%) became seizure free, including 1 patient with hemimegalencephaly who presented in non-convulsive status epilepticus, was treated with 40 mg/kg on day 1, 60 mg/kg on day 2, became stable, and proceeded to functional hemispherectomy, 2 patients with carbamazepine induced and idiopathic neutropenia, respectively, 2 patients with low grade tumor, 1 patient with autism. 1 patient(12.5%) required weaning of Levetiracetam because of behavioral problems observed 5 weeks latter at dose of 60 mg/kg/day. 62.5% were on LEV monotherapy.

Conclusions: Rapid titration of Levetiracetam has shown to be an effective in childhood epilepsies with partial or generalized seizures under curtain circumstances. No increase in side effects had been observed in our series. More data are needed to evaluate this hypothesis. That could broaden physician's choices of AEDs for use when rapid initiation of therapy is required.

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2.396
TRAINING SCHOOL HEALTH PERSONNEL IN THE ADMINISTRATION OF DIAZEPAM RECTAL GEL AS PART OF A SEIZURE EMERGENCY TREATMENT PLAN

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Rationale: Providing effective seizure treatment in the school setting is important for students, parents, and school personnel. Seizures are emergency situations necessitating rapid termination to minimize risk of long-term neuronal damage. The development of a seizure emergency treatment plan can empower school personnel to quickly and confidently treat seizures and enable students to quickly resume their usual activities. Diazepam rectal gel, a portable rescue medication for the treatment of breakthrough seizures, can be an effective part of the treatment plan. This presentation addresses strategies employed by the Central Virginia Region School District and surrounding counties to establish seizure emergency treatment plans and to train medical and nonmedical school personnel in the administration of diazepam rectal gel. It also evaluates some of the challenges encountered in adopting these plans.

Methods: We interviewed school health personnel and parents of children with seizures to assess how they were trained in the use of diazepam rectal gel and their level of satisfaction with the medication.

Results: Data represent responses from schools in 20 counties. In the majority of elementary schools, care is provided by a full time health assistant/aide and itinerant nurse who travels between schools. The majority of middle schools and high schools employ a full time nurse. Training for all school health personnel was the same. We provided direct, hands-on training at 3 schools. For the remainder of schools, we have trained the head nurse of each county program in the use of diazepam rectal gel at the State Nurses Meeting over the past 2 years; the head nurses then train the necessary health personnel in their own schools. At the meeting, the head nurses were given an instructional video, an empty syringe system for demonstration purposes, an administration sheet, and a question sheet. When diazepam rectal gel is ordered for use in a school, we send our 5-page seizure protocol that provides specific direction regarding when diazepam rectal gel should be given, when to administer a second dose, and when to call a rescue squad. The school aides reported feeling very comfortable with the administration of diazepam rectal gel; they felt that it was easy to use and very effective. Parents also reported feeling very comfortable having diazepam rectal gel in the schools. They were relieved that it was available and described it as easy to use. School health personnel in our district have demonstrated success in implementing the seizure emergency treatment plan; case studies describing effective administration of diazepam rectal gel and challenges to its use will be reported.

Conclusions: The development and implementation of a seizure emergency treatment plan incorporating diazepam rectal gel empowers students, parents, and school personnel to feel more confident in safely and quickly terminating breakthrough seizures. (Supported by Xcel Pharmaceuticals.)

2.397

NEONATAL POLISSONOGRAPHY: A NEW METHOD TO MEASURE THE MOVEMENTS IN THE SLEEP

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Objectives: To quantify the movement in each different sleep-phases in full-term newborns and comparing with number of the phases.

Methods: We analyzed the amount of movement, according to a proposed Motor Index (MI) of 32 polissonographic studies of normal full-term newborn babies born at the Hospital de Clínicas da UFPR. MI was dubbed (MI 3) when there were findings suggestive of movement in more than 50% of an EEG epoch, (MI 1) when no movements could be observed and Average MI 2 when findings of movement where observed in less than 50% of an EEG epoch. Movement features were obtained through annotations on the exam such as movement of feet, hands, head, mouth, suction movements and generalized movements, among others. An additional electromyographic channel aided in registering an increase in amplitude or irregularity of registry, when the EEG was obscured by muscular and/or movement artifacts. All of these variables were quantified in each different sleep-wake phase.

Results: The mean duration of registry was of 57.45 minutes and the total amount was of 1838.4 minutes. The mean duration of M 3 was of 18.33 minutes, M 2 of 16.36 and of M 1 of 21.5 minutes. During quiet sleep the mean duration of M 3 was of 22.3 minutes and during active sleep 323 minutes. Mean duration of M 1 in quiet sleep was of 446.33 and in active sleep was of 171.6. In quiet sleep the mean duration of M 2 was of 134.33, 240 during active sleep, 84.6 minutes in transitional sleep, and 67.6 minutes in the wake state. The sum of M 3 and M 2 was of 563 minutes (30.6% of the total time). Considering the incidence of each sleep phase, quiet sleep occurred at a rate of 3.1/exam (range 1–8/exam), active sleep 3.3/exam (ranging 1–9/exam), transitional sleep 3.9/exam (range 0–9/exam) and awake 3.9/exam (range 0–10/min). When the number of phases is compared with de movements, the instable sleep there are more movements. The statistical test used was regression multiple, with co-variance time of the electroencephalogram.

Conclusions: In all our exams the newborns remained the majority of time in sleep. Movements are observed in a greater amount during active sleep, predominantly in those patients who had a greater variation of sleep phases. There are more movements in instable sleep neonates.

In the visual analysis of neonatal EEG one must classify the different phase of the sleep-wake cycle based on polygraphic features and their changes according to each phase. In addition, quantifying the amount of each sleep phase may be of help in determining whether the polissonographic findings are those of a normal newborn or of an abnormal one.

2.398

PSYCHIATRIC PROBLEMS IN CHILDREN WITH NEW-ONSET SEIZURES AND THEIR PARENTS

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Rationale: Children with new onset seizures (NOSz) have more emotional and behavioral problems compared to siblings and classmates. Family psychiatric history is a significant risk factor for child psychopathology. Mothers of children with epilepsy have been reported to experience more psychopathology, however it has not been investigated when these problems begin. It is not known if children with NOSz have parents with higher levels of psychopathology. The purpose of this study was to evaluate the association between psychopathology in children with NOSz and their parents.

Methods: In a cross-sectional study we evaluated 30 cognitively normal children with NOSz (17girls, 13 boys), aged 5 to 15 years (mean age 9.3 $\pm$ 2.4 y) and their parents (30 mothers, 17 fathers). Data were collected within 1 month of the NOSz diagnosis confirmed by a pediatric epileptologist. The Child Behavior Checklist (CBCL) and Teacher Report Form (TRF) were used to evaluate children's emotional and behavioral problems. Symptom Checklist-90-R (SCL-90-R) was administered to assess parental psychopathology. Spearman's correlation was used to examine the relationship between the child scores on CBCL and parent scores on SCL-90-R.

Results: In a sample of children with NOSz, 13% had elevated scores ($T \geq 63$) for Total and 20% for Internalizing CBCL problems. Although more fathers (12%) than mothers (10%) had increased psychopathology ($T \geq 63$) on SCL-90-R, this may be due to the smaller number of fathers participating in the study. CBCL Total ($r = .44$, $p = .02$), Internalizing ($r = .45$, $p < .01$) and Externalizing ($r = .43$, $p = .02$) problem scores were significantly correlated with general maternal psychopathology, but not with paternal psychopathology($p = .23$; $p = .32$; $p = .26$). Higher CBCL Internalizing problem scores were significantly correlated with maternal depression, interpersonal sensitivity, somatization, paranoid ideation, and Global Severity Index (all $p < .05$).

Conclusions: Although preliminary, these findings imply that psychiatric problems in children with NOSz are associated with maternal, but not with paternal psychopathology. Mothers with higher level of psychological distress reported more psychopathology in children compared to mothers with lower levels of psychological distress. (Supported by Eli Lilly and American Academy of Child and Adolescent Psychiatry.)

2.399

INITIAL MONOTHERAPY WITH LEVETIRACETAM IN CHILDREN 3 YEARS OLD AND YOUNGER

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Rationale: Levetiracetam is a relatively new antiepileptic medication. Initial monotherapy in young children has not been evaluated extensively. This report addresses the use of levetiracetam in children 3 years old and younger, as initial treatment.

Methods: Charts of children were reviewed alphbetically until 25 were found with levetiracetam as the initial treatment for epilepsy. To be included, the child had to be 3 years old or younger, have the diagnosis of epilepsy. They could only have been treated to stop an acute seizure, for example in the emergency room, but not with a chronic medication. The charts were reviewed for seizure characteristics, demographics, does, adverse side effects, and effectiveness.

Results: There were 14 females, 11 males, mean age 17 months. 24 had complex partial or partial secondarily generalized seizures, one had myoclonic seizures. All but 6 had abnormal EEG. Average duration of follow-up was 12.7 months, and 21(84%) were seizure free. The mean dose of levetiracetam was 32.2 mg/kg. Three reported adverse effects, 1 rash, 2 bad behavior. The child with myoclonic seizures did not bennefit from treatment.

Conclusions: Levetiracetam was effective and well tolerated as initial monotherapy in young children and infants with partial onset seizures. It was easy to administer as either liquid form or as tablets dissolved or crushed, and all patients were treated on a bid schedule.

2.400

EFFECT OF DIAZEPAM RECTAL GEL USE ON QUALITY OF LIFE IN PEDIATRIC PATIENTS

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Rationale: Pediatric patients with epilepsy and their caretakers must contend not only with the challenge of uncontrolled seizures, but also with the impact of this chronic condition on their quality of life and daily activities. Breakthrough seizures may occur at any time; as a result, it

is important that parents be able to manage their child's seizure emergencies. The underlying anxiety and stress about seizure emergencies impact the entire family and may unnecessarily limit a child's activities. These considerations underscore the value and importance of having a portable rescue medication available. Diazepam rectal gel is the only portable rescue medication approved by the Food and Drug Administration for the at-home treatment of breakthrough seizures. The purpose of this study is to investigate the impact of diazepam rectal gel use on the quality of life of patients with epilepsy and their caregivers.

Methods: A survey including quality of life issues pertaining to diazepam rectal gel use was given to consecutively treated children with epilepsy who are currently using the drug and to their caregivers. Survey questions assessed patient medical history, experience with diazepam rectal gel, and consequent changes in lifestyle, if any. Demographic data, including duration of epilepsy and developmental level, seizure type, and number/types of concomitant medications were evaluated to provide a comprehensive background of the range of patients using diazepam rectal gel. Patient history included seizure types for which diazepam rectal gel is used, length of time patient has been using the drug, and number of times used. Questions about patient and caregiver experience with diazepam rectal gel assessed its effect on the following parameters: duration of lasting effect following use, change in duration of seizures, and number of visits to the emergency department. The level of caregiver education was also queried. To evaluate whether diazepam rectal gel affects patient and caregiver involvement in daily activities, the questionnaire sought information about the following areas: travel outside the home (eg, shopping, vacations), time lost from work or school, perceived ability to participate in activities typical of the patient's age group, perceived sense of control over one's life, and incorporation of diazepam rectal gel as part of an emergency seizure treatment plan at school.

Results: Preliminary results indicate that, overall, patients with epilepsy and their caregivers reported a high level of satisfaction with diazepam rectal gel and improvement in aspects of quality of life.

Conclusions: Diazepam rectal gel is associated with improved quality of life for patients with epilepsy and their caregivers. This survey will provide valuable data in further elucidating the ways in which diazepam rectal gel assists patients and their families in maintaining usual activities and living a more "normal" life. (Supported by Xcel Pharmaceuticals.)

2.401

LONG-TERM CLINICAL EXPERIENCE WITH CHLORAZEPATE AS AN ADJUNCTIVE THERAPY IN REFRACTORY EPILEPSY

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Rationale: Clorazepate is an older established antiepileptic drug (AED) indicated as an add-on therapy for patients with partial seizures. In this retrospective anaysis, we evaluated the long-term efficacy of clorazepate as an adjunctive treatment in refractory seizures of all types.

Seizure types included generalized onset (n = 13), focal (n = 4), and mixed (n = 4). Currently, 24% of the patients have been seizure free for more than 6 months, 67% demonstrate >50% seizure reduction, and 10% are still poorly controlled. Sedation was reported in several patients and it occurred predominantly during initiation or when dosing increases occurred.

Key words: anticonvulsants, antiepileptic therapy, seizures, benzodiazepines, refractory epilepsy

Grant provided by Ovation Pharmaceuticals

Methods: Twenty-one patients treated in a community setting were prescribed clorazepate for a period of at least 5 years with a minimum dose of 11.25mg/day. Patient demographics, efficacy, tolerability, seizure types, current medications and treatment failures were included in the retrospective chart review.

Results: Of the 21 patients evaluated, 13 were male and 8 were female with a mean age of 22.9 years (8.5–36.6 years). Patients were on clorazepate treatment for an average of 9.92 years (5.5–20.2 years). All patients were on a minimum of 11.25 mg (11.25–28.125 mg) with an average maintenance dose of 17.5 mg. 81% of the patients are currently on a minimum of two AEDs (mean 2.43). This patient population has failed an average of 3.57 AEDs.

Conclusions: Clorazepate can be conveniently administered in a single daily dose or in multiple doses per day. In this retrospective clinical review, we concluded that clorazepate was safe and efficacious for long-term use in refractory epilepsy. (Supported by a grant provided by Ovation Pharmaceuticals.)

2.402

EFFICACY AND TOLERABILITY OF LAMICTAL AS MONOTHERAPY IN PEDIATRIC EPILEPSY

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Rationale: Lamotrigine (LTG) is a new antiepileptic drug (AED) that has been approved for use as adjunctive therapy in patients above 2 years for partial epilepsy (PE) or generalized epilepsy (GE) of the Lennox-Gastaut type. The objective of this study was to evaluate the efficacy and tolerability of LTG monotherapy in children.

Methods: We retrospectively reviewed the records of epileptic children seen at our institution during 2001–2003. Twenty patients (9M, 11F), ages 5–21 years (mean 13 years) were identified.

Results: Fifty percent had developmental delay, mental retardation or learning disability. Type of epilepsy was PE in 50%, idiopathic GE (IGE) in 35%, and symptomatic GE (SGE) in 15%. Range of LTG dose was 2–11 mg/kg/day (mean 5 mg/kg/day). Follow-up range was 0.5–9 years (mean 3.2 years). LTG was started as first-line monotherapy in 3 patients (15%), and as adjunctive therapy in 9 (45%), or due to side effects of other AEDs in 8 (40%). Mean number of previous AEDs was 1.6 (range 0–3). Global seizure reduction was as follows: seizure free for an average of 3.5 years in 12 (60%), 75–99% in 4 (20%), 50–74% in 1 (5%), and <25% in 3 (15%). Overall, 17 (85%) patients showed >50% reduction in seizure frequency. According to epilepsy type, seizure reduction was as follows: PE: >50% in 90%, 70% seizure-free, and <25% in 10%. IGE: 71% seizure-free, and no change in 29%. SGE: >50% in 100%, none seizure-free. The only side effect reported was worsening of myoclonic seizures in one patient.

Conclusions: LTG proved to be effective and safe as monotherapy in various types of pediatric epilepsy.

2.403

THE USE OF ALTERNATIVE/COMPLEMENTARY THERAPIES IN CHILDREN WITH EPILEPSY AND OTHER NEUROLOGIC DISORDERS

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Rationale: The use of alternative/complementary therapies among adults with chronic illness is reported. In adult studies, (50% report using these therapies and more than half did not report this to their physician. Use of alternative medications in children with neurological problems has not been systematically examined. Use of these therapies without physician knowledge puts the child at risk for adverse events and interactions.

Methods: This study was conducted at the Penn State Children's Hospital between 6/03 and 3/04. Parents/caregivers of established patients with neurological disorders completed a questionnaire regarding use of complementary/alternative therapies. This was comprised of 13 questions addressing diagnosis, length of illness, present treatment, use of alternative therapies, patient perceptions of effectiveness and reporting use to providers. This study was approved by the IRB. Consent was obtained from each participant.

Results: 350 of 356 (98%) questionnaires were completed. Mean age was 8.6 years (range 4 months to 20 years). Epilepsy was the most common diagnosis (60%). 74% were receiving therapy for their underlying condition. The majority felt it was effective. 37% (129/350) reported

either use or prior use of alternative therapies which included herbal, massage, chiropractic and vitamin therapy. The majority were patients with epilepsy (45%) and this was significant ($p < 0.01$). The use of these therapies was significantly more likely if the duration of illness was one year or less ($p < 0.01$). An individual with a duration of less than one year, was 2.4, 4 and 3.8 times more likely to use alternative therapies than someone with a duration of 1–4, 5–9 and >10 years respectively. 87% of the entire group felt the alternative therapy was effective. 40% knew if there were side effects to this treatment. There was no significant difference between perceptions of effectiveness by caregivers of medically prescribed versus the alternative therapy. 69% reported use to either their primary care provider or neurologist.

Conclusions: More than one third of children with neurologic conditions are exposed to alternative therapies. Patients with epilepsy were significantly more likely to use alternative therapies than children with other neurological disorders. A shorter duration of illness was significantly associated with alternative therapy use suggesting increased availability of information and awareness. Caregivers perceive both types of therapy effective. Most caregivers report use of these therapies to at least one care provider. (Supported by the Children's Miracle Network.)

Non-AED/Nonsurgical Treatments–All Ages

2.404
SUBPECTORAL IMPLANTATION OF VAGUS NERVE STIMULATOR

Joel A. Bauman, Orrin Devinsky, and Werner K. Doyle (Comprehensive Epilepsy Center, New York University School of Medicine, New York, NY)

Rationale: Vagus nerve stimulation (VNS) is an effective treatment option for specific patients with medically refractory epilepsy. The generator component is typically implanted in the subcutaneous space of the superior left chest region. Cosmetic and mechanical concerns especially in children and aesthetic adults were addressed with an alternative implantation of the generator. We report a series of VNS cases in which the generator was inserted into a subpectoral plane between the pectoralis major and minor. Merit of this surgical modification was assessed by comparing a subpectoral VNS population to a subcutaneous control group.

Methods: We retrospectively reviewed and compared demographics, complications, and side effects, from patients receiving either subcutaneous (SQ) or subpectoral (SP) VNS implants, performed by one neurosurgeon from 1999–2003. Selection of implant location was made during the preoperative surgeon-patient consultation based on patient preferences and surgeon recommendations.

Results: There were 107 SP implants in 106 patients; 55 patients (51.9%) were female. Median age was 19 years (95% CI, 15 to 23; range 2–72 years). Thirty-one SP patients (29.2%) were younger than 12 years. The SQ group was comprised of 138 implants in 138 patients; 66 (47.8%) were female. Median age was 29 years (95% CI, 25 to 32; range 6–73 years). Nineteen SQ patients (13.8%) were younger than 12 years. In the SP group, there were 4 infections occurring in 3 patients, or 2.8% per patient. In the SQ group there were 4 infections, or 2.9% per patient. Average follow up times for the SQ and the SP groups were 52.0 months and 28.4 months, respectively. Infections tended to present longer after implant in the SP group than the SQ group.

An additional 16 patients (including seven from the control SQ cohort) were revised from a previous SQ to SP placement. Including these patients, overall infection rate per SP patient was 2.5% (3.3% per implant). In at least three patients within this group, specific complaints of pain and/or looseness of the generator contributed to the decision for SP conversion. One planned SP patient was converted to a SQ implant due to obesity that compromised telemetry with the generator when it was SP. This patient was included in the SQ group. There were no intraoperative complications in either group.

Conclusions: The subpectoral VNS implant is an acceptable alternative to standard subcutaneous implants. Compared to the SQ group, our SP population was younger and had a slightly higher female ratio; the SP group also had more co-morbidities, which may reflect the surgeon's selection bias. Advantages of the SP implant include: cosmesis and protection from mechanical complications such as migration and pain. SP implantation offers broader utility in the younger population. Infection rate of SP is comparable to SQ implants. Surgical technique and recommendations for appropriate patient selection are discussed. (Supported by Fight Against Childhood Epilepsy and Seizures.)

2.405
REAL-TIME AUTOMATED SEIZURE DETECTION AND QUANTITATIVE ANALYSIS IN ANALOG: METHOD AND PERFORMANCE EVALUATION

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Rationale: Novel antiseizure therapies or delivery modalities are being actively developed and tested. One of the most desirable outcomes of these efforts would be the development of a fully implantable device for automated detection, quantitative analysis and blockage of seizures. We developed a new Percentile Tracking Filter (PTF) that replaces the digital order-statistic filter in the original the Osorio-Frei Algorithm (OFA) in an analog implementation, demonstrate the feasibility of its implementation for real-time quantitative seizure detection and analysis, and assess its performance. The analog implementation of the order statistic filter, a key operation of the OFA, facilitates full device implantation due to its low power consumption, which decreases battery size requirements or frequency of recharging.

Methods: The original OFA comprises an FIR band pass filter, a squaring operation and an order statistic filter that are performed digitally. These operations were carried out in analog by an analog band pass filter matching the pass band and sharpness of the FIR, an absolute value circuit in place of the squaring operation, and the PTF circuit to perform the order statistic filtering. The performance of the analog implementation was evaluated using 20 ECoG segments, each about 500 seconds long containing a seizure beginning after about 300s. The output of the analog circuit was digitized, normalized and compared with the output of the validated digital OFA.

Results: The analog implementation detected all the seizures without false positive detections. Sample-to-sample comparison of the performance of the analog circuit and the digital SDA are in Table 1. Sensitivity, specificity, and kappa were obtained by classifying each output sample during a seizure or a non-seizure segment as above or below a threshold, which determined TP, FP, TN and FN. The speed of detection was determined at the generic threshold and duration constraint of the validated SDA.

TABLE 1. *Comparison of the Algorithms*

Classifier vs Visual	Analog	OFA
Sensitivity	92%	91%
Specificity	94%	94%
Kappa	0.86	0.85
Speed of detection (mean, median, sd, iqr)	−0.13s, 1.88s, 11.2s, 1.9s	0.85s, 2.18s, 9.8s, 1.8s

Conclusions: The results showed that the performance of the analog implementation is nearly identical to the validated SDA. This analog implementation can be realized into an application specific integrated circuit (ASIC) that may be used in a fully implantable device for seizure monitoring, warning, and treatment, increasing acceptability. Preliminary analysis showed that this ASIC consumes very little power compared to a digital device and can last for several years without the need for recharging or replacing its battery. The savings in power result from eliminating data sorting and storing, which are essential operations in a digital order statistic filter. (Supported by Flint Hills Scientific, LLC.)

2.406

ANTIEPILEPTIC DRUG WITHDRAWAL AFTER VNS IMPLANTATION

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Rationale: To determine how often antiepileptic drugs can be decreased after VNS implantation.

Methods: We reviewed all clinic records of VNS implants at the Regional Epilepsy Center between November 2001 - April 2004. The demographic information included age, gender, seizure type, number of AEDs at time of implant, seizure frequency at time of implant, and seizure reduction after implant. The results were recorded. We evaluated the number of AEDs at time of implant and whether the AEDs could be decreased, increased, or no change.

Results: 88 patient charts were reviewed. From those charts we excluded the following patients: 1 explanted VNS, 2 VNS turned off, 8 charts with incomplete data, and 5 research patients. Ages ranged from 8–82 years and there were 40 males and 44 females. See Table for results of AED changes post-VNS implantation.

TABLE 1. *AED Activity Table*

Number of AEDs at Implant	Total Patients	Decrease in AEDs	No Change	Increase in AEDs
1	14	8 (56%)	3	3
2	32	12 (38%)	15	5
3	18	9 (50%)	4	5
4	8	6 (75%)	2	0
All Patients	72	35 (48%)		

Conclusions: We conclude many patients can successfully decrease their seizure medications after VNS implantation. Early decreases were possible in the majority of patients evaluated. (Supported by Aurora Health Care.)

2.407

CHANGES IN LARYNGOSCOPIC EVALUATION BEFORE AND AFTER VAGUS NERVE STIMULATOR IMPLANTATION

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Rationale: Vagus nerve stimulation (VNS) is an FDA approved treatment used in patients with intractable epilepsy. Intermittent voice alteration is commonly reported by patients following implantation of the device. In the second pivotal device study, 62% of patients at 3 months and 55% of patients at 12 months reported this side effect. In addition, reversible vocal cord paralysis was seen in two patients. The purpose of this study is to retrospectively determine if there are visible changes in vocal cord function by pre- and post-VNS implantation laryngoscopy.

Methods: This is a retrospective chart review of patients implanted with the VNS device, who underwent pre-operative and post-operative laryngoscopy. Each patient underwent visualization and evaluation of larynx and vocal cord function. An attempt made to visualize these structures through at least one VNS activation cycle.

Results: Thirty-one patients met the criteria for inclusion into our study. 24 of the 31 patients (77%) were newly implanted patients. Another seven patients (23%) were revisions of previously implanted devices by other surgeons. In the newly implanted patients, 18/24 (75%) had normal pre-operative and post-operative vocal cord function on laryngoscopy. Five patients (21%) were noted to have decreased abduction and rhythmic contraction of the vocalis muscle on the left side when the VNS was activated. When the stimulator cycled off, vocal cord function returned to normal. One patient (4%) developed left sided vocal cord paralysis 11 months after implantation, which persisted after revision. Of the patients undergoing revision, 4/7 (57%) had no change in their vocal cord function following surgery. 2/7 (29%) patients had some mild worsening of left vocal cord function when the stimulator became active, but neither had subjective complaints. Four of 31 (13%) patients complained of dysphonia with activation of the stimulator, but there were no laryngoscopic changes noted. Two patients complained of neck discomfort from the stimulator, but did not require removal or turning off of the device.

Conclusions: This retrospective study demonstrates that most patients undergoing vagus nerve stimulation device implantation have no demonstrable change with visualization of vocal cord function after surgery. Some patients had decreased left vocal cord function when the stimulator was active, but this effect resolved when the stimulator cycled off and did not cause any patient discomfort or problems. Also, our study demonstrates that most patients that undergo replacement of their VNS device have no change in their post-operative function. One of the patients developed left vocal cord paralysis 11 months after implantation, without a clear etiology. During replacement of the lead, there was no visible damage to the vagus nerve. Few of our patients complained of dysphonia.

2.408

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND BRAIN CORTICAL MALFORMATIONS

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Rationale: Slow rTMS may decrease cortico-spinal excitability, suggesting that this technique might be used to decrease cortical excitability in patients with refractory epilepsy. A few animal and human studies indicate that this technique might be effective in seizure control. However, others have failed to find beneficial effects of rTMS on epileptic activity. Herein, we explore the question of whether rTMS might be clinically useful in patients with malformations of cortical development (MCD) and refractory epilepsy.

Methods: Patients were prospectively selected if they fulfilled the following criteria: diagnosis of MCD based on MRI; refractory epilepsy; non-surgical and AED compliance. Patients were excluded if they had ferromagnetic metallic implants, history of major head trauma or were unable to cooperate with the procedure. Eight patients (mean age 24.2 $\pm$ 9.5y) participated in the study. EEG*:* All patients underwent EEG before, immediately after, 15 and 30 days following rTMS. The number of epileptiform discharges (ED) on EEG was counted in two epochs of 5 minutes. Clinical Outcome*:* Subjects recorded number of seizures in a calendar in the month before and two months after rTMS treatment. In order to minimize placebo effect all patients were told that the primary aim of the study was to investigate the effects of rTMS on EEG. TMS: The site for stimulation was determined according to EEG 10–20 system. We targeted the foci in patients with focal ED and Pz in patients with multifocal or diffuse ED and lesions. In one of the patients with bilateral lesions and ED, we stimulated two areas that seemed to be equally active on EEG. Stimulation parameters were frequency of 0.5Hz and intensity of 65% of maximum output stimulator intensity in one session of 20 minutes (600 pulses).

Results: EEG: rTMS significantly decreased the number of ED immediately after rTMS by 30% compared to baseline ($p = 0.011$). The comparison between the baseline EEG and the EEGs performed 15 and 30 days after the treatment showed an average reduction of 52% and 46%, respectively, in the number of ED ($p = 0.016$ and $p = 0.017$). Clinical Outcome: rTMS markedly reduced the number of seizures in 7 patients. After 15 and 30 days of the stimulation, the patients reported a significant reduction in the number of seizures, showing a decrease of 53% and 47%, respectively ($p = 0.018$ and $p = 0.027$). Only one patient with periventricular nodular heterotopia had no alteration in frequency of seizures and EEG showed an increase in the number of ED after 15 and 30 days of treatment. No seizures were induced by low frequency rTMS in any of these patients.

Conclusions: In this study, clinical and neurophysiological outcome corroborates the evidence obtained with animal models, decreasing

cortical excitability, even in lesions with a high epileptogenicity such as MCD.

2.409
VAGUS NERVE STIMULATION: PREDICTORS FOR SEIZURE FREEDOM

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Rationale: To identify predictive factors for the seizure-free outcome of vagus nerve stimulation (VNS)

Methods: We included all patients who had undergone VNS implantation at our centre and had at least 1-year follow-up. All patients underwent a complete presurgical evaluation including a detailed clinical history, MRI, and long-term video-EEG with ictal and interictal recordings. After the implantation, the adjustment of stimulation parameters and concomitant antiepileptic drugs were at the discretion of the treating physician.

Results: The mean age of the patients was 22.7±11.6 (range 7–53) years. Six of 47 patients (13%) became seizure-free after the VNS implantation. Only two variables showed a significant association with the seizure-free outcome: absence of bilateral interictal epileptiform discharges (IED) and presence of malformation of cortical development (MCD). The epilepsy duration showed a non-significant trend towards a negative association with the outcome. According to the logistic regression analysis, only absence of bilateral IED correlated independently with successful VNS therapy ($p < 0.01$). Bilateral IED (independent or bilateral synchronous) was found in one of six seizure-free patients and in 33 of 41 non-seizure-free patients. When bilateral IED were absent, the sensitivity for a seizure-free outcome was 0.83 (95% confidence interval: 0.44–0.97); and the specificity was 0.8 (95% confidence interval: 0.66–0.9).

Conclusions: Bilateral IED was independently associated with the outcome of VNS. Our results are preliminary because they were based on a relatively small patient population. However, it may facilitate other prospective VNS studies enrolling larger numbers of patients to confirm our results**.** [Supported by a grant from the *Deutsche Forschungsgemeinschaft (DFG-Eb 111/2–2*).]

2.410
MEDICATION TRIALS BEFORE VNS IMPLANTATION: NO INFLUENCE ON VNS SEIZURE REDUCTION

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Rationale: To determine the success of VNS seizure reduction dependant on prior medication trials.

Methods: We reviewed clinic records of all VNS implantations for 2001–2004. Their demographic information included age, gender, type of seizures, number of AEDS, frequency of seizures at time of implant and reduction of seizures after implant. The results were recorded. We evaluated the number of medication trials and the subsequent effectiveness of the VNS therapy for 4 groups: 1–3 AEDS trialed, 4–6 AEDS trialed, 7–9 AEDS trialed and > 10 AEDS trialed.

Results: 88 patients charts were reviewed. From those charts, we excluded the following patients: 1 explanted VNS, 2 VNS's turned off, 8 charts with incomplete data, and 5 research patients. Ages ranged from 8–82 years and there were 40 males and 44 females. Please see Table for results from VNS dependant on prior medication trials.

TABLE 1. *Medication Trials and VNS Seizure Reductions*

Number of Trials	Patients Implanted	Patients with Significant Reductions
1–3	15	10 (66%)
4–6	26	19 (73%)
7–9	20	12 (60%)
10 or Greater	7	5 (71%)

Conclusions: We conclude that there is not a significant decrease or change in the outcome of success using the VNS for refractory seizures regardless of the number of failed trial AEDs the patient has been on. VNS should continue to be a viable treatment option for all epilepsy patients. (Supported by Aurora Health Care.)

2.411
SUBNECROTIZING DOSES OF MODULATED 100-MeV PROTONS PRODUCE LONG-LASTING EFFECTS ON RAT CNS ELECTRICAL AND CHEMICAL EXCITABLITY

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Rationale: The number of centers performing stereotactic radiosurgery continues to increase, as does interest in radiosurgery as an alternative to invasive surgery for the treatment of refractory epilepsy. The basis for the anti-epileptic effects of radiation as currently practiced is likely related to the necrotizing effects of ionizing radiation. The present studies were undertaken to determine whether sub-necrotizing doses of inonizing radiation can produce long term effects on CNS tissue excitability.

Methods: Animal radiation procedures were performed as previously detailed by Kennedy et al (*Invest Radiol* 1995; 30:214–20). Hemibrain radiation dose (0, 10, 20, or 30 Gy) was delivered to Sprague-Dawley rats in a single fraction with a modulated proton beam. Eight months after treatment, animals were either subjected to amygdala kindling (stimulating electrode located in the irradiated hemisphere) OR administered a chemical convulsant (kainic acid, 8 mg/kg i.v.) and monitored for one hour to assess hemispheric EEG spike activity and to grade seizure activity.

Results: Prior radiation exposure was found to exert a dose dependent effect on amygdala kindling (See Table 1, ADT = afterdischarge threshold, ADD = afterdischarge durgation). Similary, radiation treatment reduced the severity/duration of the motor convulsions observed during the first hour after kainate administration ($p < 0.05$, Kruskall-Wallis test) as well as the epileptic spike activity in the irradiated but not the contralateral hemisphere (10 Gy = 66% decrease, 20 Gy = 55% decrease vs sham irradiated animals, $p < 0.05$, 1-way ANOVA, Fisher PLSD tests). Post-mortem histology showed no indication of radiation necrosis in any of the treated animals.

TABLE 1. *Effect of Radiation Dose on Amygdala Kindling*

Dose (Gy)	Latency (trials)∗	Amygdala ADT (uA)∗	Amygdala ADD (s)	Seizure Duration (s)∗	Generalized Seizure Duration (s)
0	7.4 +/- 2.7	140 +/- 103	165 +/- 185	345 +/- 191∗	43 +/- 37
10	11.5 +/- 4.2	325 +/- 163	63 +/- 29	141 +/- 102∗	27 +/- 21
20	17.7 +/- 6.7∗∗	430 +/- 273 ∗∗	78 +/- 33	96 +/- 28∗	17 +/- 10
30	16.4 +/- 8.3∗∗	404 +/- 151 ∗∗	71 +/- 22	157 +/- 114∗	15 +/- 6

Radiation dose delivered 240 days prior to kindling. ∗$p < 0.05$ 1-way ANOVE Factor = Dose, ∗∗$p < 0.05$ vs 0 Gy (No treatment) Fisher PLSD

Conclusions: It has been previously shown that radiation doses up to and including 30 Gy produce NO detectable behavioral, histological, or radiolgocial (MRI) indication of radiation necrosis for up to 300 days following irradiation under identical treatment conditions used in the present study, and we conclude that the effects of radiation treatment on amygdala kindling and kainic acid seiaures observed in these studies occur below the necrotizing dose threshold for proton hemibrain irradiation. (Supported by H.L. Guenther Foundation.)

2.412

AUTOMATED SEIZURE ABATEMENT IN HUMANS USING ELECTRICAL STIMULATION

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Rationale: The need for novel, efficacious anti-seizure therapies is widely acknowledged. Seizures may be blocked by electricity if delivered in close proximity to their onset. This study investigates in humans, the feasibility, safety and efficacy of high frequency stimulation (HFES; 100–500 Hz.) triggered by automated seizure detections.

Methods: Eight subjects undergoing surgical evaluation were enrolled in this study, which consisted of a control (CP) and an experimental phase (EP). HFES was delivered to the epileptogenic zone (Local-closed loop; LCL) to 4 subjects and to the anterior thalamic nuclei of the other four (Remote-closed loop; RCL). Seizures were detected and quantified using a validated algorithm. Interphase (CP vs. EP) and intra-phase (stimulated vs. non-stimulated seizures) comparisons of clinical seizure frequency (*Sf*) and relative seizure severity (RSS; clinical and electrographic) were performed and differences assessed using effect size (ES). Subjects were deemed "responders," if *Sf* was reduced by at least 50% and "non-responders" if not.

Results: All subjects completed the study; rescue medications were not required. There were a total of 1491 HFES (0.2% triggered after-discharges). Mean decrease in *Sf* in the LCL group was 55.5% (-100 to +36.8%); (3/4 "responders": 86% (-100 to -58.8%)) and in the RCL 40.8% (-72.9 to +1.4%) (2/4 "responders": 74.3% (-75.6 to -72.9%). Effect size on RSS was 0 in the LCL ("responders": medium to large in magnitude) and negligible in the RCL group ("responders": medium to large). HFES effects on epileptogenic tissue were immediate and also long-lasting.

Conclusions: This is the first study in the history of epileptology to demonstrate the feasibility and short-term safety of closed-loop anti-seizure therapy and provide preliminary evidence of efficacy. (Supported by Medtronic, Inc. and the Kansas Technology Enterprise Corporation.)

2.413

A BIDIRECTIONAL PHARMACOKINETIC INTERACTION STUDY OF LAMOTRIGINE AND THE COMBINED ORAL CONTRACEPTIVE PILL IN HEALTHY SUBJECTS

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Rationale: To investigate the effects of Microgynon 30®("COC; " 30 mcg ethinylestradiol+150 mcg levonorgestrel) upon the pharmacokinetics (PK) and tolerability of lamotrigine and of any effect of lamotrigine upon the PK of the COC.

Methods: Sixteen healthy young female subjects completed this open-label study. Day 1 was defined as the first day of the COC after enrollment into the study. Subjects took the COC once daily for 21 days, followed by a 7 day pill-free period. A PK profile of the COC components was performed on Day 21. After a 7 day pill-free interval, subjects restarted the COC on Day 29 and commenced titration of lamotrigine up to 300 mg/day. On Day 105 of the study, when subjects had received lamotrigine 300 mg for 35 days and were on Day 21 of the COC cycle, PK profiling for the COC components and lamotrigine was performed. Subjects discontinued the COC on Day 105, but continued with 300 mg lamotrigine for a further 3 weeks. On Day 126, PK profiling for lamotrigine was performed. A 25% change in the PK of lamotrigine and a 30% change in the PK of the COC components were determined a *priori* as being clinically meaningful effects. Predose PK samples were also collected during the first week after discontinuation of the COC. Additional blood samples were taken on Days 20–22 and Days 104–106 for determination of progesterone concentrations.

Results: (a) the COC had a clinically relevant effect on the pharmacokinetics of lamotrigine (on average, AUC(0–24) decreased 52% and Cmax decreased by 39% in the presence of the COC); (b) lamotrigine had no effect on the pharmacokinetics of the ethinylestradiol component of the COC; (c) lamotrigine had a modest effect on the PK of the levonorgestrel component of the COC (on average, AUC(0–24) decreased 19% and Cmax decreased by 12% in the presence of lamotrigine) which is unlikely to be of clinical relevance; and (d) Relative to the COC co-administration period, predose serum lamotrigine concentrations were, on average, 27%, 63% and 116% higher on the 3rd, 5th and 7th days, respectively, of the first week after COC withdrawal. A lack of change in progesterone levels between Days 20–22 and Days 104–106 is supportive of maintenance of the COC pill efficacy during co-administration with lamotrigine. In general, lamotrigine was well-tolerated at doses of up to 300 mg in healthy young females when co-administered with the COC.

Conclusions: Systemic lamtorigine exposures in the presence of the COC pill were found, on average, to be approximately 50% of exposures in the absence of the COC pill. This interaction may result in a change in the efficacy of lamotrigine, particularly in women on a stable lamotrigine dose who start the COC. In contrast, lamotrigine appears to have no clinically relevant effect on the PK of the COC pill components.

2.414

THE EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION (TMS) ON THE VAGUS NERVE STIMULATOR (VNS)

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Rationale: The electrical effects of TMS-produced high intensity magnetic fields on the VNS is unknown. Understanding these effects is important before exposing individuals with an implanted VNS to TMS, as could occur in epilepsy research involving TMS.

Methods: VNS leads and electrodes were embedded in a normal saline gelatin matrix while connected to an operating VNS unit in order to measure the current induced in the leads during maximal intensity biphasic TMS pulses. TMS was delivered by the Magstim model 220 with a 70 mm figure-of-eight coil. We also assessed whether the TMS pulses had a detectable effect on the pulse generator by oscilloscope measurement of the output of the VNS before, during, and after stimulation by the TMS unit.

Results: At the highest TMS intensity and with the TMS coil held directly over the VNS wires, a 200 nA, 1.0 msec current was induced by the coil. This translates to an induced charge density of 24 pC/cm^2/phase based on the 6 mm^2 surface area of the VNS electrodes. The VNS pulse generator continued to function normally during and after this stimulation. The VNS was unaffected even when its case was directly stimulated by the TMS coil.

Conclusions: The induced charge density measured in this experiment is well below the charge densities that are known to be safe for direct peripheral nerve stimulation, and below the threshold of nerve activation (1). Therefore, using TMS in individuals with VNS should not result in nerve damage. Furthermore, TMS does not affect the function of the VNS pulse generator, including any influence on the stimulation settings. Although the results of these tests under artificial conditions were consistent with low risk, the safety of using TMS in individuals with VNS remains to be systematically studied in a population of patients.

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2.415

THE ANTICONVULSANT EFFECT OF COOLING IS PRESYNAPTIC

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Rationale: Over the past decade there has been great interest in the therapeutic potential of brain cooling for epilepsy and other neurological diseases (*Epilepsy Currents* 2003;3:153–6). Because we have found that hypothermia can rapidly reduce synaptic potentials, we decided to directly test the hypothesis that cooling blocks central neurotransmitter release.

Methods: We used conventional, submerged rat entorhinal-hippocampal slices and recorded the field potential in the stratum radiatum. A Peltier device embedded in the bottom of the slice chamber directly contacted the slice and enabled us to determine the effects of rapid cooling (latency less than 5 sec) on the evoked synaptic response. We cooled other slices with a bath perfusion system to determine the effect of slow cooling on synaptic responses. In a second set of experiments, we microinjected a portion of the CA1 region with the fluorescent vesicular label FM1–43, which was taken up by presynaptic terminals in a stimulation-dependent manner. We then used 2-photon microscopy to monitor the effect of cooling on evoked transmitter release. One Hz pulses were applied, and Z-stacks (5 image planes) were obtained every minute and analyzed to quantify loss of fluorescence.

Results: Over the temperature range 33°- 20° C, rapid cooling over several seconds caused a 49% reduction in the evoked synaptic response. When we perfusion cooled over the same temperature range, which required 30 minutes for temperature equilibration, we observed a similar reduction in synaptic response. Interestingly, however, at 28° C, there was a transient increase in the size of the synaptic potential, indicating some differences in the effects of slow and fast cooling. When we loaded slices with FM1–43, we found very little loss of dye under control, unstimulated conditions for up to 60 minutes ($\tau = .015$ sec^{-1}). When we stimulated (1 Hz; 50 μsec) in stratum radiatum, there was an exponential loss of FM1–43 fluorescence ($\tau = 0.16$ sec^{-1}). When the slices were cooled to 22° C and then stimulated in an identical manner, the rate of fluorescence decay was dramatically reduced ($\tau = .027$ sec^{-1}).

Conclusions: Both slow and rapid cooling diminish synaptic currents, although the former can induce a paradoxical increase in current over a narrow temperature range. This may be the result of pump inhibition and elevated neuronal excitability. In either case, the FM1–43 experiments suggest that the dominant effect of cooling is a reduction in evoked neurotransmitter release. The temperatures required to reduce transmitter release parallel temperatures that abort seizures in our epilepsy models. These temperatures are, however, considerably lower than temperatures associated with neuroprotection in stroke models, suggesting that diminished neurotransmitter release cannot account for this observation. [Supported by NINDS (R01 NS 42936 and R21 NS 045652 to SMR).]

2.416

VALPROIC ACID EFFECTS ON HIPPOCAMPAL CA3

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Rationale: The periodic discharge of the in vitro hippocampal CA3 pyramidal cell network is a well-studied model of pathological network synchronization. Many experimental manipulations that induce seizures in vivo also produce episodic depolarizations and bursts of action potentials in CA3. We have described convulsant and anticonvulsant effects on spontaneous CA3 population bursts (Yee et al. JNP, 2003). Now, we attempt to validate this model by examining effects of anticonvulsants used in clinical practice on the CA3 system.

Valproic Acid (VPA) is used to treat status epilepticus and generalized and partial epilepsy. However, the underlying mechanisms of VPA remain unclear. We examined the effects of VPA on CA3 when burst probability was low by measuring changes in the interburst interval, burst duration, and thresholds for burst initiation and termination with and without the inhibitory $GABA_A$ system intact.

Methods: In adult rats, 400 micron slices were prepared in artificial cerebral spinal fluid in standard fashion. We used extracellular field recordings to examine spontaneous bursting induced under conditions of "low burst probability" in modified ACSF ($[K^+]_o$ 3.3mM, $[Mg2^+]_o$ 0.9mM, $[Ca2^+]_o$ 1.3mM) with and without addition of 100uM picrotoxin (PTX). Effects of VPA 5mM were evaluated.

Results: 1. When the inhibitory system was intact, 5mM VPA increased the interburst interval by 300% and decreased burst duration by 23% (n = 6).

2. When the inhibitory system was blocked by 100uM PTX, 5mM VPA increased the interburst interval by 154% and decreased the burst duration by 13% (n = 4).

3. When we examined changes in the burst start and burst end thresholds, addition of VPA 5mM did not significantly change the *difference* between the bursting thresholds [control 0.27; 5mM VPA 0.25; (n = 6; ttest = 0.48)].

4. Similarly, when the inhibitory system was *blocked* with 100uM PTX, the difference between the bursting thresholds also did not significantly change in control conditions vs 5mM VPA [control 0.37; 5mM VPA 0.33; (n = 6; ttest = 0.54)].

Conclusions: 1. The changes in the interburst interval and burst duration suggest that an intact inhibitory system augments VPA effects on CA3 spontaneous bursts.

2. However, the lack of significant changes in the bursting thresholds suggests that the effects of VPA are independent of the inhibitory systems in CA3.

3. We are in the process of performing additional experiments to reconcile these seemingly disparate findings on the effects of VPA on CA3 spontaneous bursts. (Supported by AES, NIH.)

2.417

ANTERIOR THALAMIC DEEP-BRAIN STIMULATION INHIBITS PENTYLENETETRAZOL SEIZURES: POSSIBLE SEROTONERGIC MECHANISM OF ACTION

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Rationale: The Anterior Thalamic Group (AN) has been shown to modulate generalized seizures in rodents (1–3). AN deep brain stimulation (DBS) raises seizure threshold in both PTZ & pilocarpine convulsant animal models (4–5), and has demonstrated potential efficacy in human pilot trials (6–7). How DBS prevents seizures in AN is unclear. Direct electrical perturbation vs. transmitter alterations may be involved. Our laboratory has recently shown that anticonvulsant DBS resulted in site-specific and selective increase in serotonergic activity in AN (8). We thus suspect that regional AN serotonergic systems, particularly 5-HT_7, may play a role in DBS seizure modulation.

Methods: P&V Sprague-Dawley male rats (200–300 gm) were anesthetized with halothane and implanted with surface EEG and bipolar AN & posterior thalamic (PT, as control) electrodes. Non-stimulated (NOSTIM) animals were treated, with and without the 5-HT_7 receptor agonist 5-carboxamidotryptamine (5-CT, n = 7) or 5-HTantagonist methysergide (n = 5), and compared to AN-DBS (STIM) animals (n = 7), each under 0.5% halothane and infused with i.v. PTZ (5.5 mg/kg/min). Microdialysis samples (1 uL/min) were collected in AN every 20 min and measured by HPLC for 5-HT, 5-HIAA (5-HT metabolite), norepinephrine, dopamine. 5-CT (50 :M) or Methysergide (100 :M) was delivered into mock-CSF infusion medium starting 40 minutes prior to PTZ administration. Bilateral AN Stimulation was delivered using a Grass Instruments Constant Current stimulator: 0.1–10 V; 150mA; 0.1 msec pulse duration beginning 40 minutes prior to PTZ infusion.

Results: 5-CT infusion resulted in an increase in 5-HIAA (but not 5-HT) in AN during PTZ infusion to the first seizure. AN DBS during PTZ produced higher elevations of 5-HIAA in AN (but not PT). Although PTZ infusion alone resulted in an increase in norepinephrine (NE) in both STIM and NOSTIM animals, 5-CT infusion did not alter NE or dopamine (DA) levels. In controls, PTZ resulted in EEG seizures at 3832 $\pm$ 300s (total 319 mg/kg PTZ). AN DBS delayed the onset (4980 $\pm$ 240s) and 5-CT was similarly effective (4920 $\pm$ 480s) (p = 0.02). AN-Methysergide lowered PTZ seizure threshold (2795 $\pm$ 293).

Conclusions: AN DBS during PTZ infusion raises 5-HIAA levels, and thus suggests that stimulation is effective by means of AN serotonergic mechanisms. In support, the data also show that serotonin agonism within AN blocks PTZ seizures as effectively as DBS, while antagonism lowers the convulsant threshold. These data suggest DBS mechanisms of action, and may implicate new pharmacological approaches towards clinical seizure control.

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Surgery–All Ages

2.418
SISCOM-GUIDED DEPTH ELECTRODES IN EPILEPSY SURGERY

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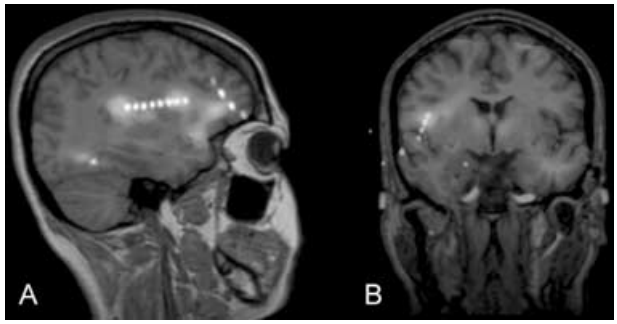
Rationale: Subtraction ictal SPECT coregistered with MRI (SISCOM) has proved a valuable localizing method in epilepsy surgical workup. Our purpose is to demonstrate that SISCOM-guided stereotactic implantation of depth electrodes using a framed stereotactical system can localize the ictal onset zone in patients where SISCOM indicates areas difficult to assess with subdural electrodes.

Methods: Implantation of depth electrodes with stereotactical technique, guided by SISCOM was performed in two patients with intractable epilepsy and normal findings on MRI. In both patients, SISCOM showed more than one area of hyperperfusion, of which at least one was unsuitable for investigation with subdural electrodes.

Results: Depth electrodes were implanted using SISCOM-guided stereotactical technique within the regions of hyperperfusion and also in the ipsilateral hippocampus. Multimodal fusion images were constructed, confirming the intended placement of the electrodes (Fig. 1). Invasive EEG recording localized the ictal onset zone in both patients. The first patient underwent a right sided temporal lobe resection. The second a right lateral temporal lobe resection under stereotactical surgical guidance. Neither patient is seizure free at short term post-operative follow up.



Conclusions: These cases suggest that combination of SISCOM, stereotactically implanted depth electrodes and stereotactically guided surgery can be reliably used in patients with intractable epilepsy where the suspected epileptogenic region is difficult to access with subdural EEG-electrodes or problematic to localize without guidance. Furthermore, in some cases this method might reduce the risk of complications by optimizing the electrode placement and thereby minimizing the number of intracranial electrodes required.

2.419
IMMEDIATE POSTOPERATIVE SEIZURES IN EPILEPSY SURGERY: PATIENTS TAKING LAMOTRIGINE SHOULD RECEIVE THE DRUG VERY EARLY IN THE POSTOPERATIVE PERIOD

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Rationale: Immediate (<24 hours) postoperative seizures occur in approximately 10% of the patients submitted to epilepsy surgery. These seizures are more often distinct from the patient's habitual seizure's type and bear no correlation to the long-term seizure's outcome. This paper reports on a specific subpopulation of patients that are highly prone to present immediate postoperative seizures.

Methods: Eleven consecutive adult patients who were receiving lamotrigine (minimal dose = 150mg/day; mean = 200mg/day) and who had been submitted to cortical resections were studied. Seven patients have been submitted to cortico-amygdalo-hippocampectomy (CAH) and 4 to extra-temporal resections. Concomitant medication included carbamazepine (n = 8; mean dose = 1400mg/day), oxcarbazepine (n = 3; mean dose = 2400mg/day), valproate (n = 4; mean dose = 2000mg/day), fenobarbital (n = 10; mean dose = 100mg/day) and clobazam (n = 7; mean dose = 20mg/day). All were submitted to standard CAH under the same anesthetic procedure as the other patients in the temporal lobe surgery series, which basically consisted of propofol and forane (with or without precedex). All patients received IV phenytoin preoperatively (15mg/kg bolus).

Results: All patients left the operating room awake and without deficits. Nine patients presented tonic-clonic generalized seizures during the first postoperative hours. In all, administration of lamotrigine through a nasogastric tube abolished the seizure's cluster.

Conclusions: A high prevalence of early postoperative seizures was noted in patients using lamotrigine preoperatively (81% versus 10% in the general series). Lamotrigine should be administered very early intraoperatively or early postoperative in patients submitted to epilepsy surgery. Especial caution is advised in patients receiving lamotrigine and valproate concomitantly. (Supported by Sao Paulo's Secretary of Health.)

2.420
ANTERIOR TEMPORAL LOBECTOMY VERSUS SELECTIVE AMYGDALOHIPPOCAMPECTOMY FOR TEMPORAL LOBE EPILEPSY DUE TO HIPPOCAMPAL SCLEROSIS: SEIZURE OUTCOME OVER THE YEARS

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Rationale: The increasing ability to visualize the sclerotic hippocampus by magnetic resonance imaging (MRI) and the evolving knowledge about the pathogenic bases of mesial temporal lobe epilepsy due to hippocampal sclerosis (MTLE/HS) have raised questions about the best surgical approach to treat these patients. We compare two groups patients with MRI and pathology-confirmed MTLE/HS, who were uniformly evaluated, presented a very homogeneous clinical picture, and were operated by the same surgeon through either an anterior temporal lobectomy (ATL) or a selective amygdalohippocampectomy (SAH).

Methods: Surgical outcome in regard to seizure control was analyzed for 161 consecutive patients operated in Porto Alegre for MTLE/HS, from January 1992 to March 2002. These were drawn from a total of 569 patients operated for intractable epilepsy in the same period, 285 of whom in the temporal lobe. Eighty patients had an ATL (Spencer

technique) and the other 81 had a SAH, in which mesial structures were removed according to the technique originally described by Niemeyer. Data is presented in regard to the outcome at the last updated visit and also as a Kaplan–Meyer survival analysis in each Engel's outcome class.

Results: After a mean follow up of 5.8 years (range, 24-132), 116 patients (72.0%) had been completely seizure free since surgery (class IA), 143 (88.8%) were in outcome class I, and 151 (93.7%) were either in outcome classes I or II (Table 1). Fifty-eight (72.5%) of the 80 ATL patients (mean follow up of 7.5 years) and also 58 (71.6%) of the 81 patients undergoing a SAH (mean follow up of 4.2 years) continued to be completely seizure free since surgery (outcome class IA). Tests for equality of survival distributions comparing both techniques in outcome classes IA, I, and I or II were not significantly different at any point in time. Only one of the 161 patients (0.6%) with MTLE/HS was lost to follow up. Patients were followed for two to 11 years, with a mean of 5.04.

Last follow up						
Class	ATL		SAH		ALL	
		n		*n*		*n*
IA	72,5%	58	71,6%	58	72,0%	116
IB	6,3%	5	0,0%	0	3,1%	5
IC	8,8%	7	11,1%	9	9,9%	16
ID	3,8%	3	3,7%	3	3,7%	6
I	91,3%	73	86,4%	70	88,8%	143
II A/B	0,0%	0	3,7%	3	1,9%	3
II D	3,8%	3	2,5%	2	3,1%	5
II	3,8%	3	6,2%	5	5,0%	8
III	3,8%	3	3,7%	3	3,7%	6
IV	1,3%	1	2,5%	2	1,9%	3
Lost FAU	0,0%	0	1,2%	1	0,6%	1
	100,0%	80	100,0%	81	100,0%	161

Conclusions: Surgical results for TLE/HS are stable over time and highly satisfactory, irrespective of the chosen technique. These highly satisfactory results can be achieved with a limited incision of the temporal neocortex. Since both (ATL and SAH) lead to extremely satisfactory results, it is likely that a neocortex-sparing technique (SAH) should be preferred.

2.421
POSTSURGICAL SEIZURE OUTCOME OF FRONTAL LOBECTOMIES

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Rationale: Frontal lobectomy is the second most frequently performed type of epilepsy surgery. The postsurgical seizure outcome has been reported to range between 30% in non-lesional cases to 60% among patients with structural lesion. The purpose of this study is to assess the post-surgical seizure outcome in a group of 17 consecutive patients who underwent a frontal lobectomy at Rush Epilepsy Center for management of medicaly intractable epilepsy and to compare our patients' seizure outcome to that reported in the literature.

Methods: This is a retrospective study of 17 patients, 12 men and 5 women, with a mean age of 34.1±15.5 years and a mean duration of seizure disorder of 10.2 ± 9.1 years. Patients had a mean post-surgical follow-up period of 6.8 ± 7.5 years. We analyzed the post-surgical seizure outcome according to Engel's classification (Class I –Free of disabling seizures, Class II- Rare disabling seizures, Class III- Worthwhile improvement [>90% reduction of seizure frequency], Class IV- No worthwhile improvement [<90% seizure frequency reduction]). We compared the outcome between patients with and without a structural lesion and established the degree to which Subtraction Ictal Single-Photon Emission Computed Tomography Co-registered on MRI (SISCOM) studies were associated with a better outcome in non-lesional patients.

Results: Post-surgical seizure outcome: Class I: n = 12 (70%), Class II: n = 1 (6%), Class III: n = 3 (18%), Class IV: n = 1 (6%). Among the 12 Class I patients, six were lesional and six were non-lesional. SISCOM studies were done in five patients, four non-lesional and one lesional. Among the four non-lesional patients, three had a class I outcome. Among the Class II – IV outcome patients, four were lesional and one was not. Among these four lesional patients, one had a recurrent oligodendroglioma (class III), one had a focal Rasmussen's encephalitis (Class III), one had a neuropathologic diagnosis of a diffuse inflammatory process (Class III) and one had encephalomalacia (Class II).

Conclusions: Frontal lobectomies can result in a better post-surgical outcome than suggested in the literature, even among non-lesional patients. The availability of SISCOM appears to improve the localization of the seizure focus and the surgical success. A limiting factor of these data is the relatively small number of patients included in this study.

2.422
IMAGE-GUIDED KEY-HOLE CRANIOTOMY FOR SELECTIVE AMYGDALOHIPPOCAMPECTOMY

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Rationale: Selective amygdalohippocampectomy (SAH) is an effective treatment for intractable mesial temporal lobe epilepsy with an excellent opportunity for cure in appropriately selected patients.[1]

Methods: At West Virginia University Medical Center, all individuals since August 2003 with mesial temporal seizure onset proven by chronic stereoelectroencephalography underwent a minimally invasive image guided key-hole craniotomy for SAH. This approach utilizes a small curvilinear temporal skin incision, a 2 cm size temporal craniotomy, image guided corticectomy over the upper bank of T2, and an image guided corridor to open the temporal horn and expose the mesial temporal structures. The SAH consists of subpial emptying of the entorhinal cortex and parahippocampus, en bloc removal of the hippocampal head and body, subpial emptying of the uncus, and removal of 4/5 of the amygdala.

Results: Six patients underwent an image guided key-hole craniotomy for SAH and were included in this study. Three are seizure free (50%). One has over 90% seizure reduction, one has over 60% seizure reduction, and 1 individual had 3 seizures in the early postoperative period only. There were no complications. Hospital stay averaged 3 days postoperatively.

Conclusions: Image guided key-hole craniotomy for SAH is an effective treatment for mesial temporal lobe epilepsy. Despite a small scalp incision and keyhole cranial opening, excellent exposure of the mesial temporal structures is achieved. The approach requires the use of image guidance to confirm the location of T2 and the posterior extent of the T2 corticectomy in the dominant hemisphere. The goal of keyhole surgical approaches is to limit operative risk and patient discomfort while providing the best possible benefit. The image guided key-hole craniotomy for SAH achieves these goals.

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2.423
SURGICAL OUTCOME OF HEMISPHERECTOMY FOR MEDICALLY INTRACTABLE EPILEPSY PATIENTS

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Rationale: The surgical techniques for the treatment of catastrophic hemispheric epilepsy have evolved since first introduced in the 1950's. Techniques for hemispherectomy include anatomical, functional, hemispherical deafferentation, peri-insular hemispherotomy, and hemidecortication. Despite a multiplicity of techniques, surgical outcome remains

overall excellent across the variety of pathologies treated. Little has been described regarding the applicability and efficacy of individual surgical techniques applied to specific pathologies. We examined 87 patients undergoing functional and anatomical hemispherectomy to determine whether one technique was more successful than another in relation to the underlying pathology.

Methods: A retrospective review was performed of 87 patients who underwent hemispherectomy for treatment of intractable epilepsy. All of the operations were performed by a single neurosurgeon during 1996–2003. Surgical techniques included functional, anatomical, and modified anatomical hemispherectomy. Surgical outcome and complications were described. The mean follow-up was 26.3 months (6–79 months).

Results: The mean age of the patients was 7.9 years (4months-55yrs). The mean body weight at the time of surgery was 27.9 kgs (6.9–94kgs). The mean operative blood loss was 330 ml. The mean duration of admission was 10 days. Morbidity included coagulopathy (34%), aseptic meningitis (25%), hydrocephalus (5%), and infection (3%). There was no mortality. Pathology included hemispheric dysplasia (n = 30, 34.5%), hemimegalencephaly (n = 14, 16.1%), perinatal stroke (n = 29, 33.3%), Rasmussen's encephalitis (n = 10, 11.5%), and Sturge Weber disease (n = 3, 3.4%). Forty eight percent of the hemispheric dysplasia group (including hemimegalencephaly) underwent modified anatomical or anatomical hemispherectomy. Seventy-one percent of perinatal stroke group underwent functional hemispherectomy. The chance of freedom from seizures (Engel I) after optimal resection was 100% in Sturge-Weber disease, 80% in hemispheric dysplasia, 71% in perinatal stroke, 60% in Rasmussen's encephalitis, and 53% in hemimegalencephaly. Reoperation for persistent seizures after surgery was more common in the hemimegalencephaly (21%) and hemispheric dysplasia groups (13%). The basal frontal region was the most common area of incomplete disconnection. Hydrocephalus was also more common in the hemimegalencephaly group.

Conclusions: Hemispherectomy is an effective and safe operation for the treatment of catastrophic hemispheric epilepsy. Functional hemispherectomy was an excellent technique for perinatal stroke and Sturge Weber disease. Our experience in Rasmussen's encephalitis has led to additional removal of the insular cortex. Our experience with malformative lesions (especially hemimegalencephaly) has led to abandonment of the functional operation in favor of anatomical removal of the abnormal hemisphere.

2.424
THE PROGNOSTIC VALUE OF INTRAOPERATIVE DEPTH ELECTRODE RECORDING IN TAILORED HIPPOCAMPAL RESECTION FOR TEMPORAL LOBE EPILEPSY

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Rationale: Intraoperative depth electrode recording (IDER) is a technique used widely to guide the extent of resection in temporal lobectomies for refractory epilepsy based on the assumption that epileptiform discharges recorded intraoperatively relate to outcome. The usefulness of IDER in surgery for temporal lobe epilepsy, however, has not been established.

Methods: Patients undergoing temporal lobectomy for refractory epilepsy at the University of Maryland from 1997 to 2003 were reviewed. IDER was used to tailor temporal lobe resections in 54 consecutive patients, either with or without mesial temporal sclerosis (MTS). Following resection of temporal neocortex, a depth electrode was placed freehand into the hippocampus for a brief recording of electrical activity. This recording was followed by an initial routine resection of the mesial tissue. Recordings were then repeated using depth electrode insertions following additional resections until no further spikes were evident or no additional resection was possible. Patient outcomes were correlated with the presence or absence of spike activity.

Results: 54 patients underwent hippocampal resection with IDER. 34 (63%) patients had spikes detected. The presence of spikes prompted modification of the initial routine resection in 30 (56%) patients. Of 33 patients with spikes identified by IDER and known outcomes, 22 (67%) had Engle Class I/II outcomes 11(33%) had Class III/IV outcomes. Of 16 patients with no spikes recorded by IDER. 14 (87.5%) had Class I/II and 2 (12.5%) had Class III/IV outcomes. Although the presence of spikes detected at any point during surgery was associated with poorer seizure outcomes, this was not statistically significant. Of the 4 patients with residual spikes at the conclusion of surgery, 2 (50%) had Class III/IV outcomes whereas of 25 patients with no residual spikes, 6 (24%) had Class III/IV outcomes. The presence of residual spikes at the conclusion of resection similarly appeared to predict poorer outcome, but the correlation did not reach statistical significance. In 23 patients with MTS, the presence or absence of residual spikes was not predictive of seizure outcome. In 21 non-MTS patients, 68% (13 of 19) of those without residual spikes had Class I/II outcomes compared to 0% (0 of 2) of those with residual spikes. The absence of spikes in non-MTS patients appeared predictive of better seizure outcomes, but the trend was not statistically significant. Only the presence of MTS as evidenced by MRI was significantly predictive of good outcome ($p = 0.045$).

Conclusions: The presence of spikes recorded by IDER either pre- or post- hippocampal resection tended to correlate with poorer seizure outcomes, but did not reach statistical significance. The prognostic value of IDER in the surgical management of temporal lobe epilepsy, especially in comparison to other predictive data, such as MTS, may be limited.

2.425
REFERRAL PATTERNS IN 537 PATIENTS FOR SURGICAL TREATMENT OF INTRACTABLE PARTIAL EPILEPSY

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Rationale: We investigated the referral practice of patients with intractable partial epilepsy to one comprehensive epilepsy center. All individuals subsequently underwent a surgical procedure for treatment of their seizure disorder. The rationale for this study was to identify the patient's state of residence, age at referral, duration of intractable epilepsy, and the physician referral pattern for epilepsy surgery.

Methods: A retrospective study was performed using the Mayo Clinic epilepsy surgery database that includes all individuals who underwent treatment for a medically, physically, and socially disabling seizure disorder from December 1, 1987 to December 1, 1996. All patients were evaluated and treated at Mayo Clinic in Rochester, MN.

Results: 537 consecutive patients were identified who underwent a surgical procedure for intractable partial epilepsy during this period. The mean age was 32 years (range, 3–69 years). The mean age at seizure onset was 13 years (range, 0–65 years). The mean duration of epilepsy was 19 years (1–39 years). The state of residence could be identified in 442 patients. These individuals were from 34 states and the District of Columbia. Ten individuals were international patients. 378 patients (85%) were from the midwest, 37 patients (8%) from the south, 15 patients (3%) were from the west, and 3 patients (<1%) from the northeast. The most frequent states of residence were Iowa (N = 78), Minnesota (N = 67), Michigan (N = 51), Wisconsin (N = 48), and Illinois (N = 44). All patients were evaluated by a neurologist(s) prior to undergoing a presurgical evaluation in Rochester, MN. However, over 50% of the 537 patients were self-referred or referred by a non-neurologist to Mayo Clinic for epilepsy care. Common precipitating factors for referral included recent generalized tonic-clonic seizure, status epilepticus, loss of drivers license, physical trauma related to seizure, and antiepileptic drug toxicity. The long-term operative outcome (mean duration of 6 years) was available in 516 patients. 348 patients (67%) were seizure-free, 31 patients (6%) experienced rare and non-disabling seizures, 37 patients (7%) had >80% reduction in seizures, and 100 patients (19%) were surgical failures.

Conclusions: Patients with surgically remediable epileptic syndromes during this period were often not identified early in the course of medical treatment, even by the treating neurologist, despite an intractable seizure disorder. Frequently, the patient or primary care provider initiated the epilepsy evaluation after an adverse event. (Supported by Mayo Clinic College of Medicine and Mayo Foundation.)

2.426

TECHNIQUE PADRONIZATION OF HUMAN HIPPOCAMPAL SURGICAL RESECTION: THE IMPACT OF IN VITRO SURVIVAL

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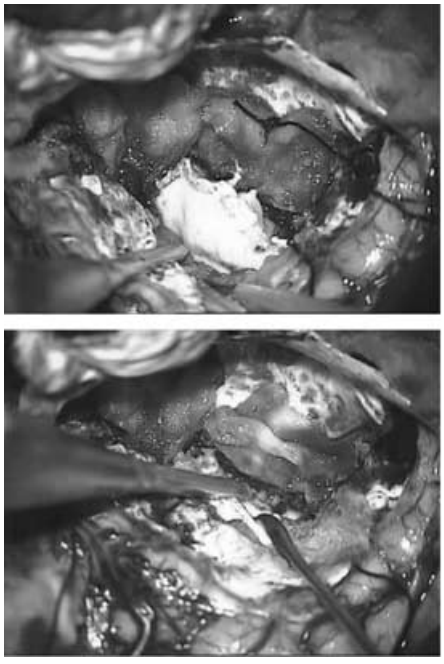
Rationale: Our service is based on human epileptogenic tissue study, and since the begining we try to solve the problem of hippocampal survival for *in vitro* studies. In this paper we show our techinique padronization of surgical ressection and its impact on hippocampal survival.

Methods: We studied 55 patients of our service with mesial temporal sclerosis and divided them in two groups: with (16) or without (39) hippocampal ressection padronization; and compared the hippocampal survival for *in vitro* studies. We divided the hippocampal ressection in five steps: first, the temporal horn of lateral ventricle openning and hippocampal exposure; second, anterior ressection of intralimbic girus and amigdala, preserving the head of hippocampus; third, posterior delimitation of hippocampus ressection at the level of body-tail transition; fourth, aspiration of parahippocampal girus; and fifth, medial ressection close to fimbria fornix where vascularization was cuted and hippocampus was delivered to neurophisiology team (Figs. 1 and 2).

Results: The hippocampus ressected before padronization had 38,5% survival against 75% in those after padronization, showing an outstanding improvement in its survival.

Conclusions: In our experience the padronization of ressection of human hippocampus was really important to garantee the hippocampal survival for *in vitro* studies. The time reduction of ischemia during the surgical ressection was remarkable to improve the hippocampus survival index and it was directly related with the padronization of ressection techinique.



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2.427

DETERMINANTS OF SATISFACTION AFTER RESECTIVE EPILEPSY SURGERY

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Rationale: Resective surgery for refractory epilepsy has beneficial impacts on seizure occurrence and on health-related quality of life. However, patients' perceptions of the impact of surgery and their willingness to undergo surgery if they had that decision to make again, as well as determinants of those perceptions, are key outcomes to consider in evaluating a highly invasive elective procedure. Large, prospective studies to evaluate satisfaction are lacking.

Methods: At 7 US centers, 396 adolescents and adults were enrolled in an observational cohort study and underwent resective surgery for refractory epilepsy. Data were collected by interview and medical record review at baseline (except satisfaction) and at 3, 12, and 24 months after surgery. Satisfaction measures obtained included: (1) overall impact of surgery, and (2) willingness to undergo surgery if he/she had that decision to make again. Data were analyzed using multivariate ordered logistic regression, adjusted for clustering by site. Seizure freedom, change in employment, temporal vs. extra-temporal resection, gender, complications at discharge, age, epilepsy duration, and side of surgery were assessed for associations with each satisfaction measure.

Results: The majority of patients at 3 ($n = 356$), 12 ($n = 354$), and 24 ($n = 318$) months reported a very strong positive overall impact (51.5%, 58.7%, and 59.3%, respectively); a minority reported a negative impact (4.4%, 5.1%, 3.4%, respectively). A large majority of subjects at months 3, 12, and 24 would definitely do it all over again (73.8%, 77.4%, 75.5%); a minority would not (3.3%, 4.8%, 6.6%). Multivariate modeling showed that being completely seizure free since surgery was associated with more positive perceptions of both satisfaction measures at each time point (all $p < 0.04$). Improved employment status was also generally associated with higher satisfaction at 12 and 24 months, although fewer than 15% of patients had an improved employment status. Right-sided resection (at 12 and 24 months) and female gender (at 3 and 12 months) were each positively associated with overall impact. Surgery type, age, epilepsy duration, and discharge complications were not associated with either satisfaction measure.

Conclusions: A large majority of this cohort who had resective epilepsy surgery reported a strong positive impact of surgery and would "do it all over again." Over time, seizure freedom and improved employment were consistently associated with satisfaction, but only a small proportion became regularly employed. Although these associations are not necessarily causal, they suggest that efforts to re-integrate these patients into employment should be enhanced. (Supported by NIH R01 NS 32375; RWJ Foundation.)

2.428

SURGICAL OUTCOME FOR THE FRONTAL LOBE EPILEPSY

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Rationale: Frontal lobe is the largest lobe in the cerebral hemisphere, and has diverse functions spread on the widest surface area. Because of this, frontal lobe epilepsy is not well characterized compared with medial temporal lobe epilepsy.

Methods: Our preoperative investigations are not different from other centers, and included EEG, interictal and ictal with video monitoring, and MRI basically. However, FDG-PET and SPECT were used more often in frontal lobe epilepsy than in other lobe origin epilepsies because cases without any apparent abnormalities in MR imaging were more common in frontal lobe epilepsy. Functional MR study was performed routinely to localize language and motor areas in most cases.

Results: Our epilepsy surgery program experienced 97 patients during the past 10 years. In order to localize ictal onset zone and functional areas, subdural electrodes were implanted in most patients (87/97). However, 3 out of these 87 patients could not undergo further surgical treatment because of poor localization of ictal onset zone. Once ictal onset zone localized, this zone was resected. In selected cases, callosotomy or multiple subpial transection was performed also. After a mean follow up

of 55 months, 69% had more than worthwhile improvement including 43.5% seizure free rate.

Conclusions: Frontal lobe epilepsy still imposes difficulties on surgical treatment, especially in cases of no apparent abnormalities in MR images. Recent progresses in neuroimaging field, to mention a few, MEG, DTI, etc, are expected to resolve these difficulties.

2.429

PRESURGICAL LOCALIZATION OF LANGUAGE: A PRELIMINARY COMPARISON OF MULTIPLE TECHNIQUES

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Rationale: The intracarotid amobarbital procedure (IAP) has historically been the gold standard for lateralization in language function. Localization of language cortex has previously been performed through cortical stimulation studies and more recently with functional neuroimaging procedures. Good concordance has been reported in lateralizing language. Systematic comparison of techniques that localize language cortex has been limited. The current study reports our preliminary experience comparing fMRI, magnetoencephalography (MEG) and electrocortical stimulation in patients with language dominance established by IAP.

Methods: The subjects were 13 patients who were candidates for epilepsy surgery (8 M; 5 F). Ages ranged from 7 to 47 yrs. Eleven patients were right-handed, one was left-handed and one was ambidextrous. Eleven of the patients were left-hemisphere dominant by IAP and two were undetermined. Eight patients underwent fMRI with language testing in multiple modalities and also underwent cortical stimulation mapping using subdural electrode array. Four patients underwent mapping with MEG and cortical stimulation. One patient underwent all procedures. Anatomical localization of language cortex was compared between techniques.

Results: Eleven patients demonstrated left hemisphere language lateralization on all procedures. One patient yielded discordant data, with the IAP undetermined, fMRI suggesting right dominance, and stimulation identifying expressive language in the left hemisphere. For the remaining patient, language lateralization was undetermined on IAP, but clearly left on fMRI and cortical stimulation. When the localization of language areas was compared across techniques, fMRI activation suggested larger areas of language cortex compared to results of stimulation mapping for a majority of cases. In contrast, MEG appeared to underrepresent language cortex compared to stimulation mapping in two of four patients. Language areas appeared more consistent in the remaining two cases. The patient who underwent all procedures demonstrated consistent localization of language areas.

Conclusions: Reliance on functional neuroimaging alone to guide surgical resection remains uncertain. Continued language mapping using electrocortical stimulation is essential to the application and interpretation of function neuroimaging.

2.430

THREE-STAGE EPILEPSY SURGERY

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Rationale: Surgery for extra-temporal & non-mesial temporal epilepsy often fails due to epileptic regions that are expressed only after a primary focus is resected. This may represent a network pathophysiologic process. In 69 patients who underwent diagnostic invasive monitoring prior to therapeutic resection, intracranial electrodes were replaced for a 2nd invasive monitoring & further resection. These 3 stage cases were retrospectively reviewed. Efficacy, complications, seizure characterization, rationale for, and findings supporting network behavior is described.

Methods: All procedures were between 1994 & 2003. Each patient was managed by a multidisciplinary team & had a typical epilepsy surgery evaluation. A 2 stage procedure was initially planned, but data from the initial invasive monitoring compelled the additional diagnostic & therapeutic stage. Engel score was used to describe efficacy. Outcome data at a minimum of 1 yr from surgery was available for 95%.

Results: All cases had non-concordant VEEG, MRI, Wada, & physiologic imaging, or had broad VEEG onsets. There were 30 females. The ave age was 25.4 yrs. In 50/69 (72.5%) additional resection was performed at the 3rd operation. For Engel Class 1, 2, 3, & 4 there were respectively 36 (55%), 10 (15%), 13 (20%) & 7 (10%), of 66 cases (3 were unavailable.) In 24 cases 1 lobe was involved, in 33 two lobes, in 11 three lobes & in 1 four lobes. Pathology was cortical dysplasia or neuronal migration defect in 35, nonspecific in 12, gliosis in 8, cavernous hemangioma in 2, old infarct in 2, low grade neoplasm in 1, hamartoma in 1, foreign body reaction in 1, & hippocampal sclerosis in 3. There were 29 right, 36 left, & 4 bilateral seizure onsets. Neural network node combinations defined by invasive monitoring were temporal frontal (23%), frontal parietal (13%), temporal only (10%), & temporal parietal (4%).

Complications were: 2 infections, 1 hydrocephalus, 1 motor/sensory deficit, 2 bone plate resorptions, 1 DVT, & 1 pneumonia. There were no deaths, hemorrhages, subdural hygromas, pathologic ICP, permanent occulo-cranial nerve injuries, significant language or memory deterioration.

Conclusions: The population described are difficult cases since 45/69 (65%) had multi-lobar seizure onsets & only 7 had sole temporal onsets, characterizing the population as extra-temporal or temporal plus syndromes. Histopathology included mesial sclerosis in only 3. Three stages can be considered when there is suspicion of complex, multi-lobar, or non-contiguous multi-foci seizure onset. Three stage procedures have acceptable risks. Many of these patients can be sub-grouped into 1 of 5 specific epilepsy networks suggested by Spencer (1). Since the network theory predicts variable nodes of noncontiguous seizure onsets, 3 stage surgery may be a viable treatment option.

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2.431

OUTCOME OF SURGERY FOR POSTTRAUMATIC EPILEPSY

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Rationale: Traumatic brain injury may result in diffuse, focal and/or multifocal changes with sites of epileptogenesis coinciding with the site of apparent injury and/or remotely. Surgical outcomes in temporal and extratemporal epilepsy cases may therefore reflect certain mechanisms underlying the injury and possibly differ from those achieved in nontraumatic cases.

Methods: An archival review of operated cases of epilepsy over a 10-year period (1993–2003) was undertaken. Both resections and vagus nerve stimulator implants were included in the review. Patient profile, duration of epilepsy, age at injury, mechanism, site of epileptogenicity and surgical outcome of posttraumatic epilepsy (PTE) cases were assessed and compared with certain features found in the overall review of surgical epilepsy cases.

Results: Posttraumatic epilepsy accounted for 16% of the total surgical epilepsy case load. The mean age at injury was 12.5 y and the duration of epilepsy was 19.8 y. There was no lobe-specific predilection towards epileptogenesis for injuries sustained before the age of 10 y. Of the 52 patients (31M, 21F), 31 required prolonged extraoperative electrocorticography. A total of 46 resections were performed with 2 patients undergoing 2 resections each. Pure temporal lobe resections (TLRs) occurred in 26 patients (12R, 14L) with a further 11 requiring an additional extratemporal resection. Vehicular accident cases accounted for 35% (18 patients) of cases. In the latter category, 12 (67%) had undergone pure TLRs. Overall, 14 patients underwent vagus nerve stimulator implants, 6 of whom had prior resections. Of the pure TLR cases, 58% remain free of disabling seizures after a minimum of 1 year of followup and of the

total number of surgically treated posttraumatic cases, 44% are free of seizures.

Conclusions: A selective lobar vulnerability towards epileptogenicity exists with medial temporal structures predominating. Age at injury appears not to dictate a preferential site of epileptogenicity. Surgical outcomes with posttraumatic TLE mirror those obtained in nontraumatic cases. Vehicular trauma accounts for a high proportion of posttraumatic temporal lobe epilepsy.

2.432
FACTORS INFLUENCING SURGICAL OUTCOME IN PATIENTS WITH NONLESIONAL MEDICALLY REFRACTORY EPILEPSY

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Rationale: It is widely accepted that surgical outcome in non-lesional epilepsy cases is not comparable to the outcome of anterior temporal lobectomy or amygdalohippocampectomy with MRI documented mesial temporal sclerosis. Fortunately, non-lesional cases make up a small percentage of epilepsy surgery series. In our current communication, we present our experience in treating patients with non-lesional, mainly extra temporal, epilepsy and we also try to identify the prognostic factors that might predict a seizure free outcome.

Methods: Our retrospective clinical series included 51 patients who were surgically treated in our institution over a period of 11 years (1992–2003). The patients' age ranged between 3 and 47 years while their mean age was 22.5 years. Regarding their pre-operative work-up, this included thorough clinical examination with emphasis in the seizure semiology, ictal and interictal surface EEG, invasive EEG monitoring with depth and subdural electrodes and MRI in all of our patients while MEG was obtained in 9 of our patients (17.6%). Based on the patients clinical semiology, EEG and MEG (whenever available) findings the patient underwent surgical resection by employing standard subpial aspiration/resection technique.

Results: Engel's modified classification system was used for the evaluation of the surgical outcome at one year post-operatively; 25 patients (49%) were class I, 6 patients (11.7%) were class II, 6 patients (11.7%) were class III while 14 patients (27.4%) were class IV. Regarding their age at surgery, 34 patients were older than 18 years while 17 patients were younger than 18 years; among the older patients, 16 patients (47.0%) were class I while the respective percentage in the younger group of patients was 52.9% (9 out of 51). In regards to the inter-ictal surface EEG findings, among the 13 patients with localizing findings 8 patients (61.5%) had class I outcome while in 38 patients with non-localizing findings 17 patients (44.7%) were seizure free. Regarding the surgical resection site and the outcome, in 24 frontal resections 10 patients (41.6%) were seizure free, in 4 patients with temporal resection 2 (40%) were seizure free, in 3 patients with occipital resection only 1 patient (33.3%) was seizure free, in 5 patients with fronto-temporal resection 4 patients (80%) were seizure free in 8 patients with temporo-parietal resection 5 patients (62.5%) were seizure free and finally in 2 patients with occipito-temporal resection one patient (50%) had class I outcome. Finally, in the group of 9 patients where MEG studies were available, only 2 (22.2%) were seizure free.

Conclusions: Our clinical series confirms the inferior surgical outcome of non-lesional cases compared to the one of well-defined temporal lobe seizure foci resection. Early surgery and localizing inter-ictal EEG findings might represent favorable prognostic factors in the surgical outcome of this challenging group of patients.

2.433
SEIZURE AND QUALITY-OF-LIFE OUTCOME AFTER CALLOSOTOMY FOR LENNOX-GASTAUT SYNDROME IN A BRAZILIAN CENTER

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Rationale: Lennox-Gastaut Syndrome (LG) is a severe form of epilepsy in which drop-attacks are the most hazardous type of seizure. Callosotomy has been advocated as a palliative treatment option in order to reduce the severity of such seizures. We studied the clinical outcome and quality of life op LS patients undergoing callosotomy.

Methods: From September 1995 to May 2003, 23 patients with LG underwent callosotomy and of those 13 were further studied. All of them had multiple types of seizures that were refractory to medical treatment, with drop-attacks as the most severe type and were followed for at least 1 year after surgery. Demographic data, etiology, neuroimaging, VEEG, medical treatment, seizure type and family satisfaction after surgery were evaluated.

Results: 86% were male, onset of seizures was in infancy in the majority of patients, all had cognitive impairment, 5 patients had an unknown etiology. All were dependent on their caregivers for daily activities, such as feeding, taking their medications and walking. Drop-attacks were the most severe and incapacitating seizures. Iterictal EEG had typical LG features and ictal VEEG had diffuse eletrodecremental and generalized run of rapid spikes or generalized slow spike-and-wave. Seizure frequency reduction was $> 50\%$ in 8(61,5%), $< 50\%$ in 3(23%) and without significant changes in 2(15,3%). Quality of life in the opinion of caregivers was better in 11(84,6%), and 10(76,3%) patients had a fewer behavioural disorders.

Conclusions: In our series, callosotomy reduced seizure frequency in the majority of patients and led to a better behavioural outcome.

2.434
LOCAL CHANGES IN CORTICAL ACTIVITY AFTER 50-HZ STIMULATION IN HUMANS

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Rationale: Chronic intermittent cortical stimulation to abort seizures in humans is under investigation. Ideal electrode placement and stimulating parameters are unknown, largely due to a poor understanding of the volume of tissue affected by a stimulus, and the duration and nature of its effect on cortical activity. To help answer these questions, we have analyzed changes in ECoG activity adjacent to stimulated electrodes during and after stimulation in patients undergoing functional cortical mapping with subdural electrodes.

Methods: Two patients undergoing intracranial electrode monitoring for seizure localization were chosen for analysis. During routine stimulation for mapping of language and motor function, one strip was chosen for bipolar stimulation at sequentially larger distance intervals between 1 and 10 cm between electrode contacts. ECoG was recorded from contacts not stimulated. Stimulation parameters were identical to those used for functional mapping: 50 hz, 0.2 ms pulse width, 2–10 mA, with 5 sec. duration. Average Teager energy was calculated for a baseline period 5 sec. prior to stimulation, a 3–5 sec. period during stimulation, and for 5 sec. intervals after the stimulus ended. Average energy was also calculated for delta, theta, alpha, beta, and gamma frequency bands.

Results: Teager energy was considerably increased in adjacent electrode contacts during stimulation. This increase fell as a function of distance from the stimulus. Average Teager energy was also increased (230–570%) compared to baseline during the first 5 second interval after stimulation (4, 6, 8, and 10 mA) in electrode contacts immediately adjacent to a stimulation site. The increases seen 1 cm from stimulated contacts were significantly higher than those at contacts 2 cm from stimulation ($p \leq 0.05$). There was no difference between the response of contacts within the stimulated pair of contacts and those outside the bipolar pair.

Conclusions: Bipolar stimulation of the human cortex at 50 Hz resulted in elevated ECoG energy measurements persisting ≥ 5 seconds after stimulus termination in adjacent electrodes. Contacts more than 1 cm from a bipolar stimulation electrode contact, inside or outside the bipolar pair, showed significantly smaller responses. Separating bipolar stimulating contacts > 2 cm on the cortical surface may be of questionable benefit at common stimulation intensities (2–10 mA). Local changes in ECoG activity should also be measured at stimulation frequencies currently used in therapeutic trials to confirm cortical response profiles at those frequencies. (Supported by NIH R01 NS044102.)

2.435
THE ROLE OF SISCOM IN EPILEPSY SURGERY WORKUP: A CRITICAL APPRAISAL
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Rationale: To assess the role of subtraction ictal SPECT coregistered with MRI (SISCOM) in surgical candidates with diffuse or multiple lesions and with non-lesional epilepsy.

Methods: Data from twenty consecutive patients with post-surgical seizure outcome who had undergone pre-surgical ictal SPECT was re-evaluated. Patients, either with no MRI lesion, or multiple or widespread non-circumscribed lesions were included, i.e. complicated patients in need of extensive surgical work-up. Concordance between electrophysiological data and SISCOM results was evaluated for patients in different outcome categories.

Results: In 13 out of 14 patients undergoing intracranial VEEG, guided by SISCOM, seizure onset was recorded from locations indicated by SISCOM.

Eight of 14 lesional patients underwent invasive VEEG. Five of these had an unfavorable outcome despite concordance between invasive VEEG and SPECT.

All six non-lesional patients underwent invasive VEEG, and five patients, including four with unfavorable outcome showed concordance between VEEG and SPECT. In six lesional patients operated without VEEG three showed favorable results, of which two showed concordance between extracranial EEG and SPECT, and three showed unfavorable outcome (all showed concordance).

Conclusions: SISCOM is helpful in guiding the implantation of intracranial electrodes, especially in patients with diffuse or widespread lesions and in patients without discernable lesions in MRI, but this is not a guarantee for favorable outcome, which is presumably determined by the nature and extent of the epileptogenic lesion itself.

2.436
INFECTION RATES IN PATIENTS WITH INTRACRANIAL RECORDINGS
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Rationale: To determine frequency of intracranial recording infections.

Methods: We reviewed the rates of treated infections following the use of intracranial electrodes for epilepsy surgery resection at St Luke's Medical Center in Milwaukee, Wisconsin. Review of follow-up visits and hospital charts were used as source documents. With explantation of grid electrodes, sentinel cultures were done in the subglial space. Antibiotics were used if cultures are positive.

Results: From 2/2002 to 5/2004 a total of 83 epilepsy surgery resections were undertaken and 75 resections performed. Eight patients were not candidates due to functional capacities in the focus or multi-focal seizure onsets. Intracranial subdural strip and/or grid electrodes were used in 26 patients. There were no positive sentinel cultures obtained and no anitbiotics used for cranial infections. Three reoperations for suspicious fluid on CT Scan failed to document infection.

Conclusions: Intracranial electrode use is not associated with a higher post-operative infection in our institution. Sentinel cultures will continue to be used.

2.437
ROLE OF CENTROMEDIAN THALAMIC STIMULATION IN TREATING INTRACTABLE EPILEPSY
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Rationale: 2 groups have demonstrated the safety of Centromedian thalamic stimulation in the treatment of intractable epilepsy. One study showed no significant benefit but the other group demonstrated significant reduction in seizure frequency with this treatment option. We present the experience at our Center with Centromedian Thalamic stimulation in patients with intractable epilepsy.

Methods: This is a retrospective study of four patients (all Caucasians; age range 7 - 34 years; 2 male, 2 female) who were implanted with Centromedian Thalamic stimulator between August 2001 and November 2003. All of them had intractable epilepsy, had tried a minimum 4 anti-epileptic medications. They had obtained no benefit from vagal nerve stimulator implantation. One patient had partial seizures with secondary generalization. 3 patients had multiple seizure types with multifocal epileptiform discharges. All patients had undergone video-EEG monitoring. DBS Medtronic stimulator was implanted in the Centromedian nuclei by stereotactic method. Initial stimulation parameters were between 50 to 185 Hz, 4.0 to 6.2 volts, 90 ms pulse width, and the stimulation was on for 1 min and off for 4 mins in every 5 min cycles. Stimulation parameters were adjusted in the subsequent clinical visits to control the seizure frequency. Pre-implant baseline seizure frequencies were compared to the seizure frequencies observed on the last follow up clinical visit.

Results: Three patients tolerated the procedure well and did not have any cognitive or behavioral side effects during the follow-up period (4 - 31 months). One patient was taken off the stimulator after a period of 19 months due to infection. 3 out of 4 patients showed at least a 50% reduction in seizure frequency on their last clinical visit as compared to their baseline preoperative seizure frequency. After the removal of an infected stimulator the patient had worsening of seizures.

Conclusions: Centromedian Thalamic stimulation is a potential therapeutic option available for the treatment of intractable epilepsy, when patients fail to respond to medications, resective surgery and VNS. It appears to be a safe and effective novel method of seizure control in patients with intractable epilepsy in our experience. Our sample size is small and to establish this as an approved form of epilepsy therapy a large randomized multi-center study is needed.

2.438
PARIETAL RESECTIONS FOR TREATMENT OF REFRACTORY EPILEPSY
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Rationale: Parietal resections are seldom performed for treatment of refractory epilepsy. This paper reports our experience with parietal resection performed either as an isolated procedure or as part of multilobar resective procedures.

Methods: Forty-four patients were studied. Sixty percent of them had lesions seen on MRI; there were 10 patients with gliotic/anoxic lesions, 6 with cavernoma, 7 with cortical dysplasia, 2 with tumor and 1 with arteriovenous malformation. All patients with normal MRI were submitted to invasive evaluation using subdural grids' electrodes. Fifteen patients were submitted to parietal resection alone; in 22 patients, parietal resection was part of posterior quadrantectomy and in 7 part of other multilobar resections (4 frontal and 3 temporal). Five out of the 15 patients submitted to exclusively parietal resections had total parietal, 6 had superior parietal and 4 inferior parietal lobe removals. In non-dominant hemisphere posterior quadrantectomy, total parietal lobe resection was performed; in dominant hemisphere posterior quadrantectomy, the antero-inferior parietal lobe quadrant was spared. Two out of 7 patients submitted to other multilobar resections had complete, 4 had superior and 1 had inferior parietal resection. Eight patients were submitted to subpial resection of the postcentral gyrus.

Results: Fourteen patients were submitted to surgery on the dominant hemisphere. Sixty-nine percent of the patients have been seizure-free after surgery. Transient postoperative dysphasia was present in 6 patients and in one patient it persisted chronically; this patient also presented with other characteristics of Gerstmann syndrome. No aspect of Gerstmann syndrome was observed in patients submitted to resections sparing the inferior parietal lobe. There was no morbidity associated to resection of the postcentral gyrus.

Conclusions: Parietal resection are safe and can be performed isolately or as part of multilobar resections. Postcentral gyrus resections are well tolerated as far as the vessels related to the central sulcus are preserved during the procedure. Only somatosensitive partial seizures could be considered localizatory. All patients with normal MRI should be submitted to invasive studies during the preoperative work-up. Patients with mesial parietal lobe foci may present with seizures that resemble those arising from the supplementary motor area or tonic spasms (similar to West's). (Supported by Sao Paulo Secretary of Health.)

2.439

OUTCOME RESULTS AFTER SURGICAL TREATMENT OF TEMPORAL LOBE EPILEPSIES WITH HIPPOCAMPAL PATHOLOGY OF NON-HS TYPE

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Rationale: There has been extensive discussion about whether hippocampal sclerosis (HS) is the best prognostic factor concerning outcome measurements after surgical treatment of mesial temporal lobe epilepsy (TLE). HS is characterised by pronounced cell loss and gliosis in various regions of the hippocampal formation. On the other hand there are temporal lobe epilepsies with no HS. Due to the grading system as proposed by A. R. Wyler et al. (1992) tissue changes graded as Wyler 0 up to Wyler 2 are considered to be non-HS, whereas changes graded as Wyler 3 and 4 are grouped as HS. We were interested in how far outcome results would differ in regard to the above mentioned grouping between these two groups in our TLE patients (pts) treated surgically (temporal lobe resection/TLR).

Methods: We identified 164 pts who underwent TLR at our centre between December 1996 and December 2003 (7 years). The group comprised of 76 female and 88 male pts of a mean age of 35,2 years at the time of operation (Range: 4 – 68 yrs.). 77 patients underwent a TLR on the right side and 87 on the left side. We excluded for further analysis all pts with insufficient follow-up of less then 6 months or missing histopathological data. We were left with 159 pts which we subdivided according to the postoperative histological results of the resected specimen into HS (Wyler 3° and 4°), Non-HS (Wyler 0°,1° & 2°), Neoplasias, Dysplasias, and others (e.g. traumatic lesions). We evaluated outcome results following the classification proposed by J. Engel jr. We also worked up electroclinical and history differences in these groups.

Results: Of the 159 pts in whom we were able to obtain all the target data 90 were classified as HS following the histopathological results. The specimen of 14 pts was graded as Wyler 0°, 1° or 2° (non-HS). 55 pts belonged to the other groups.

Outcome results showed that seizure freedom (Engel class1) was achieved in 74 of the 90 HS-pts [equals 82%], in 9 of the 14 pts graded as non-HS [equals 64%], in 15 out of 19 pts belonging to the Neoplastic lesion group [equals 79%] and in 3 pts of 6 pts with Dysplasias [equals 50%] and 19 pts of 30 pts in the "others" group [equals 63%]. It was astonishing to find that all 9 pts in the non-HS-group became completely seizure free (also without auras) according to Engel's class: 1A.

Conclusions: Even though significantly more patients with a histologically proven HS became completely seizure free in the long run, we found a high degree of excellent outcome (completely seizure free) in the patient group with a non-HS finding in the histopathology. This shows that even slight hippocampal changes (graded as non-HS type) seems to be a relatively important prognostic factor for this group of epilepsies.

2.440

SURGICAL OUTCOME OF TEMPORAL LOBE EPILEPSY DUE TO HIPPOCAMPAL SCLEROSIS: A SINGLE-ETIOLOGY GROUP-SURVIVAL ANALYSIS

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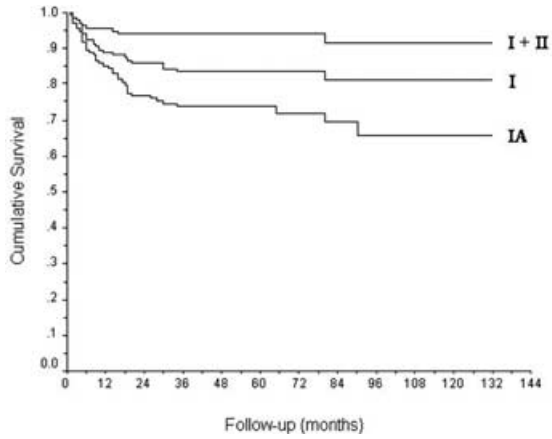
Rationale: Surgical treatment is usually indicated for patients with medically refractory mesial temporal lobe epilepsy due to unilateral hippocampal sclerosis (MTLE/HS). Nonetheless, there is still debate on the actual rates of postoperative seizure control and the stability of surgical results over time. Most outcome studies of temporal resections include patients with different etiologies, and this may preclude preoperative prognostication based on specific etiological substrates.

Methods: Surgical outcome in relation to seizure control and postoperative motor and language complications were analyzed yearly for all 135 consecutive patients operated for MTLE/HS, from January 1992 to December 2000. These were drawn from a total of 437 patients operated for intractable epilepsy in the same period, 226 of which had surgery for TLE. In addition to the 135 with HS (60%), 49 patients with TLE had low-grade gliomas, nine had nonspecific gliosis, seven had cavernomas, and five had dysgenetic lesions, and in the remaining 21 MRI and pathology were normal. Patients were followed for a minimum of two up to 11 years, with a mean of 5.47. One (0.7%) was lost to follow up. Outcome was analyzed using Engel s classification through Kaplan-Meier estimated survival curves (as a function of the time to seizure recurrence) and at the last updated follow up.

Results: The probability of a given patient to remain in outcome class IA after one, two, five, and 10 years post-surgery was 85%, 77%, 74%, and 66% (see Fig. 1). Mean survival time in this outcome class was 8.03 years (95% CI: 7.22 - 8.84). Furthermore, the probability of survival in outcome class I (A, B or D) at the same post-operative points in time was 89%, 86%, 83%, and 81%. With a mean survival time of 9.23 years (95% CI: 8.57 - 9.89). Finally, probability of survival in either outcome class I or II at years one, two, five, and 10 after operation was 96%, 94%, 94%, and 91% (mean survival time, 10.26 years; 95% CI: 9.80 - 10.73).Only nine patients (6.7%) had outcome classes III or IV at any point during follow up.



Conclusions: Seizure free rates in patients with MTLE/HS are considerably higher than those reported when patients with different etiologies of TLE are pooled as a group. High rates of seizure freedom can be obtained and remain stable over the years in patients operated for unilateral MTLE/HS, even in countries with limited resources.

2.441

SEMIOLOGY, NONINVASIVE, AND INVASIVE ICTAL EEG IN MEDICALLY INTRACTABLE POSTTRAUMATIC EPILEPSY

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Rationale: Intractable epilepsy with head trauma (HT) as risk has been associated with both mesial temporal (MTLE) and neocortical localization (NE). There is limited information on the semiology, ictal and interictal EEG characteristics of post-traumatic epilepsy (PTE). We wished to review the ictal features of our cohort with medically intractable PTE undergoing epilepsy surgery.

Methods: The epilepsy surgery database from Henry Ford Hospital was reviewed to identify those individuals who underwent epilepsy surgery with a minimum of 1 year follow-up and whose sole risk factor

for epilepsy was HT. Each monitoring was reviewed in a blinded fashion for: seizure (Sz) type, Sz onset location, Sz onset frequency, and Sz duration. Semiology was classified as suggestive of MTLE or NE and combined with noninvasive ictal and interictal EEG localization to form an overall impression of noninvasive monitoring as being MTLE, NE or unclear localization. Interhemispheric propagation times (IPT), and presence of ictal spiking (IS) was determined from invasive recordings. Age at HT, duration of epilepsy, surgical procedure performed, Sz outcome as of last follow up was determined. A database was created. Statistics used included Student t-test and Chi-square.

Results: Thirty six patients were identified from the database; 3 were excluded due to missing EEG data, and 1 for prior resection. All underwent noninvasive monitoring and 24 invasive monitoring. A total of 653 Sz were reviewed. Ten had recorded simple partial Sz, 33 complex partial Sz, 19 generalized tonic clonic Sz, and 19 subclinical Sz (SCSz). Summarized ictal features of both groups are presented in Table 1. Review of noninvasive impression indicated 20 with MTLE, 10 NE, and 6 unclear localization. Impression was compared to ultimate localization and was correct for 19/20 with MTLE, all with ES, and 4/6 which were unclear localized to MTLE. Twenty three underwent anterior temporal lobectomy (ATL) with 15 Engel Class I; 13 underwent various neocortical resections with 4 Engel Class I. The ATL group was more likely to have Engel Class I outcome ($p < 0.05$). Neither age at HT or duration of epilepsy correlated with outcome for either MTLE ($p = 0.63$, $p = 0.57$) or NE ($p = 0.72$, $p = 0.58$).

Conclusions: Noninvasive EEG and semiology correctly differentiated MTLE from NE in the majority with PTE. No ictal feature predicted good seizure outcomes. Those who underwent ATL were more likely to be seizure free. Age at HT and duration of epilepsy did not impact outcome or localization.

TABLE 1.

FEATURE	MTLE	NE	Significance
AVG # electrodes	67.4±28.9	100.4±27.6	p<.01
Sz duration noninvasive	81.1±32.9 s	68.2±33.7 s	p = .3
Sz duration invasive	105.6±59.9 s	81.5±42.3 s	p = .3
Sz Onset frequency	5.7±2.5 Hz	4.6±3.3 Hz	p = .3
SCSz present	9/13	8/11	p = 1.0
IPT	24.4±9.9 s	14.7±22.4 s	p = .27
IS present	4/13	2/11	p = 1.0

2.442

REOPERATION AFTER FAILURE OF EPILEPSY SURGERY

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Rationale: Treatment of patients who fail epilepsy surgery is problematic. There are few other treatment options available for this group of patients. Indeed many of these patients may be candidates for further resective surgery. The purpose of this study was to study the outcome following re-operation and identify factors predictive of good outcome in these patients.

Methods: We performed a retrospective consecutive chart review of patients that underwent re-opertion for medically intractable epilepsy at our institution from 1990–2001. Seventy patients underwent re-operative epilepsy surgery with 57 having a minimum of 1 year follow-up. Factors associated with outcome were studied.

Results: Histopathology of re-operated cases included tumors (31.6%), cortical dysplasia (CD) (21.1%), hippocampal sclerosis (HS) (17.5%), dual pathology (10.5%) and non-specific pathology (19.3%). There were no significant differences in outcome in patients undergoing temporal versus extra-temporal lobe re-operations. Febrile seizure, family history of seizures, or the seizure-free period after the first surgery were not predictive of final seizure outcome. Fifty percent of patients had favorable outcomes (Engel I and II) following re-operations. Patients with tumors and CD on initial pathology had better outcomes although this did not reach statistical significance.

Conclusions: Re-operation in selected patients failing epilepsy resective surgery should be considered as 50% of patients with limited other treatment options may benefit. Patients with neoplastic disease or dysplastic pathology tended to have better outcomes.

2.443

EXPERIMENTAL CALLOSOTOMY: ELECTROPHYSIOLOGICAL AND METABOLIC APPROACH

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Rationale: In pediatric epilepsy surgery, seizure-free rate of callosotomy is lower than that of vagal nerve stimulation. And cost-effectiveness of callosotomy is also controversial. In the present study, experimental callosotomy was performed in cats and in rats. Electrophysiological and metabolic approaches were made.

Methods: Six adult cats and 19 Wistar rats were used. Exp.1. Under intraperitoneal pentobarbital anesthesia, craniotomy was made in all cats and the dura was opened unilaterally. Bipolar electrodes were implanted and EEG recording was made. Three micrograms of kainite was injected into unilateral sensori-motor cortex and focal cortical seizures were elicited. Callosal section was performed using stereotactic coordinates. EEG analysis was made. Exp. 2. Under intraperitoneal pentobarbital anesthesia, femoral artery and femoral veins were canulated. Craniotomy was made in all rats and the dura was opened unilaterally. Two micrograms of kainite was injected into unilateral sensori-motor cortex and focal cortical seizures were elicited. Callosal section was performed using stereotactic coordinates. Intravenous injection of 14C-deoxyglucose was made and the rats were processed for autoradiography.

Results: All cats and rats exhibited focal cortical seizures after kainite injection. Exp. 1. Seizure propagation to contralateral cortex was clearly suppressed after callosotomy. But, kainite-induced seizures remained in the focus and seizure propagation was observed in the contralateral thalamus. Exp. 2. After callosotomy, seizure propagation to contralateral cortex(hypermetabolic area) was suppressed. Hypermetabolic area in the focus, ipsilateral basal ganglia and thalamus, and contralateral basal ganglia remained even after callosotomy.

Conclusions: Callosotomy may be a surgical option only to reduce seizure activities in the contralateral cortex. But seizure activities of the focus remained even after the callosotomy.

2.444

OUTCOME AFTER POSTERIOR RESECTIONS INCLUDING THE OCCIPITAL LOBE FOR FOCAL MEDICALLY INTACTABLE EPILEPSY

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Rationale: The surgical management of medically intractable epilepsy (MIE) arising in the occipital lobe and the parieto-occipital and temporo-occipital regions is not well characterized in the existing literature. Reasons include the relative uncommonness of epilepsy arising in this region and the paucity of outcomes data following posterior resections. The goal of this review is to elucidate the pathological processes responsible for these epilepsies, the surgical strategies adopted and the outcomes following resection.

Methods: 38 patients (age at surgery 3 months to 46 yrs, median 13 years) underwent posterior resections for MIE, at our institution, between 1994 and 2003. In 90% of these cases, non-invasive ictal electroencephalography (EEG) was localized to or predominant over one posterior quadrant. To facilitate the localization of eloquent cortex or the localization of the ictal onset zone, subdural grid electrodes (10 patients) or intra-operative electrocorticography (5 patients) were utilized. In the remaining cases, resection was tailored based on an obvious lesion on magnetic resonance imaging scans. Outcomes were categorized using the Wieser classification.

Results: In 82% of cases, abnormalities were detected by MRI scans, within and restricted to the zone of resection. Resections were restricted to the occipital lobe (12), or combined with resections of the temporal

(7), parietal (5) or temporo-parietal (14) lobes, based on imaging and EEG. 22 resections were left sided, 16 were right sided. Outcomes were assessed only for the 31 patients with at least a six month follow-up. At 26 to 481 (median 108) weeks of follow up, 26 patients (84%) had no seizures or only aura (Class 1 or 2), 2 patients experienced worthwhile improvement (Class 3 or 4), while 3 had minimal or no improvement. The most common histo-pathological findings were cortical dysplasia (50%), gliosis (26% - usually related to occipital infarction) and low grade developmental neoplasms (13%). There was no unexpected procedure related morbidity in this series.

Conclusions: Individualized surgical plans based on the MRI and localization of seizure onset can result in excellent outcomes in selected patients with posterior quadrant epilepsy. Overall, 90% of patients experienced a significant benefit from surgery. Tailored occipital resections are of value in patients with lesional epilepsy arising from the posterior quadrant. More extensive (parieto-occipito-temporal) resections, sparing the central lobe, are designed to preserve motor function in patients with less discrete disease.

2.445

CONCORDANCE OF INTERICTAL EEG, LONG-TERM ICTAL VIDEO EEG, MRI, AND INTERICTAL SPECT AND HISTOPATHOLOGY WITH OUTCOME IN PATIENTS OPERATED ON FOR INTRACTABLE EPILEPSY

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Background and Purpose: Foci localization by different techniques may overlap only partially. We compared the concordance between interictal EEG, MR imaging, interictal SPECT, ictal video EEG and histopathology of the surgically resected brain tissue in the localization of epileptic foci in patients operated for intractable epilepsy at All India Institute of Medical Sciences (AIIMS), New Delhi.We studied the outcome data at 1 year followup and coreelated this with the concordance of the various modes of investigations done presugrgically.

Methods: This prospective tudy which included 187 consecutive patients of intractable epilepsy undergoing presurgical evaluation for epilepsy surgery admitted for long term video EEG epilepsy in the neurology wards from april 1995 till dec 03. The concordance rates for interictal EEG, interictal SPECT, MRI and ictal video EEG (VEEG) were calculated and compared with pathological diagnosis outcome data was also seen.

Results: The mean age was 19.6 yr + 11.6(range 4 months-59yr). Histopathology (HP) was concordant with ictal video EEG, interictal EEG, MRI and SPECT in 66.6%, 43.85%, 86.76%, and 66.6% respectively. Ictal video EEG was concordant with interictal EEG, MRI and interictal SPECT in 66%, 72% & 74% of cases respectively. MRI was concordant with interictal EEG and SPECT in 52% and 90% of cases while SPECT was concordant with routine EEG in 46% of cases.The outcome GOOD (Group I and II Engel scoring was seen in 92% of DNET, 75% of MTS, 32% in CD).The seizure outcome was also good in patients who underwent a hemispherotomy.Quality of life outcome were also done, pre and post surgical neuropsychological evaluation by the All India Institute Of Medical Sciences Neurosychological battery (standardised to our population modified Luria Nebraska) was done.

Conclusions: The best outcome was seen in DNET, followed by Mesial temporal sclerosis and the worst in Cortical dysplasia.There is a definite improvement in qualty of life and memory function after surgical treatment of intractable epilepsies done with minimum modalities of EEG, VEEG, MRI, SPECT (Ictal and Interictal) in a developing country like India.

2.446

SUBDURAL GRID ANALYSIS IN FOCAL CORTICAL DYSPLASIA: PREDICTORS OF OUTCOME

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Rationale: Focal cortical dysplasia (CD) is a common cause of focal epilepsy amenable to surgical resection. Complete resection of the dysplastic tissue will result in seizure freedom in a high proportion of patients. The preoperative localization of the epileptogenic zone may require an invasive subdural grid evaluation (SGE). We recently showed that patients undergoing SGE for cortical dysplasia had worse outcomes than expected, compared to patients not undergoing SGE. The goal of our study is to determine the variables that contributed to the poor outcome.

Methods: The charts and SGE data from thirty-nine patients with isolated CD who underwent SGE-guided epilepsy surgery between 1990 and 2002 were retrospectively reviewed. The success of the surgery was determined by the Engel score at the latest follow-up date. The details of the SGE evaluation were studied: they included the number of grids and electrodes, localization of eloquent cortex and its relationship to ictal and interictal electrodes. The presence of bilateral noninvasive features, diffuse or multifocal onset were also identified. When available postoperative MRI and EEG data were reviewed.

Results: Using a multiple regression analysis model, a poor surgical outcome was associated with the following features: postoperative surface EEG interictal epileptiform activity ($p = 0.0032$), >1 grid ictal onset zones ($p = 0.044$), the presence of interictal epileptic activity within eloquent cortex ($p = 0.00037$), a previous SGE ($p = 0.0041$) and bilateral features (on EEG, MRI and/or PET) in the noninvasive evaluation ($p = 0.0195$). A diffuse grid ictal onset, the number of grids used, number of electrodes with interictal or ictal activity (outside eloquent cortex), a non-lesional MRI, and the number of clinical seizure types were not associated with poor surgical outcome. Absence of residual CD on postoperative MRI (when available) did not predict a successful outcome. The occurrence of perioperative complication(s) did not affect the seizure outcome.

Conclusions: Careful selection of surgical candidates should result in better postoperative outcomes. The presence of epileptic cortex within eloquent areas, and/or the identification of multifocal/widespread epileptogenicity are associated with worse postoperative outcome. The identification of various predictors of surgical outcome may assist in the risk and benefit counseling of patients in the preoperative period.

2.447

INTRACRANIAL EEG SEIZURE-ONSET PATTERNS AND SURGICAL OUTCOMES IN NONLESIONAL EXTRATEMPORAL EPILEPSY

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Rationale: Patients with normal MRI (non-lesional) and medically intractable extratemporal epilepsy make up a disproportionate number of non-excellent outcomes from epilepsy surgery. We investigate the usefulness of intracranial EEG (iEEG) in the identification of surgical candidates.

Methods: Twenty-seven consecutive patients (1990–2001) with normal MRI, extratemporal epilepsy who had iEEG and subsequent surgery were identified. The implantation of intracranial electrodes was determined by seizure semiology, interictal and ictal scalp EEG, and in some SPECT and PET studies. The anatomic location of the seizure onset zone, as determined by iEEG, and subsequent surgical resection was divided into frontal, parietal, and occipital. The seizure onset iEEG pattern was characterized by the waveform morphology, frequency of discharge and spatial extent (focal, regional, lobar, multilobar). The Engel classification system was used to identify excellent (Class I, and IIA) and non-excellent (Class IIB, IIC, IID, III and IV) outcome from surgery.

Results: The presumed seizure onset zone as determined by iEEG was frontal lobe in 25 (92%) patients and parietal lobe in 2 (7%) patients. The iEEG seizure onset frequency was a beta or gamma frequency discharge in 11(40%) of patients, and in 7(63%) of these patients the ictal discharge was focal (< 5 electrodes). In 16(60%) the seizure onset frequency was less than beta frequency (<12 Hz), and of these patients only 3(18%) had a focal onset. A total of 11 (41%) patients had excellent outcome, but none had been able to discontinue medications at follow-up (average follow-up 36 months). Of the patients who achieved excellent surgical outcome, 8(72%) had focal beta or gamma frequency seizure

onset patterns compared to 2(13%) of the non-excellent outcome patients [$p < 0.005$].

Conclusions: Focal high frequency (beta or gamma frequency) seizure onset discharge on intracranial EEG seizure may identify patients likely to have an excellent outcome from surgery for non-lesional extratemporal epilepsy. [Supported by the National Institutes of Health (K23 NS047495–01).]

2.448
LONG-TERM FOLLOW-UP OF PATIENTS WITH NORMAL MRI SCANS WHO UNDERWENT ANTERIOR TEMPORAL LOBECTOMY FOR SEIZURE CONTROL

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Rationale: The success and guidelines for surgery in patients with temporal lobe epilespy (TLE) due to a lesional or non-lesional focus have been well documented. However, the effectiveness and indications for surgery in patients with TLE and normal MRIs is unclear. We report our surgical outcome in TLE patients with normal MRI's undergoing anterior temporal lobectomy and propose a treatment paradigm for patients with intractable TLE.

Methods: From March 1991 – July 2001, 57 patients with normal MRI scans underwent surgery for intractable TLE. There were 30 males and 27 females between 12 and 53 years (mean 32 $\pm$ 10 years). Prior to surgery, all patients underwent a screening protocol that was developed by a multidisciplinary epilepsy team (Neurosurgery, Neurology, and Neuropsychology) at our institution. This paradigm consisted of MRI scans, surface electroencephalography looking for ictal events (Phase I video/EEG), positron emission tomography (PET) attempting to localized the seizure focus, and subdural or depth electrode monitoring (Phase II EEG) for patients whose seizure focus cannot reliably be identified. All patients went through MRI and Phase I EEG testing. Among patients, 37 proceeded to have PET scan (which localized the seizure focus in 30) and 22 required Phase II testing. Outcomes were classified as seizure free (Grade I), at least 90% reduction of seizures (Grade II), between 50% – 90% reduction of seizures (Grade III), and failures or less than 50% reduction of seizures (Grade IV).

Results: All 57 patients identified through our TLE treatment paradigm underwent an anterior temporal lobectomy and amygdalohippocampectomy. 82.5% of patients (n = 47) had Grade I outcome. 12.3% patients (n = 6) had Grade II outcome. 1.8% of patients (n = 1) had Grade III outcome, and 3.5% of patients (n = 2) had Grade IV outcome. Mean follow-up period was 118 $\pm$ 30 months.

Conclusions: Our findings show that excellent surgical outcome for patients with MRI normal TLE can be achieved. Functional imaging using PET and neurophysiologic monitory via surface and intracranial electrodes can be used to identify optimal surgical candidates.

Neuropsychology/Language/Behavior–Adult 2

2.449
MEMORY FOR NEWS EVENTS IN TEMPORAL LOBE EPILEPSY

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Rationale: New episodic memory or the ability to retain new information has been the primary focus of memory research with temporal lobe epilepsy (TLE) patients. Semantic memory has received less attention. Semantic memory refers to culturally shared information and factual knowledge that has no specific temporal-spatial context. This study of TLE patients and controls assessed memory for news events reported in the United States during the 1990s. The goal of the investigation was to further elucidate the status of semantic memory ability in patients with TLE.

Methods: The participants were 27 healthy controls and 14 temporal lobe epilepsy (TLE) patients. Individuals with left, right or bilateral TLE were included. The two groups did not differ in mean age or level of education. Because there was a significant between group difference in IQ, this variable was used as a covariate in the statistical analyses (see Results).

The Transient News Events Test (O'Connor, M. G. et al., 2000) was administered to both groups. Because the majority of the participants were relatively young, only data for news events from the 1990s will be reported here. A question was asked about six news events that occurred between 1991 and 1998. For each event, a participant received one point for each of the two critical aspects that was correctly identified. If necessary, one or two recognition questions were presented in a forced choice format. A participant received one point for each recognition question answered correctly. Thus, the maximum score was 12 for the free recall and recognition components of the test. All participants were at least 15 years old in 1991. Assessment of the participants began in late 2002.

Results: With IQ as a covariate, there was a significant group difference for both the free recall and recognition TNET scores ($p < .05$). The TLE goup scored lower on both components of the test. The relationship between the TNET and demographic, seizure history, and cognitive test variables was examined. This analysis revealed that the Boston Naming Test (BNT) and a new Famous Faces Naming Test were the measures that correlated best with TNET recall and recognition performance.

Conclusions: TLE patients have not often been assessed on measures of semantic memory or culturally shared knowledge. In this study, TLE patients performed worse than controls on both the recall and recognition components of a news events test covering widely reported stories from the 1990s. Interestingly, TNET performance correlated more strongly with other tests of semantic memory (BNT, Famous Faces Naming) compared to measures of episodic memory (WMS-III), IQ and other cognitive abilities and demographic and seizure history variables. Semantic memory and its association with episodic memory and mesial versus lateral temporal lobe pathology merits further study in TLE patients. [Supported by K23 NS42251, NS 37738, and MO1 RR03186 (G.C.R.C.).]

2.450
DIURNAL MOOD VARIABILITY AFTER RIGHT AND LEFT TEMPORAL LOBECTOMY

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Rationale: Findings of mood-related laterality effects following anterior temporal lobectomy (ATL) have been inconsistent at best. Although previous studies have examined mood at isolated points in time post-surgery, this approach provides little information about intrinsic diurnal variability. In the current study, we explored for the first time whether "variability" in emotional reactivity would be more associated with right versus left ATL and how this variability related to biologic markers of stress (i.e., cortisol).

Methods: Patients with unilateral ATL (N = 16) and age- and education matched controls completed multiple measures of stress and mood, 5 times a day over the course of 5 days. Mood measures included ratings of stress level, affect intensity, and valence using likdert scales. Ratings were made by participants in their home enviroment at predetermined times relative to wakening. They also simultaneously provided spit samples for analysis of salivary cortisol. The right and left ATL groups were matched for age, seizure onset, and time since surgery. All were left language dominant and had nonlesional temporal lobe epilepsy prior to surgery. To index variability in mood, we calculated daily standard deviations for each participant on each measure. These data were analyzed using repeated measures ANOVA's.

Results: The Left ATL group showed significantly less variability in their daily ratings of stress, affect intensity, and valence than the Right ATL and Controls. These findings were not due to differential use of antidepressants, the use of medications with mood stabilizing effects (i.e., Depakote), or the occurrence of seizures. The right and left ATL groups did not differ on standard depression or anxiety measures (Beck, STAI). Analysis of corresponding diurnal salivary cortisol levels revealed

no significant differences among the groups. All showed the expected pattern of increased cortisol levels upon awakening that progressively decreased over the course of the day.

Conclusions: This is the first report that Left ATL patients displayed diurnal mood variability that is more restricted in range than that of Right ATL patients and Controls. This difference in mood variability was not related to scores on traditional mood measures, diurnal patterns of cortisol, patient age, time since surgery, seizure control, or medications. Potential factors underlying this difference will be discussed. Laterality effects may suggest that left temporal lobe systems may play a special role in modulating mood and stress. Analyzing standard deviations of repeated mood measures is a useful and unique way to study emotional changes in epilepsy patients. (Supported by University of Florida Opportunity Fund.)

2.451

CONSTRUCTIONAL PRAXIA IS ASSOCIATED WITH HIPPOCAMPAL VOLUMES IN TEMPORAL LOBE EPILEPSY

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Rationale: Neuroimaging research in temporal lobe epilepsy (TLE) has documented that verbal material-specific functioning is often associated with the integrity of the hippocampal structures in the language dominant hemisphere. However, similar research has produced inconsistent empirical support that nonverbal material-specific functioning is associated with the integrity of nondominant hippocampal structures. We hypothesized that decreasing perceptual-motor clustering performances on a complex design copying task would be correlated with right, as compared to left, hippocampal volumes in patients with intractable TLE.

Methods: We evaluated 45 patients with intractable, unilateral TLE and left hemisphere language dominance. We scored each patient's design copying performance on the Rey-Osterrieth Complex Figure Test using a perceptual-motor clustering scoring system. We obtained hippocampal volumes from T2-weighted MRI images using our previously published protocol and evaluated the correlation between perceptual-motor clustering and hippocampal volumes.

Results: We found that decreased design copying performances were significantly correlated with decreasing right ($p < .05$), but not left ($p > .20$), hippocampal volumes. These results were significant after statistically removing the effects of the WAIS-R Full Scale IQ and chronicity of seizures.

Conclusions: Our findings, using a perceptual-motor clustering scoring system, document a previously unreported relationship between design copying and right, but not left, hippocampal volumes in patients with unilateral TLE. Although constructional praxia is generally believed to be more closely related to parietal lobe functioning, the current results are consistent with hypothetical contributions of anterior and inferior-mesial structures in visual-motor and perceptual-organizational functioning.

2.452

PSYCHOGENIC PSEUDOSYNCOPE: AN EXPLANATION FOR "SYNCOPE OF UNKNOWN ORIGIN"

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Rationale: Nearly 50% of the syncope cases remain unexplained after a complete evaluation, i.e., "syncope of unknown origin." Unlike seizures, a psychogenic etiology for refractory syncope is not usually investigated. The purpose of this study was to estimate the frequency of psychogenic pseudosyncope in these patients.

Methods: Patients referred to our epilepsy center for recurrent syncope-like episodes and negative work-up (brain imaging, EEG, ECG, 2D-ECHO, Holter monitoring, tilt table) underwent EEG-video monitoring with activation by suggestion ("induction"), similar to what is used for psychogenic seizures. Activation was done in standing or sitting position. The diagnosis of psychogenic pseudosyncope required: 1) activation procedure that triggered the habitual event; 2) fall and limp motionless unresponsiveness with eyes closed; 3) normal EEG before during and after the clinical event.

Results: Habitual episodes were triggered in 9/10 (90%) patients. Age ranged from 21 to 60 (mean 36). Illness duration was 6 months to 15 years (mean 4.2 years). Event frequency was 3–4/day to 2/month. EEG showed preserved alpha rhythm before, during and after the clinical event. There were no epileptiform discharges, background suppression or slowing typically seen in syncope, resulting in a definite diagnosis of psychogenic pseudosyncope.

Conclusions: Many cases of "syncope of unknown origin" may represent psychogenic pseudosyncope. Patients with syncope-like events and a negative evaluation should undergo EEG-video monitoring with induction in order to demonstrate a possible psychogenic etiology and avoid further repeated work-up.

2.453

SELF-REPORTED WORD-FINDING DIFFICULTY AND VISUAL NAMING TEST PERFORMANCE IN TEMPORAL LOBE EPILEPSY

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Rationale: Subjective memory complaints typically correlate at least as well with degree of mood disturbance as they do with objective memory test performance. In addition to memory deficits, temporal lobe epilepsy (TLE) patients often show mild object naming impairment. The relationship between self-reported word finding difficulty and standardized objective naming test performance has not been well examined in this group. The goal of this study was to examine the association between TLE patients' perception of word finding problems and objective naming test performance, other neuropsychological measures and mood.

Methods: The participants in this study were 31 individuals with TLE. They had a mean age of 38.4 (11.2) and the mean educational level was 13.9 (2.5) years. The mean age of seizure onset was 11.1 (6.3) years. All participants were administered a battery of neuropsychological tests and self report questionnaires. The measures of interest in this study were the Boston Naming Test (BNT), the Beck Depression Inventory (BDI) and the Naming Self-Report Questionnaire.

The Naming Self-Report Questionnaire constructed for this study consisted of eight items rated on a seven-point scale, with low scores representing the minimal level of subjective complaint. The Naming Self-Report variables that correlated best with the BNT were a subtotal score consisting of four items (everyday ability to name objects, places, famous people and friends/relatives) and the score from a single item rating distress related to word finding difficulty. Thus, analyses for this study were restricted to these two variables.

Results: The composite score of word finding difficulty correlated significantly with the BDI ($r = .53$, $p < .05$), but not the BNT. Naming Self-Report rating of distress correlated significantly with the BNT ($r = -.37$, $p < .05$), but not with the BDI. Both Naming Self-Report variables also correlated with other cognitive variables, including verbal memory, IQ and reading level.

Conclusions: Self-reported level of the distress related to word finding problems correlated significantly with objective visual naming ability, as measured by the BNT. In addition, this particular naming self-report variable did not correlate with mood, as measured by the BDI. This finding suggests that patients' dissatisfaction with their everyday word finding ability can be a relatively accurate measure of objective visual naming test performance. A possible limitation of the data is that the Naming Self-Report rating of distress correlated not only with the BNT, but also with other cognitive measures. [Supported by NIH K23 NS42251, NS R0137738 and MO1 RR03186 (G.C.R.C.).]

2.454

CONSTRUCTIVE PRAXIS IN PARTIAL EPILEPSY

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Rationale: In partial epilepsy patients, poor attention has been given to constructive praxis, although copying abilities are usually involved in neuropsychological tests assessing visuospatial memory and learning. In particular, questions have been arisen as to whether these patients show constructive praxis deficits and if these deficits are related to specific cognitive impairment and different brain damage. Given the frequent use of Rey's complex figure in memory assessment, we have analysed constructive praxis, as expressed by figure's copying before memory reproduction.

Methods: A hundred and ninety-seven patients with left temporal lobe epilepsy (TLE) ($n = 80$), right TLE ($n = 72$), left frontal lobe epilepsy (FLE) ($n = 27$), right FLE ($n = 20$) and 31 healthy subjects, undergoing an extended neuropsychological battery, were compared in Rey's Complex Figure copying (RCFC), Rey's Complex Figure recall (RCFR), Raven's Coloured Progressive Matrices (RCPM), and Trail Making Test part A (TMTA), as measures of constructive praxis, visuospatial memory, visuospatial perception/reasoning, and spatial exploration/visuomotor coordination. Patient and control groups has similar age and education.

Results: Separate Kruskall-Wallis one-way ANOVAs showed significant between-group differences in RCFC ($chi^2 = 17.43$, $p = 0.0016$), RCFR ($chi^2 = 32.27$, $p < 0.0001$), RCPM ($chi^2 = 12.967$, $p = 0.01$), and TMTA ($chi^2 = 21.40$, $p = 0.0003$). Post-hoc Mann-Whitney tests revealed that right TLE patients ($U = 801.5$, $p = 0.0068$), left FLE patients ($U = 195$, $p = 0.0001$), and right FLE patients ($U = 195.5$, $p = 0.0049$) were impaired in RCFC. Left TLE patients showed normal RCFC scores. Correlation analyses showed that the RCFC scores significantly correlated with RCPM and TMTA scores in right TLE patients and right FLE patients, and with TMTA scores in left FLE patients. In left TLE patients and healthy subjects, RCFC scores correlated with RCPM scores. In all patient groups, but left TLE patients, and healthy controls, the RCFR scores correlated with RCFC scores.

Conclusions: The results of the study reveal that partial epilepsy patients may show constructive apraxia, as revealed by the copying of a complex design. The impairment may be related to the involvement of visuospatial abilities, spatial exploration, and visuomotor coordination, depending on the site of the epileptic zone. Visuospatial memory is also related to praxis abilities. All this suggests that apraxia is a consistent facets in the neuropsychological scenario of epilepsy patients, although it does not necessarily influence daily performances. In particular, the interpretation of visuospatial memory deficits should take into account of basic constructive and spatial abilities.

2.455
MULTIVARIATE PREDICTION OF PSEUDOSEIZURE DIAGNOSIS BASED ON MEDICAL, PSYCHIATRIC, AND MMPI PROFILES

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Rationale: To differentiate epileptic (ES) and psychogenic non-epileptic seizures (NES), psychological testing is often performed as an adjunct to long-term video-EEG monitoring (VEEG). The Minnesota Multiphasic Personality Inventory (MMPI) is the most commonly used measure for this purpose. Correct overall classification rates of 70% may be expected using the decision rules of Wilkus et al. (1984). In this study, we examined whether combining MMPI profiles with other medical and psychiatric history variables may enhance diagnostic accuracy as compared to classification based on personality profiles alone.

Methods: Subjects were drawn from a consecutive series of adult patients who underwent VEEG to characterize seizures. Those with a definite diagnosis of NES or ES based on ictal EEG findings and clinical semiology were included. Excluded patients had documented concurrent NES and ES, only subjective spells, or did not complete the MMPI-2. 105 patients with NES and 109 patients with ES met these criteria. The MMPI classification rules of Wilkus et al. were applied without modification to MMPI-2 profiles. Routine medical and psychosocial histories were abstracted on standardized data sheets. Multiple variables were recorded, including age, sex, age at onset and duration of seizure disorder, number of other current and past medical diagnoses, number of current medications, presence of chronic pain disorder, number of psychiatric conditions, and history of physical or sexual abuse. Stepwise logistic regression was used to identify the variables giving the best diagnostic classification.

Results: Significant differences were observed between the ES and NES groups on all of the aforementioned variables. MMPI profiles correctly classified 87% of the NES subjects, and incorrectly classified 28% of the ES patients, for an overall correct classification rate of 79%. A total correct classification rate of 82% was acheived by a combination of 6 variables that were more closely associated with NES: Female sex, short duration of seizure disorder, history of chronic pain, higher number of past and current medical diagnoses, and the total number of documented psychiatric problems. The highest overall accuracy was 85.5% (86% sensitivity for NES, 85% specificity) when these clinical variables were combined with the MMPI data.

Conclusions: Differentiating NES from ES patients on the basis of psychometric measures such as the MMPI may be useful as an adjunct to other diagnostic studies, but the probability of making false positive errors (classifying ES patient as NES) based on this method alone is a significant limitation. Classification accuracy is enhanced when other simple clinical data are considered along with MMPI scores.

2.456
DOUBLE DISSOCIATION OF PARAHIPPOCAMPAL AND AMYGDALAR *f*MRI ACTIVATION IN PATIENTS WITH MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Functional magnetic resonance imaging (fMRI) of limbic mesial temporal lobe structures may help to taylor epilepsy surgery in patients with refractory mesial temporal lobe epilepsy (MTLE). We have shown earlier that a simple fMRI memory paradigm (Roland's Home Town Walk) well lateralizes the side of MTLE by activation of the parahippocampal gyri (Jokeit et al. Neurology 2001;57:1786). In addition, information about the integrity or dysfunction of the amygdala may influence the decision about the anterior extension of the resection. Although only in a minority of surgical patients, postoperative deficits in social and emotional cognition and behaviour can occur. We present data showing that activation of amygdala and parahippocampus can be dissociated in patients with MTLE by appropriate fMRI tasks.

Methods: Five male patients (aged 25 to 45) with refractory MTLE (three left-sided) were investigated. Three patients had hippocampal sclerosis, the others a neoplasia or cavernoma. Using BOLD fMRI, we measured language related activity by a verbal fluency task, parahippocampal activity by Roland's Home Town Walking Task, and amygdala activity. Amygdala activation was induced by presentation of scenes from thriller and horror movies showing animated fearful faces. This paradigm has before been validated in fifteen healthy controls (10 males, 5 females, aged 23–57). All subjects elicited bilateral amygdala activation ($p < .001$). Reproducibility of the paradigm was demonstrated by restudying 5 of the control subjects after one week. Activation patterns were reproducible and the activation intensity did not differ significantly over both measurements.

Results: All patients predominantly activated left hemisphere regions during a verbal fluency task and demonstrated significant parahippocampal and amygdala activity. In three patients contralateral amygdalar and parahippocampal activity was higher compared to ipsilateral activity. In one patient with right-sided MTLE and questionable hippocampal sclerosis a comparable activity of both amygdala was detected while parahippocampal activity was asymmetric corresponding to the side of MTLE. In one patient with left-sided MTLE and a paraamygdala neoplasia only contralateral activity of the amygdala was detected while parahippocampal activity was symmetric.

Conclusions: In three out of five patients parahippocampal and amygdalar activity were asymmetric corresponding to the side of MTLE. Two patients, however, demonstrate a double dissociation of amygdala and parahippocampal activation.

In patients with MTLE, the use of two simple paradigms allows an individual dissociation of amygdalar and parahippocampal activation within limbic mesial temporal lobe structures. The prognostic value of this information for surgery and counseling of patients has to be evaluated in prospective studies. (Supported by Novartis Pharma AG Schweiz.)

2.457

INTRACAROTID SPEECH AND MEMORY PROCEDURE: ETOMIDATE BETTER THAN AMOBARBITAL?

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Rationale: For 45 years the intracarotid amobarbital procedure (IAP) has been used to lateralize cerebral dominance for speech and evaluate memory in each hemisphere independently. This has been done by anesthetizing one hemisphere briefly while the awake hemisphere performs simple speech and memory tests. The drug most used in this procedure was sodium amobarbital. Due to repeated shortages and other problems, attempts have been made to find another anesthetic agent. Methohexital (brevital) has been used with some success, and propofol has been tried. However, methohexital is not readily available and is so short-lived that re-injection is usually required. Propofol is contained in a lipid emulsion. We report our experience using etomidate, a widely-used agent for the induction of anesthesia.

Methods: Patients requiring IAP to evaluate memory or for speech lateralization were tested. A catheter was placed in the internal carotid artery and an angiogram was performed prior to the procedure. EEG was recorded and read online by an EEGer. The drug was injected under the supervision of an anesthetist using an algorithm that would reproduce local plasma levels identical to those achieved by a usual systemic dose (0.3 mg/kg over 30 to 60 sec). Administration was by bolus followed by an infusion, which was maintained during the initial speech and memory tests. Upon termination of infusion, cognitive testing continued until all tests were completed and baseline levels were observed on EEG, handstrength, and language (in dominant hemisphere injections).

Results: Six patients (10 hemispheres) were tested. In all cases a satisfactory contralateral hemiplegia followed injection without affecting the ipsilateral hemibody. EEG slow waves were confined to the injected hemisphere in 4 injections, with some contralateral slowing in 6, consistent with our usual EEG findings in IAP. Dysarthria was observed in nondominant hemisphere injections, and global aphasia with preserved attention and cooperation in dominant injections. These phenomena remained throughout the period of infusion. After ending the infusion a gradual return to baseline was observed for about four minutes, allowing speech testing as the aphasia cleared, passing through a stage of dysphasia and then recovery. Trembling of the contralateral arm was observed during the drug effect in 8 of 10 injections. No patient complained of discomfort, and most had no memory of weakness, visual defects or speech disturbance that had occurred during the drug effect.

Conclusions: Etomidate administration by bolus followed by infusion offers more than a viable alternative to the traditional IAP; it presents a considerable improvement for performing all cognitive tests during an assured hemianesthesia of the injected hemisphere. We have observed no contraindications in patients tested so far.

2.458

SIDE OF SURGERY AND HIPPOCAMPAL SCLEROSIS ARE SOLE PREDICTORS OF VERBAL MEMORY DECLINE AFTER ANTERIOR TEMPORAL LOBECTOMY

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Rationale: Absence of hippocampal sclerosis (HS) indicates a more 'functionally adequate' ipsilateral memory system and higher risk of verbal memory decline after dominant anterior temporal lobectomy (ATL). Patients vary in other ways (other MRI abnormalities, EEG focality, baseline verbal memory, Wada memory results, gender, age at first risk, age at surgery) that may reflect functional adequacy and capacity of non-resected areas to mediate recovery ('functional reserve'). We examined whether such factors predicted decline, beyond effects of HS, speech laterality and baseline memory.

Methods: Patients had ATL in the Multicenter Study of Epilepsy Surgery, a prospective, observational study. MRIs were coded for presence/absence of non-incidental findings in ipsilateral and contralateral temporal and extra-temporal regions. Scalp ictal and interictal EEG was summarized as the presence vs. absence of exclusively focal, consistent abnormalities in the ipsilateral medial temporal lobe. Memory decline was change in Long Delay Free Recall on the California Verbal Learning Test at 1–2 years post-surgery. Variables were included in a multivariate prediction model only if a univariate relationship was suggested.

Results: 36/132 patients (27%) had MRI findings other than exclusively unilateral HS (77/132 (58%)) or normal MRI (19/132 (14%)). Of these, 21/36 (16% overall) had MRI findings outside the ipsilateral temporal lobe (e.g. atrophy, contralateral HS, developmental anomaly). EEG other than exclusively focal and consistent in the ipsilateral medial temporal lobe occurred in 30% with exclusively unilateral HS on MRI and in 48% with other MRI findings. Speech laterality ($p < .01$), early age at injury ($p < .05$) and unilateral HS ($p < .01$) were associated with memory decline in univariate analyses. Those with poor baseline memory tended to be less likely to decline ($p = .09$). Only unilateral HS and speech laterality were significant predictors in multivariate analyses ($p < .01$).

Conclusions: EEG and MRI abnormalities outside the ipsilateral temporal lobe were unrelated to verbal memory decline after ATL, suggesting that 'functional reserve' (as reflected by these indices) plays a minor role in mediating memory changes in the majority of ATL patients. As in prior studies, memory decline was more strongly related to the functional adequacy of the ipsilateral medial temporal memory system. Failure of baseline memory function and WADA memory assessment to predict decline may reflect insensitivity of single memory measures, prevalence of HS in this sample and cross-center variability in Wada methods. [Supported by RO1 NS32375 (NINDS).]

2.459

COMPARISON OF REY-OSTERREITH FIGURE QUALITATIVE ERRORS ON RECALL PERFORMANCE BETWEEN RIGHT AND LEFT TEMPORAL LOBE EPILEPSY PATIENTS

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Rationale: Lateralization of temporal lobe epilepsy can be difficult. The present study was aimed at investigating qualitative differences in recall performances of patients diagnosed with right versus left temporal lobe epilepsy (TLE) and to determine whether or not qualitative analysis of errors suggest laterality of temporal lobe dysfunction.

Methods: Data were prospectively collected from patients with TLE undergoing neuropsychological evaluation for anterior temporal lobectomy at the University of South Florida - Tampa General Hospital Comprehensive Epilepsy Program. The Rey Complex Figure Test (RCFT) was administered as part of the preoperative neuropsychological assessment. The RCFT stimulus card was presented and subjects were instructed to copy the figure using the administration instructions from the RCFT professional manual. Delayed recall performances for right and left TLE were compared.

Results: In this preliminary analysis, we analyzed data from 10 patients with TLE, 6 right and 4 left. Table 1 shows the number and

distribution of errors in the two groups. The left TLE group made 2 or 3 errors, whereas the right TLE made 0 or 1.

TABLE 1. *Errors in right versus left temporal lobe epilepsy.*

Right Temporal	Left Temporal
1. I, VIII	1. No errors
2. IV, VIII	2. IX
3. IV, VIII, IX	3. IX
4. VIII, XI	4. No errors
5. VI, VIII, XII	
6. II, VIII	

Conclusions: The present findings support the use of the Loring qualitative scoring approach to differentiate between right and left TLE patients with the RCFT delayed recall performances.

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2.460

EFFECTS OF AGE AT ONSET AND DURATION OF EPILEPSY ON COGNITION IN THE FRAMEWORK OF CATTELL'S THEORY OF FLUID AND CRYSTALLIZED ABILITIES

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Rationale: Course and etiology of cognitive impairments in chronic epilepsy still remains controversial. By using a factorial model of cognitive domains, a new approach to characterize the effects of age at onset and duration of epilepsy on cognition was chosen.

Methods: A comprehensive neuropsychological test battery including measures of intelligence, language, spatial abilities, verbal and nonverbal memory, executive function, and psychomotor processing was administered to a sample of $n = 158$ patients with medically intractable epilepsy. Patients were tested in the context of preoperative evaluation. A factor analysis with varimax rotation was calculated, and factor scores were correlated to age at onset/duration of epilepsy while controlling for age and other variables.

Results: Factor analysis using test scores adjusted for age, gender, and education disclosed seven factors accounting for 62% of variance. Factors were: verbal episodic memory, attention, language based knowledge system, executive function, numerical, visuospatial and visual memory functions, and a seventh, bad defined factor. At least four of these factors can be seen as meaningful according to the factor loadings. Duration of epilepsy and onset of disease were significantly associated only with language based knowledge [age at onset: $r = .190$, $p = 0.017$ (positive association); duration: $r = -.203$, $p = .011$ (negative association)]. This relationship remains significant after controlling for several other factors (e.g., polytherapy, side and site of lesion, verbal episodic memory). As a trend, the effect seems to be stronger in patients with left-sided lesions.

Conclusions: Factor analysis of an extensive neuropsychological test battery for the preoperative evaluation of patients with focal epilepsy resulted in 7 cognitive domains, with the first four factors representing verbal episodic memory, attention, language based knowledge system, and executive functions. Partialling out the effects of ageing, education and gender on performance in these domains, an earlier onset of chronic epilepsy was associated with significantly poorer performance in language based knowledge. Results can be discussed in the framework of Cattell's theory of fluid and crystallized abilities: Focal epilepsy first of all impairs fluid intelligence (Gf), and this diminishes the potential to acquire crystallized intelligence (Gc). Following this, the cumulative development of Gc through the life span is reduced particularly in association with an early onset of disease. Taking into account earlier results from our center, it can be concluded that impaired Gc in association with an early onset is mainly caused by reduced Gf rather than by reduced episodic memory. The former may be associated with neocortical damage.

2.461

COGNITIVE INHIBITION, MOOD, AND BEHAVIOR IN FRONTAL LOBE EPILEPSY: RELATIONSHIP TO SEIZURE LATERALIZATION AND STRUCTURAL MRI FINDINGS

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Rationale: Frontal lobe epilepsy (FLE) is the most common form of extratemporal epilepsy, comprising between 15 to 30 percent of patients with medically refractory seizures. Despite its prevalence, few studies exist describing the cognitive and behavioral characteristics of FLE. Past research suggests that patients with FLE demonstrate significant impairments in executive functioning, especially in cognitive inhibition. Patients with FLE also report higher levels of depression and experience more social behavioral problems than their healthy counterparts. What is unclear is whether problems with cognition inhibition, mood, and behavior differ depending on the side of the seizure focus and/or the presence or absence of a structural lesion on MRI. This investigation explored cognitive inhibition, mood, and behavior in patients with FLE and addressed whether the side of the seizure focus and/or lesion status influence performances.

Methods: Participants were 15 patients with FLE documented by EEG and clinical history. Five patients had left and 10 had right seizure foci. Eight patients had MRI-confirmed lesions, whereas seven were nonlesional. All patients completed the Color-Word Interference Test (CWIT) of the Delis-Kaplan Executive Functions System (DKEFS), the Frontal Systems Behavior Scale (FrSBe), and the Beck Depression Inventory-II.

Results: Patients with FLE, as a unified group demonstrated mild impairments on the CWIT Inhibition/switching condition of the DKEFS and reported mild levels of depression. Significant subgroup differences emerged, however, when the side of the seizure focus and lesion status were considered. Patients with left FLE showed poorer cognitive inhibition and reported higher levels of depression than those with right FLE. In addition, patients with structural lesions on MRI demonstrated poorer cognitive inhibition and reported higher levels of apathy on the FrSBe than patients without structural lesions. Correlational analyses in the whole sample revealed that higher levels of self-reported executive dysfunction were associated with poorer cognitive inhibition on formal testing. Neither variable correlated with self-reported depression.

Conclusions: In patients with FLE, cognitive inhibition, mood, and behavior may differ depending on the side of the seizure onset and the presence or absence of a structural lesion. Thus, considering these patients as a unified group may obscure important cognitive and behavioral differences. Furthermore, there appears to be a significant relationship between self-reported executive dysfunction and actual test performance in patients with FLE, regardless of the side of seizures or lesion status. (Supported by the Epilepsy Foundation through the generous support of the American Epilepsy Society and the Milken Family Foundation.)

2.462

COGNITIVE CHANGES AFTER UNILATERAL ANTERIOR TEMPORAL LOBECTOMY AND TRANSYLVIAN SELECTIVE AMYGDALOHIPPOCAMPECTOMY

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Rationale: Thirty-six patients who had unilateral anterior temporal lobectomy with amygdalohippocampectomy (ATL) or transsylvian selective amygdalohippocampectomy (TSA) were evaluated using a selection of cognitive tests before and one year after surgery, to examine whether the TSA produces less cognitive impairment than a standard *en bloc* resection.

Methods: We described 36 patients who had temporal lobe surgery between 1991–2003. The patients had either a left or right ATL or a left or right TSA. In 17 patients ATL and in 19 patients TSA was performed. All patients received comprehensive neuropsychological testing of IQ and verbal/non verbal memory before and one year after operation.

Results: There were no differences between groups on the ratio of seizure free (ATL 70.6%, TSA 73.7%). IQ was improved postoperatively in ATL and TSA groups. For ATL, verbal memory was impaired in left-side resections while non-verbal memory was impaired in right-side resections. Although a decline in verbal memory was found for the left-side TSA, significant improvement in verbal memory was found for the right-side TSA and no apparent decline of memory function except verbal memory in left-side TSA were indicated.

Conclusions: The results clearly indicate that, particularly, left-side ATL and TSA can lead to a significant decline in verbal memory functions. However, in general, the preservation of memory function in the TSA group was better than in the ATL group. TSA may thus minimize the cognitive consequences of temporal lobe surgery.

2.463

ANALYSIS OF DECLARATIVE MEMORY CHANGES PRODUCED BY TEMPORAL LOBE EPILEPSY SURGERY IN SPANISH-SPEAKING PATIENTS

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Rationale: The aim of this study is to analyze declarative memory changes in temporal lobe refractory epilepsy patients, before and after anterior temporal lobectomy.

Methods: We selected 30 patients (p.) with refractory temporal lobe epilepsy surgically treated between January 2000 and December 2003. All the patients were evaluated, before and 6 months after surgery, with a Neuropsychological Protocol that includes the assessment of intelligence, attention, handedness, verbal memory, visual memory, language and executive function. A z-score were applied to raw values for each patient. These results were compared with normal population according to age and education. Patients were classified as "normal" when tests results presented values above z-2. After surgery, a chi-square test were applied in order to analyzed both samples.

Results: From the total population evaluated, 73% (22p.) have memory deficits. Patients were divided in 2 groups for their analysis: Patients with left anterior temporal lobectomy (LATL) (n = 13) and patients with right anterior temporal lobectomy (RATL) (n = 17). After surgery, on LATL group, 3 p. presented with a significant decline on declarative memory while 3 p. improved on verbal memory. Two p. presented a significant decline on visual memory and 7 p. remained without changes. On RATL group, after surgery, 2 p. improved significantly their visual memory deficits, 2 p. presented no significant changes on visual memory, 2 p. have a significant verbal memory deficit and 9 p. were normal. One year after surgery, 23 patients (77%) were in Engel's class I.

Conclusions: On the studied patients the neuropsychological profile was characterized by material-specific (verbal/visual) memory deficits. After surgery we found a variable outcome with a better prognosis on RATL group, as was described by other authors on the English-speaking population. We also analyze memory findings produced by temporal lobe epilepsy and surgery, in the framework of the declarative/procedural memory model.

2.464

ORGANIZATION OF RECEPTIVE LANGUAGE-SPECIFIC CORTEX BEFORE AND AFTER LEFT TEMPORAL LOBECTOMY

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Rationale: We used magnetoencephalography (MEG) to examine brain activation associated with receptive language in patients with left temporal lobe epilepsy (TLE) before and after an anterior temporal lobectomy. We evaluated which patients were most likely to show a change in the lateralization and localization of the mechanisms supporting receptive language and if such changes were associated with neuropsychological function.

Methods: Fifteen patients with left TLE underwent pre-operative Wada testing, and pre- and post-operative neuropsychological testing and MEG language mapping. The anatomical location of receptive language-related activity sources observed with MEG was determined by co-registering MEG data with structural MRI scans. Language laterality indices were calculated based on the number of activity sources in each hemisphere. The location of language-specific activity was also examined in relation to its proximity to Wernicke's area.

Results: Patients with atypical (bilateral) language lateralization on the Wada test were significantly more likely than patients with left-hemisphere dominance to show a shift in language representation toward greater right hemispheric activity after surgery. Patients with left hemispheric dominance pre-operatively were more likely to show intrahemispheric changes involving a slight inferior shift of the putative location of Wernicke's area. Patients with bilateral representation tended to perform worse on neuropsychological test measures pre- and post-operatively.

Conclusions: MEG can contribute significantly not only to the precise localization of Wernicke's area for presurgical planning, but is also an important tool for documenting post-operative language reorganization. [Supported by NINDS grant (NS 37941) to Andrew C. Papanicolaou and Austrian Science Fund (J2224-B02) to Ekaterina Pataraia.]

2.465

LANGUAGE OUTCOME AFTER LEFT TEMPORAL LOBECTOMY (LTL) IN ADULT PATIENTS WITH BILATERAL LANGUAGE (BL) REPRESENTATION

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Rationale: LTL of left language dominant patients for the treatment of intractable epilepsy has rarely resulted in frank aphasic symptomatology, provided the resection remains anterior to primary language cortex identified by electrical stimulation. However, recent reports have documented that some decline in language processing including visual confrontation naming is frequently present in these patients postoperatively. The possibility that BL representation as determined by the Intracarotid Amobarbital Procedure (IAP) might be associated with some sparing of these deficits has been reported for pediatric patients, but to date, has not been evaluated in an adult population. The present study compares the postoperative language outcome of adult patients with BL to a similar group of LTL patients with left hemisphere language dominance (LD).

Methods: The records of 39 patients who had undergone LTL, IAP and neuropsychological testing pre and postoperatively were reviewed. 26 patients were LD, while 12 had BL. The two groups did not differ in age at surgery (x = 29.6 yrs.), education (x = 13.4 yrs.) or Full Scale IQ (x = 92.4). 50% of LD and 75% of BL patients had early seizure onset (<13 yrs.). A majority of patients underwent language mapping with cortical stimulation prior to surgery. Neuropsychological variables included measures of vocabulary, abstract verbal reasoning, visual confrontation naming, phonemic verbal fluency and category fluency. Pre to postoperative difference scores were calculated for each variable and the two language groups compared for absolute level of performance and degree of change using paired t-tests. Individual change scores for each patient were also reviewed, with significant decline defined by the Reliable Change Index or a drop of one standard deviation or more on at least one language measure.

Results: As a group, BL and LD patients performed similarly on language measures both before and after LTL. A significant difference was found on confrontation naming postoperatively, with the LD patients scoring lower than the BL patients ($p < .05$). For both groups, postoperative performance and pre-post change scores suggested greater impairment for patients with late seizure onset. 65% of LD patients and 50% of BL patients declined on at least one language measure. Among

BL patients, postoperative language decline was less for patients with higher right hemisphere language scores on IAP.

Conclusions: The presence of BL in association with early seizure onset may predict a better language outcome following LTL. This effect appears to be maximized in patients with relatively greater right hemisphere language.

2.466

SUBJECTIVE PREFERENCE FOR LAMOTRIGINE OR TOPIRAMATE: RELATIONSHIP WITH MOOD AND COGNITIVE FUNCTIONING

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Rationale: The cognitive and behavioral effects of lamotrigine (LTG) and topiramate (TPM) were compared to the self-reported drug preference of healthy adults. Drug preference is important for patient compliance and antiepileptic drug (AED) therapy. Subjective perception of cognitive and behavioral effects contribute to drug preference. Evaluating the effects of AEDs in healthy volunteers minimizes the confounding factors associated with epilepsy.

Methods: A randomized, double-blind, double-dummy, two-period crossover study in healthy adults. Subjects were randomized (1:1) in the first treatment period to receive either LTG or TPM for 12 weeks (7 weeks of dose escalation followed by 4 weeks of maintenance therapy, and then a 1 week taper). Maintenance dose was 300mg/day for both AEDs. Subjects then received the alternate therapy for the next 12 weeks with the same dosing format. Evaluations were conducted at Screening, end of the First Maintenance Phase, end of the Second Maintenance Phase, and in the Post-treatment Period. Subjects were queried as to their preference for LTG vs. TPM at their last visit of the Second Maintenance Phase (subject and investigator blind). Side effects were recorded at each evaluation. Measures included mood assessment (QOLIE-89, SEALS, and POMS), and cognitive tests of attention, memory, language, and executive functioning.

Results: A total of 37 adults (mean age = 38 yrs) completed the study. Significantly more participants (26/37, 70%) preferred LTG (LTG-P). Six (16%) preferred TPM (TPM-P) and 5 (14%) had no preference (No-P). There was no difference in age or IQ between groups ($p > .05$). Overall, participants reported improved attention, memory, and language (QOLIE-89) along with less worry, tension, fatigue, and dysphoria (SEALS) on LTG regardless of drug preference. Within group differences were found. A total of 73% of subjects in the LTG-P group reported fewer side effects on LTG, while 67% of the TPM-P group had fewer problems on TPM. POMS ratings were consistent with drug preference, in which 4 of the 6 subscales favored TPM for the TPM-P group, and favored LTG for the LTG-P and No-P groups. Counter to self-report, performance on most cognitive variables declined on TPM in all 3 groups.

Conclusions: Seventy percent of healthy volunteers preferred LTG to TPM. Congruent with their stated preference, 73% of these subjects voiced fewer drug side effects and 100% objectively performed better while on LTG. Interestingly, the 16% who preferred and reported less toxicity while on TPM all showed impairment of cognitive function objectively. Thus, factors other than cognitive performance led to preference of TPM in a subgroup of patients. (Supported by GlaxoSmithKline.)

2.467

ANATOMIC DISSOCIATION OF CONFRONTATION AND RESPONSIVE NAMING: A FUNCTIONAL MRI STUDY

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Rationale: Visual confrontation naming requires patients to generate the name of visually presented objects. Auditory responsive naming requires the generation of an object name in response to an auditorally presented short definition of the target word. The later type of naming task may more closely approximate everyday language. Research suggests responsive naming is more sensitive to post-surgical naming deficits than confrontation naming. Intra-operative mapping studies show responsive naming to be more widely distributed than confrontation naming, in particular involving anterior temporal regions which are the target of resection in a standard temporal lobectomy. Functional MRI (fMRI) examining language lateralization has shown confrontation naming to be less lateralizing than many other language paradigms. No study has compared fMRI activation associated with responsive naming versus confrontation naming.

Methods: Participants included 20 healthy right-handers: 10 completed the fMRI confrontation naming paradigm and 10 completed the responsive naming paradigm. Imaging was acquired using a 1.5 tesla scanner. All tasks were block design paradigms. During the active condition of the confrontation naming paradigm subjects viewed line drawings and were instructed to covertly name the drawing. The baseline task consisted of sets of lines that were viewed passively. During the active condition of the responsive naming task subjects heard short definitions and covertly generated the word associated with the definition; the baseline consisted of short sentences read backwards. Specific regions of interest (ROIs) were defined within the frontal and temporal lobes, and hippocampus. A laterality index (LI) was calculated for each ROI and volume of activation was also measured.

Results: The LIs associated with auditory responsive naming were significantly higher than for visual confrontation naming in all frontal and temporal ROIs except for the fusiform gyrus. Responsive naming produced significantly more activation (as measured by extent of activation) within the left middle and superior temporal gyri as compared to confrontation naming. The activation within the dominant temporal lobe also extended more anteriorly during responsive naming, as was suggested by previous brain mapping studies. Both confrontation naming and responsive naming produced hippocampal activation.

Conclusions: Findings suggest that auditory responsive naming may be a more useful fMRI paradigm in assessing language lateralization than confrontation naming. Responsive naming also activates large portions of the temporal lobe, which may enable it to be useful as a predictor of post-surgical language changes. Both naming tasks activated the hippocampus, findings that are consistent with several other studies that also implicate this structure as part of the neural network involved in naming.

2.468

ADJUNCTIVE LEVETIRACETAM IMPROVES QUALITY OF LIFE IN LINE WITH PATIENT PRIORITIES IN EPILEPSY

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Rationale: To determine the effect of levetiracetam (LEV) on health-related quality of life (HRQOL) when added to other antiepileptic drugs (AEDs) for community-based patients in Spain.

Methods: LEV was added to other AEDs in a open-label study of adjunctive therapy. Patients $\geq$16 years of age with partial-onset seizures were evaluated for changes in HRQOL with the QOLIE-10-P, a new version that includes the 10-items from the original QOLIE-10 (scores ranging from 0 – worst HRQOL – to 100 – best HRQOL), one item on overall distress, and one item on the relative importance of each QOLIE-10-P domain. Assessments were made at baseline and after adjunctive treatment with 1000–3000 mg/day LEV for 16 weeks. Change from baseline in overall HRQOL was additionally assessed at follow-up on a 5-point scale.

Results: A total of 342 patients were evaluated (mean age 39 years, 54% female, mean duration of epilepsy 21 years). Adjunctive LEV reduced the weekly frequency of partial seizures and all seizure types by a median of 55%. QOLIE-10-P total scores were significantly improved from baseline (mean $\pm$ SD: 54.2 $\pm$ 18.1) to final follow-up (64.4 $\pm$ 18.7), an increase of 10.2 $\pm$ 17.8 points (paired t-test: $p < 0.001$). All item/domain scores were also significantly improved from baseline to follow-up (all $p < 0.001$, except energy-fatigue $p = 0.004$). Score changes from baseline were greatest for seizure worry (+13.7 points), social function (+13.5) and overall QOL (+10.5). The epilepsy effects factor improved from baseline by +9.1 points, mental health factor by

+7.5 points, and role function factor by +12.9 points (all $p < 0.001$). At baseline and at follow-up, seizure worry, overall QOL and social function were listed by the patients as the three most important domains. Patients' global assessment of change revealed that 59% of patients felt their HRQOL had improved with the addition of LEV (25% a lot better, 34% a little better) while 15% felt unchanged.

Conclusions: The addition of LEV to other AEDs resulted in improved HRQOL in this cohort of community-based patients in Spain. Largest improvements were observed in those items/domains reported as the most important by the patients, i.e. seizure worry, social function and overall QOL. (Supported by UCB Pharma S.A.)

2.469

LONG-TERM FOLLOW-UP STUDY OF PATIENTS WITH PNES

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Rationale: In an earlier study we showed that patients diagnosed with psychogenic nonepileptic seizures (PNES) at our facility had a dramatic decrease or cessation of nonepileptic seizure events in the 24-hour period after patients were informed of their diagnosis using the Shen protocol. We suggested that a follow up study should evaluate whether the decrease was maintained over time, and whether cessation of PNES was followed by the development of other psychiatric or somatic complaints. This study addresses these points.

Methods: Study subjects were chosen consecutively from the database of all patients admitted to the UC Davis Medical Center inpatient video-EEG monitoring unit from January 2000 through March 2004. Definitive diagnosis of PNES required vEEG monitoring in which the patient was observed having typical seizures without accompanying abnormality on EEG, and family members or witnesses familiar with the patient's events agreed that the recorded episodes were typical events. 53 patients were eligible for the study. Three physicians with standardized protocol training contacted subjects by telephone and administered a 15-item survey about their PNES and other factors. Survey results were analyzed using the SPSS for Windows program.

Results: Of the 52 eligible patients, 23 patients (44%) completed the survey, 25 patients (48%) were lost to follow up, 2 patients (4%) declined to participate and 2 patients (4%) were in jail. There was no significant difference in age between participants and non-participants ($p = 0.42$), but participants were more likely to be female ($p = 0.01$, t test). Mean length of follow up since diagnosis of PNES was 17.3 months (range 2–60 months). Three patients (13%) were seizure-free; 15 patients (65%) had a greater than 50% reduction in seizure frequency; 5 patients (22%) were having the same or greater frequency of seizures. 20 of 23 patients (87%) were still having some PNES. Patients were categorized as responders (more than 50% reduction in seizure frequency) or nonresponders (increase, no change or less than 50% decrease in seizure frequency). Responders were more likely to believe the diagnosis of nonepileptic seizures at the time of the survey than nonresponders ($p < 0.001$, t test) and were less likely to be on disability ($p = 0.04$, t test). There were nonsignificant trends indicating that responders were less likely to have other somatization symptoms and were more likely to have experienced abuse. They did not differ in rates of AED use (~40%), psychotropic use (~80%), emergency visits for NES (~30%) or comorbid psychiatric diagnoses (~78%).

Conclusions: Results suggest that the substantial decrease in NES frequency shortly after diagnosis is not maintained long term, but that the majority responded well with a greater than 50% reduction in seizure frequency from before diagnosis.

2.470

AFFECT IN EPILEPSY PATIENTS UNDERGOING VIDEO-EEG MONITORING: RETROSPECTIVE VERSUS MOMENTARY ASSESSMENT AND TEMPORAL RELATIONSHIP TO SEIZURES

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Rationale: A large proportion of epilepsy patients suffer from mood disorders. However, there is little research on whether traditional retrospective reporting of mood/affect accurately reflects how epilepsy patients feel at specific times. The goals of this study were to: 1) examine the relationship between *retrospective* and *momentary* assessment of affect (Rate how you feel *at this moment*) and 2) examine the temporal relationship between momentary affect and seizures.

Methods: Participants were 24 epilepsy patients (10 males; ages 20–62) undergoing inpatient video-EEG monitoring. While hospitalized, each patient was loaned a watch that beeped at random intervals several times daily, signaling him/her to complete a 44-item *momentary* affect questionnaire (e.g., enthusiastic, miserable, tired). Items yielded 6 scales: activated positive, positive, unactivated positive, activated negative, negative, and unactivated negative. Prior to discharge, patients *retrospectively* rated their affect with these items (Rate how you felt during your hospital stay).

Results: Correlations between average momentary ratings and retrospective ratings were strong for all scales, $rs = .57$ to $.79$, $ps < .01$. Thus, patients who, on average, reported negative (or positive) affect on their momentary ratings also gave negative (or positive) retrospective ratings. Despite strong correlations, t-tests comparing the *means* for retrospective and momentary ratings showed significantly more positive retrospective ratings for all 3 positive scales, $ps < .05$. Thus, patients retrospectively recalled feeling more positively during their stay than they reported feeling at the time.

Temporal relationship between affect and seizures: Twelve patients had EEG-verified seizures during their stay. Their momentary ratings were divided into 5 periods: prodrome, preictal, early postictal, late postictal, interictal. The only comparison with enough data for analysis was between prodromal and interictal ($N = 7$). There was significantly more unactivated negative affect, $p = .026$, and less activated positive affect, $p = .056$, in the prodromal period.

Conclusions: Finding that retrospective ratings were more positive than momentary ratings suggests that retrospective ratings may not accurately capture how patients feel at specific times. Retrospective ratings can suffer from forgetting, as well as biasing effects, such as recency and halos. The finding of more negative and less positive affect in the prodrome than in the interictal period is consistent with a prior study that obtained *daily* mood ratings. This suggests that the biological mechanisms responsible for seizures may also be responsible for negative affect. (Supported by Albrecht/FSU Epilepsy Fund.)

2.471

DEPRESSION, STATE AND TRAIT ANXIETY, AND GENERAL HEALTH PERCEPTION IN PATIENTS WITH EPILEPSY

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Rationale: The most common psychiatric disorder in epilepsy is interictal depression, which a lifetime prevalence is of 10–60%. Depression and anxiety symptoms in epilepsy are often underrecognized and undertreated. The aetiology of depression and anxiety in epilepsy has not been determined, but it can include: the brain pathology, the negative psychosocial impact of epilepsy and side effects of antiepileptic drugs. This study was designed to assess depressiveness, state and trait anxiety and general health perception in patients with epilepsy.

Methods: 1495 patients, 16–80 years old, with newly diagnosed or treated epilepsy and experiencing any seizure type classifiable by the International Classification of Seizures. These patients has to be free of additional chronic diseases and to were able fulfil questionnaires. The following assessments were obtained: medical history, seizure history and frequency, serious negative life events, current treatment and mood assessments including the Beck Depression Inventory (BDI), Spielberger's State and Trait Anxiety Inventory (STAI) and Goldberg's General Health Questionnaire (GHQ-28).

Results: The mean BDI score in patients with epilepsy was 16,9, suggesting mild depression. 59,5 per cent of patients have BDI scores above 13, including 15.1 per cent having BDI scores above 29. The trait

anxiety scores were significantly higher than state anxiety scores, but lower than I community samples. The BDI scores were significantly correlated with age. There was no correlation between mood scores and epilepsy variables including seizure frequency.

Conclusions: Depression is a common comorbidity in epilepsy patients, but the level of anxiety seems not to be significantly higher than in general population. (Supported by GlaxoSmithKline.)

2.472

THE DELAYED DIAGNOSIS OF PSYCHOGENIC SEIZURES AND THE SUBSEQUENT NEGATIVE EFFECTS

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Rationale: The diagnosis of psychogenic seizures may not be established for several years, during which antiepileptic drugs (AEDs) may be used unnecessarily and appropriate psychiatric intervention delayed. Because some of our patients had taken more than four AEDs for more than ten years before the diagnosis of the psychogenic seizures, we elected to systematically study this population to determine the frequency and causes for delayed diagnosis and to analyze the negative effects of the delay.

Methods: Data from 215 patients admitted for video-electroencephalography (VTEEG) during a nine month interval were analyzed. The diagnosis of psychogenic seizures was considered definite if clinical events were recorded on VTEEG that (1) were typical of that patient's usual episodes, (2) were devoid of epileptiform discharges, and (3) were characteristic of psychogenic seizures by visual inspection of the videotaped event. We analyzed patient demographic distribution, stratified risk factors, the duration from onset to diagnosis, and subsequent negative effects such as numbers and duration of unnecessary AED treatment, working status. Delayed diagnosis was defined as more than six month from onset to diagnosis.

Results: A total of 109 patients (50.6%) had psychogenic seizures. 33% (35) were male and 67% were female. The most significant risk factors are history of sexual abuse and psychiatric disorders. 30.3% of them had concomitant or history of psychiatric disorders, 28% had history of sexual abuse. Only eight patients were referred and diagnosed on presentation. 74% of these patients were diagnosed after six months. In the group of delayed diagnosis, the mean time from onset until diagnosis of psychogenic seizures was 54.3 months with range from six to 372 months. 36.8% of them were on one AED with mean duration of 37.03 months; 27.6% were on 2 AEDs with a mean duration of 87.9 months; 10.5% were on 3 AEDs with duration of 41.8 months; and 2.6% were on 4 AEDs with duration of 108 months. 41.3% of these patients were on more than one anti-epileptic drug with average duration of 79 months. About 60% of these patients were not working and 20% of them were on disability.

Conclusions: The diagnosis of psychogenic seizures is often delayed even with the wide availability of VTEEG. Delayed diagnosis of psychogenic seizure can impede appropriate medical management and have significant negative effects resulting in unnecessary AED treatment and loss of productivity. Neurologists should have a high index of suspicion and be sensitive to risk factors when encountering patients with "pharmaco-resistant epilepsy" and patients with symptoms suggestive of psychogenic seizures. Early referral to VTEEG should be considered. With this in mind, achieving earlier diagnosis and avoiding unnecessary use of AEDs in this population is a challenging yet achievable task.

Neuropsychology/Language/Behavior–Pediatric

2.473

IMPAIRED SOCIAL COMPETENCE IN PEDIATRIC EPILEPSY: INSIGHTS INTO UNDERLYING MECHANISMS

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Rationale: Children with epilepsy have impaired Child Behavior Checklist (CBCL) (Achenbach, 1991) social competence scores involving school, social relations, and activities (Austin et al., 1994; Hermann et al., 1988; McCusker et al., 2002; Schoenfeld et al., 1999). Social competence scores are inconsistently related to seizure control, illness duration, and antiepileptic drug (AED) (Hermann et al., 1988; McCusker et al., 2002; Schoenfeld et al., 1999). We examined if social difficulties in pediatric epilepsy reflect the underlying seizure disorder and/or associated behavioral, cognitive, and linguistic problems. We compared social competence in children with epilepsy to normal children controlling for demographic, cognitive, and linguistic group differences. Using seizure factors derived from a principal components analysis, we examined the role of seizure-related, cognitive, behavioral, linguistic, and demographic variables in the social competence scores.

Methods: 90 complex partial seizure disorder (CPS), 62 childhood absence epilepsy (CAE), and 91 normal children, aged 5–16 with average IQ scores participated in a structured psychiatric interview, cognitive, linguistic, and social communication testing. Parents completed CBCL forms, provided seizure-related information, and had a structured psychiatric interview about the child.

Results: Controlling for cognition, language, and demographics, ANCOVAs demonstrated similar social competence in the CPS and CAE goups, significantly reduced total social competence ($p < .05$) and more school problems ($p < .0001$), but no significant differences in social relations and activities in the patients compared to the normal subjects. Modeling total social competence with demographic, cognitive, linguistic, psychiatric disorder, CBCL scores, social communication, and seizure variables in the model yielded significant findings for IQ ($p < .0001$), ethnicity ($p < .01$), and psychopathology ($p < .01$) among patients. There was no main effect for the seizure components: onset age/duration; EEG lateralization/localization/severity; seizure frequency/number of AEDs; and prolonged seizures/febrile convulsions. Lower IQ, externalizing CBCL scores and disruptive disorders accounted for 42% and 40% of the variance of total social competence and school scores, respectively. Fewer peer interactions were related to reduced IQ ($p < .0004$) and externalizing behaviors ($p < .0001$). Less involvement in organized activities was associated with lower IQ ($p < .06$) and disruptive behaviors ($p < .03$). Ethnicity predicted total social competence ($p < .01$), social ($p < .008$), and activities scores ($p < .01$).

Conclusions: Average IQ children with epilepsy with school and social problems need cognitive and behavioral assessments. (Supported by RO1 NS 32070.)

2.474

BEHAVIORAL AND PSYCHOSOCIAL OUTCOME IN PEDIATRIC EPILEPSY AFTER TREATMENT WITH TOPIRAMATE

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Rationale: The incidence of behavioral and psycho-social problems in epilepsy children is known to be 5–6 times higher than normal. This study is subjected to reveal the influence of topiramate on behavioral and psycho-social outcome in the treatment of epilepsy children

Methods: 233 patients (male,121; female,112 and mean age $\pm$ SD, 8.4 $\pm$ 3.8 year) are enrolled in this study from 22 medical centers in Korea. Topiramate was added and titrated for up to 3 months starting with 1 mg/kg/day for 2 weeks with increment of 1 mg/kg/day for 1–2 weeks as tolerated with maximal doses up to 9 mg/kg/day. The psycho-behavioral batteries {Korean Child Behavior Check List (K-CBCL), Yale Children's Inventory (YCI), Children's Depression Inventory (CDI), Family Environment Scale (FES), Piers-Harris Children's Self Concept Scale(PCSCS)} were used for assessment at baseline, 6 months, and 12 months after starting topiramte.

Results: The seizure frequency at 1 year after topiramate treatment was decreased; more than 50%, 79% (seizure free, 51.5%); 25–50%, 8.7%; no change, 11.4%; worsening, 0.9%. The anti-epileptic efficacy

of topiramate was inversely correlated with DOI ($p < 0.001$). The adverse effects of topiramate were noticed in 6.2%, which were fatigue, vertigo, and weight loss, etc. In the K-CBCL, total behavior problem ($p < 0.01$) and internalizing behavior problem ($p < 0.05$) were significantly improved at 1 year after topiramate treatment. Total and internalizing behavior scores were significantly improved in patients with higher seizure frequency and the patients whose seizures were significantly improved after topiramate($p < 0.05$). There were no significant changes in YCI, CDI, FES and PHSCS.

Conclusions: The add-on use of topiramate was quite effective in controlling seizures and improving behavioral, and psycho-social outcome in pediatric epilepsy children. (Supported by Janssen Korea Co.)

2.475

DO ATTENTION PROBLEMS AND INTERNALIZING PROBLEMS PREDICT SEIZURE RECURRENCE IN CHILDREN?

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Rationale: Hauser et al. and Hesdorffer et al. (*Epilepsia* 1998; 39(suppl. 6):222) found that ADHD and depression were both more frequent in and a possible risk factor for new-onset seizures in children. We looked for evidence of these disorders in a sample of children with new-onset seizures and asked if the presence of symptoms of attention and internalizing problems predicted recurrence of seizures.

Methods: The sample consists of 224 children with new-onset seizures. The comparison group was 103 children with asthma whose symptoms had recently worsened. Parents completed the Child Behavior Checklist (CBCL) within 6 weeks of the first recognized seizure or change in asthma symptoms. Parents were asked to base behavior ratings on the six months prior to the first recognized seizure or change in asthma symptoms. For this analysis, we used the internalizing score, a combination of anxiety/depression, withdrawal, and somatic complaints, and the attention problems syndrome score. Logistic regression analyses, controlling for demographic variables, were used to compare children with seizures to children with asthma and children with recurrent seizures to children without additional seizures on mean CBCL T-scores and dichotomized data for at risk and clinical CBCL categories.

Results: At baseline, the children with seizures had higher mean attention scores ($p = 0.04$) and were more likely to be in the at-risk category for attention problems ($p = 0.01$) than children with asthma. In contrast, the children with asthma had higher mean internalizing scores ($p < 0.01$) and were more likely to be in the at-risk category for internalizing problems ($p < 0.01$) than the children with seizures. Comparing the children with no additional seizures to those with at least one recurrent seizure 3–24 months after the first seizure, we found a borderline significant association between the total attention problems T-score and recurrent seizures ($p = 0.05$) but no association between total internalizing score and recurrent seizures. The children with recurrent seizures were significantly more likely to be in the clinical category for attention problems at baseline than were the children with no additional seizures (17.9% vs. 5.0%, $p = 0.01$). There was no significant association between recurrent seizures and internalizing problems.

Conclusions: We confirmed the increased frequency of attention problems in children with new-onset seizures and found that attention problems at onset predict recurrent seizures. We did not find an association between internalizing problems and recurrent seizures. We suspect that seizures and attention problems may be due to a common underlying central nervous system dysfunction. (Supported by grant PHS R01 NS22416 from NINDS.)

2.476

SUBJECTIVE AND OBJECTIVE VIEWS OF MEMORY OUTCOME AFTER PEDIATRIC EPILEPSY SURGERY

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Rationale: This study examined the potential effects of epilepsy surgery on memory in children and adolescents. It is novel in that it includes a nonsurgical comparison group, tracks change over time, and includes qualitative and quantitative methods. The qualitative component illuminates the experiences of the participants and how they make sense of their memory difficulties. While it may be hoped that an improvement in seizure status coupled with on-going maturation would result in benefit to memory, work with adults suggests that outcome is not a static process, and decline in verbal memory over time after left temporal lobectomy has been observed. This possibility has not been investigated with the pediatric population for whom there is little information on long-term cognitive change after surgery.

Methods: Memory was investigated in 27 participants in a longitudinal study before (T1), and at one (T2) and two to four years (T3) after epilepsy surgery. A comparison group with intractable epilepsy ($n = 15$) matched in age, sex, age of seizure onset and IQ, was studied at the same time points. Methods included qualitative interviews to probe the participants' perceptions of their memory over time and administration of standardized tests of story recall and face recognition.

Results: At T1, 20 (74%) youth in the surgery group and 9 (60%) in the comparison group reported memory problems. The following changes were reported by the surgical group: at T2, 9 improved and 4 declined; from T2 to T3, 5 improved and 3 declined. In the comparison group, 0 improved and 6 declined at T2; 2 improved and 1 declined by T3. Narrative themes were similar in both groups, with persistent deficits in retention of information and academic performance reported most frequently. On-going problems included difficulties with word-finding and memory for personal semantic information. Transient memory problems were worsened by seizures, medication and fatigue, which in some instances affected memory by reduced concentration, attention and understanding. Persistent and transient memory deficits caused fragmented learning and poorer academic performance. There was no significant change over time in either group on the standardized measures. Site and laterality of excision, age at surgery and seizure outcome were not predictive of change in the surgical group.

Conclusions: Up to 4 years after surgery, little benefit with respect to memory was documented. Of importance, there was also no evidence of decline in the majority of participants. The narratives revealed a complex of factors that impacted on memory. Although objective tests did not show change, these tasks emphasize episodic memory. The narratives indicated that semantic memory may be affected by surgery, suggesting that the effects of surgery on this type of memory warrant further investigation. (Supported by The Ontario Mental Health Foundation.)

2.477

ADHD CLASSIFICATION IN CHILDREN WITH CHRONIC EPILEPSY: DISCREPANCIES BETWEEN MEASURES OF ATTENTION AND SCHOOL CLASSIFICATION

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Rationale: Research suggests that children with epilepsy might have an increased risk for symptoms of attention deficit hyperactivity disorder (ADHD). Unfortunately, many children with epilepsy may go undiagnosed with ADHD. This study compared the rates of children classified with ADHD in the school with the rates of children meeting cutoff criteria for attention problems on standardized measures. It was hypothesized that children would be under-classified for ADHD in the school based on scores from standardized measures of attention.

Methods: Participants were 85 children with chronic epilepsy. Children were assessed at baseline, 12 months, and 24 months. The mean age was 13.07 ($SD = 1.94$) at 24 month assessment, age of seizure onset was 7.00 ($SD = 3.71$), and 51% were females. Parents completed an educational services survey, on which they indicated whether the child was currently classified as having one of several diagnoses including ADHD (yes = 1, no = 2). Additionally, a parent-report measure of attention problems (Child Behavior Checklist) and an objective measure of attention (Continuous Performance Test) were administered.

Results: 2 × 2 (Cutoff Score × Classification) Chi-Square analyses were conducted to determine whether significant differences emerged between those with or without a classification of ADHD. On the CBCL, results demonstrated a significant difference between those scoring in the "at-risk" ($T \geq 67$) range for attention problems and those classified with ADHD ($\chi^2 = 11.57$, $p = .001$), where several children met cutoff scores for attention problems yet were not classified with ADHD. However, when using the clinical cutoff score ($T \geq 71$), differences no longer remained significant ($\chi^2 = 1.59$, $p = .21$). On the CPT, participants scoring 2 SD from the mean ($T \geq 70$) on omission rates were considered to demonstrate attention problems. Results yielded a significant difference between children demonstrating attention problems and those classified with ADHD ($\chi^2 = 5.45$, $p = .020$). Of note, 14 children were not able to complete the CPT, which may suggest that these results underestimate the rate of attention problems.

Conclusions: Children with chronic epilepsy may go undiagnosed with ADHD when symptoms are present. However, these instruments are screening measures and do not replace diagnostic measures. Thus, measures incorporating DSM-IV criteria will be a critical follow-up to this study. Future studies should compare the rates of those children who are classified as ADHD with diagnostic measures utilizing DSM-IV criteria. (Supported by PHS R01 NR04536 from NIH/NINR to J.K.A.)

2.478

EFFECT OF SEIZURE CONTROL ON NEUROPSYCHOLOGICAL PERFORMANCE AND ACADEMIC ACHIEVEMENT OVER TIME IN CHILDREN WITH EPILEPSY

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Rationale: Children with chronic epilepsy often exhibit cognitive impairment; some show decline, especially with early age of onset, persistent seizures, and/or toxic levels of some antiepileptic drugs (Bourgeois et al., 1983; Rodin, Schmaltz, & Twitty, 1986). One study suggests that children might be more susceptible than adults to the effects of persistent seizures (Bjornaes et al., 2001). These studies have been limited to IQ. A study of academic achievement showed no adverse changes over four years in a chronic sample (Austin et al., 1999). The present study examined the effects of persistent seizures over time on specific neuropsychological functions that are commonly affected in children with epilepsy. It was predicted that neuropsychological performance would decline but only in those children with incomplete seizure control.

Methods: The sample consisted of 173 children with chronic epilepsy (ages 8–15 years; 49% female, 91% White/Non-Hispanic; 79% one seizure type, 79% on one medication, 69% with active seizures). Children diagnosed with mental retardation were excluded. There were 164 children at baseline and 130 children at 24 months later who completed a comprehensive neuropsychological battery assessing 9 cognitive domains and academic achievement in reading, writing, and math. For seizure control, participants were classified at baseline and at 24 months as active (seizure within past 12 months) or controlled (no seizures in 12 months). A repeated-measures analysis of covariance, which controlled for age, age at onset, and gender, was used to test the main effects and the interactions of Time and Seizure Control for the neuropsychological functions.

Results: There was a Time × Seizure Control interaction (decline over time but only for children with active seizures) for two of the nine neuropsychological domains: executive processing [Category Test, $F(1, 123) = 5.07$, $p = 0.03$] and rapid automatic naming [Stroop Word Trial, $F(1, 123) = 4.76$, $p = 0.03$]. A main effect for seizure control (active worse than controlled) was observed for two other domains: receptive language [Tokens Test, $F(1,32) = 8.74$, $p = 0.006$] and verbal memory [WRAML Story Memory, $F(1,32) = 4.39$, $p = 0.04$]. No other main effects or interactions were observed, $p > .05$.

Conclusions: Consistent with research on IQ, uncontrolled seizures were associated with lower performance in two neuropsychological domains at baseline and were associated with declines (or less improvement) in two other domains. Also consistent with prior research, academic achievement was stable over the time period of this study. (Supported by PHS R01 NR04536 from NIH/NINR to J.K.A.)

2.479

TEMPORAL LOBE EPILEPSY IN CHILDHOOD: NEUROPSYCHOLOGICAL ASSESSMENT

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Rationale: Cognitive deficits in childhood temporal lobe epilepsy (TLE) is not well defined. The objective of this study is to attempt to identify specific neuropsychological deficits in children with TLE.

Methods: We evaluated 11 children with clinical, electroencephalographic and MRI findings of TLE. They underwent a comprehensive neuropsychological examination aiming to assess: cognitive level, visual perception, attention, handedness, visuo-motor praxis, executive functions, language, memory and learning (verbal, visual and global). Tests were: WISC III, color and shape perception test, trail making test, Wisconsin card sorting test, Boston naming test, verbal fluency test, WRAML test.

Results: MRI showed right temporal lobe lesion in 7 patients. We identified memory (in 7 patients), language (naming; in 7 patients) and verbal fluency (executive function; in 4 patients) deficits. Mental flexibility was impaired in 9 patients. Despite the deficits, global IQ was normal in all patients.

Conclusions: Children with TLE may present specific neuropsychological deficits that are not directly correlated with the lesion itself, but may suggest dysfunction of other cerebral areas, particularly the frontal lobes. (Supported by CAPES and FAPESP.)

2.480

THE INFLUENCE OF EEG FOCUS LATERALIZATION AND LOCALIZATION ON VISUAL MEMORY IN CHILDREN

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Rationale: To compare neuropsychological performance regarding visual memory, of two groups children with focal epilepsy: those who have the EEG epileptogenic focus in left hemisphere (L), and those who have rigt (R) sided epileptogenic focus.To compare also, performance on visual memory testing between two groups children with EEG focus localized temporal (T) vs. extratemporal (ExT).

Methods: Visual memory both immediate (reproduction of figure after 3 minutes) and delayed (reproduction of figure after 40 minutes) were measured in 80 children with focal epilepsy aged 7–16 years, using Rey complex figure. The effects of age at seizure onset, number of seizures and type of seizure were also examined.

Results: All groups had high rates of impairment in comparation with healthy children controls ($p < 0.0001$). Group differences were not found neither left (L) vs. right (R) ($p > 0.05$), nor temporal (T) vs extratemporal (Ex T) ($p > 0.005$).Age at seizure onset (before years of 7) and type of seizure were related to performance on Rey complexe figure. The high number of seizure was not correlate with poor performance on test mentioned above.

Conclusions: Children with focal epilepsy have visual memory deficit (both immediate and delayed). There is no significant relationship between EEG focus localization and lateralization and severity of measured visual memory impairment. Age at seizure onset and type of seizure are very important predictive factors for cognitive functioning in children with focal epilepsy.

2.481

NEUROPSYCHOLOGICAL STATUS IN NEW-ONSET PEDIATRIC EPILEPSY

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Rationale: Chronic epilepsy in adults is often associated with widespread neuropsychological dysfunction. Whether this cognitive morbidity is due to adverse progressive effects of epilepsy and its treatment, the impact of initial etiological factors, or the combined effects of cause and consequence of epilepsy remains to be deteremined. We have reported that children with *chronic* epilepsy also exhibit relatively widespread cognitive difficulties. By examining children shortly after diagnosis and following them over time, the etiology of cognitive morbidity may be better understood.

Methods: Of an anticipated final sample of 75 children with new onset epilepsy and 75 controls, this preliminary report describes results from 24 children; 15 with epilepsy (localization-related = 8, primary generalized = 7) with an average duration of 12.4 months, and 9 age-matched controls (first degree cousins). Recruitment is ongoing from two major health care systems in Wisconsin. Average age of the sample is 13.2 years (range 8–18); average grade level is 7 (range 2–13), and mean age of diagnosis for the epilepsy sample is 11.6 years. Subjects were administered a comprehensive battery of tests assessing intelligence, academic achievement, language, memory, executive functions, and motor speed.

Results: Pair-wise comparisons indicated no statistically significant differences between the children with epilepsy and the controls across measures of cognition. All children performed within the average range of intelligence (controls = 108.6, epilepsy = 111.7) and performances were similarly average/high average across tests of expressive and receptive vocabulary, immediate and delayed verbal and visual memory, executive function, and motor dexterity. Examination of academic achievement scores revealed that 20% of the children with epilepsy versus 0% of the controls exhibited significant learning disability or delay.

Conclusions: These preliminary findings indicate that children with new onset epilepsy perform comparably to healthy controls across measures of cognition. Examination of individual subject data demonstrates higher rates of academic underachievement in new onset epilepsy (20%) compared to controls (0%). Increasing accrual of new onset cases and controls will facilitate additional comparisons (e.g., between epilepsy syndromes) as well as increased statistical power to identify the clinical and cognitive correlates of academic underachievement. [Supported by NIH NS R01-44351, F32 MH649882, and MO1 RR03186 (GCRC).]

2.482
PSYCHIATRIC COMORBIDITY IN CHILDREN WITH NEWLY DIAGNOSED EPILEPSY

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Rationale: Chronic epilepsy can be associated with significant psychiatric co-morbidity. The nature, timing, and etiology of this co-morbidity remain to be fully characterized. Prior investigations of children with *chronic* epilepsy using standardized psychiatric interview procedures (e.g., K-SADS) have revealed high rates of psychiatric disorder (approximately 50%) which could have been apparent from the onset of the disorder or developed over time. This investigation examined children with new onset epilepsy (<12 months since diagnosis) to determine whether psychiatric co-morbidity was present closer in time to the onset of the epilepsy.

Methods: Of an anticipated final sample of 75 children with new onset epilepsy and 75 controls, this preliminary report describes results from 24 children; 15 with epilepsy (localization-related = 8, primary generalized = 7) and 9 age-matched controls (first degree cousins). Recruitment is ongoing from two major health care systems in Wisconsin. Average age of the sample is 13.2 years (range 8–18) and mean age of diagnosis for the epilepsy sample is 11.6 years. Subjects and their mothers independently underwent a standardized psychiatric interview (K-SADS) and the primary caretaker completed a Child Behavior Checklist (CBCL).

Results: K-SADS revealed that 46.7% of the children with epilepsy and 11.1% of the controls had a current Axis I disorder. Lifetime-to-date Axis 1 disorders were found in 60% of the epilepsy and 22.2% of the control group. The most common current disorders in the epilepsy group were mood (major depression, depressive disorder NOS) and anxiety (OCD, separation anxiety) disorders. There were no significant differences between the groups on the CBCL summary scores.

Conclusions: These preliminary findings indicate that children with new onset epilepsy exhibit significantly elevated rates of current and lifetime-to-date Axis I disorders compared to age and gender matched controls. This elevated psychiatric co-morbidity is present close in time to onset of the disorder, and the increased rates of lifetime-to-date disorders would appear to be consistent with the hypothesis that psychiatric co-morbidity may even be elevated prior to the diagnosis of epilepsy and associated with neurobiological factors that led to the development of epilepsy. [Supported by NIH NS R01-44351, F32 MH649882, and MO1 RR03186 (GCRC).]

2.483
INTRAHEMISPHERIC REORGANIZATION OF LANGUAGE IN EARLY-ONSET EPILEPSY

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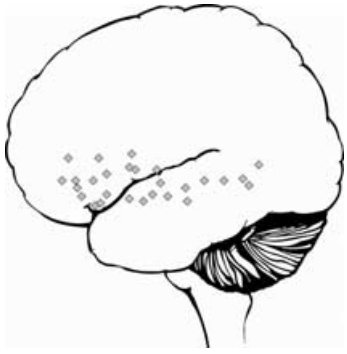
Rationale: Study of individuals with epilepsy suggests a period of increased functional plasticity of language within the first few years of life, in that those with early seizure onset demonstrate increased right- and bilateral language representation. Historically, research has focused on *inter*hemispheric shifts in language representation, without systematically assessing *intra*hemispheric effects. In this study, we developed a novel 2D-to-3D coregistration technique to assess findings from invasive language mappings. This study is the first to investigate the extent of intrahemispheric reorganization in the context of paediatric epilepsy.

Methods: Eight children, aged 5.7–17.8 years underwent extraoperative stimulation mapping (ESM) to localize language within the left hemisphere. All had left-hemisphere seizure foci with onset before 6 years. ESM permitted direct cortical stimulation and precise determination of language areas using subdural grids. Capture of digital images at the time of implant facilitated development of detailed functional maps, sensitive to each patient's unique cortical morphology. ESM data were co-registered with 3D brain representations compiled from thin-slice MRIs, spatially normalized, and assessed in standard stereotactic space. Language sites were compared to structural probability maps of the frontal operculum, or Broca's area.

Results: Language areas were observed both within and outside of canonical language regions (Broca's area and Wernicke's area; see Fig. 1). In the frontal lobe, language sites were observed in regions substantially anterior and superior to classical Broca's area, to an extent not previously described. Language sites were observed inside, bordering, and outside of epileptogenic regions.



Conclusions: In addition to *inter*hemispheric shifts in language, individuals with early onset epilepsy experience *intra*hemispheric reorganization of language. Neurosurgical teams must consider the potential

for language representation anterior to Broca's area; abnormal cortex may support language. Extensive functional mapping within and beyond canonical language areas is necessary for comprehensive characterization of the language cortex.

2.484

ACADEMIC UNDERACHIEVEMENT AND ACCESS TO EDUCATIONAL SERVICES AFTER A NEUROPSYCHOLOGICAL REPORT IN CHILDREN WITH EPILEPSY

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Rationale: Children with epilepsy (CWE) often need educational services but go unidentified. Neuropsychological testing can identify CWE who are having difficulties, and the neuropsychological report (NR) can serve as an intervention and catalyst for educational services (ES).

Methods: This study examined the number of ES that CWE received before and after a NR was provided to their parents. It was hypothesized that CWE would receive more ES after receiving the NR, especially for those who were underachieving (1 SD < IQ). At baseline, participants were 58 CWE 8–15 years old (M = 10.9; *SD* = 1.8) who were in Grade 2.7–10.2 (M = 5.5; *SD* = 1.9). IQ ranged 56–130 (M = 95.9; *SD* = 6.5); 84.5% were right-handed, and 49% were female. The children had diverse seizure types; 98% were medicated. Children were tested at baseline and at 24-month follow-up. Measures included the Woodcock-Johnson Tests of Achievement-Revised (WJ-R) and the Kaufman Brief Intelligence Test (K-BIT). After baseline testing, families received a NR. At 24-months, parents completed a survey of the number and duration of ES received.

Results: Data were analyzed with a 2 × 2 (Achievement x Time) Mixed Design Analysis of Variance (ANOVA). Achievement (normal achievement or underachievement) was the between-subjects variable, and Time (baseline and 24-month) was the repeated measure. ES at follow-up was significantly greater than ES at baseline (F (1, 56) = 117.61, $p < 0.0001$) for both groups. Additionally, there was an interaction between achievement status and services received, F (1, 56) = 6.47, $p = 0.014$; CWE who were underachieving received significantly more services than the normal achieving group at the 24-month testing compared to baseline, $F(1, 56) = 6.58$, $p < 0.001$.

Conclusions: These results suggest that receiving a NR might enhance the focus on the child's needs and encourage schools to provide more ES. As most of the CWE were referred by their doctors or school nurses, it is unlikely that enrollment in the study was due to a concurrent initiation of an Individualized Educational Plan at the school. Because it is possible that some parents did not share the NR with the school, our findings might underestimate the effect of a NR on ES. Neuropsychological testing might be an important facet to ensuring the educational success of CWE, but further research must examine the causal connection as well as the magnitude of the effect of this type of intervention. (Supported by NIH/NINR R01 NR 04536-01 to J.K.A.)

2.485

COMPARATIVE ANALYSIS OF HANDEDNESS IN CHILDREN WITH EPILEPSY

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Rationale: Study for handedness of patients with epilepsy is rare. A few studies suggested that left handedness is more common in children with injury in left hemisphere, mental retardation and epilepsy. We analysed correlation of handedness in children with epilepsy according to the cause of epilepsy and site of brain lesion by comparing with control group.

Methods: Subjects were 130 epileptic patients visited pediatric outpatient clinic of Pusan National University Hospital from June 2001 to August 2001. Controls were 130 children without history of convulsion or neurologic problem. We let them carry out or answer for each 10 items about the use of hand. We defined the handedness as the hand that carries out more than 5 items dominantly. We analyzed age of patient, type of seizure, cause of epilepsy and site of brain lesion in symptomatic group by reviewing the medical records in subject group.

Results: In 130 epileptic patients, left handedness were 20.0% which was higher than 4.6% in control group ($P < 0.05$). There was no statistical difference in left handedness between idiopathic epilepsy group and control group as 8.9% and 8.9%. But left handedness in symptomatic epilepsy group was 45.0% which was significantly higher than that of control group ($P < 0.05$). According to the site of brain lesion in symptomatic group, all patients with abnormality in left hemisphere showed left handedness. In cases with abnormality in both hemisphere or diffuse brain lesion, left handedness was 25.9%.

Conclusions: Left handedness was more common in epileptic patients than normal control group. This is due to high proportion of left handedness in symptomatic epileptic patients. Left handedness in children with epilepsy is more related with left side of brain lesion.

2.486

ACOUSTIC INFLUENCES OF CARBAMAZEPINE IN BENIGN ROLANDIC EPILEPSY

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Rationale: Although normal neurological and intellectual developments are expected in benign rolandic epilepsy (BRE), subtle specific interference with language functions were suspected because of the electric discharges are mainly distributed over the centrotemporal regions. Carbamazepine also can cause slowing effect on the motor conduction that induce speech problem.

The aims of this study are to investigate the language and speech problems in BRE with initiation of carbamazepine medication.

Methods: Eleven patients who met the BRE criteria by ILAE were investigated. We prospectively performed a standardized full language and speech assessment which covered all important aspects of language processing before and after medication of carbamazepine. Computerized Speech Lab used to assess the speech characteristics. Laryngeal articulation pattern, voicing analysis, habitual pitch, voice onset time (VOT) and total duration (TD), vowel formant were compared by acoustic parameters before and after 3 months antiepileptic medications.

Results: Laryngeal articulation patterns in all of the patients were the mainly substitutions. The rate of laryngeal articulation error patterns in stop consonants was increased from 12% (12/99) to 26% (26/99) after antiepileptic medication. VOT of stop consonants was not changed after antiepileptic medication. TD of word decreased after medication. Pitch range decreased from 209.9 ± 29 Hz to 206.2 ± 38Hz after medication. Energy range in spontaneous speech increased from 17.0 ± 5 dB to 19.4 ± 6 dB after antiepileptic medication. Duration of counting (5 to 9) was seen to decrease from 4.2 ± 1 ms to 3.1 ± 0.8 ms after medication. Total pitch of counting also decreased from 220.5 ± 23 Hz to 217.0 ± 18 Hz after medication. The first (F1) and second (F2) formant of vowels /a, u, o / decreased after medication. The first formant of vowel/i/and the second formant of vowel /e /increased in comparison with before medication.

Conclusions: The conclusions of the study as following: 1) The error pattern of laryngeal articulation was exclusively substitution of stop consonants. 2) Habitual pitch and vowel formants (F1 & F2) decreased after antiepileptic medication.

The formant frequency value was lower than normal control group. These finding suggestions those acoustic abnormalities after medication were similar to hypokinetic pattern. This pattern might be influenced by anticholinergic effects of carbamazepine, which decrease nerve conduction velocity and muscle activity. 3) VOT of stop consonants and TD of word were decreased after antiepileptic medication. Further studies are needed to interpretative the meaning of these finding. The results show that the therapeutic use of carbamazepine may induce speech problem. We recommend the logopedic and phoniatric evaluation of speech before/after carbamazepine medication.

2.487

BEHAVIORAL AND PSYCHOLOGICAL PROBLEMS IN PEDIATRIC EPILEPSY IN KOREA

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Rationale: Epilepsy has a significant impact on patient's normal life even in children. The purposes of this study were to: 1) reveal the incidence of various behavioral and psychosocial disturbances, 2) identify the factors related to various behavioral and psychosocial disturbances, and 3) provide better mental, behavioral and psychosocial outcomes in epileptic children.

Methods: Clinical interviews of 827 children with epilepsy (aged 2 to 18 years) at the 37 pediatric epilepsy centers were performed. The validated Korean version of neuropsychological assessment batteries including Korean Child Behavior Check List (KCBCL), Yale Children's Inventory (YCI), Family Environmental Scale (FES), Piers-Harris Children's Self Concept Scale(PCSCS) and Children's Depression Inventory (CDI) were used. T-test, Anova, and multiple regression were used to analyze data.

Results: The epileptic children with symptomatic etiology, longer duration of seizure, more frequency of seizures and larger number of antiepileptic drugs (AED), and presence of associated neurologic disorders revealed the higher incidences of internalizing, social and withdrawn behavior problems in KCBCL and of attention, aggressiveness and learning problems in YCI. However, patients with longer seizure duration, larger numbers of AEDs and presence of associated neurologic disorders showed the low self-concepts in PCSCS and higher incidence of depression in CDI.

Conclusions: We identified several risk factors for various behavioral and psychosocial disturbances in patients with epilepsy. These results provide the information for the correlations between neuropsychological problems and epilepsy in children that may be helpful in their neuropsychological supports, as well as drug treatment. (Supported by Janssen Korea Co.)

2.488

ANOMALOUS LANGUAGE REPRESENTATION PROTECTS AGAINST VERBAL MEMORY DECLINE AFTER LEFT HEMISPHERE EPILEPSY SURGERY IN CHILDREN

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Rationale: Anomalous language dominance (i.e., mixed or right cerebral dominant) is thought to be a good prognostic indicator of language function following surgical resection in the left cerebral hemisphere. Language dominance has also been used to help predict risk for postoperative verbal memory decline, but its predictive value is less well established for postoperative memory decline than for language preservation. Although left hemisphere resections have been associated with significant postoperative verbal memory decline in several investigations, this has not been established in a pediatric epilepsy surgery sample. Thus, the current multicenter investigation examined whether anomalous language dominance has a protective effect against verbal memory loss after left hemisphere resection for the control of intractable epilepsy in children.

Methods: Forty-five (21 male, 24 female) children, ages 6–16 years, who underwent resective epilepsy surgery in the left hemisphere served as subjects. Children were classified into one of two language dominance groups (Left or Non-left [mixed or right]) on the basis of Wada language evaluation: 34 children were Left hemisphere language dominant and 11were Non-left dominant. Verbal memory was assessed before and 1.8 mean years after surgery (range, 6 months -10 years) using either the Children's Verbal Learning Test or California Verbal Learning Test for Children. 78% of children were seizure-free (Engel Class I) after surgery. There were no significant differences between groups with regard to age, gender, duration of seizure disorder, location (TL vs. ExTL) of surgery, or interval between surgery and postoperative memory assessment.

Results: There was a significant pre- to post-surgery verbal memory decline (standard score [SS] pre = 84.9, post = 78.6) among the Left language group and a relative pre- to post-surgery improvement (SS pre = 72.0, post = 81.7) in verbal memory in the Non-left language children ($p = .02$). This group difference was also evident among individual cases. 68% of Left language dominant children demonstrated verbal memory decline after left hemisphere surgery while 64% of the Non-left children showed postoperative verbal memory improvement ($p = .06$).

Conclusions: Children with anomalous language representation (mixed or right dominant) have a better prognosis for verbal memory outcome following resective epilepsy surgery in the left hemisphere than children with typical (left) language dominance.

2.489

IMPAIRED MOTOR CONTROL IN PATIENTS WITH BENIGN FOCAL EPILEPSY OF CHILDHOOD

Marwan Maalouf, Craig D. Takahashi, David J. Reinkesmeyer, Daniel M. Cooper, and Jong M. Rho (Pediatrics and Neurology, UC Irvine College of Medicine, Irvine, CA)

Rationale: Recent reports have highlighted the spectrum of cognitive and behavioral impairment in patients with benign focal epilepsies of childhood (BFEC). In this study, we asked whether motor control and adaptation might also be impaired in these patients.

Methods: We assessed quantitatively the ability of 6 epileptic children diagnosed with BFEC (range, 7 to 11 years; mean $\pm$ SEM $= 9 \pm 0.1$ years) and 30 age-matched normal children (range, 6 to 12 years; mean $\pm$ SEM $= 9 \pm 0.2$ years) to perform arm movements in adaptation to novel force field constraints imposed by the Phantom Haptic Robot (PHR). The PHR is a commercially available device that allows investigators to precisely measure the trajectory and velocity of arm movements in the face of applied mechanical perturbations.

Results: Both motor performance and adaptation to perturbing force fields were significantly impaired in children with BFEC. Reaching distances (i.e., path lengths) were consistently longer in epileptic versus non-epileptic children ($P < 0.05$), and epileptic children did not adapt as well as controls to a variable perturbing force ($P < 0.05$). On the other hand, adaptive performance in epileptic children improved significantly with repeated exposure to a predictable force field.

Conclusions: In addition to cognitive problems, patients with BFEC may exhibit impaired motor control and adaptation. Our results further support the notion that certain "benign" epilepsies are not truly benign and warrant more careful clinical assessment and need for intervention.

2.490

NORMAL LANGUAGE EVOLUTION AFTER LANDAU-KLEFFNER SYNDROME

[1]Leticia L. Mansur and [2]Laura M.F.F. Guilhoto ([1]Speech Pathology, FMUSP; and [2]Neurology, Hospital das Clinicas, Sao Paulo, SP, Brazil)

Rationale: Landau-Kleffner syndrome (epileptic aphasia) is a rare disease and there are few cases with long follow-up. Most of these are the ones with worse evolution that are more linked to reference centers. Normal outcome is described in some reports but there is lack of quantitative data.

Methods: We describe three children that had typical Landau-Kleffner syndrome and their speech evolution after several yrs. of treatment. All of them were submitted to Boston Diagnostic Aphasia Examination (Goodglass et al., 2001) 7 to 13 yrs. after acute phase of the disease by a speech pathologist specialist.

Results: Three children, two girls and one boy, with normal IQ, presented acquired aphasia, with onset at 4 to 7 yrs. of age and epileptic seizures. Investigation revealed normal brain MRI, focal epileptiform activity on perisylvian area, two of them showing bilateral and continuous discharges, and all interictal unilateral temporal hypoperfusion. All patients received AED and two, corticosteroids. During follow-up all three patients had normal EEG and adequate scholastic performance. Language evaluation (Boston Diagnostic Aphasia Examination) obtained 7 to 13 yrs. after the onset of aphasia showed normal performance regarding the following items: auditory comprehension (word discrimination,

commands, complex ideational material), oral expression (repetition, responsive naming, visual confrontation naming), written comprehension and production.

Conclusions: Although several overlap of presentation may be seen in childhood epileptic aphasia, there are some typical pure Landau-Kleffner syndrome cases that may constitute the end of a spectrum pointing to a benign entity with good outcome. The presence of continuous epileptiform activity and temporal hypoperfusion present in some patients may urge to prompt acute treatment, but even in those cases normal language outcome can be present.

2.491

EFFECTS OF DURATION OF DISORDER AND SEIZURE CONTROL STATUS ON OBJECTIVE NEUROPSYCHOLOGICAL PERFORMANCE VERSUS SUBJECTIVE SELF-APPRAISAL IN CHILDREN WITH EPILEPSY

[1]Tiffany J. McCall, [1,2]Philip S. Fastenau, [1]Kathy E. Johnson, [2]David W. Dunn, and [3]Joan K. Austin ([1]Psychology, Indiana University Purdue University Indianapolis (IUPUI); [2]Psychiatry, Indiana University School of Medicine; and [3]Environments for Health, Indiana University School of Nursing, Indianapolis, IN)

Rationale: Children with chronic epilepsy have shown cognitive deficits, and some show decline with persistent seizures. Also, Hufford et al. (2000) found inaccurate self-appraisal in children with chronic vs. recent-onset epilepsy. It was predicted that objective neuropsychological performance would be lower in children with longer duration, especially for children with persistent seizures, whereas subjective self-appraisals would be equal across groups (i.e., less accurate with longer duration).

Methods: Participants (N = 141) were ages 9–16 years ($M = 11.8$; $SD = 1.8$); 49.1% were female. Duration of disorder ranged 0.6–13.6 years ($M = 6.4$, $SD = 3.7$), 16.8% were on multiple antiepileptic drugs, and 69% had active seizures. Children completed the Subjective Awareness of Neuropsychological Deficits for Children (SAND-C; Hufford & Fastenau, in press) and a neuropsychological (NP) exam. The SAND-C is a 45-item self-report measure that asks participants to rate frequency of cognitive strengths and difficulties on a 4-point scale. These measures provided two sources of cognitive performance: Objective (NP) and Subjective (SAND-C). A global composite score was calculated for each source across six cognitive domains: attention, executive functions, psychomotor ability, language, learning and memory, and visual-spatial ability. For seizure control, participants were classified as active (seizure within past 12 months) or controlled (no seizures in 12 months). A $2 \times 2 \times 2$ Analysis of Variance (ANOVA) compared the Source (subjective v. objective) by duration (short v. long) by seizure control (active v. controlled).

Results: There was a main effect for duration at the trend level, $F(1, 127) = 2.92$, $p = 0.09$, with objective neuropsychological and subjective self-appraisal scores being lower in the increased duration group for both active seizure and controlled seizure groups. Collapsing across seizure control groups in a 2×3 (Source $\times$ Duration) ANOVA, there was a main effect for source, $F(2, 138) = 4.46$, $p = 0.04$, with subjective scores being greater than objective scores. No other main effects or interactions were observed.

Conclusions: Based on these duration cohorts, it appears that both objective performance and subjective self-appraisal might be lower in children with longer duration, and this does not seem to be due to lack of seizure control. In addition, children with epilepsy seem to view themselves more positively than their actual performance reflects. The higher, yet declining, self-appraisal might reflect lack of awareness or perhaps denial of declining cognitive performance. [Supported by PHS R01 NR04536 from NIH/NINR to J.K.A. & by Epilepsy Foundation (B. Hufford).]

2.492

LAMOTRIGINE MONOTHERAPY IMPROVES MOOD IN ADOLESCENTS WITH EPILEPSY: A RANDOMIZED, DOUBLE-BLIND COMPARISON WITH VALPROATE

[1]Chris Sackellares, [2]Alain Vuong, and [2]Anne Hammer ([1]Department of Neurology, University of Florida, Gainesville, FL; and [2]Department of Neurosciences, GlaxoSmithKline, RTP, NC)

Rationale: In adolescents with epilepsy depressive symptoms are underrecognized and may interfere with education and social functioning. Lamotrigine (LTG) has been shown to be an effective maintenance treatment for bipolar disorder, with robust efficacy in the depressive phase. LTG was noted to enhance patients' mood and well-being in patients with epilepsy. The effects of LTG monotherapy on affective symptoms have not been tested in controlled trials in adolescents with epilepsy.

Methods: In a trial comparing the effects of LTG (LAMICTAL®) to valproate (VPA, DEPAKOTE®) on weight gain, mood assessments (Beck Depression Inventory, BDI; Cornell Dysthymia Rating Scale-Self Report, CDRS; Profile of Mood States, POMS) were added as secondary measures. Patients were $\geq$12 yrs with new onset partial or generalized seizures. Patients who had used LTG or VPA for >90 days prior to screen were excluded. Patients were randomized 1:1 to LTG or VPA, entered an 8 week escalation, then a 24 week maintenance phase. Results are reported here for patients 12–20 years old, the CDC definition of adolescents.

Results: LTG group: n = 18, 33% male, mean age 16 yrs. VPA group: n = 20, 45% male, mean age 16 yrs. The mean maintenance dose was 261 mg/day for LTG, 1510 mg/day for VPA. Mean baseline BDI scores showed comparable mild depressive symptoms in both groups (6.2 for LTG, 9.6 for VPA); greater score improvements were noted at weeks 10 and 32 with LTG (1.5, 2.7) than with VPA (0, 0.4). Mean baseline CDRS scores were similar in both groups (44.4 for LTG, 50.4 for VPA); greater score improvements were observed with LTG (2.1) than with VPA (−0.5) at week 32. Mean baseline POMS scores were also comparable in both groups for all domains, with 24.9 for LTG and 30.6 for VPA for Total Mood Disturbance; at week 32 a greater score improvement was noted for LTG (12.7) than for VPA (5.0). The mean screen weights were 141 lb for both LTG and VPA. The mean weight gain at weeks 10 and 32 was negligible with LTG (1.8, 1.1 lb), and significantly higher ($p < 0.05$) with VPA (7.0, 15.4 lb). Seizure control was similar in the two treatment groups (Biton et al., J. Child. Neurol. 18(2):133–139, 2003).

Conclusions: The data suggest that LTG has mood elevating effects in mildly depressed adolescents with epilepsy, and can be useful in adolescents with epilepsy and comorbid depressive symptoms without causing weight gain. (Supported by GlaxoSmithKline.)

2.493

SUICIDAL BEHAVIOR IN CHILDREN WITH EPILEPSY

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Rationale: High rates of depression in children with epilepsy (Caplan et al., 1998, in press; Davies et al., 2003; Ott et al., 2000; Dunn et al., 1999; Etinger, et al., 1998; Oguz et al., 2002) and the reported high rate of suicide in epilepsy patients (Jones et al., 2003) highlight the importance of determining if suicide occurs in children with epilepsy. A few studies of relatively small samples of children with epilepsy report that psychopathology measures (Ettinger et al., 1998), cognition (Ott et al., 2001), type of antiepileptic drug (Brent et al., 1991), but not seizure control (Ott et al., 2001) are associated with the presence of suicidal ideation or plan (SI/P). We examine suicidal behavior in a large sample of children with epilepsy and the association with psychopathology, cognition, language, and seizure variables.

Methods: The Kiddie Schedule for Affective disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997), the Child Depression Inventory (Kovacs, 1985), the Multidimensional Anxiety Scale for Children (March et al., 1997), cognitive and language testing were administered to 167 children with epilepsy (99 complex partial seizures, 68 childhood absence epilepsy) and 92 normal children, aged 5–16 years. Parents were interviewed about the child with the K-SADS, completed the Child Behavior Checklist (Achenbach, 1991), and provided demographic and seizure-related information.

Results: Although none of the patients had made a suicide attempt, the children with epilepsy (20%) had a significantly higher rate ($X^2 = 5.94$, $p < .01$) of SI/P than the normal group (9%). Among the 34 patients with SI/P, 79% had a DSM-IV diagnosis compared to 52% in those without SI/P ($X^2 = 8.16$, $p < .004$). Regarding type of psychiatric diagnosis, 21%

had disruptive disorders, 9% had major affective or anxiety disorders and 50% had combined disruptive and affective/anxiety diagnoses. In contrast, only 10% of the epilepsy patients without SI/P had combined disruptive and affective/anxiety disorder diagnoses (X^2 (3) = 29.31, p < .0001). In addition to a high rate of psychiatric diagnoses, the children with SI/P had significantly higher scores in the borderline/clinical range for total (p < .0001), internalizing (p < .001), externalizing (p < .02), and anxiety/depression CBCL scores (p < .0001), CDI scores (p < .009), and MASC scores (p < .004) than those without SI/P. Other than longer duration of illness in the patients with SI/P compared to those without SI/P (p < .005), seizure, cognitive, and linguistic variables were unrelated to the presence of SI/P.

Conclusions: Increased suicidal ideation/plan and the association with severe psychopathology in children with epilepsy with these symptoms emphasize the need for psychiatric evaluations in children with epilepsy. (Supported by RO1 NS 32070.)

2.494
SEVERITY OF FOCAL CORTICAL DYSPLASIA AND FUNCTIONAL ORGANIZATION OF THE BRAIN

Mary Lou Smith, Byron Bernal, Michael Duchowny, Catalina Dunoyer, Prasanna Jayakar, and Nolan R. Altman (Psychology, University of Ontario, Mississauga, ON, Canada; Radiology/Brain Institute; Neurosciences/Brain Institute; Brain Institute; and Radiology/Brain Institute, Miami Children's Hospital, Miami, FL)

Rationale: There is somewhat contradictory evidence for whether malformations of cortical development (MCD) may support motor, visual or cognitive function. Factors that may determine whether or not function is retained are the type of malformation and the stage of brain development at which the malformation occurs. To date, severity of MCD has not been examined as a potential causative factor. To address this possibility we examined one type of MCD, focal cortical dysplasia (CD), and compared two subtypes, distinguished by severity as defined by histopathology of surgical specimens.

Methods: Severity of CD was based on detailed histopathological analysis and cases were classified into mild (n = 9) and severe (n = 14) subtypes. Mild CD was defined by evidence of dyslamination, and severe CD by dyslamination as well as the presence of balloon cells and/or giant dysmorphic neurons. Cases were relevant to the question when the area of CD overlapped with the expected area of cortical representation of function; hence the number of cases per type of activation paradigm varied. Cortical representations of functions were established with fMRI paradigms for language (n = 7), motor (2), visual (6) and auditory function (6). Altered cortical specification for function was defined as absence of activation at expected sites, shift within the same hemisphere, transferring to the contralateral hemisphere or bilateral representation.

Results: For language paradigms, activation was absent at expected sites in 2/7 patients, with 1 showing intrahemispheric shift and 4 showing bilateral activations. For motor, visual and auditory tasks, activations at expected sites were absent on the epileptogenic side in 9/14 patients, the rest showing intrahemispheric or bilateral scatter. There was no difference between the two CD groups in terms of the number of cases showing altered cortical specification.

Conclusions: Our findings indicate altered cortical specification in almost all patients with CD. Absence of activation correlates with the epileptogenic region, but the rates of altered specification are no different between the two grades of CD. The abnormal hemisphere often retains significant language function even with severe grades of CD, a finding relevant to the planning of surgical strategies.

December 7, 2004
Plenary Session 1—Treatment of Epilepsy: Improving Outcomes with Innovative Surgical Techniques
9:00 a.m.–11:00 a.m.

December 7, 2004
PL2.01
TREATMENT OF EPILEPSY: IMPROVING OUTCOMES WITH INNOVATIVE SURGICAL TECHNIQUES

Elaine Wyllie, Ajay Gupta, William E. Bingaman, Frank G. Gilliam, Nicholas M. Barbaro, Helen Cross, and Howard Weiner (Cleveland Clinic Foundation, Cleveland, OH; Washington University, St. Louis, MO; University of California, San Francisco, CA; The Wolfson Center, Institute of Child Health, London, England; New York University Medical Center, New York, NY)

The theme of the symposium is innovative surgical techniques for epilepsy. Three topics (hemispheric syndromes, temporal lobe epilepsy, and tuberous sclerosis) will each include two topics addressed by a neurologist and a neurosurgeon. The talks on hemispheric syndromes will address: 1) selection of candidates for hemispherectomy, with emphasis on innovative approaches to difficult clinical problems; and 2) experience related to seizure outcome and complications of hemispherectomies performed in different clinical settings, and the strategy for choosing the best surgical approach. The talks on temporal lobe epilepsy will address: 1) challenges related to offering temporal resection that is substantial enough to achieve seizure control in the face of concerns about postoperative memory outcome; and 2) the data available so far from surgical trials that may have bearing on this issue. The talks on tuberous sclerosis will address: 1) the available data concerning the roles of conventional MRI, scalp EEG, PET (FDG, flumazenil, and AMT), ictal SPECT, and diffusion-weighted MRI in identifying the epileptogenic tuber(s) for resection; and 2) the overall surgical strategy for patients with tuberous sclerosis, and the experience with multi-staged procedures as a technique to identify the epileptogenic tubers that need to be resected to achieve freedom from seizures.

December 7, 2004
Plenary Session 2—Astrocytes and Epileptogenesis
9:00 a.m.–11:00 a.m.

PL3.01
ASTROCYTES AND EPILEPTOGENESIS

Jack M. Parent, Magdalena Gotz, Christian Steinhäuser, Harald Sontheimer, and Peter B. Crino (Neurology, University of Michigan Medical Center, Ann Arbor, MI; Stem Cell Institute, GSF-National Research Center for Environment and Health, Neuherberg, and Neurosurgery, University of Bonn, Bonn, Germany; Neurobiology, University of Alabama at Birmingham, Birmingham, AL; and Neurology, University of Pennsylvania Medical Center, Philadelphia, PA)

The role of astrocytes in the development of seizures and epilepsy remains elusive. This symposium will explore recent advances in understanding astrocytic contributions to normal brain development and epileptogenesis. The radial glial cell is a subtype of astrocyte now recognized as a neural stem cell that gives rise to most, if not all, cerebral neurons. The stem cell function of radial glia and their potential involvement in seizure-induced neurogenesis will be described. Astrocytes are also pivotal in the generation of hyperexcitability and seizures in many localization-related epilepsies. Astrocyte dysfunction is specifically implicated in the pathogenesis of epilepsy associated with mesial temporal sclerosis, cortical dysplasias, tuberous sclerosis and cerebral gliomas. Potential mechanisms underlying altered astrocytic function in these disorders, based upon recent studies of human tissue or animal models, will be discussed. Speakers will focus in particular on dysregulated glutamate handling and altered potassium buffering by astrocytes in epileptic brain. An improved understanding of astrocyte biology and the involvement of glial cells in epileptogenesis offers the potential for developing novel pharmacological strategies to treat epilepsy.

December 7, 2004
Platform Session D: Translational Research
3:00 p.m.–5:00 p.m.

D.01
DELETION MUTATION IN THE CHAC GENE CAUSING FAMILIAL TEMPORAL LOBE EPILEPSY

[1]Eva Andermann, [1]An Jansen, [1]Abdullah Al-Asmi, [2]Carol Dobson-Stone, [2]Anthony Monaco, [3]Anthony Lang, [4]Francine Robert, [1]Aman Badhwar, [1]Suha Mercho, [1]Francois Dubeau, [5]Adrian Danek, and

[1]Frederick Andermann ([1]Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada; [2]Monaco Group, Wellcome Trust Centre for Human Genetics, Oxford, United Kingdom; [3]Movement Disorder Clinic, Toronto Western Hospital, Toronto; [4]North Bay Genetics Clinic, North Bay, ON, Canada; and [5]Neurologische Klinik und Poliklinik-Groshadern, Klinikum der Universitat Munchen, Munchen, Germany)

Rationale: Chorea-acanthocytosis (CHAC; OMIM 100500) is a neurodegenerative disorder characterized by the gradual onset of involuntary movements, dysarthria, areflexia, seizures, and dementia, and the presence of acanthocytes in peripheral blood smears. Seizures rarely constitute a predominant or presenting feature of the disease, and have been poorly described to date. In the majority of CHAC families, the disease is inherited as an autosomal recessive trait which maps to chr 9q21, and has recently been cloned (Rampoldi et al., 2001).

Methods: We have studied 4 large French-Canadian kindreds with CHAC. Detailed medical and family histories, as well as medical records, of affected family members were obtained. Detailed biochemical tests and peripheral fresh blood smears for acanthocytes were performed. EEG, video-telemetry, MRI, volumetric and neuropsychological tests were carried out. Bloods were collected for DNA studies in 75 individuals.

Results: 11 patients in 6 sibships had clinical features of CHAC. 4 of the 6 sibships had clear parental consanguinity. 7 patients presented with epilepsy, 6 with confirmed temporal lobe epilepsy, years before developing involuntary movements including chorea, dysarthria, orofacial dyskinesia and unusual tics. The epileptic aura consisted of a sensation of déjà vu, fear, palpitation and vertigo. Epilepsy was intractable in most patients. Lamotrigine and carbamazepine worsened the involuntary movements. The patients had mood disorders and slowly progressive cognitive and memory dysfunction. EEG with video-telemetry confirmed ictal and interictal temporal epileptic abnormalities. Brain MRI showed caudate atrophy and abnormal signal in the basal ganglia. Peripheral blood smears showed acanthocytosis in all patients. Molecular tests ruled out Huntingdon disease, oculopharyngeal muscular dystrophy and MERRF. All 4 kindreds were homozygous for a large deletion mutation spanning exons 70–73 of the CHAC gene, and shared a common haplotype in the region.

Conclusions: We describe 4 French-Canadian kindreds, three of which manifested familial mesial temporal lobe epilepsy as a presenting feature, delaying the diagnosis of CHAC. Parental consanguinity, the finding of a common haplotype and a shared deletion mutation, all suggest a founder effect. CHAC represents the first gene mutation associated with the clinical features of familial mesial temporal lobe epilepsy, to our knowledge. (Supported by an operating grant from CIHR to EA)

D.02
PROGRESSION FROM FRONTAL-PARIETAL TO MESIAL-TEMPORAL EPILEPSY AFTER FLUID PERCUSSION INJURY IN THE RAT

[1,2]Raimondo D'Ambrosio, [3]Donald Born, [2]Ednea Simons, and [1,2]John Miller ([1]Neurological Surgery; [2]Neurology and Regional Epilepsy Center; and [3]Pathology, University of Washington, Seattle)

Rationale: Traumatic brain injury is the single most important cause of acquired epilepsy and often manifests itself as complex partial seizures, which are frequently resistant to treatment with antiepileptic drugs. We have recently described, for the first time, an *in vivo* model of posttraumatic epilepsy (PTE) in the rat where chronic recurrent seizures appear following a single episode of rostral lateral fluid percussion injury (rpFPI; D'Ambrosio et al., 2003). PTE was studied during the first 2 months post-injury. It was focal and seizures predominantly originated from the frontal-parietal neocortex at the injury site. However, rarer bilateral seizures originating from a different and undefined focus were also observed. To shed light on the posttraumatic epileptogenic mechanisms and on the generation of bilateral seizures, we studied rats up to 7 months post-injury.

Methods: Severe in vivo rpFPI was induced in 32–35 days old Sprague Dawley male rats. Chronic electrocorticography (ECoG) with 5 epidural electrodes placed on frontalparietal and parietal occipital cortex, or paired epidural- and depth electrode recordings (in anterior and posterior ipsilateral hippocampus) were performed from 2 weeks to 7 months post-injury. Data are shown as mean ± standard error.

Results: Two epileptic foci were identified with different temporal evolution. The firing rate of the frontal-parietal neocortex was 2.04 ± 0.49 events/hour at 2–4 weeks and remained constant at 2.05 ± 0.86 events/hour at 17–18 weeks and at 2.6 ± 1.53 events/hour at 27–28 weeks post-injury. Conversely, the hippocampal firing rate was 0.090 ± 0.026 event/hour at 2–4 weeks and increased to 2.94 ± 1.25 at 26–27 weeks post-injury. The most common ictal behavioral at 2–4 weeks post-injury was stereotyped freeze-like pauses, sometimes followed by facial automatisms, and without loss of body posture. However, the ictal behavior 5 months post-injury typically consisted of stereotyped complex partial seizure with loss of posture with or without contralateral ictal limb dystonia.

Conclusions: These results demonstrate for the first time that rfFPI-induced frontal-parietal epilepsy progresses to a multi-focal form of mesial-temporal lobe epilepsy. In addition, the different temporal evolution indicate distinct epileptogenic mechanisms at work in cortex and hippocampus. The data also extend the observed similarities between rpFPI-induced PTE and the human posttraumatic condition and further validate it as a clinically relevant model of PTE for antiepileptic and antiepileptogenic drug screening.

1) D'Ambrosio, Fairbanks, Fender, Doyle, Born, Miller (2003) Posttraumatic epilepsy following fluid percussion injury in the rat. Brain. 2003 Nov 7 [Epub ahead of print]. (Supported by NIH/NINDS, grant NS 40823 (RD).)

D.03
ENVIRONMENTAL ENRICHMENT REVERSES THE IMPAIRED EXPLORATIVE BEHAVIOR AND ALTERED GENE EXPRESSION INDUCED BY EARLY-LIFE SEIZURES

[1,2]Sookyong Koh, [2]Hongjing Xia, [1]Hyokwon Chung, [1]Amit Mahadevia, and [1]Amanda L. Young ([1]Pediatrics, Children's Memorial Hospital; and [2]Neuroscience, CMIER/Northwestern University, Chicago, IL)

Rationale: Behavioral problems, school failure and memory impairment are common among children with epilepsy. No effective treatment exists to promote recovery and neuron regeneration after seizures; currently used antiepileptic drugs only prevent further seizures. Growing evidence suggests that a stimulating environment and rehabilitation enhance recovery from neuronal injury. We investigated the efficacy of environmental enrichment in reversing seizure-induced changes in behavior and gene expression in developing rats.

Methods: Postnatal day 20-25 LE male rats were injected with kainic acid (KA, 10mg/kg, i.p.) or saline and placed in either singly in a cage, or as a group of 8 in an enriched environment (control-isolated, KA-isolated, control-enriched, and KA-enriched). After 7–10 days, exploratory behavior in a novel environment was quantified in the open field test by counting number of squares crossed by an animal during 5 minutes and seizure susceptibility was measured by latency to KA-induced seizures. Microarray-based gene analysis was performed on total RNA isolated from hippocampi dissected from 4 animals per chip. Three independent hybridizations were performed on Affymetrix Genechip® per condition (total of 12 RAE230A profiles) and analyzed using Affymetrix GDAS, Genespring® and SAM softwares. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) was performed on select genes to confirm microarray data.

Results: Exploratory behavior in KA-isolated rats were decreased in open field while KA rats housed in enriched environment behaved similarly to controls ($n = 37$, ANOVA, $p < 0.001$). Exposure to enriched environment following KA also reversed heightened seizure susceptibility at P30. Correlated with an improvement in behavior, an effector immediate early gene and growth factor, Arc (activity regulated cytoskeletal associated protein) as well as zinc finger transcription factors, Erg (early growth response)1 and Erg4, that were decreased by KA seizures, were enhanced in KA-enriched rats. Conversely, increases in inflammation related genes (Cebpd (CCAAT/enhancer binding protein, delta), C1, C3 (complement component 1 & 3), CD74 (MHC class II antigen), Aif1 (allograft inflammatory factor 1) following seizures were reversed by rearing in the enriched environment. Quantitative RT-PCR confirmed these gene expression changes.

Conclusions: Our results show the therapeutic efficacy of environmental enrichment in reversing a decrease in exploratory behavior and an increase in seizure susceptibility after early-life seizures. These behavioral changes are accompanied by parallel changes in pro-inflammatory genes and in specific genes involved in learning, memory consolidation and cell proliferation. Our results provide an experimental basis for promoting enriching education programs for children with epilepsy. (Supported by KO8NS02068 and CURE)

D.04

ADENO-ASSOCIATED VIRUS (AAV) VECTOR-MEDIATED EXPRESSION AND SECRETION OF GALANIN IN THE PIRIFORM CORTEX PREVENTS KAINIC ACID SEIZURES

Thomas J. McCown (Gene Therapy Center, University of North Carolina School of Medicine, Chapel Hill, NC)

Rationale: Using AAV vectors it has previously been shown that in vivo expression and secretion of the neuroactive peptide galanin significantly attenuates electrically elicited, focal seizure activity and prevents hippocampal damage after kainic acid-induced seizures (Haberman et al., Nat. Med. **9**:1076,2003). However, intractable temporal lobe seizures represent the most likely application of this gene therapy. Therefore, it is important to demonstrate that limbic seizure activity can be attenuated using this gene therapy approach.

Methods: AAV vectors were constructed where the fibronectin secretory signal sequence preceded the coding sequence for galanin, and a hybrid chicken beta actin promoter drove gene expression (AAV-FIB-GAL). This construct provided a means to both express and constitutively secrete galanin. Rats were anesthetized and subsequently received bilateral stereotaxic infusions of the recombinant AAV-FIB-GAL vectors (8 X 10e12 viral particles/ml) into the piriform cortex (2 microliters/side over 20 minutes; −0.26 mm anterior to Bregma, 5.6 mm lateral, 7.8 mm vertical; N = 6). One week after the AAV-FIB-GAL vector infusions, the rats received a 10 mg/kg, i.p. injection of kainic acid, and the appearance of limbic seizure behaviors was determined.

Results: In control untreated rats (N = 5), the first class IV limbic seizure activity appeared 61 ± 5 minutes after the kainic acid injection, while the first class V limbic seizure activity appeared 86 ±10 minutes after the kainic acid injection. This seizure activity proved to be repetitive with bouts of class III seizure activity that evolved to class V seizures. For the AAV-FIB-GAL treated rats, wet dog shakes first appeared 51 ± 3 minutes after the kainic acid treatment, and continued sporadically throughout the observation period. These animals also exhibited hyperactive and stereotyped behaviors throughout the observation period. However, in marked contrast to the controls, none of the AAV-FIB-GAL treated animals exhibited any class IV or class V seizure activity over a period of 240 minutes post-kainic acid treatment. Furthermore, only one of the five animals exhibited a single, brief class III seizure 129 minutes after the kainic acid treatment.

Conclusions: AAV vector transduction of the piriform cortex and subsequent expression and secretion of the neuroactive peptide, galanin prevented limbic seizure activity evoked by peripheral administration of kainic acid. Thus, this gene therapy approach can effectively attenuate limbic seizure activity. (Supported by NINDS grant 35633 to TJM.)

D.05

EFFECT OF STATUS EPILEPTICUS AND INTERICTAL DISCHARGES ON VISUAL-SPATIAL MEMORY AND LEARNING IN THE RAT

Meghana Raghavendra, Qian Zhao, and Gregory Holmes (Neurology, Dartmouth Medical School, Hanover, NH)

Rationale: Prior studies from our laboratory have demonstrated that status epilepticus (SE) at postnatal (P) 20 results in significant impairment in visual-spatial learning and memory in the water maze. It is not known whether interictal discharges contribute to this cognitive impairment. Our first goal in this study was to determine if SE in immture rats results in impaired visual-spatial memory in the radial eight-arm maze and second, to determine whether interictal discharges influence cognitive ability.

Methods: Rats (n = 6) underwent lithium-pilocarpine-induced SE at P20 while controls received normal saline (n = 10). On P60, electrodes were implanted in both the SE and the control groups. A recording electrode was implanted in the right CA1 area and the stimulating electrode in the contralateral ventral hippocampus. After a period of one month, the rats were pre-tested with gradually increasing intensity of stimulation. Stimulation at 1 Hz, with a duration of 0.2 millisecond and intensity 50–80 microamperes produced a population spike with an amplitude of 3 millivolts.The rats were monitored for five minutes after this stimulation to confirm there were no afterdischarges. Rats then underwent training in the radial eight-arm maze. To mimic interictal spikes a set of control rats received continuous 1 Hz stimulations using an current sufficient to induce a 3 millivolt population spike through the stimulating electrode during the training pattern while other control rats were not stimulated.

Results: Rats with SE showed considerably impaired performance in the radial eight arm maze as compared to the control rats. In control rats receiving 1 Hz stimulations there was a significant impairment in performance in the radial eight-arm compared to non-stimulated controls.

Conclusions: SE in P20 rats results in substanial impairment in visual-spatial memory in the radial eight-arm maze ($p < 0.05$). In addition, interictal discharges impaired learning and memory in this behavioral task. Our findings suggest that interictal epileptiform discharges can impair visual-spatial memory. However, even in the absence of interictal epileptiform abnormalities SE in young rats causes cognitive impairment. (Supported by National Institutes of Health, NINDS (NS044296 and NS41595) and the Western Massachusetts Epilepsy Awareness Committee.)

D.06

REORGANIZATION OF BARREL CIRCUITS LEADS TO THALAMICALLY-EVOKED CORTICAL EPILEPTIFORM ACTIVITY

Qian-Quan Sun, John R. Huguenard, and David A. Prince (Dept. Neurology and Neurological Sciences, Stanford School of Medicine, Stanford, CA)

Rationale: Transcranial freeze lesions in neonatal rat pups produce microgyri that can be used to model human cortical polymicrogyria. The cortical area surrounding the microgyrus (paramicrogyral zone, PMG) was previously found to be epileptogenic (Jacobs et al., 1996, 1999). Inhibitory and excitatory neurons located in rodent barrel cortex are known to form functional circuits mediating vibrissal sensation. Here, we examined the hypothesis that reorganization of the barrel microcircuits occurs in the PMG, leading to sensory evoked epileptiform discharges.

Methods: We made transcranial freeze lesions in P0-P1 rats, resulting in single microgyral malformations that extended over 1-2 barrels in the face representation of the somatosensory cortex by P10. Thalamocortical slices were prepared according to methods described by Agmon and Connors. Dual whole-cell patch-clamp recordings were made from identified neurons in the barrel. Extracellular multiple-unit activities were recorded from cortex using monopolar tungsten electrodes and a Grass amplifier (bandwidth, 0.3–10 kHz). Bipolar extracellular stimuli were delivered to the VB nucleus through sharpened tungsten electrodes.

Results: (1) Single electrical stimuli applied to the thalamic VB nucleus evoked transient cortical multiunit activity (65 +/− 42 ms) in untreated thalamocortical (TC) slices from naive rats and robust paroxysmal discharges (850 +/− 100 ms) in similar slices from freeze lesioned cortex. (2) The epileptiform discharges originated from the PMG and propagated laterally, with a latency of about 100 ms, over a distance of about 5 mm. (3) The discharges were occasionally highly synchronous between two adjacent recording sites (<0.5 mm), and had a complex frequency spectrum including alpha, beta and gamma bands. (4) Paroxysmal discharge duration was significantly shortened by about 70% when slices were perfused with ACSF containing APV, and epileptiform activity was totally abolished by CNQX. (5) The cortical paroxysmal discharges did not evoke thalamic oscillations in TC slices (n = 5). (6) Raising $[K^+]_o$ from 2.5 to 5 mM and adding glutamine (0.3 mM) increased the incidence of spontaneously occurring cortical bursts discharges and the duration of the paroxysmal oscillations by 25%, and shortened the latency for horizontal propagation by 35%. (7) Dual whole-cell patch-clamp recordings

from layer 4 of barrel cortex showed a selective loss of inhibition from a subgroup of interneurons.

Conclusions: (1) Reorganization of the barrel microcircuits occurs in the PMG, leading to sensory evoked epileptiform discharges. (2) Inhibitory networks in the PMG are preferentially affected. Selective loss of inhibition from a subgroup of interneurons was likely a major factor leading to unconstrained cortical recurrent excitation and epileptiform activity in the somatosensory cortex. (Supported by NIH grant NS06477 and NS12151 from the NINDS.)

D.07

CHRONIC LOW-DOSE CORTICOSTERONE SUPPLEMENTATION ENHANCES ACQUIRED EPILEPTOGENESIS IN THE RAT AMYGDALA KINDLING MODEL OF TLE

[1]Taufik Taher, [3]Michael Salzberg, [2]Margaret Morris, [1]Rink-Jan Lohman, [1]Bianca Jupp, and [1]Terence J. O'Brien ([1]Department of Medicine, RMH; [2]Department of Pharmacology, The University of Melbourne, Parkville; and [3]The Department of Psychiatry, St. Vincent's Hospital, Fitzroy, Victoria, Australia)

Rationale: It has long been noted that temporal lobe epilepsy (TLE) patients have high rates of depression and anxiety. Recently it has been suggested that these psychiatric co-morbidities may play a role in enhancing epileptogenesis in TLE, with one possible mechanism being an effect of the associated hypercortisolaemia. The electrical amygdala-kindling model is one of the best-studied and validated models of TLE. We compared the effects of chronic supplementation with low-dose corticosterone on the number of stimulations required to reach the fully kindled state in rats undergoing electrical amygdala kindling.

Methods: Sixteen week old non-epileptic wistar rats were ovariectomized and implanted with a bipolar electrode into the left amygdala complex. After a one week recovery period one group of rats ($n = 7$) had corticosterone (CS; 3mg/100mls – approx. 4.5 mg/kg/day) added to their drinking water while in the control group saline (0.9 mg/100mls) was added. Twice daily electrical stimulations (200 mA, 1 msec duration, 50 Hz for 1 second) were applied via the bipolar electrode. With this technique, initially the stimulations result in no behavioral effects, but after repeated stimuli the rats start having increasingly prominent seizures. The number of stimulations required to reach the fully kindled state (defined as five Class V seizures) was compared between the two treatment groups.

Results: Fewer stimulations were required in the CS supplemented rats than in controls to reach the fully kindled state (32 vs 81, $p < 0.03$, Student *t*-test) and the first Class V seizure (14 vs 57, $p < 0.05$, Student *t*-test). There was a trend for less stimulations to the first seizure and the first convulsive seizure (both, $p = 0.05$). The mean length of the after discharges (electrographic seizures) was significantly greater in the corticosterone treated group ($p = 0.03$, repeated measures ANOVA).

Conclusions: These data demonstrate that low-dose CS supplementation enhances epileptogenesis in the amygdala kindling rat model of TLE. This provides support for the hypothesis that chronically elevated cortisol levels, as a result of stress, anxiety and/or depression, may facilitate the development and progression of epilepsy in patients with TLE.

D.08

DISRUPTIONS IN GLUTAMATE-GLUTAMINE CYCLING ALTER GABA FUNCTION

[1]Anne Williamson, [2]Cheryl L. Garganta, and [3]Ognen A. Petroff ([1]Neurosurgery; [2]Genetics; and [3]Neurology, Yale University School of Medicine, New Haven, CT)

Rationale: Temporal lobe epilepsy (TLE) is associated with a disruption in glutamate-glutamine cycle between neurons and glia. The effect of this disruption on synaptic functioning has not been well established. We tested the hypothesis that a disruption in glutamate synthesis from glutamine by phosphate-activated glutaminase (PAG) will alter GABAergic function by limiting the availability of glutamate for GABA synthesis by glutamic acid decarboxylase (GAD).

Methods: We used a combination of electrophysiology and mass spectrometry to test this hypothesis. Field potential studies in hippocampal slices from young adult rats were used to assess the effects of diazo-oxo-norleucine (DON), a specific PAG inhibitor, on synaptic inhibition. A parallel series of experiments were done to assess the changes in the metabolite content of incubated slices and the rate of synthesis of glutamate, glutamine and GABA using sodium 2-13C-acetate. The levels of these compounds and the degree of isotopic labeling were measured using quantitative mass spectrometry.

Results: We found that DON was associated with profound excitation with the loss of paired pulse inhibition in the dentate granule cells studied using field potential recordings. These effects were first apparent as 1) an increase in the amplitude of the population spike such that there was a shift in the threshold stimulus intensity and 2) a decrease in paired pulse inhibition at 10 ms and 150 ms, corresponding roughly with the peaks of the fast and slow IPSP. There was a $43.6 \pm 12.5\%$ decrease in PPI at 1 hour following bath application of DON, $n = 4$. In half of the slices tested, prolonged field bursts could be evoked in DON.

The responses to DON in the CA1 region were different from those seen in the dentate in two respects. First, while we saw a similar increase in the amplitude of the population spike and a reduction of paired pulse inhibition 1 hour following bath application of DON, we never saw the prolonged fields noted in the dentate. Second, the evoked response faded completely over the course of four hours such that a single population spike could not be evoked, even in slices where there were prolonged field bursts in the dentate.

In slices treated with DON in a static bath, we found the expected decrease in glutamate and GABA content and a slight increase in glutamine content. Surprisingly, the rate of GABA synthesis was not changed by the addition of DON.

Conclusions: These data suggest that 1) there are differences in the dependence of GABA synthesis on PAG-generated glutamate between the dentate and CA1; 2) GABAergic function may be disrupted earlier that glutamatergic transmission when glutamate-glutamine cycling is impaired and 3) the levels of GABA in the whole slice may not correlate with functional GABAergic neurotransmission. (Supported by NIH grants RO1NS45792 and PO1139092)

December 7, 2004
Platform Session E: Clinical Neurophysiology
3:00 p.m.–5:00 p.m.

E.01

PREDICTORS OF SEIZURE CONTROL FOLLOWING INITIAL ANTICONVULSIVE TREATMENT IN NEWLY DIAGNOSED EPILEPSY

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Rationale: Approximately 50% patients will achieve early seizure control on the first drug regimen. There is little information on predictors of success.

Methods: We have evaluated factors associated with seizure control on the first AED (defined as $\geq$12 months seizure free) in an unselected cohort of 890 adolescent and adult patients with newly diagnosed epilepsy of whom 814 were followed longitudinally. We examined demographic characteristics, prior medical history, family history of epilepsy, seizure characteristics (including, duration of seizures, number of seizures prior to first AED, seizure semiology, seizure clusters and status epilepticus), and results of neurodiagnostic studies (imaging and EEG) to identify predictors of seizure control. Multivariate Cox proportional hazard models adjusting for age were constructed.

Results: There were 178 adolescents (21.9%) and 92 (11%) people age 65 and older. There were 422 males (51%). Generalized tonic clonic seizures occurred in 670 cases (82%), partial seizures in 135 (16%), and other seizure types in 9 (2%).

Table 1. *Multivariate cox proportional hazards regression for predictors of remission among 814 subjects with newly diagnosed epilepsy treated with a first AED*

Factors	Rate Ratio	95% CI
One sz before 1st AED	1.5	0.9–2.5
Two szs before first AED	1.4	1.04–1.9
3–5 szs before 1st AED	1.4	1.04–1.8
6–10 szs before 1st AED	1.1	0.8–1.6
11–20 szs before 1st AED	0.95	0.6–1.4
>20 szs before 1st AED	1	Referent
History of sz cludters	0.35	0.1–0.8
No history of sz clusters	1	Referent

Etiology was identified in 247 (30.3%). Only number of pretreatment seizures and a history of seizure predicted seizure control. The likelihood of seizure control increased with decreasing number of pretreatment seizures and when there was no history of seizure clusters.

Conclusions: Frequency and pattern of seizures were the only predictor of seizure control with the first anticonvulsant regime in this large cohort of newly diagnosed patients. Etiology, seizure type, and demographic characteristics were not predictive. This suggests that seizure severity and response are determined prior to initial therapy.

E.02

EPILEPTIFORM EEG CHANGES. FREQUENCY IN A POPULATION BASED INCIDENCE COHORT OF UNPROVOKED SEIZURES

Elias Olafsson, W. Allen Hauser, Petur Ludvigsson, Dale Hesdorffer, and Olafur Kjartansson (Department of Neurology, Landspitali University Hospital, Reykjavik, Iceland)

Rationale: Epileptiform changes on EEG are frequently important for the diagnosis of epilepsy. Very little has been reported on the frequency of EEG changes in newly diagnosed cases in the general population. We report the findings of a population based incidence study of unprovoked single seizures and epilepsy in Iceland. We present the relative distribution of epileptiform EEG changes.

Methods: Cases were identified through a surveillance system which screened all health care facilities in Iceland during the 39 month study period. We have analyzed the frequency of epileptiform activity based on the gender, seizure type, age at onset, etiology and epileptic syndrome.

Results: Overall 31% of all had epileptiform activity with the highest proportion seen among children. EEG findings by age group are presented in table.

Epileptiform changes in newly diagnosed unprovoked seizures

Age groups	0–15	16–64	≥65	All
	n = 145	n = 244	n = 112	n = 501
EEG results				
Normal	39%	49%	21%	40%
Epileptiform pattern	60%	22%	13%	31%
Slow activity only	1%	17%	31%	15%
Not done	1%	12%	35%	14%

Conclusions: We present a population based study which describes the proportion of newly diagnosed seizures and epilepsy who have epileptiform changes on EEG. The results are useful when evaluating the usefulness of EEG as a diagnostic tool for individuals with newly diagnosed epileptic seizures. (Supported by the National Institute of Health)

*Abstract E.03 has been withdrawn.

E.04

THE CONTRIBUTION OF HIPPOCAMPAL DEVELOPMENTAL CHANGES (HcDC) TO EPILEPTOGENICITY: A SEEG STUDY OF 15 PATIENTS WITH FOCAL EPILEPSY

Demet Kinay, Eliane Kobayashi, Andrea Bernasconi, Neda Bernasconi, Frederick Andermann, Jean Gotman, Andre Olivier, and Francois Dubeau (Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada)

Rationale: Abnormal hippocampal shape and orientation have been previously reported in patients with focal epilepsy (Baulac et al. *Ann Neurol* 1998;44:223–233). Typical MRI appearance consisted of incomplete folding of the hippocampus (Hc) with abnormal medial location along the choroid fissure, globular shape or verticalization. The purpose of this study is to assess the epileptogenicity of HcDC through evaluation of depth electrode recording (SEEG).

Methods: We retrospectively analyzed all epileptic patients (n = 69) who had at least bilateral temporal lobe depth electrode implantation between 1995 and 2003. We performed hippocampal volumetric study and analysis of the hippocampal shape and orientation abnormalities and reviewed interictal and ictal SEEG findings. Fifteen of 69 patients were found to have abnormal shape and orientation of the Hc (unilateral in 10 cases and bilateral in 5, hence there were 20 Hc with HcDC and 10 without). Eleven had extratemporal depth or peg electrodes in addition to temporal implantation.

Results: Fifteen patients (7 men) with HcDC were studied. Eight had only HcDC on MRI. Seven also had extraHc lesions: three had ischemic lesions in the posterior quadrant and four periventricular nodular heterotopia. There was concomitant hippocampal atrophy in nine (unilateral in 6 and bilateral in 3). Ictal semiology suggested widespread or multifocal neocortical involvement with temporal predominance in nine and extratemporal in six patients. Surface EEG interictal findings were mainly temporal, but ictal onsets were predominantly bilateral or widespread.

Eighteen (90%) of 20 Hc with developmental abnormality showed active interictal epileptiform abnormalities (IEA) during SEEG whereas five of 10 without such abnormality had IEA ($p = 0.02$, Fischer's exact test). All patients showed in addition extraHc IEA: amygdala, 12 (6, bilateral); temporal neocortex, 10 (2, bilateral); and extratemporal, 3 (1, bilateral). Eleven (55%) Hc with HcDC had ictal onset restricted to the abnormal Hc whereas only one (10%) without HcDC showed this ($p = 0.02$). All patients except one however had in addition seizure onsets involving other temporal or extratemporal structures.

Conclusions: In a highly selected group of patients with intractable focal epilepsy we found abnormal shape and orientation of Hc in 21.7%. Although we recorded interictal and ictal SEEG epileptiform activity coming from the HcDC in the majority of patients, large and multiple epileptogenic zones were found in most (14/15). These findings suggest that HcDC have intrinsic epileptogenicity, but very likely as part of a more extensive disturbance of brain development. (Supported by the Savoy Foundation for Epilepsy and EK by the Preston Robb fellowship (MNI).)

E.05

HEART RATE ACCELERATION ACCOMPANYING EPILEPTIC SEIZURES

Richard C. Burgess, Elia M. Pestana, and Paul Shkurovich (Neurology, Cleveland Clinic, Cleveland, OH)

Rationale: We look for tachycardia as an adjunct to EEG analysis for on-line detection of epileptic seizures in our adult and pediatric epilepsy monitoring units. While acceleration of heart rate is a robust indicator of seizures, it occurs in only some patients. In temporal lobe epilepsy tachycardia occurs typically in more than 50%; an inconsistent correlation to the right hemisphere has been found. In addition, the time relationship between the tachycardia and other clinical manifestations is variable.

The pattern of tachycardia during seizures is unique in comparison with heart-rates during activities of daily living, showing an acceleration significantly higher and more abrupt (as seen in figure 1) than that in pseudoseizures. Partly to refine our tachycardia-based seizure detector, we sought to further characterize the tachycardia associated with seizures and to compare the acceleration pattern with normal controls.

Methods: Video-EEG of seizures from patients manifesting seizures accompanied by tachycardia recorded over a 3 year period were

reviewed. The EKG during each seizure and a 2–3 minute pre-ictal baseline period was converted to heart rate over a 5 minute epoch. Epochs were compared within and across patients. Handedness was determined by subjective report and by Wada testing. Side of seizure onset was determined by visual EEG analysis.

Six, healthy college-age control subjects were recruited for simultaneous EEG/EKG monitoring. The control subjects attempted to elevate their heart rates as quickly as possible during bicycle exercise and vigorous hyperventilation. Cardiotachographs of these recordings were also generated and compared with those from the epilepsy patients.

Results: Ictal tachycardia occurred in patients with both left and right temporal lobe epilepsy, as well as in patients with generalized motor activity. The tachycardia that occurred in temporal lobe epilepsy was either more abrupt or reached a higher maximum than the tachycardias induced in the control subjects. The heart rate acceleration pattern accompanying seizures was remarkably consistent within individual patients. Tachycardia was more likely during seizures with certain manifestations (e.g fear).

Conclusions: In patients with tachycardia preceding other clinical manifestations, the pattern of acceleration is remarkably consistent and unique. This signatory pattern can be used as an early indicator of epileptic seizures.

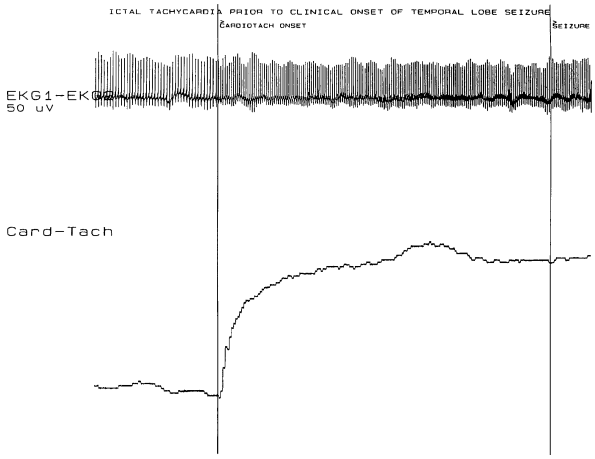

FIG. 1. In this temporal lobe seizure, the increase in heart-rate occurred approximately one and a half minutes before any clinical manifestations. (Supported by Cleveland Clinic Foundation)

E.06
DOES SCALP EEG AND IMAGING ANTICIPATE THE RESULTS OF SUBDURAL GRID EVALUATION?: A RETROSPECTIVE STUDY IN MEDICALLY REFRACTORY FOCAL EPILEPSY

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Rationale: To identify patient categories in those not proceeding to resective surgery after subdural grid evaluation (SDE), and to correlate them with the results of noninvasive investigation.

Methods: Retrospective review of medical records of all patients (n = 140, aged 15 years and over) undergoing SDE over an 8-year period at the Cleveland Clinic Foundation, when a single surgeon (WB) performed all grid placements. Patient clinical details, and results of scalp interictal and ictal EEG, cranial MRI, ictal SPECT, interictal PET, and interictal and ictal subdural grid recordings, were obtained.

Results: 25/140 patients (=17.9%) did not proceed to subsequent resective surgery; 22 were selected for further analysis. Reasons for patients not proceeding to resective surgery were (i) ictal onset confirmed over eloquent cortex (8/22 = 36.4%; Category I), (ii) no seizures despite prolonged monitoring (2/22 = 9%; Category II), (iii) complications related to grid placement (2/22 = 9%; Category III), and (iv) nonlocalizing (diffuse or multifocal) ictal onsets (10/22 = 45.5%; Category IV).

The majority of Category IV (8/10 patients) had nonlesional MRIs. A subgroup analysis compared these patients with those nonlesional MRI patients who underwent resective surgery after SDE (22 patients). A simple scoring system to quantify the degree of concordance between the remaining noninvasive investigations (ictal EEG, interictal epileptiform EEG discharges, interictal PET and ictal SPECT) was devised. The range of scores was 0 (no concordance; generalized ictal and interictal EEG) to 3 (perfect concordance; focal ictal and interictal EEG). A statistically significant difference ($p < 0.001$; 2-sample t test) was found between the mean scores of the two subgroups.

Conclusions: 55% of patients not proceeding to resection after SDE had causes that could not have reasonably been anticipated in advance (Categories I-III). Resective surgery on the remainder was precluded by diffuse, or multifocal, ictal onsets on SDE. The majority (80%) of these patients had nonlesional MRIs. A simple scoring system to quantify the localizing value and mutual concordance of four noninvasive investigational parameters (interictal and ictal EEG, PET and SPECT) delineated, on average, these patients from those nonlesional MRI patients whose SDEs subsequently allowed for surgical resection. Segregation of SDE patients into subgroups based on the noninvasive data may allow for prognostication of invasive evaluation.

E.07
SUMMATED BICOHERENCE IS SIGNIFICANTLY ELEVATED IN THE IMMEDIATE PREICTAL STATE

[1]Charles Hall, [1]Gregory Worrell, [2]Brian Litt, and [1]Terrence Lagerlund ([1]Neurology, Mayo Clinic, Rochester, MN; and [2]Neurology and Bioengineering, University of Pennsylvania, Philadelphia, PA)

Rationale: Bicoherence quantitatively measures the degree of frequency coupling in a signal. Previous studies have shown that the electroencephalogram exhibits frequency coupling that varies with state of vigilance and with seizure onset. The hypothesis tested in this study is that the degree of frequency coupling increases as seizure onset is approached from the interictal-wake state.

Methods: We studied 5 patients admitted consecutively to the Epilepsy Monitoring Unit for presurgical evaluation with intracranial depth electrodes for medically intractable temporal lobe epilepsy. This study was conducted with the approval and written consent of each patient. We collected sets of intracranial electroencephalogram in the interictal-wake state (defined as unequivocal wakefulness at least 2 hours before seizure onset or after seizure termination), the preictal-wake state (defined as unequivocal wakefulness immediately prior to seizure onset), the ictal-wake state (defined as a seizure occurring out of unequivocal wakefulness), and the interictal-sleep state (defined as slow wave sleep occurring at least 2 hours before seizure onset or after seizure termination). We performed a Kruskal-Wallis analysis to determine if the means of bicoherence summated over all frequency pairs (summated bicoherence) differed significantly between each of the above mentioned states.

Results: The summated bicoherence was significantly elevated in the preictal-wake state and the ictal-wake state with respect to the interictal-wake state in all 5 patients studied. In 3 of 5 patients, the degree of frequency coupling was significantly increased in the lead of seizure onset with respect to the other channels in the interictal-wake state. Summated bicoherence was also increased in the interictal-sleep state with respect to the interictal-wake state.

Conclusions: Our results indicate that the degree of frequency coupling in the intracranial electroencephalogram, as measured by summated bicoherence, increases progressively from the interictal-wake state, to the preictal-wake state, and into the seizure state. These results suggest that summated bicoherence may be a useful metric in a seizure probability function. We also found increased frequency coupling in the seizure onset zone. Therefore, summated bicoherence may also prove to be a useful metric in identifying epileptogenic brain regions.

E.08
CHARACTERISTICS OF MEG SPIKE SOURCES IN CHILDREN WITH INTRACTABLE EPILEPSY SECONDARY TO TUBEROUS SCLEROSIS COMPLEX

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([1]Pediatrics, Division of Neurology; and [2]Radiology, Hospital for Sick Children, Toronto, ON, Canada)

Rationale: Seizures are very common among individuals with tuberous sclerosis complex (TSC) and are often medically intractable. Epileptogenic lesions of tuberous sclerosis are the result of a complex developmental disorder of neuronal migration including cortical/subcortical tubers and areas of cortical dysplasia. As most patients with TSC have multiple potentially epileptogenic tubers and interictal scalp EEG often reveals multifocal epileptic discharges, epilepsy surgery is often discouraged. Magnetoencephalography (MEG) provides an additional tool for localization of interictal epileptiform discharges and is able to more precisely localize spike sources than scalp EEG. The primary goal of this study is to characterize MEG spike sources (MEGSS) in TSC as part of presurgical evaluation and to examine the correlations and possible divergence between MEG, EEG and MRI in TSC.

Methods: We studied seven children with TSC and intractable epilepsy. Age at MEG study ranged from 43 months to 12 years and duration of epilepsy ranged from 3–11 years. As part of presurgical evaluation, all patients underwent prolonged scalp Video-EEG monitoring, EEG single moving dipole analysis, 151 channels MEG with single moving dipole modeling and brain MRI. We defined MEGSS distribution as a cluster of $\geq$6 dipoles with less than 1 cm apart, and a scatter of <6 dipoles or more than 1 cm apart. We compared MEGSS distribution to interictal and ictal EEG findings, EEG dipole distribution and MRI.

Results: Four patients had one or more MEGSS clusters, and all patients had scattered MEGSS. The MEG distribution patterns were classified into three groups. Group A in two patients with unilateral single cluster, Group B in two patients with bilateral clusters and group C in three patients with bilateral scattered MEGSS and no clusters. Both patients in group A had a single MEG cluster that was concordant with a single epileptic region determined by EEG dipoles and ictal onset zone and a prominent tuber on MRI. Patients in group B and C had divergent epileptic regions between MEG, EEG and MRI.

Conclusions: This study provides evidence for the potential value of MEG in the presurgical evaluation of intractable epilepsy in TSC. A single MEG cluster that correlates to the interictal EEG dipole lateralization, ictal onset zone and the prominent tuber on MRI indicates a simple epilepsy network that can be surgically managed for optimal seizure control. Bilateral MEG clusters and scattered MEG dipoles with multiple tubers on MRI indicate a more complex epilepsy network involving both hemispheres.

December 7, 2004
Platform Session F: Clinical Epilepsy
3:00 p.m.–5:00 p.m.

F.01
THE FEQUENCY OF EPILEPSY AND SEIZURE DISORDERS AMONG PERSONS WITH TRAUMATIC BRAIN INJURY: A POPULATION-BASED EVALUATION OF HOSPITAL DISCHARGES AND EMERGENCY DEPARTMENT VISITS IN SOUTH CAROLINA, 1996–2001

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Rationale: South Carolina records an average of 12,500 new cases of traumatic brain injury (TBI) annually and 2.9% have a comorbid diagnosis of epilepsy and seizure disorders. Seventy-five percent were treated and released from the Emergency Department (ED). Individuals with epilepsy have an increased risk of injury, with as many as 30% reporting injuries compared to the general population. Of adults with epilepsy in the U.K. who answered questions on injuries sustained from an epilepsy attack, 22.5% reported a head injury in the previous year. In the U.S., patients with seizures may make up almost 1% of all patients seen in an urban ED, with 6% having serious trauma resulting from the seizure. However, there is no concrete, population-based, estimate addressing the rate of TBI among persons with epilepsy. This study examines the relationship between TBI and epilepsy to, 1) determine the occurrence of epilepsy among persons with TBI, 2) identify the seizure types frequently associated with brain injury, 3) characterize the demographic characteristics, and 4) identify the mechanism of injury.

Methods: We defined TBI using the standard CDC case definition and ascertained cases with ICD-9-CM codes of 800–801, 803–804, 850–854, and 959.01. All persons who visited ED or were admitted to any one of the 62 non-federal hospitals were included in the study. Cases were unduplicated using personal identifiers. Observations with a comorbid diagnosis of 345 and 780.39 were selected as cases. A random sample of 893 observations was selected for detailed medical record review and evaluations.

Results: Preliminary analysis indicates that 75,006 individuals were diagnosed with TBI. About 2.9% (2,169) have a comorbid diagnosis of epilepsy and seizure disorders. Most common comorbid diagnosis was seizure not otherwise specified (780.39), followed by grand mal seizures (345.1) and convulsive epilepsy (345.3). In 71% of the records, there was evidence of seizure. Males with seizure were 3 times more likely to experience head trauma than females. Falls were the most commonly recorded mechanism of injury. The rate of occurrence of TBI among persons with seizure disorder is nearly 11 times that of the rate noted in the general population of South Carolina.

Conclusions: These preliminary population-based findings suggest that TBI occurs at an alarming rate among persons with epilepsy. Repetitive head injuries are likely to exacerbate the seizure frequency and severity. Further study is needed to assess the specific clinical and behavioral factors that predispose persons with epilepsy to TBI. (Supported by the CDC under Cooperative Agreement # U17/CCU421926)

F.02
MAJOR DEPRESSION AND ATTEMPTED SUICIDE AS RISK FACTORS FOR INCIDENT UNPROVOKED SEIZURES AND EPILEPSY IN ICELANDIC CHILDREN AND ADULTS

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Rationale: Two prior studies in adults suggest that depression is associated with an increased risk for epilepsy. Following the diagnosis of epilepsy, some studies suggest that suicide is a more common cause of death than expected in the general population. We undertook a population-based case-control study of epilepsy in Icelandic adults and children to address whether DSM-IV diagnosis of major depression is associated with an increased risk for developing unprovoked seizures.

Methods: Population surveillance was used to identify individuals with first unprovoked seizure or incident epilepsy. Age-matched controls were selected from the population registry as the next two same sex births who were alive, resided in Iceland at the time of the index seizure, and did not have a history of unprovoked seizure on the date of the case's incident seizure. Symptoms of major depression were ascertained, using the lifetime module of the DISC for Diagnostic and Statistical Manual IV (DSM-IV) for children $\geq$3 years, and using a standardized interview based on the SCID for adults. Odds ratios and 95% confidence intervals were obtained, using logistic regression for matched sets.

Results: 387 cases and 773 controls were enrolled. Major depression (DSM IV) prior to the onset of seizures occurred in 10.6% of cases and 6.3% of controls (OR = 1.8, 95% CI = 1.1–2.8). In a multivariate model, examining individual symptoms of depression suicide attempt was associated with an increased risk for epilepsy (OR = 4.3, 95% CI = 1.6–11.9). This increased risk remained even after controlling for major depression and bipolar disorder (adjusted OR for suicide attempt = 4.2, 95% CI = 1.8–9.8). The increased risk for seizures associated with suicide attempt was present for suicide attempt with depression (OR = 4.2, 95% CI = 1.7–10.5) and for suicide attempt without depression (OR = 16.0, 95% CI = 2.0–129.2).

Conclusions: Major depression is associated with an increased risk for developing unprovoked seizures in children and adults. Coherent with some studies showing an increased risk for completed suicide following the diagnosis of epilepsy, attempted suicide is independently associated with an increased risk for developing unprovoked seizures. This is consistent with a common antecedent. Further exploration of these associations is needed. (Supported by a Grant R01 NS 32663 from the National Institutes of Neurological Disorders and Stroke)

F.03

A POPULATION BASED COHORT STUDY ON THE INCIDENCE OF FRACTURES AMONG PATIENTS WITH EPILEPSY

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Rationale: The incidence of fractures among patients with epilepsy has never been studied in a large, population-based primary-care database. The objective of this study was to assess and compare the incidence of fractures among epilepsy patients and non-epileptic control patients.

Methods: This study of a UK-based primary-care database covered a period from 1990–1998. Patients were included in the epilepsy cohort if there was sufficient evidence of active epilepsy, as indicated by either medical diagnoses or the use of antiepileptic drugs (AEDs) after the start of the General Practice Research Database (GPRD) follow-up of the practice. The control cohort comprised randomly selected patients from the GPRD without epilepsy. Two control patients were matched to each epilepsy patient by practice and index date. Study outcomes were occurences of fractures during follow-up. Fractures were identified through relevant Oxford Medical Information System (OXMIS) and Read codes. Incidence rates were calculated by dividing the number of fractures by the total number of person-years. Poisson regression analysis was used to estimate age and gender adjusted incidence density ratios (IDRs).

Results: The study population comprised 40,485 and 80,970 patients in the epilepsy and control cohort, respectively. The median duration of follow-up was about 3 years. The median age was higher in the epilepsy cohort (39.1 vs. 34.1 years), while the gender distribution was similar. In the epilepsy cohort, 3,489 fractures occurred during 143,754 person-years of follow-up, yielding an overall incidence rate of 241.9 per 10,000 person-years. This rate was about double the incidence rate of the control cohort: crude IDR 1.96 (95% CI: 1.87–2.05). The IDR decreased slightly to 1.89 (1.81–1.98) after adjustment for age and gender. When comparing IDRs among the different groups of fractures, the highest risk estimate was found for hip and femur fractures (adjusted IDR 2.79, 95% CI: 2.41–3.24). The IDRs for hand/arm, lower leg/foot and other fractures were 1.70 (95% CI: 1.57–1.84), 1.89 (95% CI: 1.70–2.10) and 1.94 (95% CI: 1.80–2.09), respectively.

Conclusions: The risk of a fracture was nearly twice as high among patients with active epilepsy compared to the general population in this population-based study in a UK-based primary-care setting. The fracture risk was highest for hip and femur. (Supported by GlaxoSmithKline)

F.04

MORTALITY IN PATIENTS WITH NEWLY DIAGNOSED EPILEPSY

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Rationale: Patients with epilepsy have increased mortality compared to the general population. Most of this excess mortality is attributable to the underlying cause of epilepsy such as brain tumours; however seizures themselves are also believed to cause death. Whether risk of death should be discussed with patients at the time of diagnosis is a controversial issue. We analysed mortality data in a cohort of 890 patients with newly diagnosed epilepsy to quantify the risk of excess mortality.

Methods: All patients diagnosed with epilepsy at the Epilepsy Unit, Western Infirmary, Glasgow between July 1981 and May 2001 were included in the study. The patient list was matched against the Death Database at the General Register Office for Scotland in August 2002. Death certificate copies were obtained for patients whose demographic information matched. All surviving patients were prospectively flagged on the National Health Service Central Register. All deaths reported till September 2003 were included in the analysis. Comparison was made with an age- and sex- matched cohort constructed from the UK Government Actuary's Departments Interim Life Tables to reflect the expected mortality in the Scottish population. Expected number of deaths was calculated by summing individual expected mortality over the study period. Observed and expected deaths were compared using a χ^2 statistic on 1 degree of freedom.

Results: Overall, 93 deaths were observed in the cohort (crude death rate 10.4%), compared 65.54 deaths expected (Rate ratio 1.41 95% CI 1.15–1.74). Kaplan Meier method with log-rank test was used to compare survival in patients with idiopathic generalised, symptomatic partial and cryptogenic partial epilepsies. Symptomatic epilepsy had the worst survival prognosis compared to both idiopathic and cryptogenic epilepsies ($p < 0.0001$). Age- and sex-specific standardised mortality ratios (SMRs) were calculated for the cohort to quantify excess mortality. The highest SMRs were seen for patients aged less than 40 years at diagnosis (SMR 4.25 95% CI 2.70–6.30, $p < 0.0001$). This was especially high in patients diagnosed with symptomatic epilepsy under the age of 40 (SMR 8.64 95% CI 3.78–13.50, $p < 0.0001$). There was significant excess mortality in patients aged <40 with idiopathic generalised epilepsy (SMR 4.62. 2.01–8.94), as the expected mortality was low in this predominantly younger group of patients.

Conclusions: Patients diagnosed with epilepsy are at significantly higher risk of dying compared to age and sex matched controls. This excess mortality is highest in younger patients, especially those with symptomatic epilepsy. Higher number of deaths was also observed in younger patients with idiopathic generalised epilepsy, suggesting that seizures themselves contribute to mortality. These factors should be taken into account while counselling patients diagnosed with epilepsy.

F.05

IS REDUCED HIFH FREQUENCY HEART RATE VARIABILITY ASSOCIATED WITH SUDDEN UNEXPLAINED DEATH IN EPILEPSY (SUDEP)?

Rita R.C. Schaumann, Nina Eppinger, Hennric Jokeit, and Gunter Kramer (Hospital, Swiss Epilepsy Center, Zurich, Switzerland)

Rationale: The experience of sudden unexpected death in epilepsy (SUDEP) obliges clinicians to consider possible etiologies and investigate possible preventing mechanisms. A reduction of the heart rate variability (HRV) has been reported in several cardiological and neurological diseases (Kamath MV et al. Crit Rev Biomed Eng 1993;21:245–311) and an association between reduced HRV and sudden death has been suggested. Several studies on HRV and epilepsy provide evidence of a sympathetic/parasympathetic dysbalance.

Methods: Central modulation of autonomic function was studied by spectral analysis of HRV. Subjects: 7 patients who died from SUDEP, 21 with epilepsy, 15 with psychogenic seizures, and two healthy drug free controls for each SUDEP patient matched for age and sex. Patients and controls underwent a 15 min standard electroencephalogram (EEG) with electrocardiogram (ECG)- channel. High frequency HRV (HF-HRV) was analyzed by an algorithm developed by Porges (Porges SW et al. Biol Psychol 1992;34:93–130). Twenty-one consecutive 30 second epochs of interbeat intervals were submitted to the polynomial filter providing estimates of HF-HRV. These estimates were analyzed by a repeated measure analysis of variance using epoch-number as within-subject factor and group membership as between-subject factor.

Results: Post hoc contrasts revealed that the SUDEP patients had significantly lower HF-HRV than epilepsy patients ($p = .045$), patients with psychogenic seizures ($p = .029$) and healthy controls (<0.01).

Discussion: Our study provides evidence that SUDEP patients have an altered autonomic control of the heart, with a reduction in HF-HRV

measures. This suggests a decreased parasympathetic tone, which may be related to drug therapy, epilepsy as such or a concomitant maturation deficit of the central autonomous network.

Conclusions: Decreased HF-HRV may be associated with an increased risk for SUDEP.

F.06

20 YEARS AFTER THE ONSET OF CHILDHOOD SYMPTOMATIC GENERALIZED EPILEPSY (SGE) THE SOCIAL OUTCOME IS USUALLY COMPLETE DEPENDENCY OR DEATH: A POPULATION-BASED STUDY

Carol S. Camfield, and Peter R. Camfield (Pediatrics, Dalhousie University and the IWK Health Centre, Halifax, NS, Canada)

Rationale: The long term social outcome is unknown for children who develop symptomatic generalized epilepsies (SGE). The seizures in SGE are typically thought to be refractory and mental handicap is frequent – features that suggest that social outcome will be poor.

Methods: We used the Nova Scotia population-based childhood epilepsy cohort to identify all children in Nova Scotia who developed SGE between 1977 and 1985. They were followed up in 2003–4. ILAE syndromes included were Lennox Gastaut, West, Myoclonic-astatic(MAE) and SGE undefined (>1 generalized seizure types including myoclonus, tonic, atonic/akinetic + slow spike wave or multifocal EEG). Social outcome was assessed using a semi-structured interview with patients and/or caretakers.

Results: 76 children developed SGE, 11% of all childhood epilepsy. Syndromes at onset were: SGE undefined 28 (37%), West 32 (42%), Lennox 4, MAE 9, other 3. During follow up, 19 died between ages 1.5 and 20 years (7/19 died <10 years old). Six (8%) were lost to follow up. For the 51 survivors, the average age of seizure onset was <2 years (1month -12 years) and follow up averaged 20 ± 6.5 years. Twenty-seven (47%) survivors had intractable seizures at the end of follow up. During the entire course 25 (40%) never had an entire year seizure free and 25 never attempted to discontinue AEDS. By the end of follow up, 21 (38%) had a terminal remission of >4 years and 18 (32%) no longer received AEDs. For social outcome we focused on the 46 patients older than 18 years at the end of follow up (average age 23 ± 3 years). 48% were unable to walk and 35 (76%) were mentally handicapped. Assessment of social outcome indicated that only 3 were living independently, although 9 were judged potentially capable. 57% still lived at home and 35% lived in group homes or institutions. Financial dependency was marked—complete dependence on parents or state in 86%. Only 5 earned enough money to support themselves. 60% required assistance with all aspects of care and 38% were spoon or tube fed. Functional reading literacy was achieved by 22% and 40% had some safety literacy. 12 (26%) were judged capable of managing their own finances. 20% were considered socially isolated, although only 8/45 (18%) had their greatest social interaction in normal community activities. Current health was considered satisfactory by 93%. None of the 19 women had become pregnant. Overall only 3 (6%) (all normally intelligent) were seizure-free, off AEDs, living independently and financially independent.

Conclusions: The social outcome of children with SGE 20 years after diagnosis is usually disappointing. Most are mentally handicapped and/or highly dependent with ongoing frequent seizures. 25% die and only a tiny percent are seizure free and independent. (Supported by Epilepsy Nova Scotia)

F.07

IDIOPATHIC GENERALIZED EPILEPSY (IGE) BEGINNING IN CHILDHOOD – HOW MANY PATIENTS ARE THERE, WHICH SYNDROMES AND WHAT HAPPENS IN THE LONG RUN? INSIGHTS FROM THE NOVA SCOTIA POPULATION-BASED STUDY

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Rationale: Idiopathic Generalized Epilepsy (IGE) is generally thought of as common and relatively benign. We examined the Nova Scotia Childhood Epilepsy Cohort to better understand the frequency of IGE syndromes and their outcome.

Methods: All children in Nova Scotia who developed epilepsy (two or more unprovoked seizures) between 1977–85 were identified from a central EEG reading facility for the entire Province (population ~850,000). Cases were followed by chart review, telephone or in person 5–20 years later. Children were included if their first two seizures occurred before age 16 years.

IGE was diagnosed when the first seizure type was absence, generalized tonic-clonic or myoclonic and the child had normal intelligence, normal neurologic examination and no alternative cause. All initial EEGs showed normal background and spontaneous or provoked (hyperventilation, photic stimulation) bursts of generalized spike-wave.

Remission was defined as seizure free and no longer receiving daily anti-epileptic medication at the end of follow-up.

Results: The entire NS cohort included 692 patients. At the time of diagnosis, there were 140 with IGE; therefore, IGE accounts for 20% of all incidence cases *of* childhood epilepsy. Among the 140 with IGE, syndromes were Childhood Absence Epilepsy (CAE) (n = 81, 58%), Juvenile Absence Epilepsy (n = 12, 9%), Juvenile Myoclonic Epilepsy (JME) (n = 14, 10%), benign myoclonic epilepsy of infancy (n = 1), IGE not otherwise defined (n = 32, 23%). The overall long term remission rate for all IGE was 55% (75/140). The remission rates by syndrome were CAE (65%), Juvenile Absence (60%), JME (14%) and IGE not otherwise defined (44%). We note that 15% of those presenting with CAE evolved over time to meet all the criteria for JME. For those with IGE otherwise not defined, the long term remission rate for those with onset ≤10 years was 71% (10/14) compared 22% (4/18) for those with onset >10 years ($p = 0.01$).

Conclusions: At the time of diagnosis, IGE accounts for only one-fifth of all childhood epilepsy and is made up from a relatively uncommon group of syndromes. Childhood Absence Epilepsy represents the majority of IGE cases. About one-quarter do not fit into a clearly defined IGE syndrome at diagnosis. Long term remission occurs in 55% of IGE with varying rates depending on the IGE syndrome. The most favorable remission rate appears to be for IGE, otherwise not defined, provided that the epilepsy begins before age 10 years.

F.08

LONG TERM PROGNOSIS FOLLOWING DISCONTINUATION OF ANTIEPILEPTIC DRUG THERAPY IN CHILDHOOD-ONSET EPILEPSY

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Rationale: The majority of children who are seizure free on antiepileptic drug (AED) therapy for 2 or more years will remain so when AEDs are discontinued. Few data are available on the long term prognosis of these children and in particular what happens to those whose seizures recur following AED withdrawal.

Methods: Between 1983 and 1990, 264 children and adolescents (median age 11.9 years) who were seizure free for a minimum of 1 year on their AEDs and who were being withdrawn from AED therapy were enrolled in a prospective study and followed. The cohort has now been followed for a mean of 15.3 years with 10 or more years of follow-up available in 248 (94%). Median age at last follow-up was 27.4 years. The distribution of etiologies was 82 (31%) idiopathic, 85 (32%) cryptogenic and 97 (37%) with remote symptomatic epilepsy. Outcomes analyzed included recurrence of seizures as well as final outcome at last follow-up.

Results: To date, 110 subjects have experienced a recurrence. Of these 86 (78%) occurred within 2 years of medication withdrawal, 13 (12%) between 2 and 5 years, 9 (8%) between 5 and 10 years and 2 (2%) more than 10 years after AED withdrawal. At last follow-up 70% of the cohort was seizure free for 10 or more years, 83% were seizure for 5 yrs and 77% were not on AEDs. At last follow-up, 3 (1%) children were still having frequent seizures and 8 (3%) were having occasional seizures (6 on AEDs, 2 off AEDs). Etiology was associated with prognosis. At last follow-up 88% of those with idiopathic etiology, 85% with

cryptogenic etiology and 78% of those with remote symptomatic etiology were >5 years seizure free ($p = 0.2$). However, at last follow-up, 85% of idiopathic, 76% of cryptogenic and 67% of remote symptomatic cases were seizure free for one or more years off AEDs ($p < 0.02$). There were 5 deaths in the cohort all of which occurred in children with severe neurological abnormalities. Of these 5, one was having frequent seizures but the other 4 were all seizure free for 6 to 11 years (2 on AEDs due to earlier recurrence, 2 off AEDs who never recurred).

Conclusions: The majority of children who are withdrawn from AEDs after a seizure free interval have a favorable long term prognosis. Late recurrences occur but are uncommon. The majority of those who do recur will reenter remission though not necessarily as soon as AEDs are restarted. (Supported by grant 1 R01 NS26151 from NINDS)

December 7, 2004
Platform Session G: Imaging
3:00 p.m.–5:00 p.m.

G.01
FLUMAZENIL PET IN CHILDREN WITH INTRACTABLE PARTIAL EPILEPSY OR INFANTILE SPASMS: DOES IT PROVIDE ADDITIONAL LOCALIZING INFORMATION?

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Rationale: Scalp ictal EEG and 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) PET are commonly used to localize epileptic foci during presurgical evaluation of children with extratemporal epilepsy. PET scanning with [^{11}C]flumazenil (FMZ) may be useful in further localizing neocortical epileptic foci, but its added clinical value has not been systematically evaluated in children who have undergone intracranial EEG monitoring. The purpose of this study was to evaluate the added localizing information of FMZ PET as compared to scalp ictal EEG and FDG PET in children with non-lesional neocortical epilepsy.

Methods: Twenty-six children (mean age: 7.3 years) with intractable partial epilepsy ($N = 19$) or infantile spasms ($N = 7$) were studied prospectively. All of them had normal MRI scans. Focal cortical areas of decreased FMZ binding were delineated objectively as regions with abnormal asymmetry and correlated with localizing information provided by ictal scalp EEG and FDG PET and, subsequently, by intracranial EEG monitoring.

Results: Decreased cortical FMZ binding was found on objective analysis in the lobe(s) of seizure onset in 20 children (77%). Sensitivity of FMZ PET was higher in children with partial epilepsy (89%) than in those with infantile spasms (43%; $p = 0.028$). FMZ PET provided additional information as compared to scalp ictal EEG findings in 14 patients (54%), including: (1) further localization of the seizure onset zone when scalp EEG onset was poorly localizing ($N = 7$); (2) identification of an additional region of seizure onset ($N = 4$); (3) and identification of an area remote from the onset with rapid involvement in seizure spread or frequent interictal spiking on intracranial EEG monitoring ($N = 3$). FMZ PET also provided localization information in addition to FDG PET in 12 patients, including: (1) showing a smaller PET abnormality that was more specific for seizure onset than corresponding areas of glucose hypometabolism ($N = 7$); (2) detecting a seizure onset area that was missed by FDG PET ($N = 2$); (3) and showing an additional area of either rapid spread ($N = 2$) or frequent interictal spiking ($N = 1$) on intracranial EEG. Altogether, FMZ PET provided localization information for intracranial EEG abnormalities in addition to *both* scalp ictal EEG *and* FDG PET in 7 patients, including 2 children with infantile spasms.

Conclusions: FMZ PET detects extratemporal seizure foci in about four-fifth of children with intractable partial epilepsy and provides independent localizing information in addition to scalp ictal EEG and FDG PET in a considerable proportion of these children. Focal FMZ abnormalities are less likely to occur in children with infantile spasms, but can still be useful in presurgical evaluation of such children. (Supported by NIH grant NS 34488)

G.02
ATYPICAL LANGUAGE DOMINANCE AND PATTERNS OF REORGANIZATION IN EPILEPSY AS ASSESSED BY A PANEL OF fMRI TASKS

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Rationale: fMRI provides a non-invasive way to assess the reorganization of language networks in patients with localization related epilepsy. We sought to identify the patterns and location of language activation in atypical language dominant epilepsy patients.

Methods: We studied 24 atypical language dominant patients (14 right handed, 7 left handed, 3 ambidextrous; 13 M, 11 F; aged 8.5–45 years), mean age of seizure onset, 8.3 years (range 0.5–29), with vEEG, MRI, and fMRI. 5 patients had mesial temporal sclerosis, 4 had stroke, 5 had tumor/dysplasia, and 10 had normal MRI. Twenty patients had a temporal lobe focus (11 left, 4 right, 1 bitemporal), 4 had an extratemporal focus (2 left, 2 right). Whole brain EPI BOLD fMRI at 1.5T, employed a box car design; the task panel included verbal fluency, category description, reading comprehension, and auditory comprehension. Data were analyzed using semi-automated methods and displayed as t-maps. Data were visually inspected and coded to determine activation in brain regions (left, right, or bilateral for frontal lobe (inferior frontal gyrus, midfrontal gyrus, or temporal lobe (Wernicke's area) regions).

Results: Seven of 24 patients (29.2%) had consistently right hemisphere lateralized language representation across brain regions; 11 of 24 (45.8%) had bifrontal, but uniformly lateralized temporal activation (5 right temporal, 6 left temporal); 3 of 24 (12.5%) had bifrontal and bitemporal activation; and, 3 of 24 (12.5) had a diaschisis where frontal and temporal language areas were represented in opposite hemispheres. Only two patients had activation outside of typical or homologous brain regions.

Conclusions: Atypical language representation is expressed within homologous language areas in the typically non-dominant hemisphere, and rarely in areas outside classic language areas. Four distinct language patterns were identified. Larger series are necessary to draw firm conclusions regarding the influence seizure focus and remote symptomatic etiology on atypical language patterns. (Supported by Clinical Epielpsy Section, NINDS, NIH and NINDS, NIH R01NS44280)

G.03
VOXEL-BASED ANALYSIS OF GRAY MATTER IN FOCAL CORTICAL DYSPLASIA

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Rationale: In patients with malformations of cortical development, there is evidence for extensive structural abnormalities beyond the visually identified lesion. In focal cortical dysplasia (FCD), histological abnormalities may be disseminated rather than confined to a single patch (Taylor et al., 1971). To date only a few structural imaging studies based on a limited number of patients have addressed the question of structural changes distant to the FCD lesion. Our purpose was to investigate gray matter (GM) changes in individual FCD patients using voxel-based morphometry.

Methods: We studied 30 patients (20 females, mean age: 26 yrs $\pm$ 8) with known FCD lesions and partial epilepsy and 39 healthy controls (21 females, mean age: 29 yrs $\pm$ 8). 20 (67%) patients underwent surgery and Taylor type FCD was confirmed by histopathology in all of them. FCD was seen on pre-operative MRI in 28 patients and in two others subtle dysplastic changes were found in the tissue removed at surgery. High-resolution MRI was acquired on a 1.5T scanner using a T1-FFE sequence (1mm slice thickness, isotropic voxels). Image processing included: (i) automated correction for intensity non-uniformity; (ii) linear registration to a standardized stereotaxic space; (iii) classification of brain tissue into GM, WM and CSF; (iv) blurring of GM masks with an isotropic Gaussian kernel (12 mm FWHM) to generate 3D-maps of GM concentration. We compared the GM map of each

subject (controls and patients) with the average GM map of all controls and obtained a GM z-score map for each individual. To detect significant differences in GM concentration, a voxel was considered abnormal if its value fell outside the mean of the controls ±4.5 SD (this cutoff was chosen to exceed the maximum GM changes seen in any control subject).

Results: Among the 28 patients with an MRI-visible FCD, z-score maps showed an increase in GM that coincided with the lesion in 21 (75%) patients. In 12/21 (57%) of them there were additional areas of GM increase distant from the primary lesion. In 7/28 (25%) patients, no GM increase was found at the FCD location. However, 5 (71%) of these patients had areas of GM increase distant from the primary lesion. In the two patients in whom FCD was diagnosed only at histopathology, areas of increase in GM were found in the region of the corticectomy. Areas of GM decrease were found in 9/30 (30%) patients.

Conclusions: Individual analysis of GM using voxel-based morphometry identified the FCD lesion in the majority of our patients. Moreover, this method allowed the detection of subtle FCD that was overlooked by visual MRI evaluation. Extra-lesional GM increase distant from the primary FCD lesion in more than half of our patients demonstrates that FCD is often associated with widespread structural abnormalities. (Supported by Epilepsy Canada Canadian Institutes for Health Research The Scottish Rite Charitable Foundation of Canada)

G.04
IMPLICATIONS OF LOW NAA/CR IN HIPPOCAMPAL EPILEPSY

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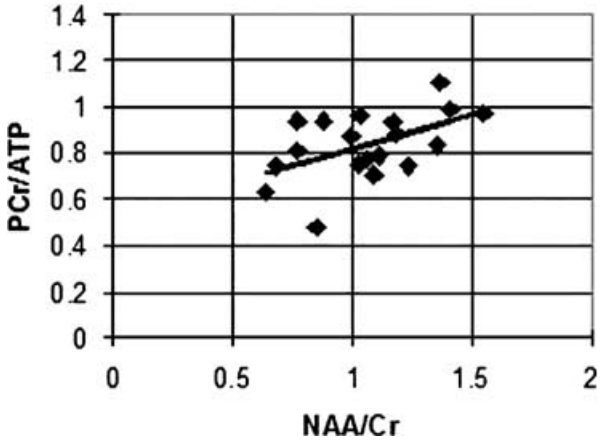
Rationale: Many studies have reported declines in NAA/Cr in the hippocampus (ipsi-worse than contralateral) in MTLE. This measure is believed to reflect neuronal mitochondrial dysfunction. Although the sensitivity and specificity of the decline in NAA/Cr for seizure lateralization in MTLE is high (>90%), few studies have reported how NAA/Cr relates to other measures, such as volumetry and neuropathology. Also, although methods exist to measure direct energetics (31P spectroscopic evaluations of PCr/ATP), no studies have evaluated both NAA/Cr and PCr/ATP in a common pool of MTLE patients. This abstract reports correlations of NAA/Cr with volumetry and neuropathology as well as 31P spectroscopic measures of energetics.

Methods: We acquired high field structural imaging, 1H and 31P spectroscopic imaging studies in $n = 19$ surgical MTLE patients together with neuropathologic measures. Hippocampal volumetry was performed using the methods of Watson and Jack. Neuropathology data included total gliosis, neuronal counts and quantitative glial fibrillary acidic protein (GFAP) staining. 1H spectroscopic imaging was performed using a 3D localized adiabatic moderate echo sequence. In a second study (acquired 30 min after completing the 1H study), the 31P spectroscopic imaging was acquired. Analysis of the 1H and 31P data has been previously described. Pearson correlations were used for analysis, $p < 0.05$.

Results: A correlation between NAA/Cr with ipsilateral volumetry was significant ($n = 18$) with $r = 0.50$, $p < 0.04$. Neuropathologically, the NAA/Cr correlated with total GFAP (averaged across CA1-3, hilus) and total glial count ($r = -0.54$, $p < 0.025$ $n = 17$ and $r = -0.50$, $p < 0.03$ $n = 19$ respectively) while it did not correlate with neuronal counts. Finally, the hippocampal NAA/Cr significantly correlated ($r = +0.52$, $p < 0.03$, $n = 19$) with amygdala PCr/ATP. The pes was similarly correlated.

Conclusions: Declines in NAA/Cr are positively correlated with direct measures of energetic state, suggesting that if mitochonodrial functionality is low, then PCr/ATP is also low. The correlations with GFAP and total glial count suggest that NAA/Cr and energetics are more related to injury, rather than direct neuronal number. The positive correlation with hippocampal volumetry suggests that the remaining tissue in an atrophic hippocampus is energetically depressed in comparison to non-atrophic tissue. These multiple correlations between the energetics (PCr/ATP), volumetry, glial and GFAP counts with NAA/Cr suggest that neuronal loss and injury are linked with energetic depression.



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G.05
HIPPOCAMPAL APPARENT DIFFUSION COEFFICIENT (ADC) FOLLOWING PROLONGED FEBRILE CONVULSION IN CHILDHOOD

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Rationale: There is mounting evidence that prolonged febrile convulsion (PFC) causes acute hippocampal oedema (prolonged T2 relaxation time and large hippocampal volume). The hippocampal diffusion characteristics associated with PFC may be useful in the understanding of the mechanisms of the oedema. In addition, the age dependency of apparent diffusion coefficient (ADC) in the hippocampus is not well characterised. Therefore the aims of the study are (1) to characterise ADC abnormalities within 5 days of a PFC, and to determine whether any such abnormalities had evolved 4–8 months later and (2) to characterise ADC age dependency in the hippocampus.

Methods: Diffusion weighted imaging, with calculation of ADC maps, was acquired in 23 patients (median age 18 months, range 7–21 months) within 5 days of a PFC, and in 14 of these children a mean of 5.5 months later. 20 control subjects (median age 12 months, range 6–39 months) were also enrolled. A region of interest was placed in the hippocampus on the ADC map and the mean ADC for the region was recorded.

Results: The PFC was generalised at the time it was first observed in all patients. 3 children had a further PFC between the magnetic resonance investigations. One patient has developed non-febrile seizures, with no associated structural brain abnormality. In control subjects there is a strong dependence of ADC on age ($p = 0.001$) but no age dependence was identified in patients at the initial timepoint ($p = 0.35$) or at follow-up ($p = 0.65$). On a paired analysis there is a reduction in ADC between the acute and follow-up investigations in patients investigated within 2 days of a PFC ($p = 0.048$), but not in those children investigated 3–5 days after the PFC ($p = 0.9$).

Conclusions: The 2 major findings in the current study are (1) the reduction in ADC over time in patients investigated within 2 days of a PFC but not in those investigated 3–5 days after the event, and (2) the difference in the age trajectory between patients and controls. The reduction in ADC over time provides additional evidence for hippocampal oedema, that is vasogenic in nature, within 2 days of PFC. The oedema has largely recovered within 5 days of the PFC. The difference in the dependence of ADC upon age in the children with a PFC, compared to control subjects, at either the initial or follow-up timepoints, supports the view that hippocampal development is abnormal in children who are prone to PFC. Understanding the cellular mechanisms for such developmental

differences may provide insight into mechanisms of a predisposition to PFC. (Supported by The Wellcome Trust)

G.06
MESIAL TEMPORAL SCLEROSIS IN CHILDREN IDENTIFIED BY MRI

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Rationale: We sought to determine the age at which mesial temporal sclerosis (MTS) can be identified using MRI in children with seizure disorders, and to assess the factors associated with MTS in children.

Methods: We reviewed records in 104 children with MTS identified by MRI performed to evaluate children with a history of seizures. MRI was performed at 1.5T and included a high resolution oblique coronal Fast Spin Echo sequence perpendicular to the hippocampal formation. MRI studies were reviewed by a pediatric neuroradiologist blinded to patient identity. Studies were scored on a scale of 1–5 (1 normal, 2 probably normal, 3 equivocal, 4 probably abnormal, 5 abnormal) for both signal and atrophy. Scans with a score of 4 or 5 for both signal and volume were determined to have MTS. Patients were identified between 1993 and 2004. Records were reviewed for associated risk factors.

Results: Mean age at age at MRI study was 8.7 (SD 4.7) with a range between 0.5 and 17.5 years; Median was 8.5, and Mode was 5 and 6 years (eleven each). 35 children were found to have MTS identified by age 5 and younger. Seven children had MTS identified before two years (four during infancy). 40 children had MTS identified between 6 and 10. 12% children had bilateral MTS; 30% had a history of febrile seizures; 14% had acute illness (CNS infection, acute encephalopathy); 12% had dual pathology (perinatal stroke, dysplasia); 6% had a history of prematurity with evidence of ischemic brain injury.

Conclusions: MTS is readily identified by high resolution MRI throughout childhood. MTS was present in one third of our patients by age 5, and may be identified during infancy. Historically MTS has been associated with risk factors that occur by age 5. Risk and causative factors may be found in nearly two thirds of children with MTS, and generally occur before age five. (Supported by NICHD 1P30HD40677)

G.07
A COMPARISON OF TWO fMRI HIPPOCAMPAL ACTIVATION PARADIGMS IN PREDICTING SIDE OF SEIZURE FOCUS IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: The success of epilepsy surgery hinges on the accurate identification of a seizure focus. Relatively few studies have examined the potential of functional magnetic resonance imaging (fMRI) in lateralizing the side of seizure focus. The purpose of this study was to compare the clinical utility of two different fMRI hippocampal activation protocols and Wada memory testing in identifying the side of seizure focus in patients with temporal lobe epilepsy (TLE).

Methods: Twenty-seven TLE patients (15 left & 12 right) who underwent Wada memory testing and preoperative fMRI were included in this study. Wada memory testing closely modeled the procedures of Loring et al. (1992). Wada memory asymmetries (WMAs) were derived by subtracting memory scores obtained by the right hemisphere (inject left) from scores obtained by the left hemisphere (inject right). Whole brain fMRI was conducted using two activation protocols that have previously been shown to produce bilateral medial temporal lobe activation in healthy individuals. In the definition naming (DN) task, patients heard a series of spoken definitions and were required to name aloud the concept to which the definition refers. In the scene encoding (SE) task, patients viewed photographs and had to decide whether they represented indoor or outdoor scenes. Appropriate control tasks were used for each activation paradigm. Region of interest (ROI) volumes were created for the anterior and posterior hippocampus. Laterality indexes (LI), reflecting the interhemispheric difference between voxel counts in the left and right ROI's, were calculated.

Results: WMA scores were significantly correlated with both the anterior ($r = .665$, $p < .001$) and posterior ($r = .433$, $p = .026$) DN fMRI LIs. No significant correlations were found between WMA scores and the SE task or between the DN and SE task (p's $> .05$). Using the anterior hippocampal ROI and an optimal LI cutoff score to predict side of seizure focus, the percent of patients correctly classified was: 78% (21/27) with the DN LI, 63% (17/27) with the SE LI, and 85% (22/27) with the WMA score. A Chi-square analysis revealed both the DN LI and WMA score were significantly better than chance ($p < .05$) in predicting side of seizure focus whereas the SE LI was not ($p > .05$).

Conclusions: Consistent with previous findings, our results show that WMA scores are predictive of side of seizure focus in TLE patients. This is the first study to use a fMRI DN paradigm for lateralizing relative memory functions in pre-operative TLE patients. This task appears to be a better measure of lateralized memory functioning than a visual scene encoding task and is relatively equivalent to Wada memory testing in its ability to accurately predict side of seizure focus. (Supported by NINDS RO1 NS35929)

G.08
PET AND SISCOM IN PATIENTS WITH COMPLICATED INTRACTABLE PARTIAL EPILEPSY

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Rationale: To assess the localization value of interictal F-18-FDG PET and Subtraction Ictal SPECT Coregistered with MRI (SISCOM, 99 Tc-ECD) in correctly determining the ictal EEG onset zone and the epileptogenic focus in patients with complicated intractable partial epilepsy.

Methods: The study consists of consecutive patients who had both PET and SISCOM because their seizures were not localized sufficiently with MRI and noninvasive video-EEG recording. Localization of PET and SISCOM was determined by two nuclear medicine specialists who were blind to other data. The locations of PET and SISCOM foci were compared with that of intracranial ictal EEG focus. We also determined the association between resection of the foci and post-surgical seizure improvement (excellent or favorable outcome; mean follow up of 17.4 months).

Results: Thirty-four patients (17 male, 17 female, mean age 26.8, range 0–50 years) were identified. Twenty-one (62%) had concordant PET and SISCOM localization (PET/SISCOM focus). Sixteen of these 21 patients (76%) had intracranial EEG recordings. Eleven out of these 16 patients (69%) had concordant intracranial ictal EEG onset. Surgical resection of the PET/SISCOM/EEG site in 9 of the 11 patients resulted in seizure improvement in 8 (89%). On the other hand, the two patients whose surgical resection did not involve the PET/SISCOM/EEG site had no improvement ($P = 0.05$).

Thirteen of 34 patients (38%) had SISCOM and PET localizations that were discordant with each other. Although 12 had intracranial EEG recordings, only 5 (42%) had intracranial seizures with localized onset.

Conclusions: Co-localization of PET and SISCOM highly predicts the location of ictal EEG onset zone. The probability of seizure improvement is very high when the region localized by PET, SISCOM and intracranial EEG is resected in patients with complicated intractable epilepsy. (Supported by Mayo Fundation for Research and Education.)