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Annual Meeting of the American Epilepsy Society
Seattle, Washington, December 6–11, 2002

December 7, 2002
Presidential Symposium—Consequences of Epilepsy: Cellular to Behavioral Perspectives
2:30 p.m.–5:00 p.m.

PS.01
CONSEQUENCES OF EPILEPSY: CELLULAR TO BEHAVIORAL PERSPECTIVES

John S. Duncan, Thomas P. Sutula, Paula Schauwecker, and Bruce Hermann (Clinical and Experimental Epilepsy, The National Hospital for Neurology and Neurosurgery, Queen Square, London, England; Department of Neurology, University of Wisconsin, Madison, WI, U.S.A.; Department of Cell & Neurobiology, University of Southern California, Los Angeles, CA, U.S.A.)

For many years, physicians reassured patients that brief seizures, while disruptive, probably had minimal or no long-term effects. This reassurance was in part based on epidemiologic studies indicating that many cases of epilepsy have a favorable long-term outcome, and both experimental and human clinical studies demonstrating that damage developed primarily after intense or continuous seizures encountered during status epilepticus. In recent years, however, a growing body of experimental, clinical, and neuropsychological evidence has suggested that this simple reassurance can no longer be provided with confidence. Although it has generally been believed that the long-term effects of brief sporadic seizures are negligible, this viewpoint has increasingly been questioned as a result of experimental observations of progressive neural damage in animal models of chronic epilepsy, high-resolution imaging studies demonstrating progressive hippocampal volume loss in some patients with epilepsy, and neuropsychological studies consistent with cumulative cognitive dysfunction that increases with the duration of poorly controlled epilepsy. Seizure-induced alterations may require long duration of observation to become apparent, as indicated by emerging evidence in human epilepsy that as long as 25 years of epilepsy may be required to detect cumulative adverse cognitive effects. There is also increasing experimental evidence that many of the cumulative damaging effects of seizures may be influenced by genetic background. This symposium will focus on emerging perspectives about the possibility that poorly controlled seizures contribute to progressive functional and cognitive declines.

December 8, 2002
Investigators' Workshop
8:00 a.m.–4:00 p.m.

IW.01
STEM CELLS AND EPILEPSY: HOPES OF EPILEPTOLOGISTS

Andreas Hufnagel (Department of Neurology, University of Essen, Essen, Germany)

The discovery of human embryonic and adult stem cells in recent years and their availability has ignited tremendous scientific efforts to determine their physiologic role and possible applications in human cell-loss diseases. Degenerative diseases of the CNS have become a major target of interest. The hippocampal formation has been identified as one region of the brain that hosts adult stem cells and participates in the generation of new neurons. Because the hippocampus frequently is also a generator of epilepsy, the role of stem cells in counteracting or perhaps even solidifying epilepsy is of particular interest. Overall the role of stem cells in epilepsy is far from clear. The objective of the investigator workshop is to provide an update on the most recent advances in this field of research. In a first approach, the physiologic (natural) role of stem cells in the hippocampus will be analyzed. Next the role of neuronal precursor cells, their proliferation, migration, and differentiation in experimental models of epilepsy will be elucidated. Finally, particular interest will be directed to the role of stem cells for neurogenesis and apoptosis after stroke and epileptic seizures, as well as their possible implications for the therapy of epilepsy.

IW.02
PHARMACOGENETICS OF ANTIEPILEPTIC DRUGS

Orvar Eeg-Olofsson (Department of Women's and Children's Health, Secion of Pediatrics, University Children's Hospital, Uppsala, Sweden)

The goal of drug treatment in epilepsy is an optimal quality of life (QOL) based on seizure freedom without side effects. However, in spite of a number of new antiepileptic drugs (AEDs), many individuals with epilepsy cannot achieve this goal. An understanding of factors of importance for individual variability would be a significant progress in this treatment, and one method is to design it based on genetic characteristics. This can be summarized under the term "pharmacogenetics." Many pharmacogenetic polymorphisms have been described (e.g., in drug-metabolizing enzyme genes, in drug-metabolizing enzyme receptors, and in drug-transporter genes). Concerning the first factor, the microsomal cytochrome *c* oxidase P450 enzymes have a basic function. Nearly 100 potentially clinically relevant CYP450 allelic variants for each enzyme involved in AED metabolism have been studied. In this workshop especially CYP2C9 and CYP2C19, involved in the metabolism of phenytoin (PHT), phenobarbital (PB), valproic acid (VPA), and diazepam (DZP), and CYP3A, involved in the metabolism of PHT, carbamazepine (CBZ), DZP, ethosuximide (ESM), felbamate (FBM), tiagabine (TGB), and zonisamide (ZNS), will be discussed. For example, a poor-metabolizer phenotype for PHT is associated with elevated levels of parent drug and exacerbated neurotoxicity. It will not be long before clinicians may choose a specific drug with a specific dosage and dosage intervals based on the clinical characteristsics and genotype of their patient. At the conclusion of this workshop, participants will be able to understand the metasbolic pathways of AEDs involving polymorphic enzymes, the pharmacogenetics of CYP450 enzymes, and how to apply pharmacogenetic concepts in clinical trials in epilepsy.

IW.03
MITOCHONDRIA, FREE RADICALS, AND EPILEPSY

Manisha N. Patel (Medicine, National Jewish Medical & Research Center, Denver, CO, U.S.A.)

To manage epilepsies effectively, it is important to understand the mechanisms underlying both seizure-induced brain damage and seizure initiation. Oxidative stress is emerging as a mechanism that may play an important role in the etiology of seizure-induced cell death. Con-

versely, epileptic seizures are a common occurrence in mitochondrial diseases arising from defects in mitochondrial or nuclear genes. Therefore, oxidative stress and mitochondrial dysfunction may be important both as a consequence and a cause of epileptic seizures. Mitochondria are the principal source of cellular energy and play a key role in the control of free radical production, cell death, fatty acid oxidation, and calcium homeostasis. Each of these vital mitochondrial functions is important for normal brain function. Mitochondrial dysfunction can therefore have a major impact on epilepsy. This session will provide an overview of the data suggesting that mitochondrial oxidative stress and dysfunction can be both a consequence and a cause of epileptic seizures. A causal role for mitochondrial oxidative stress in seizure-induced cell death is supported in part by the following examples: (a) Experimental seizures can increase mitochondrial aconitase inactivation (superoxide formation), 8-hydroxydeoxyguanosine formation (oxidative DNA damage), and lipid peroxidation (F2-isoprostane formation); (b) Mitochondrial oxidative stress is an important participant in glutamate receptor–mediated excitotoxicity, which is thought to play a critical role in epileptic brain damage; and (c) Certain antioxidants such as superoxide dismutase mimetics, vitamin C, spin traps, and melatonin ameliorate seizure-induced cell death. Epileptic seizures are a common clinical feature of mitochondrial diseases such as myoclonic epilepsy with ragged red fibers (MERRF). Defects in complex I and complex IV of mitochondrial oxidative phosphorylation, which can result in increased superoxide production, are the leading mechanism by which the tRNAlys gene mutation produces MERRF. A causal role for mitochondrial oxidative stress and dysfunction in the initiation of epileptic seizures is further suggested by the occurrence of spontaneous seizures in mice deficient in Sod2. These data suggest that mitochondria and free radicals may play an important role in seizure disorders.The workshop is designed to give epilepsy researchers an overview of the sites and control of mitochondrial free radical production and the role of mitochondria in excitotoxic cell death. (Supported by NINDS, P.A.C.E., and Partnership for Pediatric Epilepsy.)

IW.04
GLUTAMATE AND γ-AMINOBUTYRIC ACID TRANSPORTERS: REGULATION AND ROLE IN EPILEPSY

John J. Hablitz, Michael W. Quick, Michael B. Robinson, Anne Williamson (Neurobiology, University of Alabama at Birmingham, Birmingham, AL; Biology, University of Southern California, Los Angeles, CA; University of Pennsylvannia, Philadelphia, PA; Neurosurgery, Yale University School of Medicine, New Haven, CT)

Amino acid transporters play multiple roles in the nervous system. Their primary role is to maintain a low level of neurotransmitter in the synaptic cleft. γ-Aminobutyric acid (GABA) and glutamate transporters fine tune synaptic transmission and may play a key role in the imbalance between the excitation and inhibition that is the hallmark of epilepsy. These systems are quite plastic. Studies in both human patients and animal models of epilepsy have shown that a complex pattern of changes occurs in both GABA and glutamate transporter density and localization. Dr. Quick will discuss the regulation of the predominant neuronal GABA transporter, GAT1. The role of changes in the rate at which substrates are translocated and alterations in the number of functional transporters on the plasma membrane will be considered. How these changes in GAT1 function are mediated by a network of protein–protein interactions and phosphorylation events to control GABAergic signaling dynamically will be discussed. Dr. Robinson will focus on the family of genetically and functionally related glutamate transporters. These transporters utilize the Na^+–electrochemical gradient to drive the intracellular accumulation of glutamate. He will present how the activity of many of the glutamate transporters can be rapidly (within minutes) regulated by a variety of signaling molecules. The same signaling pathway has opposite effects on EAAC1/EAAT3 and GLT-1/EAAT2, suggesting that it is possible to dramatically shift the balance between neuronal and glial clearance of glutamate. Dr. Williamson will give an overview of the changes that occur in transporters in epilepsy and discuss their role in the generation and maintenance of the epileptic state. Information on the link between glutamate uptake and neural energetics will be explored, as there is a possible link between hypometabolism and changes in uptake.

IW.05
FUNCTIONAL MAGNETIC RESONANCE IMAGING OF EPISODIC MEMORY IN TEMPORAL LOBE EPILEPSY

Jeffrey R. Binder, John A. Detre, M. Jones-Gotman, and Sara J. Swanson (Neurology, Medical College of Wisconsin, Milwaukee, WI; Neurology, University of Pennsylvania, Philadelphia, PA; Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, QC, Canada)

Presurgical assessment of regional brain function is one of the most common clinical applications of functional MRI (fMRI). fMRI has advantages over current methods for determining the cerebral representation of cognitive functions in that it provides information not only about lateralization but also about localization of function within a hemisphere. Studies of memory are of particular interest because memory decline is a common sequela of anterior temporal lobectomy (ATL). This workshop will examine functional activation studies of episodic memory in epilepsy surgery candidates. Participants in this workshop should be able to discuss the correlation between memory results obtained from fMRI and the intracarotid amobarbital procedure (IAP) and the usefulness of fMRI for predicting side of seizure focus and memory morbidity after anterior temporal lobectomy (ATL). Dr. Jones-Gotman will describe the memory deficits observed in patients who are candidates for surgical treatment of their epilepsy, the pattern of memory loss that may be expected after surgery, and means of predicting possible memory decline (IAP vs. fMRI). She will show normal subject and patient results from an fMRI memory task that reliably activates the medial temporal lobe bilaterally in healthy subjects, and that in TLE patients, yields results consistent with preoperative memory deficits and IAP findings. Dr. Binder will describe memory-activation protocols and results of fMRI of memory in normal subjects. He will discuss the current data examining the use of fMRI results for predicting side of seizure focus and correlations between fMRI, IAP memory, and hippocampal volumes in epilepsy surgery candidates. Dr. Detre will discuss a variety of episodic memory tasks, including encoding of complex visual scenes, which has provided the most reliable medial temporal lobe activation. His results indicate that although the correlation between fMRI and IAP memory results was highly significant in initial studies, this has not been borne out in more extensive testing. However, a significant correlation between hemispheric memory activation asymmetry and postsurgical memory change has been observed. These findings will be discussed in the context of strategies for improving the reliability of fMRI studies of memory function in TLE and other disorders.

IW.06
FUNCTIONAL IMAGING IN SMALL-ANIMAL MODELS OF EPILEPSY

Bart P. Keogh, Scott A. Small, Imad M. Najm, Harley I. Kornblum, and Philip A. Schwartzkroin (Radiology, University of Washington, Seattle, WA; Neurology, Columbia University, New York, NY; Neurology, Cleveland Clinic Foundation, Cleveland, OH; Pediatric Neurology, University of California, Los Angeles, Los Angeles, CA; Neurological Surgery, University of California, Davis, Davis, CA,)

Various "imaging" modalities [magnetic resonance imaging (MRI), positron emission tomography (PET), etc.] have provided the technical basis for significant advances in our ability to study, diagnose, and treat epilepsy. Whole-brain imaging, in the intact organism, gives the investigator a relatively noninvasive means to carry out longitudinal assessments of brain structure and function, and to pinpoint regions of abnormality. These imaging tools have been used primarily by clinicians. However, their application to experimental models offers important methods for monitoring development and spread of seizures over time and in intact brains. This workshop highlights the potential application of a number of these imaging technologies to small-animal models (rats and mice) of epilepsy. Dr. Bart Keogh (University of

Washington) will discuss recent attempts to use functional MRI (fMRI) to localize onset and spread of seizure activity in rats. Dr. Scott Small (Columbia University) will describe modifications of this fMRI theme that allow the investigator to obtain information about the level of "baseline" function. Dr. Imad Najm (Cleveland Clinic) will discuss current applications of MR spectroscopy for identifying metabolic features of epileptic brain. Dr. Harley Kornblum (UCLA) will present new developments in the use of "micro-PET" in small-animal models of epilepsy. These workshop participants have been asked not only to describe these techniques, but also to discuss a number key questions regarding their implementation in rats and mice: What are the spatial and temporal resolutions of these techniques? What are the problems in co-registering functional imaging data with EEG and structural imaging data? What is really being measured, especially with respect to seizure (i.e., electrical) activity? And how should these imaging data be interpreted: that is, what are these techniques good for in the experimental epilepsy laboratory?

IW.07
STEROID HORMONES AND EPILEPSY
Stephen Matthews, Serge Rivest, Dominique Toran-Allerand, Libor Velísek, and Jana Velísková (Physiology, University of Totonto, Toronto, ON, Canada; Anatomy and Physiology, Université Laval, Québec, Canada; Anatomy and Cell Biology, Columbia Univeristy, New York, NY; Neurology and Neuroscience, Albert Einstein College of Medicine, Bronx, NY)

At the conclusion of this session, participants will be able to discuss positive and adverse effects of corticosteroids and estrogens on brain development and function with reference to seizures and epileptogenesis. Steroid hormones have controversial effects during the brain development. Low levels of developmental corticosteroids are required for genesis and maintenance of certain brain areas, such as dentate gyrus granule cell layer and hippocampal pyramidal cell survival. However, excess of corticosteroids may induce neurodegeneration as shown in hippocampal CA1 pyramidal cells. There is almost no information on the effects of increased prenatal corticosteroids and postnatal outcome. Estrogens may help to determine sexually dimorphic features of brain nuclei during brain development. Later, estrogen excess may become harmful for the brain in terms of increased seizure propensity, yet low doses of estrogens rendering plasma levels similar to physiologic values may have significant neuroprotective effects in seizure-induced brain damage. In this session, Steve Matthews will address issues of how prenatal administration of corticosteroids may alter programming of the developing brain. Serge Rivest will discuss inflammatory response of glucocorticoids in the brain and its relevance for neuronal plasticity and epilepsy. Libor Velisek will show examples of adverse effects of prenatal corticosteroid administration in the rat on seizure susceptibility and behavior of the exposed offspring. Dominique Toran-Allerand will reveal developmental functions of estrogens mediated via a novel estradiol-sensitive and ICI 182 780–insensitive receptor type, designated estrogen receptor-X. Jana Velísková will show that in the adult female rats, small doses of estrogens may have significant neuroprotective effects after status epilepticus, and she will discuss the mechanisms that may be involved. The participants will consider relevance of their data for mechanisms of developmental epileptogenesis and for future research directions. (Supported by NIH, MRC, and private foundations.)

IW.08
RADIOSURGICAL TREATMENT OF EPILEPSY: BASIC SCIENCE AND CLINICAL MECHANISMS
Nicholas M. Barbaro, Jean M. Regis, Kevin S. Lee, and Ajay Niranjan (Neurological Surgery, UCSF, San Francisco, CA; Stereotactic and Functional Neurosurgery, Timone Hospital, Marseilles, Orsay, France; Neuroscience, University of Virginia, Charlottesville, VA; Neurosurgery, University of Pittsburgh, Pittsburgh, PA)

Radiosurgery offers a noninvasive technique of potential use in the treatment of patients with epilepsy. Recent studies have provided evidence that highly focused radiation reduces neuronal hyperexcitability and eliminates seizures in animal models of epilepsy. Preliminary data are also available from studies on humans suggesting that radiosurgery reduces or eliminates seizures in patients with hypothalamic hamartomas and mesial temporal sclerosis. The speakers in this symposium will present basic and clinical studies that provide evidence for a role of radiosurgery in the treatment of epilepsy. These studies include the reduction of seizures in animals with seizure foci induced by kainic acid microinjection and in the spontaneous limbic epilepsy model. Data from studies in rodents suggest that this effect can be produced with little or no effect on learning and behavior and with minimal changes in basic physiology or histologic morphology. Human data from European and U.S. studies will be reviewed, including effects on the radiologic appearance of the brain after radiosurgical treatment, the clinical effect on simple partial and complex partial seizures, as well as on neuropsychological testing. Rodent studies indicate that a significant effect on seizures can be obtained at "subnecrotic" doses, whereas human data suggest that a significant reduction in seizures only occurs after radiologic evidence of tissue damage. Whether these changes represent actual "radiation necrosis" or simply temporary changes in vascular permeability is not known. The speakers in this symposium will discuss the areas where further research is needed to answer the important remaining questions regarding the role of radiosurgery in the treatment of patients with seizures. This includes the exact mechanism(s) whereby high-dose radiation exerts an antiepileptic effect, whether there is a "subnecrotic" dose that is effective in humans, and whether radiosurgery may be useful in treating brain regions outside of the temporal lobes. [Supported by National Institutes of Health (NINDS), Elekta Corporation.]

December 9, 2002
Poster Session 1
11:00 a.m.–5:00 p.m.

Nonhuman/Mechanism Studies

1.001
SPECIFIC INCREASE IN NPY CONTENT OF THALAMIC RETICULAR NEURONS AFTER PROLONGED VALPROIC ACID TREATMENT IN RATS: A POTENTIAL ANTIEPILEPTIC MECHANISM
Michelle A. Lee and John R. Huguenard (Department of Neurology & Neurological Sciences, Stanford University, Stanford, CA)

Rationale: Valproic acid (VPA) has well-established efficacy in the treatment of both generalized and partial seizures, neuropathic pain, migraine, and some psychiatric disorders. Some of the proposed actions for VPA, including augmentation of γ-aminobutyric acid (GABA)ergic responsiveness or attenuation of *N*-methyl-D-aspartate (NMDA) responses, are consistent with its clinical effects, but not its therapeutic effects on nonconvulsive absence seizures. The reticular thalamic nucleus (RTN) is a shell-like group of inhibitory neurons that plays a key role in thalamocortical rhythm generation that is relevant to sleep and absence epilepsy. Previous studies support an endogenous anticonvulsant role of neuropeptide Y (NPY, which is coexpressed with GABA in RTN neurons), and we have found that application of exogenous NPY to thalamic slices results in a suppression of epileptiform activity. In this study we investigated whether the antiepileptic properties of VPA may be in part mediated by increased expression of the putative endogenous anticonvulsive substance NPY. **Methods:** VPA (200 mg/kg in 3 ml/kg H_2O) was administered to P32 to P47 rats every 8 h for 4 days via intraperitoneal injections. Control rats received equivalent doses of the structurally related but therapeutically inactive compound n-octanoic acid (OA). After prolonged treatment the animals were killed, perfused, and the brains were sectioned and processed for

immunohistochemical analysis. Using scanning laser confocal microscopy, we qualitatively surveyed the effects of VPA on NPY levels in rat cortex, thalamus, and RTN, and quantitatively examined the effects on NPY levels in RTN. For controls, we examined the immunostaining of two other thalamic neuropeptides, vasoactive intestinal peptide (VIP) and somatostatin. To quantify peptide content, we used the approach of semiautomatically locating and identifying individual neuronal somata via NeuN staining, and then assessing NPY, VIP, and SST levels on a per-neuron basis. **Results:** Prolonged VPA administration significantly increases the levels of NPY in cortical interneurons and RTN neurons compared with OA-treated rats. We found an increase of >30% in RTN cells, and a prominent expression in RTN axons that was rarely if ever observed in naïve or OA-treated animals. By contrast, levels of VIP and SST were similar in OA- and VPA-treated animals. These results were replicated in four separate OA/VPA matched trials. **Conclusions:** The marked specific increase in NPY-like immunoreactivity in RTN cells and cortical interneurons after VPA treatment, along with our recent evidence for an endogenous antiepileptic role of NPY (Y1 receptor antagonists enhance and agonists suppress thalamic epileptiform activity) suggests that the therapeutic effects of VPA and related compounds may be due in part to a specific upregulation of this endogenous antiepileptic peptide in neurons. RTN cells prominently and uniformly express NPY, and these data provide further support a role for this neurotransmitter in regulation of thalamocortical seizure activity. (Supported by NIH grants NS06477 and NS34774 from the NINDS.)

1.002

ALTERATION OF SODIUM CHANNEL EXPRESSION IN THE ENTORHINAL CORTEX OF PILOCARPINE EPILEPTIC RATS

Newton Agrawal, David Ragsdale, and Angel Alonso (Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada)

Rationale: Recently we demonstrated that principal neurons of the entorhinal cortex (EC) of pilocarpine epileptic rats display an increase in tetrodotoxin (TTX)-sensitive voltage-dependent persistent sodium current (INaP) relative to age-matched controls. Activating at subthreshold potentials and having very slow inactivation, INaP has been proposed to contribute to subthreshold oscillations, excitability, and epileptogenesis. In this study, we investigated whether the physiological increase in INaP was due to plasticity in levels of sodium channel message and/or levels of protein expression after the silent period, afterstatus epilepticus. **Methods:** Male Long–Evans rats were made epileptic with a lithium–pilocarpine protocol consisting of LiCl (3 mEq/kg, 24-h pretreatment), scopolamine methylbromide (1 mg/kg), and pilocarpine hydrochloride (30 mg/kg), with a final postapplication of diazepam (DZP; 1 mg/kg) 2 h after status epilepticus (SE). Only animals that displayed SE were selected for the epileptic population. Control animals were treated identically except with the administration of saline instead of pilocarpine. Horizontal brain slices (400 μm) were prepared, the EC layers were dissected out for (a) total RNA isolation and extraction and (b) protein extraction. Semiquantitative reverse transcription–polymerase chain reaction (RT-PCR) was performed for brain sodium channel α-subunit subtypes Nav1.1, 1.2, 1.3, and 1.6; Western blot analysis was performed for the same subtypes as well as for sodium ®-1 and ®-2 subunits. Only rats at ~10 weeks after pilocarpine and their age-matched controls were studied. **Results:** Our preliminary results indicate changes in the expression of sodium channel α subunit type III, with no detectable significant changes in the other subunits ($n = 4$). Semiquantitative real-time RT-PCR is being carried out to confirm these results. **Conclusions:** These data may indicate that changes in the expression of sodium channels in the EC of the pilocarpine epileptic rats may be correlated with an upregulation of INaP. The increase in plasticity of the persistent sodium current may contribute to neuronal hyperexcitability in the temporal lobe. Identification of localized sodium channel protein targets may help in understanding or developing improved drug therapies for the treatment of temporal lobe epilepsy. (Supported by the Canadian Institutes for Health Research, the Medical Research Council, and the Savoy Foundation. Newton Agrawal was supported by a fellowship from the Savoy Foundation.)

1.003

A NOVEL MECHANISM UNDERLYING PHARMACORESISTANCE IN CHRONIC EPILEPSY: REDUCED PHARMACOSENSITIVITY OF VOLTAGE-DEPENDENT SODIUM CHANNELS

Stefan Remy, Jian Chen, Siegrun Gabriel, Thomas N. Lehmann, Christian E. Elger, Uwe Heinemann, Albert Becker, and Heinz Beck (Epileptology, University of Bonn Medical Center, Bonn; Physiology, Charité, Berlin; Neurosurgery, Charité, Berlin; Neuropathology, University of Bonn Medical Center, Bonn, Germany)

Rationale: Insensitivity to anticonvulsant drugs (AEDs) is a crucial problem in the treatment of epilepsy, but the underlying mechanisms are unknown. We have tested whether pharmacoresistance might be due to reduced pharmacosensitivity of one major target of AEDs, the voltage-dependent sodium channel. **Methods:** We examined changes in the sensitivity of voltage-dependent sodium channels in hippocampal dentate granule cells to carbamazepine (CBZ) in both human and experimental epilepsy by using patch-clamp techniques. We also determined the sensitivity of seizure activity elicited in vitro to CBZ in human hippocampal slices from epilepsy patients with differing clinical responsiveness to this drug. **Results:** First, we demonstrated that the use-dependent block of sodium channels by CBZ that normally leads to frequency-dependent inhibition of sodium channels is completely lost in hippocampal dentate granule neurons, both in experimental epilepsy and in epilepsy patients clinically resistant to CBZ. Similarly, seizure activity induced in human hippocampal slices is virtually unaffected by CBZ in patients with CBZ-resistant epilepsy, but not in patients clinically responsive to this drug. The changes in sodium channel pharmacosensitivity in experimental epilepsy are associated with downregulation of the accessory β1 sodium channel subunit as well as the pore-forming Nav1.2 and Nav1.6 subunits in dentate granule neurons, determined by using real-time polymerase chain reaction (PCR). Expression of Nav1.1, Nav1.3, and Nav1.5 subunits was not significantly altered. **Conclusions:** These data suggest that the loss of sodium channel CBZ sensitivity may underlie the markedly diminished capacity of CBZ to inhibit high-frequency firing and seizure activity in pharmacoresistant epilepsy, with the molecular basis for this change remaining elusive. Nevertheless, development of compounds acting on altered sodium channels may be a promising approach for rational drug design in chronic epilepsy. (Supported by SFB 6006, Graduate Program of the DFG "Pathogenesis of central nervous diseases," Joint German-Israeli Research Program of the MOS and BMBF/DLR.)

1.004

DEFICIT OF A-TYPE POTASSIUM CHANNEL CONTROL OF DENDRITIC EXCITABILITY IN CA1 PYRAMIDAL CELLS IN EXPERIMENTAL EPILEPSY

Christophe Bernard, Nicholas Poolos, and Daniel Johnston (Division of Neuroscience, Baylor College of Medicine, Houston, TX)

Rationale: Three mechanisms are believed to underlie highly synchronized discharges in large groups of neurons during seizures: (a) alterations of the intrinsic membrane properties of neurons that would make them pathologically hyperexcitable; (b) increase in glutamatergic excitation, and (c) decrease in γ-aminobutyric acid (GABA)ergic inhibition. Because dendrites play an active role in the processing and propagation of synaptic inputs via the activation of voltage-gated Na^+, K^+, and Ca^{2+} channels in control tissue, we have begun to investigate the fate of these dendritic channels in experimental temporal lobe epilepsy (TLE). K^+ channels are ideally located to control pyramidal neuron excitability. Previous work has demonstrated that there is a very high density of transient, A-type K^+ channels in CA1 pyramidal neuron

dendrites in control tissue. These channels raise threshold for action-potential initiation in the dendrites, limit the backpropagation of action potentials from the soma to the dendrites, and reduce the amplitude of excitatory synaptic events. **Methods:** We used simultaneous somatic and dendritic recordings of CA1 pyramidal cells in pilocarpine-treated rats with spontaneous recurrent seizures. **Results:** We found that all action potentials were first generated in the perisomatic region during evoked epileptiform discharges or with depolarizing steps. The perisomatic region is therefore still the normal site for spike initiation in experimental TLE. These backpropagating spikes, however, had a greater amplitude in TLE than in controls, because of a downregulation of A type K^+ channel function that could be partially reversed after their dephosphorylation. The increased dendritic excitability was due to a change in the ratio of available Na/K channels in favor of Na^+ channels. Finally, preventing phosphorylation of K^+ channels dramatically reduced evoked epileptiform discharges in the dendrites. **Conclusions:** We propose that an increased endogenous phosphorylation in epileptic tissue results in decreased K^+ channel activity and increased dendritic excitability. Targeting the phosphorylation site of dendritic A type K^+ channels to upregulate their activity may be a fruitful new drug strategy in TLE. (Supported by INSERM and NIH.)

1.005

REDUCED VOLTAGE-SENSITIVE CALCIUM CURRENTS IN AN ANIMAL MODEL OF EPILEPSY

M. Steven Evans, Craig J. Cady, Kimberly E. Disney, and James J. LaGuardia (Neurology, Southern Illinois University School of Medicine, Springfield, IL)

Rationale: Genetically epilepsy-prone rats (GEPRs) are naturally susceptible to seizures. Seizures can be induced by many different stimuli, but audiogenic seizures (AGSs) are easily elicited, and the neuronal network subserving AGSs is well understood. AGSs are initiated in inferior colliculus (IC) and spread from there to other brain areas. In previous studies we found that both the fast and the slow calcium-dependent afterhyperpolarizations after action potentials are reduced in GEPRs, which leads to a marked increase in action-potential firing. In the present study, we tested the hypothesis that voltage-sensitive calcium currents are reduced in GEPRs. **Methods:** GEPRs (GEPR-9 strain) and Sprague–Dawley (SD) rats aged 6–8 weeks were compared. GEPRs had either 0 seizures or three AGSs given once daily. Dissociated IC neurons were cultured in serum-free growth medium and studied after 4–7 days in vitro. Voltage-sensitive calcium currents were studied after blockade of fast sodium and potassium currents by using tetrodotoxin, tetraethylammonium, 4-aminopyridine, and intracellular cesium. Barium (10 m*M*) was used as the charge carrier instead of calcium (0 m*M*). High-voltage-activated (HVA) currents were elicited by 200-ms step depolarizations from a holding potential of –60 mV, a protocol that elicits HVA currents. Peak current density was measured by dividing peak current by cell capacitance, and conductance was calculated from current–voltage curves. **Results:** We found that peak HVA current density was markedly reduced in GEPRs with 0 seizures (-1.86 ± 0.39 pA/pF, $n = 21$) and three seizures (-1.81 ± 0.40 pA/pF), compared with SD neurons (-4.67 ± 0.97 pA/pF, $n = 23$). The 60%/61% reduction of current density in GEPRs with 0 and three seizures was statistically significant (ANOVA, $F(2, 61) = 0.03$, with post hoc Student–Neuman–Keuls tests indicating $p < 0.05$ for each group). There was no difference in GEPRs with 0 seizures compared with GEPRs with three seizures. Plots of conductance/peak conductance versus voltage showed no difference in the voltage sensitivity of calcium currents in the three groups. **Conclusions:** Voltage-sensitive calcium currents are markedly reduced in IC neurons of this animal model of epilepsy. These data indicate that reduced calcium currents are the likely cause of the previously described deficits in calcium-dependent afterhyperpolarizations and increased action-potential firing. Reduced calcium currents are likely to be a major contributor to epilepsy in this animal model. At the end of this activity, the participant will be able to understand the possible importance of reduced calcium channel currents in epilepsy. (Supported by NINDS R29 NS34564, SIU Central Research Committee.)

1.006

HIPPOCAMPAL VOLTAGE-GATED CALCIUM CHANNEL IMMUNOHISTOCHEMISTRY IN AGING RATS AFTER KAINATE-INDUCED STATUS EPILEPTICUS

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Rationale: The importance of calcium currents in seizure generation and the establishment of epilepsy has been described in several animal and human studies, but the specific roles of the different voltage-gated calcium channel (VGCC) subtypes have not been fully delineated. Specifically, there have been no studies examining hippocampal VGCC structure or function in aged animals immediately after prolonged SE. We sought to determine whether SE resulted in aging-related changes in the expression of hippocampal VGCC α1A-D subunits immediately after convulsive SE and after attainment of the epileptic state. At the end of this activity, participants should be able to discuss the relations among status epilepticus, epilepsy, aging, and VGCC α1A-D subunit expression. **Methods:** Animals at 4–8 months (young adult; $n = 3$), 13–14 months (middle aged; $n = 2$), and 25–29 months (aged; $n = 4$) underwent kainate-induced SE or were used as controls (two young adult, one middle aged, two aged). Animals were injected with kainate (5 mg/kg in NaCl, i.p.) every hour until they demonstrated 4 h of stage 4–5 seizure activity, after which they were killed. The total dose of kainate was 12.5–20 mg/animal. Animals at 1–2 months (juvenile, $n = 2$) and 5–6 months (young adult, $n = 2$) underwent the same kainate protocol for SE but were not killed until 6 months later when they were demonstrating daily epileptic seizures. The total dose of kainate was 20–50 mg/animal. After fixative perfusion, brains were cut into 40-μm coronal sections on a sliding microtome. Nissl staining was performed on tissue sections adjacent to or near those immunostained for the α1subunit of class A-D VGCCs. **Results:** Immunoreactivity patterns of animals killed immediately after SE demonstrated marked loss of α1A staining in CA3 and hilus that was most prominent in aged animals, decreased α1B staining in SL of CA3, increased α1C staining of pyramidal and granule neurons of all ages, and markedly decreased neuropil staining in SP of CA3 and portions of CA1 that was less pronounced in older animals, and decreased α1D staining in CA3 and hilus that became more prominent with advancing age. Nissl staining demonstrated mildly dysmorphic neurons in CA3 that was most notable in aged animals. Epileptic animals demonstrated immunoreactivity similar to that of control animals. **Conclusions:** VGCC α1A-D subunit expression was differentially regulated on both neuronal cell bodies and processes during SE and may have been transient; some changes seen in aged animals were prominent in CA1 and hilus, and marked in CA3. Dysmorphic neurons suggested an aging-related regional hippocampal vulnerability to dysregulation of VGCC subunit expression that may have been associated with the metabolic stress of prolonged convulsive SE. (Supported by The Nathan Shock Center of Excellence in the Basic Biology of Aging and the Institute on Aging, Allegheny University of the Health Sciences.)

1.007

SUBSTANCE P INDUCES BURSTING IN NEOCORTICAL NEURONS RECORDED IN SLICE PREPARATIONS OF MICE

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Rationale: Substance P (SP) receptors are widely distributed in the cortex, and epileptic seizures are known to cause increased SP expression. For this reason, we examined the cellular mechanisms that underlie the modulation of cortical neurons by SP. **Methods:** Experiments were performed on male and female mice (P8-P13) that were deeply anesthetized with ether. The cortex was isolated in ice-cold artificial CSF (aCSF: 118 NaCl, 3 KCl, 1.5 $CaCl_2$, 1 $MgCl_2$, 25 $NaHCO_3$, 1 NaH_2PO_4, and 30 D-glucose, pH of 7.4) bubbled with carbogen (95%

oxygen and 5% CO_2). The cerebral hemispheres were separated at the midline. Slices (500 μm thick) were sectioned 1,500 μm from the frontal pole (motor cortex), and were immediately transferred into a recording chamber maintained at 29°C. After 30 min, the K^+ concentration was increased from 3 to 5 m*M* to obtain spontaneous rhythmic activity. Population activity recordings were obtained with suction electrodes positioned onto the surface of cortical layers 4 and 5. Intracellular whole-cell patch-clamp recordings were obtained from cortical neurons by using the blind-patch technique. Cell layer and cell type were identified by staining each neuron with biocytin. **Results:** Intracellular recordings from cortical neurons were obtained simultaneously with extracellular recordings from populations of neurons located close to the intracellular recording site. The majority of slices exhibited population activity, which was characterized by slow (<0.5 Hz), recurrent, and spontaneously generated oscillations. SP (0.1 μ*M*) had a biphasic effect: an initial increase in frequency was followed by a decrease in the frequency of these oscillations. Intracellular recordings revealed that 48% of the recorded neurons depolarized, 33% remained inactive, and 19% exhibited a biphasic response to SP (n = 21). SP caused in 33% of the recorded neurons a change in intrinsic membrane properties. Under control conditions, depolarizing current injections evoked tonic regular spiking activity, which increased in frequency when increasing the amplitude of current injections. The same stimuli evoked rhythmic bursting activity in the presence of SP. This bursting activity was voltage dependent. Increasing the amplitude of depolarizing current injections increased the frequency of bursting activity, whereas brief hyperpolarizing pulses reset the bursting activity, indicating that these bursts were intrinsic to the cortical neuron. The bursting properties persisted in the presence of Cd^{2+} at concentrations (200 μ*M*) known to block all Ca^{2+} currents. The bursting was blocked by tetrodotoxin (TTX), suggesting that the burst-generating mechanism depends on the activation of a TTX-sensitive persistent Na^+ current. In neurons that generated bursting activity in the presence of *N*-methyl-D-aspartate (NMDA), SP caused a significant increase in the frequency of bursting and the duration of individual bursts. **Conclusions:** Our data indicate that SP can enhance the excitability of cortical neurons by inducing Cd^{2+}-insensitive, but TTX-sensitive bursting activity. This increased excitability is a possible mechanism that promotes epileptiform activity. We therefore hypothesize that antagonists for SP receptor might serve as anticonvulsants by inhibiting bursting properties in cortical neurons. [Supported by Falk Foundation (WvD, CJM, KEH) Rett Syndrome Research Foundation (JMR) NIH HL 60120 (JMR).]

1.008
A CALCIUM-ACTIVATED CATIONIC CURRENT MAINTAINS ELECTROGRAPHIC SEIZURES IN EXPERIMENTAL NEOCORTICA EPILEPSY IN VITRO

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Rationale: Epileptic seizures are characterized by increased hypersynchronous electrical activity in cortical neurons. The ionic mechanisms responsible for maintaining electrical activity during seizures remain elusive. **Methods:** Concomitant whole-cell recordings from the soma and apical dendrites of layer-5 pyramidal neurons combined calcium fluorescence imaging in neocortical brain slices bathed in an extracellular slution containing either bicuculline or zero magnesium. **Results:** In bicuculline-treated brain slices, electrographic seizures were associated with an underlying sustained depolarizing waveform (SDW). The SDW had an average amplitude of 12.7 ± 1.1 mV, an average half-width of 13.3 ± 1.4 s, and average reversal potential of –9.1 ± 2.8 mV, as recorded at the soma. The SDW was calcium dependent, as it was markedly attenuated by loading neurons with the intracellular calcium buffer BAPTA via the recording pipette. Taken together, these described findings indicated the SDW was mediated by a calcium-activated cationic current. Concomitant recordings from the soma and apical dendrite of the same neuron revealed that the amplitude of the SDW was larger at the soma. Addition of flufenamic acid, a selective blocker of the calcium-activated cationic current (I_{can}), reversibly abolished the SDW. Concomitantly it reversibly eliminated spontaneous electrographic seizures and transformed evoked electrographic seizures into interictal-like discharges. Similar results were obtained in a second model of acute experimental epilepsy, neocortical slices bathed in a magnesium-free solution. **Conclusions:** The formation and maintenance of electrographic seizures critically depend on the calcium-activated cationic current, and as such the calcium-activated cationic current may serve as a novel target for antiepileptic therapy. (Supported by The Yael Foundation.)

1.009
THE GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS TYPE 2 MUTATION W1204R ALTERS VOLTAGE-DEPENDENT GATING OF rNA$_v$1.1 SODIUM CHANNELS

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Rationale: Nine mutations that cause generalized epilepsy with febrile seizures plus (GEFS+) have been identified in the *SCN1A* gene encoding the α subunit of the $Na_v1.1$ voltage-gated sodium channel. We have previously described the functional properties of two of these mutations (T875M and R1648H). T875M was shown to enhance slow inactivation, whereas R1648H dramatically accelerated recovery from inactivation. A third mutation, W1204R, changes a residue in the DII–DIII cytoplasmic linker region located approximately nine amino acids from the start of the DIIIS1 transmembrane segment that is evolutionarily conserved in vertebrate and invertebrate channels. The mutation was identified in all six affected members of a four-generation family. The clinical course was variable, including individuals with isolated febrile seizures, severe myoclonic seizures, and severe epilepsy with mental retardation (Escayg et. al., *Am J Hum Genet* 2001;68:866–73). The objective of this study was to determine the effects of the W1204R mutation on sodium channel function while attempting to define a possible common molecular mechanism by which mutations in *SCN1A* result in the clinical disorder GEFS+2. **Methods:** The mutation was cloned into the orthologous rat channel, $rNa_v1.1$, and the electrophysiologic properties of the mutant channels were determined in the absence and presence of the β1 subunit in *Xenopus* oocytes by using the cut-open oocyte and two-electrode voltage-clamp techniques. **Results:** The W1204R mutation resulted in ~11-mV hyperpolarized shifts in the voltage dependence of activation and steady-state inactivation when expressed as an α subunit alone. When the channels were coexpressed with the β1 subunit, the hyperpolarized shifts were still present but smaller, ~5 mV in magnitude. All other fast and slow-gated properties that we examined were comparable for the mutant and wild-type channels. **Conclusions:** The negative shift in activation would increase channel excitability, whereas the negative shift in inactivation would decrease excitability. The negative shifts in both properties also shifted the window current, which is the voltage region in which sodium channels can continue to open because some percentage of channels are activated, and not all of the channels are inactivated. The shift in window current for the W1204R mutation could result in hyperexcitability because the neuron's potential is more likely to reach the more negative range. These results demonstrate that a third *SCN1A* mutation that causes GEFS+2 alters the properties of the sodium channel in a different manner than the previous two mutations that were studied. The diversity in functional effects for these three mutations indicates that a similar clinical phenotype can result from very different underlying sodium channel abnormalities. (Supported by National Institutes of Health Grant NS26729.)

1.010
DEVELOPMENTAL CHANGES IN M-CURRENT FUNCTION IN RAT HIPPOCAMPUS AND NEOCORTEX

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Rationale: Mutations in K^+ channel subunits KCNQ2 and KCNQ3 are independently linked to benign familial neonatal convulsions (BFNCs), an idiopathic epilepsy that occurs in newborns and spontaneously remits after several weeks or months. KCNQ2 and 3 underlie the M current, a voltage-dependent sustained K^+ current that is critical

in regulating neuronal excitability. The mutations associated with BFNCs lead to expression of an M current that is hypofunctional. Developmental regulation of the M current could be critical to the window of vulnerability to seizures associated with BFNCs. The goal of this study was to determine whether changes in M-current expression and function during early postnatal development in rat neocortex and hippocampus could contribute to the transient expression of seizures found in BFNCs. We focused on the second postnatal week, because cortical development at this time in rat approximates human neonates. **Methods:** We made hippocampal and neocortical slices from P10 to adult rats and used intracellular voltage-clamp recording techniques to record currents in hippocampal CA1 and somatosensory cortex layer V pyramidal neurons. Standard voltage protocols were used to record M current and other sustained currents in the presence of tetrodotoxin. We characterized the pharmacologic properties of the M current using linopirdine, a selective blocker, and retigabine, a specific activator with demonstrated antiepileptic properties. We also used immunohistochemistry and Western blotting to examine expression of KCNQ2 and 3 proteins during the first 2 postnatal weeks. **Results:** In hippocampus and neocortex, we saw an increase in M-current amplitude during the second postnatal week. In CA1 pyramidal neurons from P10 to P15, M-current amplitudes were about half of those found in adults. Interestingly, M currents recorded from immature hippocampus were much more sensitive to retigabine (2–10 μM) than in adult. Linopirdine (10 μM) blocked the M current regardless of the developmental age. Concomitant to the functional increase in M current, we also observed an increase in levels of KCNQ2 and KCNQ3 protein expression in hippocampus. In neocortex, in contrast to hippocampus, M currents recorded from adult pyramidal neurons were more sensitive to retigabine than were those in immature. **Conclusions:** Our results show that in CA1 and neocortex, a developmental ?switch? occurs in M-current pharmacology. In CA1, the M current recorded from immature pyramidal neurons is more sensitive to retigabine than is that in in adult, whereas the opposite holds true in neocortex. These changes could be a reflection of differential expression of KCNQ subunits or differences in posttranslational modification. Thus, alterations in M-current expression and/or regulation could play a role in the transient nature of seizure vulnerability in neonates with hypofunctional M current. (Supported by NIH grant NS 38633 and DA 13658.)

1.011
BENZODIAZEPINES BLOCK INHIBITORY GLYCINE RECEPTORS IN CULTURED EMBRYONIC MOUSE HIPPOCAMPAL NEURONS

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Rationale: Benzodiazepines (BZDs) are among the first medications used to treat neonatal seizures. Although BZDs effectively potentiate γ-aminobutyric acid$_A$ receptors ($GABA_A$Rs) in adult neurons, they are much less effective in potentiating $GABA_A$Rs in neonatal neurons. Thus, BZDs may have additional sites of action in the neonatal brain. The inhibitory glycine receptor (GlyR) is a candidate site based on the ability of BZDs to inhibit strychnine binding. In this study, we examined the effect of BZDs on GlyR-mediated currents in cultured embryonic mouse hippocampal neurons. **Methods:** Hippocampal neurons were cultured from embryonic day 15 Swiss Webster mice by using standard techniques, which were approved by the Washington University Animal Studies Committee. GlyR- and $GABA_A$R-mediated currents were studied by using the whole-cell patch-clamp technique in neurons cultured for 4–14 days. **Results:** Glycine evoked a dose-dependent, strychnine-sensitive chloride current when applied to neurons voltage-clamped at –65 mV. At 20–100 μM, chlordiazepoxide, nitrazepam (NZP), lorazepam (LZP), alprazolam, and triazolam inhibited 50 μM glycine (EC_{50}) currents by $\geq$20%. In contrast, 100 μM DZP and 100 μM clobazam (CLB) inhibited 50 μM glycine currents by $\leq$15%. Chlordiazepoxide and NZP were studied in further detail. Chlordiazepoxide completely blocked 50 μM glycine currents with an IC_{50} of 230 ± 52μM. Nitrazepam completely blocked 20μM (EC_{20}) and 50μM glycine currents with an IC_{50} of 100 ± ± 5 and 100 ± 29 μM, respectively; 80 μM NZP increased the EC_{50} for the glycine dose–response curve from 52 ± 3 to 120 ± 10μM, increased the Hill coefficient from 1.8 ± 0.2 to 3.7 ± 1.0, and decreased the maximal response by 22%. NZP block was not voltage dependent and could not be prevented by 10 μM flumazenil (FMZ). Based on noise analysis, 50 μM NZP decreased the mean channel burst duration for 10 μM glycine from 67 ± 4 to 32 ± 4 ms. In addition, NZP increased the GlyR single-channel conductance from 3.9 ± 0.9 to 8.3 ± 1.6 pS. Although 100 μM NZP significantly prolonged the fast time constant of desensitization for 300 μM glycine (EC_{100}) currents from 0.9 ± 0.2 to 1.6 ± 0.2 s, it did not alter other parameters of desensitization. Specifically, it did not alter the slow time constant of onset, the weighted mean time constant of onset, the relative contributions of the fast and slow components, the degree of desensitization, or the weighted mean time constant for recovery from desensitization for 300 μM glycine currents. Similarly, 50 μM NZP did not alter desensitizing currents elicited by 10 μM glycine. We confirmed that BZDs do not consistently potentiate $GABA_A$R currents in this preparation. **Conclusions:** We conclude that BZDs are noncompetitive inhibitors of GlyR in embryonic hippocampal neurons. The findings exclude mechanisms involving simple open channel block and enhanced desensitization. The inhibition results in part from impaired channel gating, although an effect on binding cannot be excluded. Because GlyRs mediate a depolarizing response in neonatal neurons, their inhibition by BZDs may be important in treating neonatal seizures. (Supported by NIH.)

Experimental Animal Models (Nonhuman)

1.012
ACTIVATION OF SPHINGOMYELINASE ISOENZYMES AFTER KAINIC ACID–INDUCED STATUS EPILEPTICUS

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Rationale: We have recently demonstrated that kainic acid (KA)-induced status epilepticus (SE) results in increases in ceramide levels at 2–30 h after KA, and that such alterations lead to apoptosis in the hippocampus. The mechanisms that lead to ceramide increases during, and after, SE have not been investigated. The three isoenzymes of sphingomyelinase (SMASE) catalyze the breakdown of sphinomyelin to form ceramide and have been shown to be responsible for ceramide increases in other apoptosis models, but not in neurons after SE. The objective of this study was to determine sequentially the activity of those isoenzymes during, and after, SE in an attempt to understand the mechanisms that lead to ceramide increases after SE. **Methods:** Adult Sprague–Dawley rats (two to five/group) received, intraperitoneally, 15 mg/kg KA, were killed at 1, 2, 3, 4, 12, 18, and 24 h after KA, and were compared with vehicle-injected matched control rats. The right hippocampus was dissected, proteins were extractred, and then assayed for the activity of magnesium-independent neutral SMASE (MI-

TABLE 1. *Enzyme activity after kainic acid injection*

Hours	MI-NSMASE activity	MD-NSMASE activity	ASMASE
0 (Baseline)	32 ± 2	193 ± 42	201 ± 5
1	25 ± 1	132 ± 23	187 ± 15
2	23 ± 7	139 ± 10	156 ± 14
3	24 ± 2	155 ± 11	165 ± 2
4	109 ± 34[a]	330 ± 27[a]	159 ± 17
12	29 ± 6	155 ± 24	113 ± 30
18	130 ± 0.5[a]	288 ± 37[a]	113 ± 12
24	143 ± 18[a]	337 ± 33[a]	129 ± 16

[a] $p < 0.05$ compared with baseline; data presented as mean ± SD.

NSMASE), magnesium-dependent neutral SMASE (MD-NSMASE), and for acidic SMASE (ASMASE). Analysis of variance was used for analyzing the data. **Results:** As compared with baseline, MI-NSMASE and MD-NSMASE increased at the 4-, 18-, and 24-h time points ($p < 0.05$ in each of the paired comparisons; data presented in Table 1). Other paired comparisons were not significant. A-SMASE did not show any significant differences ($p > 0.05$, see Table 1 for data). **Conclusions:** After KA-induced SE, there is activation of MD-NSMASE and MI-NSMASE starting at 4 h after KA injection. These increases explain at least some of the increases in ceramide levels previously reported to occur after SE, and thus may be contributing to the process of SE-induced apoptosis. (Supported by DCR114170-26323.)

1.013
THE ROLE OF RETICULAR THALAMUS ON KAINIC ACID–INDUCED GENERALIZED SEIZURES IN RATS

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Rationale: Previously we investigated the features of seizure induced by kainic acid (KA) microinjection into reticular thalamus (RT), and reported that RT might be another crucial epileptogenic site in rat forebrain as rivaled by the area tempestas Gale et al. previously described. This study was designed to ellucidate the role of RT in KA-induced mesencephalic reticular formation (MRF) seizures in rats. A microinjection of KA into unilateral MRF resulted in recurrent generalized seizures in unrestrained rats (Tanaka et al., 1994). **Methods:** Twenty male Wistar rats underwent stereotactic implantation of electrodes in the left RT (LRT), the left MRF (LMRF), the bilateral dorsal hippocampus (LdH, RdH), and the bilateral sensorimotor cortex (LCx, RCx). For KA injection, a stainless steel cannula was inserted into LMRF and LRT. After recovery from surgery, all rats received KA (2.0 μg) injection into LMRF. Five hours after KA injection, while rats were exhibiting generalized seizure status, 0.5 μl of phosphate-buffered saline solution (group 1, $n = 10$) or 4% lidocaine hydrochloride (group 2, $n = 10$) was injected into LRT. Electrophysiologic and behavioral observation was made in both group. **Results:** Two hours after KA injection, synchronous spike discharges were initially observed in all records. The rats showed immobilization. Three to 5 h after KA injection, multiple synchronous spike discharges appeared, and the characteristics of these seizures were generalized tonic seizures followed by short clonic seizures. One hour after PBS injection in group 1, no electrophysiologic and behavioral change were seen. One hour after lidocaine injection in group 2, overall seizures became weak and transient, especially in the bilateral sensorimotor cortex and the LRT. Behaviorally, motor manifestations were markedly attenuated. **Conclusions:** (a) Generalized seizure status was induced by KA injection into LMRF. (b) In the rats that received lidocaine into LRT, multiple synchronous spike discharges became weak and transient, especially in the bilateral sensorimotor cortex and the LRT. Behaviorally, motor manifestations were attenuated. (c) These results suggested that RT might facilitate the development of generalized seizures induced by KA microinjection. (Supported by Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Sciences, and Culture of Japan.)

1.014
ANTICONVULSANT EFFECT OF BILATERAL INJECTION OF N6-CYCLOHEXYLADENOSINE INTO THE CA1 REGION OF THE HIPPOCAMPUS IN THE AMYGDALA-KINDLED RATS

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Rationale: In this study, the role of adenosine A1 receptors of the CA1 region of the hippocampus on amygdala-kindled seizures was investigated in rats. Results obtained showed that in kindled animals, bilateral injection of *N*6-cyclohexyladenosine (CHA), an adenosine A1 receptor agonist, at doses of 0.1, 1, and 10 μ*M* into the CA1 region of the hippocampus, significantly decreased the afterdischarge duration (AD) and stage 5 seizure duration and increased the latency to stage 4 seizure, but there were no changes in seizure stage. Bilateral injection of 1,3-dimethyl-8-cyclopenthylxanthine (CPT), an adenosine A1 receptor antagonist, at doses of 0.5 and 1 μ*M* into the CA1 region of the hippocampus did not produce any changes in the seizure parameters. Intrahippocampal pretreatment of CPT (1 μ*M*) before CHA (0.1 and 1 μ*M*), reduced the effects of CHA on seizure parameters significantly. Thus, the CA1 region of the hippocampus may play an important role in spreading seizure spikes from the amygdala to other brain regions and activation of adenosine A1 receptors in this region, and participate in anticonvulsant effects of adenosine agonists. **Methods:** Sprague–Dawley rats were stereotaxically implanted with bipolar stimulation and monopolar recording electrodes terminating in the basolateral amygdala of the right hemisphere and two 23-gauge guide cannulae also implanted in the CA1 regions of the dorsal hippocampi. One week after surgery, the AD threshold was determined in the amygdala by a 2-s, 60-Hz monophasic square wave stimulus of 1 ms per wave. In the kindled animals, the recorded parameters were seizure stage (SS), amygdala AD duration (ADD), the latency to the onset of bilateral forelimb clonus (S4L), and the duration of stage 5 (S5D). For intrahippocampal injection, CHA and CPT were dissolved in artificial cerebrospinal fluid (aCSF). Drugs were infused via two 30-gauge cannulae, which extended 1 mm below the tip of the guide cannulae. CHA at concentrations of 0.01, 0.1, 1, and 10 μ*M* or CPT at concentrations of 0.5 and 1 μ*M* were infused in situ, and 5, 15, and 60 min later, animals were stimulated at AD threshold. A two-way analysis of variance and Tukey's posttest were done to compare different groups of animals at different times after different doses of drug injections. **Results:** All amygdala-kindled rats responded with stable stage 5 seizure in either a noninfusion condition or after aCSF infusion, and there was no effect of aCSF injection on seizure parameters. At the doses used, CHA and CPT had no noticeable effect on behavioral or locomotor activity with respect to predrug or aCSF-infused rats. **Conclusions:** Results obtained in this study showed that bilateral injection of CHA into the CA1 region of the hippocampus has anticonvulsant effects on amygdala-kindled seizures. (Supported by Tarbiat Modarres University.)

1.015
A ROLE FOR THE GLuR5 KAINATE RECEPTOR IN THE CONVULSANT AND EPILEPTOGENIC EFFECT OF KAINATE

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Rationale: Kainate is a powerful convulsant and epileptogenic agent often used to produce a model for human temporal lobe epilepsy. However, the precise molecular target through which kainate acts is uncertain because the neurotoxin is a nonselective agonist of AMPA and kainate receptors. Here we used ATPA, a tert-butyl analogue of AMPA that is a highly selective agonist of GluR5 kainate receptors, to clarify the pharmacologic mechanisms underlying the seizure-inducing activity of kainate. ATPA binds to GluR5 kainate receptors at >1,000-fold lower concentrations than to AMPA receptors. Nevertheless, to exclude the possibility that the actions of ATPA are due to interactions with AMPA receptors, control experiments were carried out with AMPA. ATPA was infused directly into the basolateral amygdala, where GluR5 kainate receptors have been shown to mediate enduring synaptic facilitation, which may underlie both the acute seizure and epileptogenic effects of kainate. **Methods:** Rats were implanted with a 26- or 31-gauge stainless steel infusion cannula into the basolateral amygdala and a bipolar depth electrode into the contralateral basolateral amygdala for depth EEG recording. Screw electrodes were placed over the frontal cortex and cerebellum for surface EEG recording. After at least a 7- to 10-day recovery period, an ATPA or AMPA solution (1–40 nmol/5 μl in sterile saline) was infused over 5 min. The animals

were monitored for seizure activity by observation and EEG over the ensuing 2 months. At the end of the monitoring period, some animals underwent the intravenous (i.v.)-pentylenetetrazol (PTZ) seizure-threshold test. **Results:** ATPA caused acute seizure activity in all 14 treated animals. Seven of these animals exhibited prolonged (>30 min) status epilepticus–like generalized convulsions ("SE animals"). The remainder exhibited self-limited limbic seizures of various stages (modified Racine Scale, stages 1–4; "LS animals"). Three of the ATPA SE animals showed spontaneous limbic seizures (≥stage 3) over the subsequent 2-month monitoring period, as did one of the ATPA LS animals. AMPA also caused acute seizures in all nine treated animals. However, in contrast to ATPA, only one of five AMPA SE animals and 0 of four AMPA LS animals demonstrated spontaneous seizures over the next 2 months. The i.v.-PTZ seizure-threshold test also indicated a higher seizure susceptibility in ATPA-treated animals. **Conclusions:** Selective activation of GluR5 kainate receptors in the amygdala with ATPA induces limbic seizure activity, and in some cases, SE. In addition, animals experiencing ATPA-induced seizures may go on to exhibit persistent spontaneous seizures. Our results suggest that this can occur even in animals that do not experience SE. AMPA-receptor activation also induces seizure activity but is less likely to result in persistent spontaneous seizures. We conclude that the delayed epileptogenic effect of kainate may be related specifically to activation of GluR5 kainate receptors. (Supported by NINDS.)

1.016
HIGH-FREQUENCY STIMULATION OF THE SUBTHALAMIC NUCLEUS PREVENTS SECONDARY GENERALIZATION OF ACUTE KAINIC ACID SEIZURES IN THE RAT

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Rationale: Deep brain stimulation (DBS) is an emerging treatment for many functional neurologic disorders. One potential application of DBS is for the treatment of intractable epilepsy. The inhibition of the subthalamic nucleus (STN) by high-frequency stimulation (HFS) is believed to activate the nigral control of epilepsy system (NCES), leading to increased seizure threshold. Alternatively, STN stimulation may directly affect the cortex through the cortico-STN connection by means of antidromic inputs. We hypothesized that HFS of the STN has an anticonvulsant effect on kainic acid–induced seizures in the rat. **Methods:** Six rats were implanted with bifrontal epidural electrodes and bilateral hippocampal electrodes. Additionally, concentric monopolar electrodes were implanted bilaterally in the STN with neurophysiologic targeting. Subcutaneous injections of kainic acid (KA) (10 mg/kg) were given to induce seizures immediately. The effect of HFS of the STN on the latency to first EEG seizure activity and the duration of focal and generalized EEG seizure activity were measured. Each animal served as its own control. The animals were killed, and histology was done to confirm the location of electrode. **Results:** There was no difference in total seizure duration between the group with STN stimulation and KA injection and the control with KA injection only. However, there was a significant difference between these groups in the duration of generalized seizures, with the STN stimulation group having a shorter duration of generalized seizure activity. There was no difference in the latency to EEG seizure between groups. **Conclusions:** We therefore conclude that the main effect of HFS of the STN is to prevent secondary generalization. (Supported by Medtronic.)

1.017
OPTICAL INTRINSIC SIGNAL IMAGING OF HYPERSYNCHRONOUS ACTIVITY IN THE NEOCORTEX OF RATS WITH ACUTE SEIZURES

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Rationale: Epilepsy is probably a network disorder. It requires hypersynchronous firing of a network that comprises interconnected neuronal clusters. To study the behavior of the epileptic neuronal network in a top-down manner, a research method that could detect the network activity with satisfactory combined temporal and spatial resolution is needed. Optical intrinsic signal (OIS) imaging, which has been shown to detect seizure activity with excellent sensitivity (Chen et al., *Neurology* 2000;55:312–5), is used in this study to investigate the hypersynchronous activity of neocortical neurons of rats during acute seizures induced by penicillin. **Methods:** In Spraque–Dawley rats (n = 12), surgery and OIS imaging were performed under anesthesia. The rat was placed in a stereotactic frame, and the skull bone was thinned with a scrapper. EEG depth electrode was mounted on a stereotactic manipulator, advanced, and placed in the cortex through the burr hole at 4 mm posteriorly, 6 mm laterally relative to the bregma on the side of OIS imaging. The referential and ground electrodes were placed on the scalp and forelimb, respectively. EEG activity was monitored with an oscilloscope. OIS imaging was obtained with a CCD camera (Princeton Instruments, EEV 0206, 192 × 144-pixel array) over one hemisphere with an optical filter of 850 or 610 nm. EEG and OIS signals were synchronized and collected on a PC computer simultaneously. The EEG sampling frequency was 1,000 Hz, and the camera frame rate was either two frames per second or one frame per 3 s. The exposure time was 200 ms or 2.5 s, respectively. Acute seizures were induced by injecting or dripping 100 units of penicillin solution topically over the second burr hole 2 mm in front of the EEG electrode. The dura mater was removed in both burr holes during surgery by using the dental drill, or a sharp syringe needle. A ratio analysis was performed on the optical images by using the equation: [(data image – control image) /control image]. The control image was selected from images before penicillin application. Regions of interest (ROIs) were selected manually from separate areas showing synchronous activity after visual inspection for correlation analysis. **Results:** Various brain regions were shown to have synchronized activity on OIS imaging during seizures. In the early phase of electrographic seizures, several separate but remote brain regions had shown synchronized activity. These areas probably represent a seizure network of hypersynchronized activity. With the progression of seizures, the areas of synchronized activity expanded and convened with each other. The correlation analysis of ROIs, with a correlation coefficient of 0.96 ± 0.01 (mean ± SD, n = 12), supports the notion that hypersynchronous activity could be demonstrated with OIS imaging in seizures. **Conclusions:** (a) Hypersynchronous activity among remote brain regions during acute seizures could be demonstrated by OIS imaging. (b) OIS imaging could be used to study the behavior of epileptic networks in the neocortex. (Supported by the VA Career Development Award and NIMH grant MH52083.)

1.018
THE EFFECTS OF γ-BUTYROLACTONE AND THE KETOGENIC DIET ON THE BEHAVIOR OF MALE AND FEMALE RATS

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Rationale: Injection of γ-butyrolactone (GBL; 100 mg/kg) induces absence seizures in rats. Rats fed a ketogenic diet experience fewer and briefer episodes of the spike–wave discharges (SWDs) that characterize absence seizures but, unlike those fed a normal diet, demonstrate a profound lethargy. The purpose of this study was to evaluate the lethargic response of male and female rats to injection (i.p.) of GBL. **Methods:** Thirty-four Sprague–Dawley rats of each gender were used, and doses of 50, 75, 100, and 125 mg/kg were administered. Some animals received repeated doses in this ascending series, and others received only one dose of GBL and and were injected with saline as control in place of the other doses. Rats were scored for posture, gait, and performance on a rotorod. **Results:** The higher doses (100 and 125 mg/kg) produced a pronate resting posture, lack of spontaneous mobility, and increased failure on the rotorod behavioral test in rats fed the ketogenic diet but not in those fed standard rodent chow. In ketogenic animals, all of these effects were more evident in females than in males, and all were diminished in both genders if individual animals received repeated injections of GBL. **Conclusions:** Although the ketogenic diet is uniqure in protecting against both convulsive and nonconvulsive seizures, ketogenic rats have a cognitive/locomotor deficit when in-

jected with ictogenic doses of GBL, and this effect is more pronounced in females than in males. (Supported by Department of Biology, Georgetown University.)

1.019

LOW-FREQUENCY SINE WAVE STIMULATION DECREASES SEIZURE FREQUENCY IN AMYGDALA-KINDLED RATS

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Rationale: The search for new, effective anticonvulsant therapies that are free of side effects led us to examine the possibility that low-frequency stimulation (LFS) could effectively interfere with the generation of seizures in amygdala-kindled rats. Based on previous work by Gaito et al. and Veliskova et al., we tested the hypothesis that low-frequency sine wave stimulation, delivered during kindling acquisition and after development of the kindled state, would interfere with epileptogenesis and the generation of kindled seizures (SZs). At the end of this activity, the participants should be able to discuss the effect of LFS on kindled seizures. **Methods:** Bipolar stainless steel electrodes were implanted bilaterally into the basolateral amygdalae of adult male Sprague–Dawley rats. All animals (n = 13) were stimulated twice a day (60-Hz, 1-ms pulses, 400 μA) for 1 s. Experimental animals (n = 7) received 30 s of sine wave stimulation (1 Hz, 50 μA) immediately before the kindling stimulus. Afterdischarge (AD) duration, the number of stimulations required to elicit the first stage 5 SZ, and the number of stimulations required for each animal to become fully kindled were measured for each group. After 20 stimulations, a crossover was performed. Fully kindled rats from each group were switched, so that rats in the original control group (n = 5) received LFS plus the kindling stimulus, and rats in the original experimental group (n = 5) received only the kindling stimulus. **Results:** The addition of LFS to the kindling stimulus did not have a significant effect on AD duration, the number of stimulations to the first stage 5 SZ, or the number of stimulations required for the experimental rats to become fully kindled. However, the presentation of LFS significantly increased the number of times the kindling stimulus failed to elicit an AD. During the first 20 stimulations, the experimental rats exhibited an AD failure rate of 32.9% compared with an AD failure rate of 0.83% in control rats ($p < 0.001$, Student's *t* test). After crossover, both groups of rats received additional stimulations. The failure rate in the original control group significantly increased from 0.83 to 63.3% ($p < 0.001$), whereas the failure rate in the original experimental group decreased from 32.9 to 9.9% ($p < 0.01$). The experimental animals did not appear to alter their behavior during the LFS. **Conclusions:** These results suggest that LFS may be an effective therapy for the prevention of seizures. The observation that LFS was more effective in fully kindled animals suggests that LFS may be an effective therapy for generalized tonic–clonic seizures. LFS does not appear to have a long-lasting effect on seizure threshold, as evidenced by the decrease in the AD failure rate once LFS was discontinued. Further studies are required to determine if LFS, using different intensities or durations, will be more effective than the LFS used in this study and whether LFS interferes with normal brain function. (Supported by NeuroPace Inc. and the New York State Department of Health to J.H.G.) (Disclosure: Salary: Thomas Tcheng is an employee of NeuroPace, Inc.; Grant: from NeuroPace, Inc. to J.H.G.)

1.020

AN ENDOGENOUS CANNABINOID (2-AG) IS NEUROPROTECTIVE FOR LIMBIC SEIZURES IN RATS

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Rationale: Prior studies indicated that 2-arachidonoyl glycerol (2-AG), an endogenous cannabinoid, might have neurophysiologic roles in hippocampus, possibly by activating cannabinoid receptor-1 (CB1). This study was designed to clarify the effect of 2-AG on hippocampal neuronal damage induced by kainic acid (KA)-induced limbic seizures. **Methods:** Twenty-four rats underwent stereotactic implantation of electrodes in the left amygdala (LA), left hippocampus (LH), and the left sensorimotor cortex (LCx). A stainless steel cannula also was introduced into the LA and LH. The animals then were divided into four groups according to the pretreatment agents infused into LH; sham (phosphate-buffered saline solution; PBS), 1.0 μl, n = 6), controls (PBS, 1.0 μl, n = 6), group A (2-AG, 100 μ*M,* n = 6), and group B [2-AG, 100 μ*M* + AM251 (CB1 antagonist), 100 μ*M,* n = 6]. 2-AG and AM251 were dissolved in dimethyl sulfoxide. After 10 min, rats except shams received 1μg of kainic acid (KA) into LA via the cannula. Shams received PBS alone into the LA. After 7 days of electroclinical observation, histologic examination and statistic analyses were made. **Results:** In controls, multiple spike discharges in LA immediately propagated concurrently to the LH. Propagation involved the LCx to become status epilepticus 1–2 h after KA injection. Seizures, characterized by mastication, salivation, facial twitching, forelimb clonus, and sometimes rearing and falling, lasted 1–2 days. Microscopic examination revealed severe neuronal cell damage in the LA and LH. Unlike controls, overall seizure discharges were eliminated and neuronal cell damage in LH was reduced in group A. They only showed behavioral changes such as wet-dog shaking. In group B, seizure discharges and neuronal cell damage in LH were virtually the same as in controls. Shams showed no electroclinical and histologic changes. **Conclusions:** These results suggest that 2-AG acts neuroprotectivelyby activating CB1 in KA-indeuced limbic siezures. [Supported by Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Sciences, and Culture of Japan; grant from the La Salle High School Graduates' Association (Medical Division in Kagoshima).]

1.021

fMRI IN RAT MODELS OF EPILEPSY: PENTYLENETETRAZOL- AND KAINIC ACID–INDUCED SEIZURES

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Rationale: Fundamental to the study of epilepsy are questions about the anatomic location of seizure origination and pathways of seizure propagation through the brain. Classically, electrophysiologic measures have been used to study seizure origination and propagation. There are now magnetic resonance (MR) imaging correlates of neuronal activity that may be used to observe (indirectly) activation of anatomically distinct areas of the brain. By taking advantage of blood oxygen level–dependent (BOLD) contrast imaging techniques, we sought to determine if the onset and propagation of seizures can be observed in a small animal (rat) model of epilepsy. The participant should appreciate the potential for application of functional MRI (fMRI) to small animal models of epilepsy. **Methods:** We obtained BOLD fMRI data after the systemic administration of a convulsant, either pentylenetetrazol (PTZ; 50 mg/kg, n = 5) or kainic acid (KA; 15 mg/kg, n = 5) at a dose that induces generalized seizures in rats. Animals were anesthetized preceding placement of intraarterial, venous, and peritoneal catheters. Artificial ventilation was used throughout the experiment, and arterial blood gases were monitored. Using a single-shot gradient-echo planar imaging (EPI) technique, five slices were acquired every 2 s over the time course of the study. We defined the initiation of seizure activity as the occurrence of a statistically significant ($p < 0.0001$, unpaired *t* test) increase in baseline pixel intensity, using a simple step function and

two 10-acquisition windows. Propagation of seizure activity was measured by comparison with preseizure baseline using the same statistical parameters. **Results:** In comparing the two convulsants, we observed activation of anatomic areas that agreed with expectations based on known receptor distribution and information from other modalities [i.e., positron emission tomography (PET)]. After PTZ treatment, activation was found primarily in periventricular thalamus and diffusely over the cortex. Treatment with KA activated motor cortex, piriform cortex, olfactory bulb, and hippocampus. Moreover, the relative time courses also agreed with expectations derived from the epilepsy literature. Parallel experiments, after convulsant administration using the identical paradigm, with in vivo electrophysiologic recordings, showed characteristic seizure-associated electrical activity. The time course of the activity seen by electrophysiology correlates with the imaging studies and confirms the appearance of seizures after drug administration. **Conclusions:** Our preliminary data suggest that BOLD MRI can define the initiation and anatomic propagation of seizure discharge in the rat brain. Moreover, this general approach may be applied to seizure-prone transgenic mice, elucidating the relation between specific gene defects, cerebral anatomic abnormalities, and seizure activities. (Supported by NIH NS 8895, NIH NS07332, NIH DC03805, NIH HDO2274.)

1.022

KETOGENIC DIET: AGE-RELATED EFFECTS ON KETOSIS AND FLUROTHYL-INDUCED SEIZURE SUSCEPTIBILITY IN RATS

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Rationale: Clinically, the ketogenic diet (KD) has been thought to be more efficacious at younger ages, presumably because of the enhanced ability of the immature brain to extract and use ketone bodies. The present study was designed to investigate age-related effects of the KD on ketosis and flurothyl-induced seizure susceptibility. **Methods:** A KD [(fat: protein + carbohydrate) ratio of 4.3:1] was administered to male Sprague–Dawley rats for 3 weeks, while control animals were fed a standard rodent chow. Dietary treatment was initiated at postnatal 3, 6, 9, or 12 weeks. Blood ®-hydroxybutyrate (BHB) levels were assayed, and seizures were chemically induced by flurothyl infusion (40 μl/min) on treatment day 21. 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 (±SEM) blood BHB level in the KD-treated group was significantly higher than that of the control group in three [6.77 ± 0.79 (n = 15) vs. 0.28 ± 0.04 (n = 15) m*M,* respectively; $p < 0.001$], six [4.88 ± 0.23 (n = 20) vs. 0.25 ± 0.02 (n = 20) m*M,* respectively; $p < 0.001$], nine [2.28 ± 0.40 (n = 17) vs. 0.17 ± 0.02 (n = 16) m*M,* respectively; $p < 0.001$], or 12 [0.95 ± 0.06 (n = 18) vs. 0.27 ± 0.02 (n = 17) m*M,* respectively; $p < 0.001$] weeks old animals. The mean (±SEM) latencies to the onset of a generalized seizure were 554 ± 29 (KD-treated group, n = 15) and 457 ± 28 (control group, n = 15) s in 3-week-old rats ($p < 0.05$), 571 ± 30 (KD-treated group, n = 20) and 458 ± 24 (control group, n = 20) s in 6-week-old rats ($p < 0.01$), 508 ± 18 (KD-treated group, n = 17) and 453 ± 19 (control group, n = 16) s in 9-week-old rats ($p < 0.05$), or 494 ± 23 (KD-treated group, n = 18) and 430 ± 16 (control group, n = 17) s in 12-week-old rats ($p < 0.05$). **Conclusions:** This study demonstrates that the KD causes significant ketosis and also significant reduction of flurothyl-induced seizure susceptibility in 3- to 12-week-old rats. However, the levels of KD-induced ketosis were prominently lower, and the seizure latencies tended to be shorter at older ages. These results parallel clinical experience, where the KD has been thought to be more efficacious at younger ages. [Supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (HMP-99-N-02-0003).]

1.023

IMAGING OF DEFECTIVE MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION IN THE EPILEPTIC HIPPOCAMPUS

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Rationale: Because alterations of mitochondrial function have been shown to be involved in epileptogenesis, we investigated putative alterations of the mitochondrial membrane potential in rat hippocampal slices by using the pilocarpine model of chronic epilepsy. **Methods:** We used the mitochondrial membrane potential–sensitive fluorescent dye rhodamine 123 to follow alteration of the mitochondrial membrane potential in pyramidal neurons in living 150 μm thick rat hippocampal slices using fluorescence microscopy. To demonstrate the usefulness of this method for the quantitative measurement of mitochondrial membrane potential, we used rhodamine 123 fluorescence spectroscopy of digitonin-treated hippocampal homogenates. **Results:** Applying a potassium diffusion potential calibration procedure, this methods allows, in digitonin-treated hippocampal homogenates, a quantitative determination of alterations of mitochondrial membrane potential. In hippocampal slices, the rhodamine 123 fluorescence signal decreased if pyruvate (10 m*M*) was added to the glucose-containing slice perfusion medium. This is an indication for the substrate-dependent increase of the mitochondrial membrane potential. The stimulation of oxidative phosphorylation by KCl (10 m*M*) or the uncoupler TTFB (10 μ*M*) resulted in a dramatic fluorescence increase indicating mitochondrial depolarization. In the presence of glucose or pyruvate, we observed, in slices of pilocarpine-treated chronic epileptic rats in the CA3 and CA1 hippocampal subfields, neurons with elevated rhodamine 123 fluorescence, which did not further increase after the addition of KCl or TTFB to the slice perfusion medium. This is an indication for mitochondrial depolarization in these neurons, pointing to either insufficient substrate supply or dysfunction of mitochondrial oxidative phosphorylation. Because we were able to detect decreased activities of NADH:CoQ oxidoreductase and cytochrome c oxidase at control activities of succinate dehydrogenase and citrate synthase in the CA3 and CA1 hippocampal subfields, we suggest a dysfunction of mitochondrial oxidative phosphorylation in pyramidal neurons of chronic epileptic rats. **Conclusions:** Our findings confirm the presence of defects of mitochondrial oxidative phosphorylation in hippocampal pyramidal neurons of chronic epileptic rats. These data strongly suggest the involvement of mitochondria in epileptogenesis. [Supported by a grant from Deutsche Forschungsgemeinschaft (Ku 911/11-1).]

1.024

NEURONAL MDR-1 GENE–ENCODED P-GLYCOPROTEIN (P-170) EXPRESSION IN 3-MERCAPTOPROPIONIC ACID–INDUCED SEIZURES IN RATS

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Rationale: MDR-1 gene–encoded P-glycoprotein (P-170) is involved in the multiple drug resistance mechanism observed in cancer, and it was recently described to be expressed in brain of patients with refractory epilepsy (Tishler, 1995; Lazarowski, 1999; Sisodiya, 2002). We previously demonstrated that the expression of P-170 was induced after 4 days of treatment with i.p. administered proconvulsivant drug 3-mercaptopropionic acid (MP), in brain vessel walls, astrocytes, foot process astrocytes, and lightly in surrounding neurons (Lazarowski et al., 2002) The aim of this study was to analyze whether longer times of

MP treatment can induce a greater P-170 expression in neurons. **Methods:** Male Wistar rats (250–300 g) were daily administered 45 mg/kg i.p. of MP during 4 days (MP-4) and 7 days (MP-7). Rats daily injected with saline were used as controls. One day after the last injection, rats were deeply anesthetized with chloral hydrate (300 mg/kg) and fixed by perfusion. Brains were dissected and processed for immunohistochemistry by using monoclonal anti-P170 as primary antibody and the peroxidase–antiperoxidase technique. **Results:** Brain sections of MP-4–treated animals showed intense P-170 expression in striatum and cerebral cortex. Immunoreactivity was prominent in the capillary endothelium and surrounding astrocytes, and also evident although less intense in a few neuron fibers. In MP-7, extensive neuronal areas were stained in the same brain regions, and the imges showed sparse immunostaining on neurons, increasing highly the intensity near the vessels. In control animals, P-170 expression was minimal, showing a light and sparse labeling on a few blood vessels. **Conclusions:** These results showed a differential pattern of expression of MDR-1 gene (P-170) in brain MP-treated rats in 4 and 7 days. A longer time of MP treatment induced more extensive neuronal MDR-1 gene expression. It is the first experimental model of MDR-1 gene neuronal expression induced by proconvulsivant drug treatment. [Supported by University of Buenos Aires (UBACYT B-033), CONICET and Ministerio de Salud, Argentina.] (Disclosure: Grant: UBACYT B33, CONICET, and Ministerio de Salud, Argentina.)

1.025
EFFECT OF LOW-FREQUENCY STIMULATION ON AMYGDALA-KINDLED AFTERDISCHARGE THRESHOLDS AND SEIZURE PROFILE IN FAST AND SLOW KINDLING RAT STRAINS

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Rationale: As many individuals with temporal lobe epilepsy remain resistant to pharmacologic treatment, alternative approaches to arrest their seizures become essential. Several alternative treatments have been presented recently, including electrical brain stimulation. Previously it was reported that long trains of low-frequency stimulation (LFS) retard the kindling process in rats (Gaito, 1980). However, from a clinical perspective, a more important question would be whether that stimulation could be applied effectively against a previously epileptic site. To answer that question, we assessed the effects of LFS on a kindled amygdala focus in rats that were selectively bred to be natively seizure prone (Fast kindlers) or seizure resistant (Slow kindlers). The objective was to measure the antiepileptic potential of LFS. **Methods:** Under surgical anesthesia, 10 Fast- and 10 Slow-kindling male rats (250 g) were implanted in both amygdalae with either a twisted bipolar electrode (<0.5-mm tip separation) or a spaced bipolar electrode (i.e., two monopolar electrodes separated by 4 mm anterior to posterior). One week later, afterdischarge thresholds (ADTs) were determined, which was followed by daily kindling of one amygdala by using a 2-s, 60-Hz sine wave stimulus at the local ADT intensity. After kindling and the accumulation of six stage-5 generalized convulsions, five to 10 additional convulsions were provoked to assess the stability of the local ADT. Once ADT stability was evident, a single 30-s, 1-Hz sine wave stimulus at 100 μA was delivered to the kindled site. The ADT at that site was then redetermined 1 min, and again 1–7 days later (without repetition of the LFS). **Results:** The ADTs showed no change 1 min after presentation of the LFS in either strain, nor were there changes in the profile of the convulsive seizures. However, 1 day later, a dramatic elevation (200–500%) in the ADTs occurred, which slowly abated over 3 days and returned to baseline by ~7 days. This outcome was evident with both electrode configurations and in both strains. However, in the Slow rats, the convulsive seizure profile was also altered 24 h after LFS. Normally, without LFS, 100% of the ADTs are associated with a triggered convulsion. However, in the Slow rats after LFS, ≤30% of the ADTs did not recruit a convulsive response. With Fluoro-Jade, histologic assessment 24 h after LFS indicated no evidence of brain injury associated with the elevated ADTs. **Conclusions:** LFS of a kindled epileptic focus raises the threshold for triggering subsequent focal seizures for several days. This effect is not associated with obvious brain injury. It remains to be determined, however, whether the suppressive effects of LFS on ADTs are localized to cells at the electrode tips or represent an effect cast more broadly over the larger kindled network. (Supported by CIHR.)

1.026
SIMULTANEOUS EEG AND fMRI STUDY OF THE OCCIPITAL LOBE SEIZURES

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Rationale: Functional MRI (fMRI) has the potential to overcome limitations inherent in EEG study of epileptiform activity and provide real-time cortical and subcortical activation maps of epileptiform discharges. The feasibility of simultaneous fMRI/EEG was investigated in an animal model of epilepsy. **Methods:** Male Spargue–Dawley rats were anesthetized with isoflurane. Burr holes were made by using Paxinos and Watson's stereotactic atlas as the reference. Using an MRI-compatible stereotactic frame of our own design, carbon fiber EEG electrodes were placed above the dura. EEG was transmitted from the magnet to the recording system by using a modified version of a device developed by Ives et al. A microsyringe was advanced into the primary visual cortex (V1) of the animal. Various degrees of epileptiform activity were induced in the magnet by using by altering the dose of intracortically injected sodium penicillin G (0–100 IU) in an injection volume of 0.2 μl. Segmented and navigator-echo corrected EPI sequences developed for fMRI on our 4-T Varian whole-body MR scanner were used along with a custom-designed RF coil. A 5 × 5-cm FOV with eleven 2-mm slices was used, resulting in an in-plane resolution of 391 μm. The 11 slices could be repeated with a TR of 1.7 s at a TE of 15 ms. The animals were then killed and perfused with 4% PFA for immunohistochemistry by using C-fos and parvalbumin double labeling. **Results:** Activation maps with fMRI were made by using a pixel cross-correlation method with the low-pass-filtered EEG as a reference vector. Activated areas in fMRI bore a remarkable resemblance to the autoradiography studies of Collins and Caston (1979), showing the utility of a multimodality approach to study of epileptic activities in discerning spread of occipital seizures in a pattern predicted by functional connectivity of the cortical and subcortical visual systems. **Conclusions:** Multimodality study of seizures and other epileptiform activities is a promising tool to study the neurobiology of epileptiform discharges and their precise anatomic localization and propagation. (Supported by Canadian Institute of Health Research.)

1.027
EFFECTS OF SEIZURE REPETITION ON POSTICTAL AND INTERICTAL HEART RATE VARIABILITY IN THE RAT

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Rationale: Human epilepsy is associated with interictal abnormalities in heart-rate variability (HRV) and approximate entropy (ApEn), but it is not known how these abnormailities are related to seizure experience. We demonstrated previously that maximal electroshock (MES)-induced tonic seizures are associated with severe abnormalities in cardiac regulation, resulting in arrhythmia during the immediate postictal state. The severity of arrhythmia increased with increases in seizure severity and with daily seizure repetition. We now examine whether MES repetition induces interictal abnormalities in neurocardiac regulation. **Methods:** We obtained baseline ECG (3,000 beats) from Sprague–Dawley rats (n = 5) to calculate RR interval, standard

deviation (SD), ApEn, and normalized high- and low-frequency spectra (HFn, LFn, respectively). The rats were submitted to daily MES for a total of 10 stimulations. From the ECG recordings (3,000 beats), parameters were obtained from just before seizures for interictal data and during the late postictal phase (after the phase of obvious cardiac arrhythmia). The data were compared against baseline values by using the Friedman and Wilcoxon test (post hoc). **Results:** After a single seizure, there was a mild, but significant loss of ApEn during the last postictal state ($z = 2.0$; $p < 0.05$). No significant changes occurred in RR interval, SD, LFn, or Hfn. Before the tenth seizure, there was a significant reduction of variability shown by SD ($z = 1.8$; $p < 0.05$), and a significant reduction of HFn ($z = 2.3$; $p < 0.05$) in the interictal state. After the tenth seizure, there were significant reductions of SD ($z = 2.1$; $p < 0.05$), HFn ($z = 1.7$; $p < 0.05$), and ApEn ($z = 1.8$; $p < 0.05$) during the late postictal state. **Conclusions:** Seizure repetition with MES induces both interictal and postictal abnormalities in HRV in a kindling-like manner. The loss of HFn, which is believed to correlate with vagal function, suggests that at least some of the abnormalities induced by seizure repetition may be mediated by the vagal system. Because abnormalities in HRV have been related to sudden death in several disease states, these findings raise the question of whether seizure experience induces mechanisms that cause pathologic regulation of the cardiac autonomic system, and possibly underlie susceptibility to sudden unexpected death in epilepsy. Participants should be able to understand the effect of experimentally induced seizure repetition on neurocardiac regulation. (Supported by Southern Illinois University School of Medicine Central Research Committee.)

1.028

MARIO GOZZANO: UNFORGETTABLE EEG PIONEER AND EPILEPTOLOGIST

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Rationale: Mario Gozzano's (1898–1986) principal EEG study (1935) work reveals amazing insight and foresight but, being published in Italian, has missed acceptance by EEG epilepsy historians. **Methods:** We revisited Gozzano's essential EEG work based on data acquired while working with Kornmueller in Berlin, using EEG equipment far superior to that of Hans Berger. **Results:** Gozzano's study of the rabbit's EEG is based on strychninization of the cortex and shows single spikes as well as transition to ictal spikes, far ahead of his time. Flashes elicited single spikes from the strychninized visual cortex, thus anticipating a concept of evoked potentials—again, far ahead of his time. With painful somatosensory stimuli, the sensory cortex showed fast and presumably also ultrafast activity resembling electrodecrement, another first. **Conclusions:** Gozzano was a true EEG pioneer and visionary with profound understanding of epileptic basic mechanisms.

1.029

REGIONAL CALCIUM ACCUMULATION AND KAINIC ACID–INDUCED SUBSTANTIA NIGRA SEIZURES IN RATS

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Rationale: We reported a characteristics of substantia nigra seizures induced by a local injection of kainic acid (KA) into substantia nigra pars reticulata (SNr) (*Brain Res* 2001;911:89–95). It has been postulated that excessive influx of calcium into cells and subsequent accumulation of calcium in mitochondria leads to cell damage in various pathologic conditions. The occurrence of cell damage caused by the failure of calcium homeostasis has been reported in the following pathologic conditions: muscle cell necrosis in muscular dystrophy, myocardial infarction, hepatic ischemia, and seizures. In the present study, the sites of calcium accumulation were studied by ^{45}Ca autoradiography during KA-induced SNr seizure in rats. **Methods:** Eight Wistar male rats (250–330 g) were used. Under intraperitoneal pentobarbital (PTB) anesthesia (45 mg/kg), a stainless steel cannula was inserted stereotaxically into the left SNr for KA injection. At 7 days after surgery, 1μg of KA was injected into the left SNr (four rats), and 1μg of physiologic saline was injected into the left SNr (four rats). About 2 h after KA injection, ^{45}Ca was injected through the cannula in the femoral vein. Autoradiograms were prepared by exposing an x-ray film to the dried sections for 14 days in an x-ray cassette. **Results:** In ^{45}Ca autoradiogram, the sites of calcium accumulation were as follows: hippocampus > thalamus > pretectal area > substansia nigra > amygdala > lateral septal nucleus > caudate nucleus > globus pallidus. **Conclusions:** These results suggested that regional calcium accumulation by SNr seizures not only involved the secondary generalization of the seizures but also might be responsible for neuronal cell damages.

1.030

HIGH-FREQUENCY DIRECT CORTICAL STIMULATION AND ITS PRODUCTION OF AFTERDISCHARGES

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Rationale: During extraoperative functional mapping, direct cortical electrical stimulation (25–50 Hz) may lead to focal afterdischarges (ADs) that are usually focal, and stop spontaneously, but at times may spread and evolve into clinical seizure. It was previously shown that an additional focal stimulation may terminate the AD (Lesser et al., 1999). The effect of high-frequency stimulation on seizure generation and control remains unknown. In this study, we evaluated the effect of various stimulus frequencies on the threshold for generation of ADs and the duration of ADs in rat neocortex. **Methods:** Four Sprague–Dawley rats were used. Epidural stainless steel screws were placed over bilateral frontal cortex (A: 3.5 mm, L: ±2 mm from bregma), bilateral motor cortex (A: –1 mm, L: ±3 mm), bilateral sensory cortex (A: –1 mm, L: ±5 mm), and bilateral occipital cortex (A: –6 mm, L: ±3 mm). Bipolar, biphasic square-pulse constant-current stimuli were given between screw electrodes on motor and sensory cortex of the same hemisphere. Pulse width was 0.2 ms. Duration of stimulus train was 5 s. We used various stimulus frequencies: 50, 100, 200, 400, and 800 Hz. Simultaneous EEG recordings were performed. Stimulus intensity varied from 0.2 mA and increased 0.2 mA one by one at 10-min intervals. The threshold was defined as the amplitude of the current necessary for the production of AD. Threshold and duration of afterdischarges were compared for each frequency by using analysis of variance. **Results:** ADs were obtained for all frequencies used. Average and standard deviation of thresholds were 2.51 ± 2.07, 2.20 ± 1.88, 1.74 ± 1.29, 1.79 ± 1.50, and 2.15 ± 1.65 mA corresponding to 50, 100, 200, 400, and 800 Hz, respectively. Durations of the ADs were 10.52 ± 5.71, 7.33 ± 2.59, 8.80 ± 4.41, 8.13 ± 4.48, 8.07 ± 3.39 s, corresponding to 50, 100, 200, 400, 800 Hz, respectively. No significant differences in the threshold or duration of ADs were seen at the various frequencies used. **Conclusions:** Direct cortical stimulation at various stimulation frequencies may lead to ADs with no significant differences in the threshold of AD generation or its duration. (Supported by Medtronic.)

1.031

GLUTAMATE RELEASE AND UPTAKE AND KINDLING: REDOX EFFECT ON GLUTAMATE TRANSPORTERS AND *N*-METHYL-D-ASPARTATE RECEPTOR

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Rationale: Epileptogenesis is associated with receptors and transporters regulating glutamate, especially *N*-methyl-D-aspartate receptor (NMDA-R) and glial excitatory amino acid transporters (EAATs). However, these proteins possess regions sensitive to redox, undergoing opposite functional changes in response to oxidation or reduction of

sulfhydryl groups. This study was designed to examine redox modulation of reactive sulfhydryl components of NMDA-R and EAATs on kindling development and glutamate release in rat hippocampus. **Methods:** Male Wistar rats were used in these experiments. Kindling-like phenomena were induced with periodic release of high potassium (K^+: 100 m*M* for 5 min at 40-min intervals) through in vivo microdialysis in the rat ventral hippocampus. Extracellular glutamate ([Glu]o) levels were measured before and after K^+ stimulation by online enzyme fluorometry. During K^+-artificial cerebrospinal fluid (aCSF) infusion, [Glu]o was increased, and prolonged spike discharges were recorded. Either a disulfide reducing compound, 100 μ*M* dithiothreitol (DTT), or an oxidizing compound, 100 μ*M* 5,5'-dithio-bis(2-nitrobenzoic) acid (DTNB) was added to aCSF during the experiment. **Results:** Perfusion with DTT was associated with acceleration of kindling, with [Glu]o increasing slowly and returning rapidly to basal levels. DTNB perfusion was associated with delayed kindling development with [Glu]o increased rapidly and returned slowly to basal levels, an effect that could be caused by downregulation of NMDA-R and EAATs from an oxidizing redox reaction with protein thiol groups. Further, these data suggest that seizure-related glutamate release and either protective or destructive effects of glutamate are affected by redox effects on receptor and transporter sulfhydryl groups. **Conclusions:** Our data obtained from freely moving rats confirm that the kindling phenomena is dependent not only on extracellular glutamate, but also on the functional state of NMDA-R. We propose that redox effects may be of critical importance in the process of epileptogenesis. [Supported by a Grant-in-Aid for Encouragement of Young Scientists (12770537) from the Ministry of Education, Science, Sport and Culture, Japan (to Y.U.).]

1.032
INHIBITION OF MIDLINE THALAMIC ACTIVITY SUPPRESSES ELECTROGRAPHIC AND LIMBIC MOTOR SEIZURES IN HIPPOCAMPAL KINDLING

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Rationale: The functional anatomy of limbic epilepsy is not well understood, but there is growing evidence that the midline thalamic nuclei, which have significant reciprocal connections with multiple limbic sites, may play a role in the primary seizure circuits as well as the process of seizure generalization. In this study we wished to determine if inhibition of neuronal activity in this region has an effect on the electrographic seizure activity or the behavioral accompaniment in animals with stable kindled seizures. **Methods:** Nine adult male Sprague–Dawley rats were implanted with a bipolar electrode in the mid ventral hippocampus. They also received a cannula guide that remained outside the dura. After 1 week of recovery, the animals were kindled with a modified rapid-kindling protocol (one stimulation every hour, six stimulations per session, sessions separated by $\geq$1 day). Stimuli consisted of 2-s trains of 50 Hz biphasic, 1-ms square-wave pulses at 600 μA peak to peak. When the animals consistently had stage 5 motor seizures to each stimulation, they were given either muscimol (MUS, 30 nmol in 1 μl) or tetrodotoxin (TTX, 60 pmol in 1 μl) were injected via a cannula into the midline thalamic region 5–10 min before a stimulation. Behavioral seizure scores (Racine scale) and afterdischarge duration were measured and compared with baseline values. **Results:** All four of the TTX rats and four of the five MUS rats had a complete suppression of the motor seizure (reduced to scores of 1 or 2) and had shortening of the hippocampal afterdischarge. After the injections, the animals were behaviorally quiet, but able to ambulate when stimulated. **Conclusions:** This study suggests that the midline thalamus is involved in the process of seizure generalization. In addition, the associated reduction in afterdischarge duration suggests that this thalamic region is an integral part of the primary seizure circuit, and that modulation of the activity in this subcortical area will affect electrographic seizure activity in the limbic regions. The observation that there was no inhibition of spontaneous motor activity after the injections indicates that the suppression of limbic motor seizures was not the result of a direct inhibition of the motor system. At the conclusion of this presentation the participant will have a better understanding of the role of subcortical regions in limbic seizure activity. (Supported by NS-25605.)

1.033
INTRACEREBRAL TEMPERATURE ALTERATIONS ASSOCIATED WITH FOCAL SEIZURES

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Rationale: Because focal seizures produce an increase in cerebral blood flow and metabolic activity, they might also change brain temperature and, thereby, alter seizure susceptibility. **Methods:** We induced focal neocortical seizures in halothane-anesthetized rats by microinjection of 4-aminopyridine (4-AP; 0.5 μl of a 25 m*M* solution) and measured the temperature over the site of convulsant injection with a miniature thermocouple. In some experiments, relative blood flow was monitored with a laser Doppler probe (Laserflo Blood Perfusion Monitor, TSI). **Results:** In control animals, brain and rectal temperature remained constant at 33.5 and 37.2°C, respectively, over a 2-h period. In animals treated with 4-AP to induce focal seizures, brain temperature increased an average of 0.3°C within a few seconds of seizure onset, whereas rectal temperature remained constant. This temperature elevation was preceded by an increase in cortical blood flow. Brain temperature, but not blood flow, was also elevated 8 mm away from the seizure focus. When blood flow was increased independent of neuronal activity, by elevating pCO_2, brain temperature also rose by ~0.3°C. We did not detect any change in seizure durations when we used a Peltier device to *elevate* focal cortical temperature 1°C, so the functional significance of this 0.3°C temperature rise is unclear. **Conclusions:** Focal neocortical seizures in rats produce a small, but statistically significant increase in local brain temperature. This temperature increase is the result of increased blood flow that "clamps" brain temperature close to body temperature. In humans, seizures might cause a *reduction* in brain temperature, because brain temperature is normally higher than body temperature. Although the functional significance, if any, of this small elevation of brain temperature induced by focal seizures is unclear, this may be the first direct demonstration that elevation of physiologic brain activity can alter brain temperature. [Supported by Supported by Citizens United for Research in Epilepsy, Inc. (CURE), the Stein Fund for Pediatric Neurology Research, and NS14834 from the NIH.]

1.034
MR SPECTROSCOPIC NAA IMAGING FOLLOWING STATUS EPILEPTICUS: TIME COURSE OF CHANGES AND EFFECT OF EARLY TREATMENT

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Rationale: The time course of neuronal loss after status epilepticus is unclear, and there has been no means of evaluating loss quantitatively in a nondestructive manner so that the effect of therapy can be evaluated in vivo. In this study we used magnetic resonance (MR) spectroscopic imaging of the neuronal marker *N*-acetyl aspartate (NAA) in rats after an episode of status epilepticus to define the time course of neuronal loss and to determine if appropriate early neuroprotective therapy can be demonstrated by this method. **Methods:** Status epilepticus was induced by 90 min of electrical stimulation of the midventral hippocampus in adult male Sprague–Dawley rats. There were eight control animals and six to seven animals per experimental group. The study was performed in a 4.7-T, 9 cm diameter small-animal magnet. NAA levels (voxel size, 7.9 μl) were determined bilaterally for the frontal cortex, amygdala/piriform cortex, as well as the ventral hippocampus. The animals were scanned either at 1 day, 7 days, or 56–60 days after status epilepticus. The spectroscopic findings were

compared with the histology of the 7-day group by using a semiquantitative scoring scale. A separate set was treated with 100 mg/kg phenobarbital (PB) 1 h after stimulation onset. These animals were scanned either 7 or 56–60 days later. **Results:** There were nonsignificant decreases in the NAA levels the day after stimulation, but there were significant decreases ($p < 0.05$) at 7 days that correlated with histologic damage scores in the 7-day group ($p < 0.01$). There was no further decrease, rather a slight increase, at 56 days, an increase that was related to the demonstrated tissue shrinkage in these long-term animals. The NAA levels in these animals were significantly less than the levels in controls ($p < 0.05$) The PB-treated rats had no decrease in the NAA levels at any time. **Conclusions:** High-resolution MR spectroscopy can define the time course of neuronal loss after status epilepticus and quantify the severity. Obtaining studies early after the injury (e.g., 1 day) may establish a reliable baseline value for subsequent comparison. The beneficial effects of therapy can also be demonstrated. This technique can provide a reliable nondestructive means for determining neuronal loss and the effects of therapy in vivo. (Supported by NINDS grant NS25605.)

1.035
NEUROPROTECTIVE EFFECTS OF TOPIRAMATE IN THE KAINIC ACID MODEL OF STATUS EPILEPTICUS

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Rationale: To assess whether treatment with topiramate (TPM) after the onset of kainic acid (KA)-induced status epilepticus modifies its long-term neurologic consequences. Prior studies have shown that KA-induced status epilepticus (KA-SE) results in permanent neurologic deficits including an increased susceptibility to seizures. KA-SE rats exhibit prominent neuronal degeneration in CA3, CA1, and the hilus of the dentate gyrus and have a facilitation of their kindling rate (*J Neurosci* 1992;12:4173–87). Treatment with high doses of phenobarbital (PB; at a dose likely to block AMPA receptors) given 30 min after inducing KA-SE resulted in a dramatic reduction of degeneration in the hilar polymorphic neurons, decreased mossy fiber sprouting, and normalized the rate of kindling. TPM, an AMPA-receptor antagonist and a γ-aminobutyric acid (GABA)-A modulator, may have a similar effect in the KA-SE model. **Methods:** Three groups of rats were studied: normal controls, rats with status epilepticus induced with kainic acid (KA-SE rats; three hourly injections of 5 mg/kg s.c.), and KA-SE rats that were treated after 1 h of status epilepticus with twice daily doses of TPM (60 mg/kg s.c.) for 3–5 days. Additional groups at 20 and 40 mg/kg were also studied to evaluate a dose–response relation. Several measures of neuroprotection were assessed in the three groups: (a) the extent of cell injury using cresyl violet stain, (b) the extent of mossy fiber sprouting induced by KA, (c) the extent of terminal degeneration with the Fink-Heimer staining, (d) the rate of perforant path kindling starting 3 weeks after KA-SE as one measure of late epileptogenesis, and (e) number of late spontaneous seizures 10 weeks after KA-SE. **Results:** TPM given 1 h after KA induced SE. In female rats, the use of TPM at a dose of 60 mg/kg improved survival after KA-SE despite similar behavioral seizure scores. In both males and females, TPM at 60 mg/kg diminished the extent of neuron loss in the hilar polymorphic region and reduced the development of mossy fiber sprouting 3 weeks after KA-SE ($n = 12$) as compared with KA-SE rats ($n = 12$). At lower doses, there was a trend for improved survival after KA-SE, with more neuronal loss and mossy fiber sprouting. Prominent degeneration was observed after KA-SE in the pyramidal regions of the CA1 and CA3 regions. However, TPM at 60 mg/kg selectively protected the hilar polymorphic neurons. **Conclusions:** TPM has neuroprotective properties in a dose-dependent manner in the KA model of SE when given 1 h after KA-SE. The clinical significance of these observations deserves further study in other experimental models of SE. (Supported by Johnson & Johnson Pharmaceutical Research Institute.) (Disclosure: Grant: Johnson & Johnson Research Pharmaceutical Institute; NINDS, Consulting: Ortho-McNeil Pharmaceuticals.)

1.036
TOPIRAMATE IS BOTH NEUROPROTECTIVE AND ANTIEPILEPTOGENIC IN THE PILOCARPINE MODEL OF STATUS EPILEPTICUS

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Rationale: This study evaluated the neuroprotective and antiepileptogenic effects of topiramate (TPM) in the pilocarpine model of status epilepticus (SE). SE is a major medical and neurologic emergency associated with neuronal injury and the development of epilepsy. Development of anticonvulsant agents (AEDs) that not only treat seizure activity, but are also neuroprotective and antiepileptogenic in treating SE would have a significant impact on the treatment of this condition. **Methods:** The pilocarpine model of SE was used to evaluate the effects of (TPM as a neuroprotective and antiepileptogenic agent in SE. SE was induced by pilocarpine injections, terminated with diazepam (DZP), and animals were evaluated for the development of spontaneous recurrent seizure activity by extensive EEG and video monitoring (*Brain Res* 1998;782:240–7). Monitoring was performed at 3–6 months after the initial episode of SE. TPM was administered i.p. in different doses after 1 h of SE and qd for 4 additional days. After monitoring and analysis, animals were perfused, killed, and the brains removed for paraffin embedding and sectioning. Hippocampal cell counts were used to evaluate neuronal cell loss. All studies were performed under the guidelines of VCU animal care approved protocols. **Results:** TPM was found to be neuroprotective in a dose-dependent manner. TPM administered after 1 h of SE and in the immediate 4-day follow-up period was effective in preventing CA1 neuronal cell loss. TPM reduced cell loss from 10.3% in the epileptic animals to the baseline cell counts of sham controls. This neuroprotective effect was statistically significant. TPM in a dose-dependent manner also produced a statistically significant reduction in the development of spontaneous recurrent seizures after SE. TPM was effective in reducing the number of animals that developed epilepsy by >60% in comparison to vehicle control animals. The minimal effective dose of TPM for producing antiepileptogenic effects was 30 mg/kg i.p. **Conclusions:** The data from this study demonstrate that TPM has both neuroprotective and antiepileptogenic effects after SE and suggest that this agent may be useful in decreasing the morbidity and motatily associated with SE. The results suggest that TPM may have a direct effect in preventing or inhibiting epileptogenesis in this model. The development of novel therapeutic agents for treating some of the long-term effects of SE may have an important impact in improving the clinical outcome after this major neurologic emergency. (Supported by NIH RO1-NS23350 and Johnson and Johnson Pharmaceutical Research and Development, LLC.)

1.037
CASPASE-3 ACTIVATION IN NATURALLY OCCURRING APOPTOTIC NEURONS IN NORMAL CONTROLS AND AFTER PROLONGED SEIZURES IN THE ADULT RAT BRAIN

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Rationale: The objective of this study was to determine if activated caspase-3, the central executioner caspse in both the intrinsic mitochondrial pathway and the extrinsic Fas ligand receptor–activated extrinsic pathway, is present in TUNEL-positive morphologically apoptotic neurons in adult rats, and if prolonged seizures increase the number of these activated caspase-3–positive apoptotic neurons, compared with control rats. **Methods:** Adult male Wistar rats had skull screw implantations for EEG recording, and 3 days later, they were given lithium chloride, 3 mEq/kg i.p. The next day they were given

either pilocarpine, 30–60 mg/kg i.p., or an equivalent volume of saline i.p. After 3 h of status epilepticus (SE), diazepam (DZP; 10 mg/kg) and phenobarbital (PB; 25 mg/kg) were given i.p. to stop the seizures (or after an equivalent period of time in controls). Rats were allowed to recover for 6 or 24 h, after which they underwent transcardiac brain perfusion–fixation, their brains were removed, and left hemispheric slices were embedded in paraffin and cut into 6-μm-thick coronal sections, which were stained with TUNEL and a polyclonal antibody to the active p17 fragment of caspase-3 (CM1 antibody). Sections were counterstained with methyl green (TUNEL) and hematoxylin (CM1 antibody). Sections at the level of caudate-putamen (–0.3 mm from bregma), dorsal hippocampus (–3.3 mm from bregma), and ventral hippocampus (–5.60 mm from bregma) were examined. The numbers of TUNEL-positive and CM1 antibody–positive apoptotic neurons in the three brain sections from each rat were summed, and the data were analyzed with three-factor repeated-meaures analysis of variance and post hoc *t* tests. **Results:** The total numbers of TUNEL-positive apoptotic neurons in the three brain sections examined in each rat were significantly increased 6 h after SE (46 ± 13 in controls and 78 ± 15 after SE, mean ± SEM, $p < 0.05$, $n = 3$ and 4, respectively), but not 24 h after SE (44 ± 10 in controls and 35 ± 10 after SE, $p = 0.39$, $n = 5$ and 6, respectively), and the number 6 h after SE was also higher than that 24 h after SE ($p < 0.01$). These results must be confirmed with larger numbers of control and SE rats 6 h after SE. At both 6 and 24 h, the total number of CM1 antibody–positive apoptotic neurons were substantially fewer than the TUNEL-positive neurons, and the numbers of these neurons did not differ between control and SE rats at 6 h (1 ± 1 in controls and 16 ± 2 in SE rats, $p = 0.27$, $n = 3$ and 4, respectively), and at 24 h (0.4 ± 0.2 in controls and 1.5 ± 0.7 in SE rats, $p = 0.92$, $n = 5$ and 6, respectively). **Conclusions:** Active caspase-3 immunoreactivity is found in very few of the naturally occurring apoptotic neurons in adult rat brain, and SE does not increase the number of neurons showing caspase-3 activation. This indicates that either caspase-3 is activated in only a small fraction of apoptotic neurons, or, more likely, that caspase-3 activation occurs transiently in these neurons. Our results provide further evidence that neuronal apoptosis in the adult rat brain may not be influenced by the superimposed stress of SE, which produces widespread neuronal necrosis without caspase-3 activation, but with the DNA laddering that occurs in programmed cell death. (Supported by The Department of Veterans Affairs.)

1.038
PATTERNS OF NEURONAL LOSS AFTER PILOCARPINE-INDUCED SEIZURES IN C57BL/6 MICE

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Rationale: Previous studies have indicated that C57BL/6 mice are relatively resistant to neuronal loss after kainate-induced status epilepticus (Schauwecker, Steward. *Proc Natl Acad SciU S A* 1997;94:4103–8). The goals of this study were to determine if this mouse strain is also resistant to neuronal damage after pilocarpine-induced seizures and to compare the patterns of neuronal loss with those commonly found in pilocarpine-treated rats. **Methods:** Seizures were induced in adult C57BL/6 mice by systemic injection of pilocarpine (320 mg/kg, i.p.). The distributions of degenerating neurons were examined at short intervals (24 h to 1 week) with Fluoro-Jade methods. Patterns of neuronal loss were determined at 1–8 weeks by cresyl violet staining and immunohistochemical localization of NeuN, a general marker of neuronal nuclei. **Results:** Pilocarpine treatment produced sustained behavioral seizures in a high percentage of C57BL/6 mice. These mice resumed normal behavior within 1–2 days but then developed spontaneous seizures at 1–3 weeks after the induced seizures. Very close similarities were found between the brain regions that contained degenerating neurons at early time points, as identified by Fluoro-Jade, and the regions with neuronal loss that were evident in NeuN-labeled specimens at later time points. In the hippocampal formation, the patterns of neuronal damage were similar to those observed in pilocarpine-treated rats. Extensive damage was found consistently in the hilus and CA3, and more variable amounts of neuronal loss were observed in CA1 and CA2. Substantial neuronal degeneration was also evident in several amygdaloid nuclei. Within the thalamus of the C57BL/6 mice, severe neuronal loss was confined to specific nuclei that included the lateral dorsal, reuniens, and intralaminar nuclei. Neuronal loss in many other thalamic nuclei was less severe than that in the rat. Interestingly, very little neuronal degeneration was observed in the piriform cortex, where severe damage is generally found in the rat. Neuronal loss in other regions of the cerebral cortex was also less severe in the C57BL/6 mice than in Sprague–Dawley rats. **Conclusions:** Extensive neuronal damage occurs in the hippocampus of C57BL/6 mice after pilocarpine-induced status epilepticus, and this appears to contrast with the relative invulnerability of hippocampal neurons in this mouse strain to kainate-induced seizure damage. However, the extent and location of neuronal damage in several other regions of the CNS appears to be less severe and more selective in the C57BL/6 mice than in Sprague–Dawley rats. The consistent development of spontaneous seizures in these mice, despite the more restricted neuronal loss, suggests that the pilocarpine-treated C57BL/6 mouse could be a particularly useful animal model of temporal lobe epilepsy. These mice also could provide a baseline for evaluating the influence of various genetic alterations on neuronal damage and epileptogenesis in mice with a C57BL/6 genetic background. (Supported by VA Medical Research Funds.)

1.039
EXPRESSION OF B/K PROTEIN IN THE KAINIC ACID–INDUCED SEIZURE MODEL

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Rationale: B/K protein is a member of the double C2-like domain protein family. It is abundantly expressed in the brain, especially in the hypothalamus, pituitary gland, cerebral cortex, and hippocampus. Although its physiologic function is not evident, we found that its expression was increased in vulnerable regions under several pathologic conditions such as cerebral, renal, and retinal ischemia. **Methods:** Seizure was induced in adult male Sprague–Dawley rats by intraperitoneal injection of kainic acid. Time- and dose-dependent changes of the immunoreactivity to B/K protein and BiP were examined by immunohistochemistry. Subcellular localization of the B/K protein and colocalization with BiP were also studied by electron and confocal microscopic studies, respectively. **Results:** We demonstrated that, in the kainic acid–induced seizure model, the immunoreactivity of the B/K protein increased dose and time dependently in the CA3 and CA1 regions of the hippocampus. Expression of the B/K protein reached the maximum at 6–12 h after kainic acid injection and was partially blocked by MK-801 pretreatment. Microscopically, the immunoreactivity was not homogeneous but punctated in the cytoplasm, especially in the perinuclear region, and it was localized primarily in the endoplasmic reticulum (ER) in the electron microscopic study. Interestingly, the immunoreactivity of BiP, a marker of ER stress response, showed the similar time-dependent expression pattern to the B/K protein in the CA3 and CA1 regions. Moreover, the fluorescent signal of B/K protein was colocalized with BiP in some neuronal cells. **Conclusions:** These data suggest the possibility that the expression of B/K protein in the kainic acid seizure model may be related to ER stress response. (Supported by The Fund for the Promotion of Basic Medical Science 2001 supported by the Korean Medical Association.)

1.040
TREATMENT OF PROLONGED STATUS EPILEPTICUS: A COMPARISON OF THREE *N*-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS

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Rationale: Clinical manifestations, EEG findings, brain damage and mortality associated with convulsive status epilepticus (SE) suggest

that it can be divided into two distinct phases, an early (initiation) phase and a late (self-sustaining) phase. Treatment studies indicate that current therapy is more effective in early phase but ineffective in the late phase. Experimental studies demonstrate that *N*-methyl-D-aspartate (NMDA) antagonists are effective during the late stages of status epilepticus, when γ-aminobutyric acid (GABA) agonists begin to fail. However, these studies did not compare different classes of NMDA-receptor antagonists. It is also not known whether NMDA-receptor antagonists administered late during SE can offer neuroprotection. **Methods:** SE was induced in adult male rats by the continuous hippocampal stimulation for 90 min, as described by Lothman. Animals in behavioral and electrographic SE were treated 60 min after stimulation (150 min of SE) by intraperitoneal administration of increasing doses of NMDA-receptor antagonists. The control group was saline treated. EEG recordings of all animals were monitored continuously for 5 h after injection. Data for the logarithm of drug doses and the percentage of animals seizure free were fit to an equation for a sigmoidal curve with a variable slope; and the maximum and minimum responses were fixed to 100% and 0, respectively. All animals were evaluated for the development of chronic epilepsy by video -EEG monitoring. **Results:** Control animals had continuous seizures during 300 min of observation, and 80% developed epilepsy. MK-801 acts by a use-dependent open channel-block mechanism. MK-801 (2 mg/kg) controlled SE in 75% of animals, shortening mean posttreatment seizure duration to 81 min. Smaller doses of MK -801were less effective, and the median effective dose (ED_{50}) was 1.5 mg/kg. Epilepsy developed in 10 (52%) of 19 MK-801–treated rats. Ifenprodil is a selective NR2B-containing NMDA-receptor antagonist that increases the sensitivity of NMDA receptors to inhibition by protons. The highest dose of ifenprodil (30 mg/kg) controlled SE in only 50% of the rats, reduced posttreatment seizure duration to 180 min, and lower doses were less effective. Epilepsy developed in eight (63%) of 13 ifenprodil-treated animals. CPP binds to the agonist-binding site on the NMDA receptor and competes with the neurotransmitter glutamate. CPP (15 mg/kg) controlled SE in all animals tested, shortened SE duration to 109 min, and its ED_{50} was 6.4 mg/kg. Development of epilepsy in these animals is being studied. **Conclusions:** The rank order of efficacy in controlling prolonged SE was CPP, MK-801, followed by ifenprodil; that for shortening SE was MK-801, CPP, followed by ifenprodil; and for preventing development of epilepsy, it was MK-801 followed by ifenprodil. Both competitive and noncompetitive NMDA antagonists can control prolonged self-sustaining SE. Ifenprodil was less effective. (Supported by NINDS grants NS 02081 and NS 40337.)

1.041

LOSS OF PHASE SYNCHRONY IN AN ANIMAL MODEL OF PARTIAL STATUS EPILEPTICUS

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Rationale: The interruption of a focal and chronic infusion of ©-aminobutyric acid (GABA) in the neocortex of rats gives rise to the progressive emergence of a sustained spikes activity, associated with myoclonic jerks of the corresponding body territory. This activity remains for hours at an average frequency of 1.5 Hz and is localized to the previous site of infusion. The GABA-withdrawal syndrome (GWS) has therefore features of partial status epilepticus. The changes of neural interactions were studied in living rats by measuring the phase synchrony between epidural EEG signals bilaterally recorded in the neocortex. **Methods:** Nineteen adult rats were stereotactically implanted with a stainless steel cannula in the left somatomotor cortex. The cannula was connected, via a subcutaneous catheter, to an osmotic minipump placed under the skin of the rat's back, and filled with a Kreb's solution containing GABA (1 *M*). The infusion was delivered at a rate of 1 μl/h during 5 days, and then was interrupted. The analysis of phase synchrony between neuronal signals measured the degree to which two signals were phase-locked during a short period and was performed as previously described (Le Van Quyen, et al. *J Clin Neurophysiol* 2001;18:191–208).The level of phase synchrony between EEG signals was measured from 0.1 to 200 Hz by steps of 2 Hz, and then in specific frequency bands. Spectral analysis was performed using the fast Fourier transform. **Results:** Our results showed (a) the epileptic activity was strikingly associated with a decrease of phase synchrony that largely predominated in the 1- to 6-Hz frequency range and for all pairs of electrodes coupled to the focus (with a mean decrease of 75% between the synchrony levels before GABA interruption and after appearance of the epileptic activity), (b) the GWS-related hyposynchrony was not correlated with a difference of spectral emission, because an increase of power spectrum was observed in the signals in this frequency range, (c) no specific synchrony change was detected before the first spikes, (d) systemic injection of ketamine, an antagonist of the glutamatergic NMDA receptors, slightly delayed the appearance of the epileptic activity if injected simultaneous with the GABA interruption, or slightly decreased the epileptic activity if injected later. In both conditions, a large frequency-band decrease of synchrony was initially observed and then followed by an increase of 1–6 Hz synchrony despite reappearance of a spiking activity. (e) Spiking activity and GWS-related synchrony changes were rapidly corrected by local reperfusion of GABA. **Conclusions:** These results may suggest mechanisms underlying partial status epilepticus and may explain why and how the epileptic activity of the focus is not able to diffuse into the whole brain and to be generalized. Prolonged hyposynchrony between neuronal populations may favor the development of pathologic epileptic activities. (Supported by INSERM, FRM.)

1.042

KAINATE MODULATION OF NUCLEAR FACTOR κB ACTIVATION IN RAT HIPPOCAMPUS

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Rationale: Nuclear factor-κB (NF-κB) is activated by a wide range of stimuli and operates in several different signaling pathways. A number of these signaling pathways, including the mitogen-activated protein kinase (MAPK) cascade, modulate transcriptional activation through phosphorylation of transcription factors. Members of the MAPK family, extracellular-signal regulated kinase (ERK), p38 MAPK, and c-jun N-terminal kinase (JNK), have been shown to activate NF-κB in a variety of cell types. Previous studies in the kainate (KA) model of epilepsy have demonstrated activation of the MAPK signaling cascade in hippocampus after seizures. However, the downstream transcriptional effectors of MAPK in the KA model of epilepsy are not well understood. In these studies we evaluated KA-mediated activation of the transcription factor, NF-κB, in rat hippocampus. We also investigated whether KA-induced NF-κB activation couples to MAPK activation in hippocampus. **Methods:** We first investigated phospho-NF-κB levels and phosphorylation and degradation of total levels of IκBα, the NF-κB inhibitor in KA-treated hippocampal slices by Western blotting. ERK, p38 MAPK, and JNK activation in KA-treated hippocampal slices were evaluated by Western blotting with phosphoselective antibodies. Additionally, we sought to correlate findings from KA studies in hippocampal slices in vitro with studies in the KA model, in vivo. For these studies, we evaluated ERK, p38 MAPK, JNK, and NF-κB activation in hippocampus after KA-induced status epilepticus. **Results:** Immunoblot analysis revealed a dose-dependent increase in hippocampal NF-κB phosphorylation ($p \leq 0.05$) after KA treatment compared with controls in hippocampal slices. Similarly, we found a dose-dependent increase in phosphorylated ERK ($p \leq 0.01$) and p38 MAPK ($p \leq 0.05$) levels, but not phospho-JNK levels, after KA. Preliminary inhibitor studies are under way to evaluate MAPK coupling to KA-induced activation of NF-κB in hippocampal slices. Interestingly, we found increased levels of phospho-NF-κB ($p \leq 0.0001$) in hippocampus after KA-induced status epilepticus. **Conclusions:** We have shown that KA modulates activation of NF-κB in hippocampus, suggesting a potential mechanism for changes in gene expression that contribute to the long-term changes seen in the KA epilepsy model. We are investigating whether this KA effect is coupled

to MAPK in hippocampus. These studies provide insights into the role of KA-mediated transcriptional activation. (Supported by NINDS.)

1.043
RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS POTENTIATES NEURONAL DAMAGE IN KAINIC ACID AND PILOCARPINE SEIZURE MODELS

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Rationale: RAGE (receptor for advanced glycation end products) is a member of the immunoglobulin superfamily of cell-surface molecules with a diverse repertoire of ligands. Based on its capacity to bind AGEs (advanced glycation end products), beta-sheet fibrils, S-100/calgranulins, and amphoterin, RAGE appears to function as a progression factor promoting pathologic cellular activation in a range of situations. We hypothesized that RAGE activation promotes seizure-induced cell death after experimentally induced status epilepticus. **Methods:** Transgenic mice were generated with targeted neuronal overexpression of either wild-type RAGE (Tg wtRAGE) or dominant-negative RAGE, a form lacking the receptor's cytosolic tail (Tg DN-RAGE). Both groups of Tg mice and age- and strain-matched littermate controls were challenged with either systemic kainic acid or pilocarpine. Homozygous RAGE null mice were similarly studied. Acute seizure-induced neuronal damage was examined over the next 1–5 days with silver and FluoroJade staining. **Results:** Both Tg wtRAGE and Tg DN-RAGE displayed prominent upregulation of RAGE. Overexpression of these transgenes did not affect seizure severity or seizure-induced mortality in response to either pilocarpine or kainic acid administration. However, after status epilepticus induced by either of these agents, seizure-induced neuronal damage was significantly increased in the CA1 and CA3 hippocampal subfields in Tg wtRAGE ($p < 0.05$), compared with littermate controls. In contrast, damage was strongly reduced in Tg DN-RAGE mice ($p < 0.05$). Consistent with these data, RAGE null mice displayed a 70–80% reduction in cell death in CA1 and CA3 regions, compared with littermate controls ($p < 0.05$). **Conclusions:** After kainic acid- or pilocarpine-induced status epilepticus, RAGE promotes hippocampal neuronal damage. Blockade of RAGE–ligand interaction may provide a novel neuroprotective strategy for the prevention of seizure-induced neurotoxicity. [Supported by AG60901, AG16223 (H.P.Z., D.S., S.D.Y.); New York Academy of Medicine Elsberg Award, Klingenstein Foundation (G.M.).]

1.044
TIME COURSE OF CHANGES IN APOPTOTIC SIGNAL-TRANSDUCTION FACTORS DURING AND AFTER EXPERIMENTAL STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) results in programmed cell death (PCD) and in activation of a number of related signal-transduction factors including Bcl-2, Bax, and caspase-3. Recent data from our laboratory suggest that ceramide may also be implicated in SE-induced PCD. The exact time sequence of activation of those factors during, and after, SE is not known. The objective of this study was to determine the sequential changes in these factors in an attempt to understand potential relations that activation of those factors may have to each other. **Methods:** Adult Sprague–Dawley rats (two to six/group) were injected intraperitoneally with 15 mg/kg kainic acid (KA), underwent SE, were killed at 1, 2, 3, 6, 12, 18, 24, and 30 h after KA, and were compared with a group of six controls.The left hemisphere was cut into frozen sections for immunohistochemisty to detect Bax, Bcl-2, and CPP32/caspase-3 p20 activated fragment. The intenisity of each stain in the hippocampus was assessed blindly by using an ordinal severity scale. The right hippocampus was used to assay the level of ceramide (normalized to lipid phosphate levels) by using the diacylglycerol method. Statistical analysis was performed with the Kruskal–Wallis and analysis of variance tests. **Results:** Compared with baseline, ceramide levels increased at 2 h and remained increased at each of the subsequent time points. Bcl-2 increased at 2, 3, and 6 h, and went back to baseline after that. Bax increased at 12 h. Caspase-3–activated fragment increased at 18 h and remained increased after that ($p < 0.05$ in each of these comparisons, data presented in Table 1). **Conclusions:** SE induces early, and subsequently, sustained increases in ceramide levels starting 2 h after KA injection.This is accompanied by initial increases in the antiapoptotic factor Bcl-2, and is subsequently followed by increases in the proapoptotic factors Bax and activated caspase-3. This suggests that ceramide could, potentially, exert its effects upstream of these two proapoptotic factors. (Supported by DTS17988816700 and URB 17996074524.)

TABLE 1. *Changes after KA injection*

Hours	Ceramide/ Phosphate ratio	Bcl-2 score	Bax score	Caspase-3 fragment score
0 (Baseline)	2.35 ± 0.56	4.0 ± 1.0	7.1 ± 3.2	0.0 ± 0.0
1	2.18 ± 0.54	5.7 ± 4.6	10.6 ± 1.5	—
2	3.46 ± 0.53[a]	8.7 ± 2.3[a]	10.7 ± 1.0	0.0 ± 0.0
3	3.76 ± 0.45[a]	6.0 ± 0.0[a]	5.0 ± 0.0	0.0 ± 0.0
6	3.11 ± 0.87[a]	9.0 ± 2.8[a]	6.0 ± 2.8	0.0 ± 0.0
12	7.14 ± 2.91[a]	3.3 ± 0.5	10.8 ± 0.8[a]	1.5 ± 2.1
18	5.19 ± 0.92[a]	6.0 ± 2.0	5.3 ± 2.1	2.5 ± 0.7[a]
24	6.81 ± 2.63[a]	4.5 ± 2.1	2.5 ± 2.1	3.0 ± 0.0[a]
30	4.78 ± 0.80[a]	3.5 ± 0.7	4.5 ± 0.7	6.0 ± 1.4[a]

[a] Increased ($p < 0.05$) as compared to baseline, data expressed as mean ± SD.

1.045
NS1209, A NOVEL AMPA ANTAGONIST, EFFICIENTLY STOPS STATUS EPILEPTICUS IN RAT

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Rationale: Status epilepticus (SE) is a medical emergency with a high risk of mortality, cognitive decline, and epileptogenesis. About 40% of SE is resistant to the first-line treatments, and the risk of poor prognosis increases with a prolongation of SE. This creates a need for the development of compounds that rapidly discontinue SE. Here we describe the effect of a novel systemically administered α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) antagonist, NS1209, on electrographic and behavioral SE activity in rats. **Methods:** Self-sustained SE was induced by electrically stimulating the lateral nucleus of amygdala of adult Spraque–Dawley rats ($n = 22$) for 20–30 min (100-ms train of 1-ms, 60-Hz bipolar pulses, 400 μA, every 0.5 s). For intravenous (i.v.) drug administration, a polyethylene cannula was inserted into the right jugularis vein 1 day before induction of SE. Five rat groups were treated with various doses of NS1209 (10–100 mg/kg, i.v. or i.p. bolus continued with an i.v. infusion of 4–30 mg/kg/h for 2–24 h) 3 h after the beginning of SE. To assess the effect of NS1209 on SE activity, rats were monitored with a continuous (24 h/day) video-EEG monitoring for 3 days to assess the occurrence of high-amplitude and -frequency discharges (HAFDs) during SE, which are typically associated with behavioral seizures. **Results:** Administration of 10 mg/kg bolus (i.p.) followed with a 4-mg/kg/h infusion (i.v.) of NS1209 completely stopped the HAFDs in four (50%) of the eight animals in 122 ± 74 min. A 50-mg/kg bolus (i.v.) with a 5-mg/kg/h infusion (i.v.) stopped the HAFDs as well as all epileptiform activity in four (67%) of six animals in 14 ± 5 min without recurrence. The two remaining rats a very few HAFDs, 12 ± 11, during the next 72 h. Administration of 100-mg, 75-mg, or 50-mg bolus with 30 mg/kg/h i.v. infusion increased the mortality (seven of eight died compared with none of 14 treated with doses described earlier, $p < 0.001$, Pearson $\chi 2$ test). **Conclusions:** Systemic administration of NS1209 as long as 3 h

after the beginning of SE effectively stopped both the behavioral and electrographic SE activity. At optimal treatment regimen, response was obtained within 15–20 min without recurrence or mortality. These data show that AMPA-receptor blockage may provide a novel and efficient target for the treatment of SE. (Supported by The Sigrid Juselius Foundation, The Vaajasalo Foundation and The Academy of Finland.)

1.046

PROPOFOL INHIBITION OF LITHIUM-PILOCARPINE–INDUCED STATUS EPILEPTICUS

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Rationale: The status epilepticus (SE) induced by lithium–pilocarpine (Li-pilo) treatment in rats produces neuropathology similar to that of the organophosphrous (OP) nerve agents. Because ongoing cholinergic convulsions are difficult to arrest with current treatments, this study was designed to determine the efficacy of the nonbarbiturate anesthetic propofol against Li-pilo–induced SE. **Methods:** Anesthetized Sprague–Dawley rats were implanted with electrocorticographic (EcoG) electrodes. After 7–10 days of recovery, they were administered 3 mmol/kg LiCl, s.c., followed 20–24 h later by 25 mg/kg pilocarpine, s.c. Propofol was administered i.p. either immediately after pilocarpine exposure, after 5 min of SE, or after 3 h of SE, as defined by continuous, high-amplitude ECoG activity. Animals were killed 24 h after pilocarpine, and the brains sectioned for hematoxylin and eosin (H&E) stain. **Results:** All animals survived the 24-h period after 3 h of SE when treated with 55 mg/kg propofol, but only half (three of six) survived after 50 mg/kg propofol. All subsequent experiments tested 55 mg/kg propofol. Propofol prevented SE onset after pilocarpine exposure and terminated all seizure activity when administered during SE. The latency to inhibit SE was longer after 3-h SE than 5-min SE (20.8 vs. 12.8 min; *t* test, $p < 0.05$). Rats experiencing 3-h SE had substantial neuropathology in the perirhinal and especially the piriform cortex, with all animals demonstrating >40% necrotic or malacic tissue in that area. Significantly less neuropathology was found in the perirhinal and piriform cortex of rats treated with propofol after 5 min of SE as determined by histopathology rating (Mann–Whitney *U* test, $p < 0.025$) and optical density measurements (*t* test, $p < 0.01$) of H&E-stained sections. **Conclusions:** This study is the first to demonstrate that propofol effectively terminates ongoing Li-pilo–induced SE and decreases neuropathology associated with those seizures. Propofol may serve as effective treatment of OP nerve exposure. (Supported by Department of Army award no. DAMD 17-01-1-0794. The US Army Medical Research Acquisition Activiy, 820 Chandler Street, Fort Detrick, MD 21702-5014 is the awarding and administering acquisition office.)

1.047

cDNA PROFILING OF EPILEPTOGENESIS IN THE RAT BRAIN

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Rationale: Temporal lobe epilepsy is the most common human focal epilepsy. It typically develops in three phases: (a) initial brain-damaging insult, (b) latency period (epileptogenesis), and (c) recurrent seizures (epilepsy). The present study tested the hypothesis that remodeling of neuronal circuits underlying epilepsy is associated with altered gene expression during the epileptogenic phase. **Methods:** Epileptogenesis was triggered by inducing self-sustained status epilepticus (SSSE) with a 20- to 30-min electrical stimulation of the amygdala in rats. Animals were monitored continuously with video-EEG to ascertain that they were in the epileptogenic phase. Pattern of gene expression was examined in the hippocampus and temporal lobe by using cDNA arrays containing ~5,000 gene probes. Semiquantitative reverse transcription–polymerase chain reaction (RT-PCR) was performed to verify changes in expression for selected genes. **Results:** Changes in gene expression were found for 282 genes. In the hippocampus, 87 genes displayed changes in expression. In animals undergoing epileptogenesis that did not have spontaneous seizures, changes in gene expression were observed for 37 genes at 1 day, 12 genes at 4 days, and 14 genes at 14 days after stimulation. In epileptic animals that had spontaneous seizures by 14 days after stimulation, alterations were observed for 42 genes. In the temporal lobe, changes in expression were observed for 208 genes. In animals undergoing epileptogenesis, changes in gene expression were observed for 29 genes at 1 day, 155 genes at 4 days, and 32 genes at 14 days after stimulation. In epileptic animals, alterations were observed for 62 genes. Genes displaying changes can participate in a wide range of processes including synaptic and axonal plasticity, organization of cytoskeleton, organization of extracellular matrix or cell adhesion, gliosis, signal transduction, protein synthesis and processing, energy metabolism, regulation of cell cycle, or oxidative processes. A majority of these genes was not previously implicated in epileptogenesis or epilepsy or encodes unknown proteins. **Conclusions:** Epileptogenesis is associated with dynamic changes in expression of number of genes that can be involved in several parallel processes occurring in the brain. (Supported by the Academy of Finland, Sigrid Juselius Foundation and Vaajasalo Foundation.)

1.048

MOSSY FIBER SPROUTING AND RECURRENT EXCITATORY CIRCUIT FORMATION IN THE DENTATE GYRUS OF C57BL/6 and CD1 MICE AFTER PILOCARPINE-INDUCED SEIZURES

Ronald S. Winokur, Scott F. Davis, and Bret N. Smith (Cell and Molecular Biology, Tulane University, New Orleans, LA)

Rationale: Several rat models have examined morphologic and physiological changes in the dentate gyrus associated with the development of temporal lobe epilepsy (TLE), but analogous studies in mice have been few. Systemic kainate does not induce these changes in some murine strains, but pilocarpine injection leads to TLE and mossy fiber sprouting in C57BL/6 and CD1 mice. Because these mice are commonly used as a background for genetic mutation studies, the physiological consequences of TLE development was examined in the dentate gyrus of these strains. **Methods:** Systemic pilocarpine injection (280–290 mg/kg) was used to induce status epilepticus (SE) in adult male ICR (CD1) and C57BL/6Nhsd mice. Seizure behavior was monitored for the next 2 months. Transverse slices of the ventral hippocampus were made from pilocarpine-treated and untreated mice, and extracellular field potentials were recorded in the granule cell layer of the dentate gyrus. Recording solutions were nominally magnesium free and contained bicuculline methiodide. Population activity was recorded after electrical stimulation of the mossy fibers in the hilus and in response to photoactivation of glutamate within the granule cell layer. Slices were subsequently processed for Timm and Nissl histochemistry. **Results:** Data were obtained from 12 mice that survived pilocarpine-induced SE, eight mice that were injected with pilocarpine, but did not undergo SE, and six control mice. Most SE survivors, but not other mice, had spontaneous seizures in the weeks after treatment. Electrical stimulation of the hilus resulted in a single population spike in the dentate gyrus of slices from control mice and animals that did not experience SE. In SE survivors, similar stimulation resulted in a population spike followed by a DC shift of variable latency, which was often accompanied by repetitive afterdischarges lasting 3–60 s. Afterdischarges were blocked by glutamate-receptor antagonists. Uncaging glutamate at the recording pipette tip resulted in a negative DC shift in most slices. Negative shifts and population spikes were also elicited by glutamate uncaged in the granule cell layer at sites distant from the recording pipette in slices from SE survivors, but not other groups. Timm staining revealed robust mossy fiber sprouting in the inner molecular layer of slices from SE survivors, but not other groups. **Conclusions:** These data confirm that SE leads to development of spontaneous seizures and mossy fiber sprouting in CD1 and C57BL/6 mice. They further indicate that pilocarpine-induced SE and consequent mossy fiber sprouting results in formation of recurrent excitatory circuits between granule cells of the dentate gyrus in these murine strains. The dentate gyrus of pilocarpine-treated mice shares significant physi-

ologic and morphologic characteristics with rat models. These data support the hypothesis that SE-induced mossy fiber sprouting and synaptic reorganization are relevant characteristics of TLE. The murine model proposed may be a useful means of examining the genetic regulation of the cascade of events leading to this circuit remodeling. [Supported by Louisiana Board of Regents (LEQSF-RD-A-35) and the American Heart Association (SDG-0030284N).]

1.049

ESTROGEN ALTERS METABOLIC ACTIVITY OF DENTATE GYRUS DURING KAINIC ACID–INDUCED SEIZURES

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Rationale: Kainic acid (KA)-induced status epilepticus results in neuronal loss in the hilus and CA3 hippocampal region. In female rats, estrogen administration at low doses has a neuroprotective effect in the same regions. The neuroprotective effect of estrogen seems to be related to increased inhibition in the dentate gyrus, which serves as a gate for seizure propagation from entorhinal cortex into the hippocampus. Estrogen increases paired-pulse inhibition in the dentate gyrus. We used [^{14}C]2-deoxyglucose autoradiography to determine the changes in glucose utilization (a marker of neuronal activation) in the dentate gyrus after seizures in oil- and estrogen-treated females. **Methods:** Rats were ovariectomized 1 week before hormone replacement. Oil vehicle or β-estradiol (2 μg/day) was injected subcutaneously 48 and 24 h before saline or KA (16 mg/kg, i.p.). Cerebral glucose utilization was measured with [^{14}C]2-deoxyglucose, which was injected after 45 min of continuous seizures. **Results:** Qualitative evaluation of the autoradiograms after KA-induced status epilepticus revealed hypermetabolic activity in the granule cell layer in oil-treated rats compared with rats without seizures. In contrast, no such hypermetabolism was observed in the granule cell layer in estrogen-treated rats. **Conclusions:** These results suggest that estrogen treatment alters the entry of seizure activity into the dentate gyrus after KA-induced seizures. These findings indicate that the neuroprotective effects of estrogen on seizure-induced hippocampal damage may result from increased gating ability of the dentate gyrus. (Supported by NS 30387.)

1.050

DIFFERENCES IN C-FOS EXPRESSION PATTERNS BETWEEN SEIZURES INDUCED BY NICOTINE, COCAINE, AND PENTYLENETETRAZOLE IN NAÏVE AND KINDLED MICE

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Rationale: We previously reported that kindling can occur after the repeated administration of nicotine (1). In the present study we investigated this model further by examining the neuronal activity after a seizure, using c-Fos expression as a marker of neuronal activity. Furthermore, we compared the expression pattern of the nicotine kindling model with that of the pentylenetetrazol (PTZ) kindling (2) and a cocaine-kindling model (3). **Methods:** Kindling was induced in male NMRI mice by injection of either cocaine (48 mg/kg) every day for 5 days, PTZ (37 mg/kg) every other weekday for 3 weeks, or nicotine (2.3 mg/kg) every weekday for 2 weeks. Mice were transcardially perfused with heparinized saline on the last experimental day, and c-Fos expression patterns were determined by using standard immunohistochemistry methods. **Results:** PTZ-induced seizures increased fos expression in motor cortex (MC), paraventricular thalamic nucleus (PV), medial habenula (MHb), pirifrom cortex (PC), entorhinal cortex (EC), amygdala (AM), and to some extent in the hippocampus. Cocaine-induced seizures generally increased fos expression in MC, caudate putamen, nucleus accumbens, PV, lateral habenula (LHb), EC, PC, substantia nigra pars compacta (SNC), and in the AM. Nicotine-induced seizures increased fos expression in MC, nucleus accumbens (shell), PV, MHb, EC, SNC, and peripeduncular nucleus. In addition, a difference in activity pattern between seizures in naïve and kindled animals was observed in the nicotine kindling experiment with a decreased expression in the MHb and an increased expression in the SNC. A difference was also seen in the cocaine models with increased expression in the LHb in the cocaine-kindling mice. No observable differences were seen in expression patterns between PTZ-kindled and nonkindled mice. **Conclusions:** Nicotine seizures seemed to originate partly in the hindbrain and spread to the forebrain, as well as involve the MHb. C-fos induced by PTZ seizures was restricted mainly to the limbic system. Cocaine-induced seizures seemed to involve the limbic system, structures in the basal ganglia, and possibly also the LHb. Data in the present study also suggest that the MHb and SNC may undergo functional changes after nicotine kindling. (Supported by H. Lundbeck A/S) (Disclosure: Salary: H. Lundbeck A/S.)

1.051

LONG-LASTING ANTIEPILEPTIC EFFECT OF FOCAL COOLING ON 4-AMINOPYRIDINE–INDUCED NEOCORTICAL SEIZURES

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Rationale: Because we have previously shown that rapid, focal cooling with a small Peltier device can abruptly terminate neocortical seizures, we investigated the possibility that focal cooling could attenuate or prevent seizures when applied before seizure onset. **Methods:** Experiments were performed on halothane-anesthetized rats. Seizures were induced by a neocortical microinjection of the potassium channel blocker 4-aminopyridine [4-AP; 0.5 μl of a 25 m*M* solution in artificial cerebrospinal fluid (aCSF)]. We placed two screw electrodes symmetrically over each hemisphere and separately recorded the EEG between the two. Cortical cooling was accomplished with a Peltier device, which made direct contact with the pial surface and maintained a temperature of 20°C at the interface between Peltier and cortex. We measured seizure duration, frequency, and power in a control (uncooled) group and two experimental groups: the intermittent cooling group was cooled for 30 s every 2 min, starting 15 min after 4-AP; the precooling experimental group was cooled for 30 min before 4-AP injection by using the same 30-s cooling cycle. Seizures were quantified in 30-min observation periods for 2 h. **Results:** During the first 30-min observation period, seizures in the control group lasted 91.72 ± 33.09 s; in the intermittent cooling group, seizures were 36.97 ± 10.43 s; and in the precooled group, seizures were 19.39 ± 2.09 s. During the second 30-min observation period, seizure durations were 69.36 ± 21.68 s, 23.92 ± 11.52 s, and 17.85 ± 1.63 s in the control, intermittent cooling, and precooling groups, respectively (five animals in each group; $p < 0.001$). Seizure frequency in the three groups did not differ during the first 30 min after initial seizure onset. The seizure frequency significantly decreased to 4.6 ± 2.7 and 4.5 ± 4.95 in the intermittent cooling and precooling groups in the second 30 min, but it stayed constant at 15.2 ± 4.32 in control group ($p < 0.001$). The ratio of seizure power to baseline power was significantly higher in control seizures, compared with seizures in either of the cooling groups (4.62 ± 2.36 at control, 1.78 ± 0.46 at intermittent cooling, and 0.91 ± 0.17 at precooling group; $p < 0.001$). Although seizures persisted in the control group for the second hour of observation, no seizures were seen in the intermittent cooling and precooling groups during this period. Histologic examination of the cortex after cooling and precooling showed no evidence of neuronal injury. **Conclusions:** These results demonstrate that focal cooling not only terminates neocortical seizures, but also has long-lasting antiepileptic effects. These results, achieved in a particularly severe model of acute, neocortical epilepsy, might be even more impressive in a model of focal epilpsy that more closely modeled the human condition. When improved heat pipes and seizure-prediction algorithms become more widely available, it may be possible to permanently implant Peltier devices to prevent clinical seizures in patients with refractory neocortical epilepsy. [Supported by a grant from Citizens United for Research in Epilepsy, Inc. (CURE), the Stein Fund for Pediatric Neurology Research, and NS14834 from the NIH.]

1.052

mRNA CHANGES IN EPILEPTOGENIC AND NONEPILEPTOGENIC UNDERCUT RAT NEOCORTEX

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Rationale: Epilepsy, a frequent sequala of penetrating head injury, becomes manifest after a latent period. In the rat undercut model of posttraumatic epileptogenesis, epileptiform potentials can be evoked in neocortical slices in vitro after a latency of ~2 weeks. However, focal treatment with tetrodotoxin (TTX) in vivo during a critical period of the first 3 days after injury, prevents epileptogenesis in this model. We examined mRNA changes occurring during this critical period with and without treatment, to better understand epileptogenesis and help identify potential new treatment targets. **Methods:** Partial neocortical isolations were performed in 4-week-old male Sprague–Dawley rats, and Elvax resin with or without TTX was placed subdurally over the lesions. Control animals underwent anesthesia, but no surgery. Treated animals were selected that demonstrated some, but not severe, neurologic deficits, to ensure effective TTX treatment. Three days after injury, cortical isolations and control cortices were excised under a surgical microscope. RNA was isolated, and labeled cRNA synthesized and fragmented by using standard protocols, for hybridization to probes on Rat Genome U34A gene microarrays (Affymetrix). RNA from at least two different animals was combined per array, and three separate arrays (different animals) were used per each test condition: untreated undercut neocortex, TTX-treated undercuts, and naïve controls. To find significant changes in the amounts of transcripts present, nine individual comparisons of the three arrays of a test condition to each of the three arrays of other test conditions were performed by using Microsuite Array 5.0 (Affymetrix) and analyzed with Data Mining Tool 3.0 (Affymetrix). **Results:** Comparisons of individual undercut arrays with each array of naive control cortex revealed a significant increase of signal intensity in 11.3 ± 0.3% of transcripts, and a significant decrease in 10.5 ± 0.4%. Comparisons of epileptogenic (untreated) undercut cortex versus nonepileptogenic (TTX-treated) cortex revealed significant increases in 4.6 ± 0.6% of transcripts and significant decreases in 9.0 ± 1.2% (± values are standard error of the mean). With more stringent criteria requiring changes to be present in all possible (nine) comparisons between individual arrays of different groups, comparison of TTX-treated undercut with untreated undercut arrays revealed significant increases only in 12 transcripts, and significant decreases in 87 transcripts. Similar stringent comparisons between arrays of undercut and naïve neocortex revealed significant increases in 561 transcripts and decreases of 372 transcripts. **Conclusions:** Although there are numerous changes in RNA expression after injury, not all changes appear to be critical to epileptogenesis, as there are fewer differences between epileptogenic and nonepileptogenic-lesioned cortex, than between epileptogenic and naïve cortex. (Supported by NIH Grants NS 02167, NS12151 , and the Phil N. Allen Trust.)

1.053

EFFECT OF KETOGENIC DIET ON THE CONTINUING SEIZURES OF PENTYLENETETRAZOL-INDUCED SEIZURE MODELS IN RATS

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Rationale: Ketogenic diet (KD) significantly attenuates refractory epilepsy in certain patients. Evidence of therapeutic efficacy of the KD was proved in variety of animal models. To evaluate the effect of the KD on status epilepticus, continuing seizures in pentylenetetrazol (PTZ)-induced seizure models were analyzed. **Methods:** Postnatal 3-, 6-, 9-, and 12-week rats were divided into ketogenic diet (KD, 3, 6, 9, 12 group) and regular diet group (RD, 3, 6, 9, 12 group). Each group has >18 rats, and total number of rats was 169. After a day of fasting, KD was maintained for 3 weeks in the KD group. Seizures were induced after 3 weeks of diet, and seizure severity and duration of continuing seizures was evaluated. **Results:** Ongoing seizure was induced in 17 rats in the KD group and 19 in the RD group. Three rats were died of SE in the KD group and six in the RD group. Duration of SE was 6.07 (KD) versus 9.89 min (RD). These differences were most prominent in the postnatal 6-weeks and 9-weeks groups. **Conclusions:** KD significantly reduces ongoing seizure in PTZ-induced seizure in rats. [Supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (HMP-99-N-02-0003).]

1.054

A RAT MODEL OF CORTICAL MYOCLONUS AND EPILEPSIA PARTIALIS CONTINUA

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Rationale: Epilepsia partialis continua (EPC) is a rare condition characterized by almost continuous rhythmic muscular contraction affecting a limited part of the body for a period of hours, days, or even years. By definition, EPC is spontaneous and cortical in origin and is notoriously resistant to pharmacologic treatment. A good in vivo animal model is required to develop further treatment strategies. The objective of this study was to develop and characterize a stable and chronic seizure model of EPC in the rat with a view to investigating the seizure activity in varying conditions such as after drug administration. **Methods:** Focal, neocortical injection of tetanus toxin was used to induce a chronic seizure focus. Tetanus toxin (25–50 ng/0.5μl) was injected through an implanted cannula stereotaxically placed in the motor cortex in 16 male Sprague–Dawley rats (280–320 g), under halothane anesthesia. In eight animals, detailed EEG recordings were taken for ≤4 h daily, starting 1 day after tetanus toxin administration via recording electrodes implanted above the injection site. Behavioral responses were monitored simultaneously. All experiments were conducted under UK Home Office Animal (Scientific Procedures) Act 1986. **Results:** A single application of tetanus toxin induced frequent, mild behavioral seizures, which persisted indefinitely (at least up to 6 months, the longest measurement period) in all animals. The EEG recordings showed that the spiking activity and frequency were very similar between animals, with spiking occurring ≤80% of the time in any given hour of recording. The EEG spiking associated with seizure activity had amplitudes ≤1.5 mV and correlated with behavioral episodes of rhythmic bilateral facial twitching, myoclonic facial tremors, and periods of abrupt cessation of normal motor behavior combined with fixed staring. In between these episodes, normal behavior resumed and was correlated with "quiet" EEG periods with 6- to 8-Hz activity, amplitudes ≤0.3 mV, and with absence of spiking. Three distinct EEG patterns were associated with seizure activity, slow spiking of 0.5–2 Hz, intermediate bursts of spiking from 10 to 15 Hz, and faster bursts of >20 Hz that tended to be of shorter duration and often marked the transition from quiescent periods to periods of regular spiking. These seizure patterns remained constant over time. **Conclusions:** Previously, cortical microinjections of tetanus toxin in cats have been used to induce a chronic seizure focus as a model for EPC (Louis ED. *Electroencephalogr Clin Neurophysiol* 1990;75:548–57), but the resulting seizures varied in severity and semiology between animals and were difficult to control. This study provides a detailed characterization of the tetanus toxin model in rats that is stable over time and consistent between animals. Spontaneous almost continuous seizures occur long after the toxin has been cleared from the system and resemble the seizure activity seen in EPC, making it a good model in which to test the effects of various drugs in this condition and to investigate the underlying mechanisms of EPC. (Supported by the Brain Research Trust.)

1.055

A HISTOLOGIC ANALYSIS OF THE DENTATE GYRUS IN P35 KNOCKOUT MICE

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Rationale: Cortical dysplasia refers to a spectrum of developmental disorders that are highly associated with epilepsy. Although 20% of

epilepsy patients appear to have some form of dysplasia, the relation of specific malformations to epileptogenesis remains unclear. By studying animal models of cortical dysplasia, we hope to elucidate these relations. The p35 knockout mouse exhibits spontaneous seizures and displays both neocortical and hippocampal dysplasia. The dispersed granule cell pattern is particularly intriguing because it closely resembles a clinical picture seen in temporal lobe epilepsy. The aim of the current research is to characterize the heterotopically organized dentate during development. By elucidating developmental changes, we hope to gain a better understanding of the relation between structural abnormalities and seizure generation. **Methods:** Animals were deeply anesthetized with pentobarbital (Nembutal; PTB) and transcardially perfused with paraformaldehyde. Brains were extracted, postfixed, and cryoprotected. Forty-millimeter sections were cut on a vibratome. Histology using cresyl violet and immunocytochemistry using an antibody against parvalbumin were used to characterize dispersed granule cells (GCs) and interneurons in the dentate gyrus of p35 knockout (KO) and age-matched wildtype (WT) mice at postnatal ages P3, P7, P14, and P30 (two from each group). **Results:** Cresyl violet analysis indicates ongoing proliferation and migration of dentate GCs in both KO and WT mice at P3. At P7, in both WT and KO, the granule cell layer (GCL) and molecular layers (MLs) are differentiated, but the border between the superior blade of the GCL and the ML is indistinct. The P14 WT dentate shows an adult-like pattern in which the GCL, ML, and hilus (H) are fully developed; the ML and H are devoid of displaced GCs. P14 KOs show similar development, but the superior blade of GCL continues to lack definition; GCs blend into both the ML and the H. At P30, KOs exhibit clear dispersion of GCs into the ML and H. Immunocytochemistry first reveals parvalbumin-positive (PV+) cells, along the inner border of the GCL and in the H, in P7 WT animals; a PV+ axonal plexus is also evident in the superficial layer of GCs. KO animals show no immunoreactivity in the hippocampus at P7. In WT mice, the PV+ pattern intensifies at P14 and P30, with additional PV+ cells appearing in the inner and outer MLs. In the KO, PV+ cells and axonal plexus are first apparent at P14, with cells appearing randomly through H, GCL, and MLs. The PV+ axonal plexus is less pronounced at P30 in the KO than in the WT. **Conclusions:** Granule cell dispersion in the p35 knockout dentate gyrus is first recognized at P14; before that time, the GCL (even in WT animals) had not yet coalesced. In addition, there is a delayed appearance of PV+ cells in p35 KO mice, suggesting a slowed (and incomplete) development of inhibitory circuitry. These developmental changes in p35 KO animals may correlate with the development of spontaneous seizures in this model of cortical dysplasia. (Supported by NIH NS18895.)

1.056
IN UTERO IRRADIATION PRODUCES A SELECTIVE REDUCTION IN NEOCORTICAL INTERNEURONS DURING THE PERINATAL PERIOD

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Rationale: At the end of this presentation, participants should be able to discuss the effects of in utero irradiation on development of neocortical inhibitory neurons in the perinatal period. In utero irradiation in rats produces offspring with diffuse cortical dysplasia and heterotopic gray matter. Previous studies have shown a selective reduction of inhibition in dysplastic cortex from adolescent and adult irradiated rats (Roper et al., 1999; Zhu and Roper, 2000), but it was not known if this was a direct effect of the irradiation or some secondary effect. The current study was performed to determine if the deleterious effect of in utero irradiation could be detected in the perinatal period. **Methods:** Pregnant rats were exposed to 225 cGy of external γ-irradiation on gestational day 17 (E17). Irradiated and control litters were studied at E21 and postnatal day 6 (P6). Brains from five irradiated and five control animals at each time point were fixed and coronally sectioned at 30 μm. Sections were alternately stained for either γ-aminobutyric acid (GABA) immunoreactivity (GABA-Ir) or cresyl violet (CV). Whole brain neocortical neuronal counts were estimated by using the optical fractionator technique for both GABA and CV. The sampling parameters were optimized to reduce error coefficients to <10%. Comparisons between treatment groups were made by using the *t* test. For each brain, the percentage of GABAergic neurons within the neocortex was determined as the ratio of total GABA-Ir neurons to total CV-stained neurons. **Results:** Irradiated brains at ages E21 and P6 have significantly fewer total neocortical neurons than age-matched controls; however, both irradiated and control animals demonstrated a significant, twofold increase in total neocortical neuron counts from E21 to P6. In control animals, total number of neocortical GABA-Ir cells significantly increased from E21 ($2.9 \times 10^5 \pm 3 \times 10^4$) to P6 ($3.5 \times 10^6 \pm -3.8 \times 10^5$), and the percentage of neocortical GABA-Ir cells significantly increased from $2.8 \pm 0.15\%$ to $17.5 \pm 0.72\%$. In contrast, irradiated animals demonstrated no significant difference in total number of neocortical GABA-Ir cells between the two age groups ($6.4 \times 10^5 \pm 4.2 \times 10^4$ and $5.5 \times 10^5 \pm 1.4 \times 10^4$), whereas there was a clear reduction in the percentage of neocortical GABA-Ir cells from E21 to P6 of $17.1 \pm 0.15\%$ and $8.9 \pm 0.10\%$, respectively. At age P6, the irradiated rat brains had a significantly smaller fraction of neocortical GABAergic neurons (8.9%) compared with controls (17.5%). **Conclusions:** This study has shown that the selective deficit of interneurons in irradiated rats comes from an arrest of the addition of new interneurons to the neocortex and a persistent capacity to add new, non-GABAergic neocortical neurons. Therefore, the selective vulnerability of inhibitory neurons to in utero irradiation is not due to increased destruction of the interneurons bur rather an impaired ability to recover and generate new interneurons after the injury. This is in contrast to non-GABAergic neurons, which continue to double their numbers during the perinatal period after in utero irradiation. These findings may have important implications for cortical development after a variety of in utero insults. (Supported by NIH grants NS11129 and NS35651.)

1.057
NEURONAL DEGENERATION INDUCED BY STATUS EPILEPTICUS WITHIN THE CLAUSTRUM IS AGE DEPENDENT

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Rationale: To describe detailed topography and time course of status epilepticus–induced neuronal degeneration in the piriform cortex and the deep piriform region [including the ventral endopiriform nucleus (VEn), the dorsal endopiriform nucleus (DEn), and claustrum (CLD)] in developing rats and to find out if there is a relation to the age when status epilepticus (SE) was elicited. These structures have been identified as an area involved in the generation of epileptic seizures, and they are heavily damaged after SE in adult animals. **Methods:** Experiments were carried out in rat pups (Wistar albino) 12, 15, 18, 21, and 25 days old. Lithium–pilocarpine model of SE was used. Lithium chloride (3 mmol/kg, i.p.) was injected 24 h before injection of pilocarpine (40 mg/kg, i.p.). Only animals exhibiting clear-cut motor SE were included in this study. The rats survived for 4, 8, 12, 24, 48 h, and/or 1 week after SE. Under an overdose of urethane anesthesiam the animals were perfused with phosphate-buffered saline (PBS) followed by 4% paraformaldehyde in PBS. Coronal sections (40 μm thick) were cut on a cryostat, mounted onto gelatin-coated slides, and processed with cresyl violet or with a novel fluorescent stain (Fluoro-Jade B, FJB) used for detection of degenerating neurons. Sections were examined with an epifluorescence microscope using a filter system suitable for visualizing fluorescein or fluorescein isothiocyanate (FITC). **Results:** There was no change in the CLD of 12-day-old rat pups at any survival interval. Isolated FJB-positive neurons were scattered in the whole DEn at all survival intervals, with a prevalence in medial and basal parts fo DEn. Degenerated neurons were rarely seen in CLD of 15-day-old rats. They prevailed in the medial part of the nucleus. DEn exhibited slightly more FJB-positive neurons dispersed in its whole extent. Both subdivisions of the claustrum contained moderate to large number of FJB-positive neurons in 18-, 21-, and 25-day-old animals. Positive neurons prevailed along the medial margin of the CLD. In the Den, degenerating neurons were scattered in the whole nucleus, with a prevalence in its medial part. Animals 18 and more days old exhibited a peak in the

number of degenerating neurons in both subdivisions of claustrum 24 and 48 h after SE. **Conclusions:** Lithium–pilocarpine model of status epilepticus resulted in degeneration of neurons in the deep piriform region in all age groups studied (rat pups 12, 15, 18, 21, and 25 days old). Fluoro-Jade B–positive neurons were not numerous in the two youngest groups; they were detected in the dorsal claustrum as well as in the dorsal endopiriform nucleus. In 18-day-old and older animals, the number of degenerating neurons increased in both subdivisions of claustrum. They were mainly localized in the medial and dorsal parts of the dorsal claustrum. Degenerating neurons were found mainly in marginal parts of the rostral half of the dorsal endopiriform nucleus, whereas the medial margin represents the dominant localization in the caudal half of the DEn. Localization of neuronal loss in both dorsal and ventral claustrum are age dependent, with a marked change between postnatal days 15 and 18 in rats. (Supported by the Grant Agency of the Czech Republic, grants No. 304/99/0193 and 309/00/1644.) (Disclosure: Honoraria: Pavel Mares, speaker for Glaxo Wellcome, Janssen Cilag, Sanofi, Desitin at local meetings.)

1.058
COULD DIFFERENCES IN THE ACUTE PHASE EXPLAIN AGE-DEPENDENT OUTCOME OF STATUS EPILEPTICUS IN RATS?

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Rationale: To analyze whether differences in the acute phase of convulsive status epilepticus (SE) at different maturational stages might be a reason for less extensive neuronal damage in immature brain. **Methods:** SE was induced by lithium chloride (LiCl)–pilocarpine (40 mg/kg, i.p.) in 12- (P12) and 25-day-old rats (P25) with implanted cortical and hippocampal electrodes. Video-EEG monitoring was performed for 24 (P12) or 48 (P25) h. To decrease mortality, animals received a single dose of paraldehyde (0.3 and/or 0.6 ml/kg in the two age groups, respectively) after 2 h of SE. Because of dependence of P12 rats on the mother, EEG recording was repeatedly interrupted, and the pups were given back to the nest for 3 h. Then the registration continued. After the end of registration, the brains were used for histology. Neuronal damage was detected by Nissl and Fluoro-Jade B staining. **Results:** SE was elicited in all animals. Motor seizures slowly subsided in the younger animals, whereas they were violent in the 25-day-old ones. Reaction to paraldehyde varied among individual animals; motor seizures were always more affected than EEG phenomena. Ictal epileptic activity reappeared even in the rats with excellent reaction to paraldehyde. Nongeneralized epileptic EEG activity was common in the P12 rats and formed >60% of ictal activity. In addition, number and duration of ictal phases was lower than in P25 rats, but the total duration of seizures was much longer than the minimum necessary for marked consequences in adult rats (1 h). FJB-labeled neurons were detected in both age groups. In P12 rats, degenerating neurons were found in several telencephalic and diencephalic structures in all animals. Anterior cortical and/or medial nuclei of the amygdala and the CA1 field of the hippocampus were mostly affected. In the thalamus, FJB-labeled neurons consistently occurred in the mediodorsal and laterodorsal nuclei. No damage was detected in Nissl-stained sections. In P25 rats, neuronal degeneration was more apparent and more extensive than in P12 rats. Degenerating neurons were found in all neocortical areas, with prevalence in infragranular layers. Among subcortical structures, extensive damage was evident in the septum, in the bed nc., in the posterior half of the piriform cortex, in the endopiriform area, and in all superficial and deep amygdalar nc. In the hippocampus, degenerated neurons occurred in the CA1, the CA3, and in the hilus of the dentate gyrus. Thalamic mediodorsal, laterodorsal, and lateroposterior nc., nc. reuniens, dorsal nc. of the lateral geniculate body and medial geniculate body were affected. Decrease in Nissl staining of neurons was found in four of eight rats in the piriform cortex, CA1, and CA3 of the hippocampus and the deep amygdalar nuclei. **Conclusions:** Poor generalization of epileptic activity and low electroclinical correlation during SE in P12 compared with P25 animals might play a role in development of less extensive damage of immature brain after SE. (Supported by Grant Agency of the Ministry of Health of the Czech Republic, grant No. NF 6474-3.) (Disclosure: Honoraria: Pavel Mares, speaker for Glaxo Wellcome, Janssen Cilag, Sanofi, and Desitin at local meetings.)

1.059
THE GluR5 KAINATE RECEPTOR AGONIST ATPA INDUCES SEIZURES IN IMMATURE RATS

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Rationale: Hippocampal sclerosis, the substrate of mesial temporal lobe epilepsy, involves neuronal loss of a subset of dentate hilar interneurons. Interestingly, GluR5 kainate receptors appear to be selectively expressed in discrete subsets of neurons, including hilar interneurons, that are preferentially lost in epileptic tissue. Furthermore, loss of GluR5 immunoreactivity has been found in human epileptic hilus. (*RS*)-2-amino-3-(3-hydroxy-5-tetr-butylisoxazol-4-yl)propanoic acid (ATPA) is a selective GluR5 agonist, although at high concentrations, it also acts as an AMPA-receptor agonist. We hypothesized that systemic administration of ATPA in the immature rat might lead to excitotoxic injury of GluR5-expressing neurons, whose selective loss may be critical in epileptogenesis, and to the subsequent development of other long-term epilepsy-related changes. **Methods:** Rats aged PN5 to 20 were injected i.p. with age-specific doses of ATPA sufficient to induce limbic and tonic–clonic seizures and compared with vehicle controls. Two to 3 weeks later, rats were assessed in three ways: (a) Dentate hyperexcitability assessment by paired pulse inhibition measured extracellularly in the granule cell layer while stimulating in the outer molecular layer. The ratio of the second to the first population spike amplitude was calculated; (b) Latency for the induction of high-frequency clonus and generalized tonic–clonic seizures with the gaseous convulsant fluorothyl; and (c) Nissl staining to determine the extent of neuronal loss. **Results:** Limbic followed by tonic–clonic seizures lasting for >4 h with <25% mortality were produced by the following doses of ATPA (mg/kg): 20 for PN5–6, 15 for PN10–11, and 15 for PN14–15. Older rats required doses >30mg/kg and were not further studied. Behavioral features after ATPA administration were similar to those previously described for kainic acid: Initially immobility, scratching, and ataxia, followed (only in pups younger than PN14) by "cycling" and head wagging. Tonic–clonic seizures began as a running fit and continued as tonic seizures with additional running fits alternating with scratching and immobility. PN5–6 rats, however, did not exhibit running fts. Latency to onset of fluorothyl-induced seizure was not significantly different between ATPA-treated rats at any one of the three age groups ($n = 16$) and controls ($n = 9$). There was no significant neuronal loss in the hippocampus in rats treated with ATPA at PN10 or PN14–15 ($n = 7$) compared with controls ($n = 6$). Paired-pulse inhibition at the dentate gyrus was not significantly different between rats treated at PN10 or PN14–15 ($n = 4$) and controls ($n = 4$). **Conclusions:** Systemic injection of the partially selective GluR5 kainate-receptor agonist ATPA reliably induces limbic and secondary tonic–clonic seizures in rats younger than PN16. Despite the selective excitatory action of the drug on a subgroup of neurons selectively lost in mesial temporal lobe epilepsy, no long-term effects were induced in the model. Failure to induce long-term effects despite severe seizures could be related to the well-documented resistance of immature rats to convulsant-induced neuronal loss and epilepsy and suggests that additional pathophysiologic factors are required for damage to occur. (Supported by NS-20253, NS/HD-41366, Grass, EFA, Onassis.)

1.060
ANTICONVULSANT ACTION OF AN ANTAGONIST OF TYPE I OF METABOTROPIC GLUTAMATE RECEPTORS IN IMMATURE RATS

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Rationale: To find out whether an anticonvulsant action of MPEP, an antagonist of type I of metabotropic glutamate receptors, is present

also in immature experimental animals. The anticonvulsant efficacy of this drug was recently proved in adult rodents; therefore we studied this action at different stages of postnatal development in rats. **Methods:** Rat pups 12, 18, and 25 days old were pretreated with MPEP (Tocris, an antagonist specific for receptors containing mGluR5, freshly dissolved in isotonic saline in a concentration of 5 mg/ml) in doses of 10, 20, 40, and/or 80 mg/kg, i.p., 15 min before an injection of pentylenetetrazol (PTZ; Sigma, St. Louis, MO) in a dose of 100 mg/kg, s.c. Controls were pretreated with physiologic saline in a volume corresponding to the highest dose of MPEP. Individual age and dose groups were formed by eight to 10 rats. Animals were observed for 30 min after PTZ administration, and the presence, pattern, and latencies of minimal clonic and generalized tonic–clonic seizures were recorded. Seizure severity was quantified by using a 5-point scale (1, myoclonic jerks; 2, atypical minimal seizures; 3, minimal seizures; 4, generalized seizures without the tonic phase; 5, complete generalized tonic–clonic seizures). **Results:** Minimal seizures were not induced in 12-day-old rats even under control conditions, whereas all control animals in the two older groups exhibited this type of seizure. A dose-dependent decrease of incidence of minimal seizures was observed in 18-day-old pups; statistical significance was reached with the 40-mg/kg dose. On the contrary, even the 80-mg/kg dose did not result in a significant change of incidence in 25-day-old animals. Incidence of generalized seizures remained unchanged in all three age groups, but there was a change in their pattern: the tonic phase was selectively suppressed. This effect was best expressed in the youngest rats (a significant decrease with the 20-mg/kg dose). The dose–effect relation was clearly seen in the two younger groups. In addition, an increase of latencies of minimal seizures was observed after the highest dose of MPEP in all three age groups; latencies of generalized seizures were prolonged only in 12-day-old rats. A decrease of seizure severity from point 5 to point 4 was again age dependent. The dose of 10 mg/kg was efficient in the youngest group, whereas only the highest dose resulted in a significant change in 25-day-old rats. **Conclusions:** A specific antagonist of type I glutamate metabotropic receptors MPEP exhibited anticonvulsant effects in all age groups studied. There was an age-specific action against minimal seizures (effects in 18-day-old rats only) and a specific suppression of the tonic phase of generalized seizures in all age groups, with a developmental shift in the sensitivity demonstrating the highest efficacy of this drug in the youngest animals. Our data demonstrated a possible use of drugs with this mechanism of action as anticonvulsants even during ontogeny. Possible side effects of drugs influencing metabotropic glutamate receptors have to be studied. (Supported by a Center for Neuropsychiatric Studies, project No. LN00B122.) (Disclosure: Honoraria: Speaker for Glaxo Wellcome, Janssen Cilag, Sanofi, Desitin at local meetings in Czech Republic.)

1.061
ABNORMALITIES OF NEURONAL MORPHOLOGY IN AN ANIMAL MODEL OF CORTICAL DYSGENESIS WITH A COMPARISON TO HUMAN ACQUIRED CORTICAL DYSPLASIA

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Rationale: At the end of this activity, the participants will understand abnormalities of neuronal morphology in an animal model of cortical dysgenesis and how they compare with those seen in human acquired cortical dysplasia. Cortical dysgenesis is a major pathologic substrate for intractable epilepsy, but the etiology of the majority of these cases is unknown. In utero and perinatal insults can produce "acquired" cortical dysplasia in humans (Marin-Padilla, 1999). Abnormalities of neuronal morphology are a key feature of many cases of cortical dysplasia in humans, and the concept of a "dysplastic neuron" has received much attention. In utero irradiation was used to produce dysplastic (DC) and heterotopic cortex (HC) in rats. We then used the Golgi–Cox method to study abnormalities of cortical structure and neuronal morphology in DC and HC. These changes were compared with control rats and with findings from a collection of specimens of acquired cortical dysplasia in children. This is the first study to compare directly abnormalities of neuronal morphology in an animal model of cortical dysgenesis with a defined clinical pathological entity. **Methods:** Pregnant rats were exposed to 225 cGy γ-irradiation on E17. Offspring were killed for histologic testing at 7–8 weeks of age. Brains from eight irradiated and five control rats were processed for histologic analysis by using the Golgi–Cox method and cut into 200-μm-thick sections. Specimens were also compared with a preexisting collection of Golgi-stained sections from 36 children with acquired cortical dysplasia (Marin-Padilla, 1999). Analysis was carried out using visual examination with light microscopy and camera lucida drawings. **Results:** Irradiated animals routinely showed both DC and HC. Both DC and HC contained pyramidal neurons with loss of normal spatial orientation. DC also contained clusters of ectopic neurons near the pia. Frank abnormalities of morphology were present in pyramidal neurons in DC in the form of increased size and long and irregular dendritic branches compared with control neocortex. Similarly, some nonpyramidal (presumed inhibitory) neurons in DC were also abnormally large with longer dendrites compared with control neocortex. Neuronomegaly of this type is also seen in children with acquired cortical dysplasia. **Conclusions:** In utero irradiation produces extensive structural disorganization of the neocortex. Subpopulations of neurons within DC and HC show neuronomegaly and abnormalities in the dendritic arbor. Therefore, an injury-based model of cortical dysgenesis contains neurons that possess some properties that have been described in "dysplastic neurons." These abnormalities are also seen in human acquired cortical dysplasia. Some of these morphologic changes may be a compensatory response to loss of neighboring cells (hypertrophy of survivors) and abnormalities of afferent fiber distribution (dendritic arbor changes). [Supported by a grant from NINDS (NS35651).]

1.062
INVESTIGATION OF MECHANISMS UNDERLYING THE FORMATION OF A HIPPOCAMPAL HETEROTOPIA

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Rationale: Malformations of cortical development (MCD) can be associated with mental retardation, dyslexia, and intractable forms of epilepsy. With better detection capabilities, there has been increased interest in patients with MCD and in developing animal models that mimic the human pathology. The origin of these malformations could be a defect in cell differentiation, specification, migration, or a combination of all three. Determining the process by which a malformed brain develops would aid in creating better treatment options for patients with MCD. In rats, prenatal exposure to methylazoxymethanol (MAM) yields offspring with loss of cortical lamination, microencephaly, and nodular heterotopias in the hippocampus. MAM-exposed rats are hyperexcitable both in vitro and in vivo, possibly due to an altered potassium current on heterotopic cells, and heterotopic neurons exhibit abnormal inhibitory synaptic function. Recent work from our laboratory (Castro et al. *Neuroscience* 2002) demonstrated that hippocampal heterotopic cells share molecular and functional characteristics of supragranular cortical neurons from layers II/III. The question remains of how abnormal cell clusters arise in the hippocampi of MAM-exposed animals. Here we describe our early efforts to understand the mechanism(s) by which heterotopiae develop by characterizing, anatomically, the time span in which they appear. **Methods:** Pregnant Sprague–Dawley rats were injected with 25 mg/ml MAM, i.p., on day 15 of gestation. For preparation of hippocampal rat tissue sections, the mother was killed, and rat pup brains were removed at days 16 and 19 of gestation (E16 and E19), the day of birth (P0), and postnatal day 3 (P3). Brains were fixed in 4% paraformaldehyde, cryoprotected in 30% sucrose solution, frozen rapidly on dry ice, and then cut into 40-μm coronal sections on a vibrating tissue slicer. Hippocampal sections were subsequently stained with cresyl violet dye. **Results:** Gross analysis of rat brain sections at E16, E19, and P0 (day of birth) all show a global

effect of microcephaly with MAM prenatal exposure. At the light-microscopic level, hippocampal morphology in tissue sections from MAM-exposed animals was comparable to that of hippocampi from untreated control animals. In particular, heterotopic cells were not observed in these sections. However, analysis of tissue sections at P3 revealed the presence of distinct clusters of displaced neurons (heterotopia) and loss of hippocampal lamination. At P3, we also observed prominent expression of Id-2 mRNA in the upper layers of cortex and in a "stream" of displaced cells leading into the hippocampus. Further immunohistochemical and in situ hybridization analysis of these tissue sections will yield additional information on how these heterotopiae develop. **Conclusions:** By following, in time, the emergence of heterotopia in hippocampi of MAM-exposed rats, we ascertained that abnormal cell clusters appear postnatally. Our studies establish the time of their appearance to between birth and the third postnatal day. These studies will assist in determining the process by which experimental heterotopiae appear and may, ultimately, yield insight into the human condition of MCD. (Supported by National Institutes of Health and Parents Against Childhood Epilepsy.)

1.063

ELECTROPHYSIOLOGIC CHARACTERIZATION OF DENTATE GRANULE CELLS IN EPILEPTIC p35 KNOCKOUT MICE

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Rationale: Deletion of the p35 gene, which codes for the neuronal-specific activator of cyclin-dependent kinase 5, results in brain structural abnormalities including neocortical lamination defects. These animals also exhibit abnormal morphology of principal neurons in the hippocampus and dentate gyrus, as well as spontaneous behavioral and electrographic seizures. Therefore, this animal provides a unique opportunity to determine the electrophysiologic correlates and consequences of abnormal morphology that may result in spontaneous seizures. The goal of this investigation was to elucidate the aberrant electrical interactions that underlie the epileptic phenotype in this animal model of cortical dysplasia. **Methods:** Intracellular sharp electrode recordings of dentate granule cells were obtained from 400-μm-thick acute hippocampal slices prepared from both wild-type and knockout mice. Electrodes, backfilled with 2% biocytin in 1 *M* potassium acetate (pH 7.4, 100–220 MΩ), were used to measure the physiologic responses of granule cells to stimulation (bipolar stimulating electrode) in CA3 stratum orients [to activate mossy fiber (MF) axons]. Electrophysiologically characterized cells were filled with biocytin, fixed, and processed for light and/or electron microscopy (see accompanying poster by H.J. Wenzel, et al.). **Results:** As previously shown, GCs with abnormal axon and/or dendritic morphology exhibit normal responses to intracellularly injected current. Responses to MF stimulation, however, revealed a significant difference between p35 -/- and wild-type granule cells. Whereas no GC in wild-type dentate responded to stimulation with an excitatory synaptic event, 68% of the p35 -/- cells ($n = 25$) generate an excitatory postsynaptic potential (EPSP; z test reveals a significant difference between the knockout and wild-type animals, with a p value of 0.002); in 76% of these cases, the EPSP triggered an action potential. Furthermore, in most p35 knockout cells in which an EPSP was elicited, stimulation failed to trigger an antidromic spike; $\chi 2$ analysis indicates a significant negative correlation, with a p value of <0.001. Finally, initial analyses of early and late inhibitory postsynaptic potentials suggest a weaker inhibitory drive to GCs in p35 knockouts compared with wild-type controls. **Conclusions:** Electrophysiologic measurements of synaptic responses from granule cells in the p35-/- mice reveal a functionally aberrant dentate circuitry that may involve recurrent excitatory stimulation of granule cells. These results are consistent with morphologic observations of recurrent axon collaterals and abnormal excitatory synaptic connections. Our results also suggest that inhibition in these epileptic mice may be abnormal, and thus contribute to the hyperexcitability that generates seizures. (Supported by NIH NS 18895 and GM 07108.)

1.064

FEBRILE SEIZURES DURING A CRITICAL POSTNATAL PERIOD INCREASE SEIZURE SUSCEPTIBILITY, REDUCE INHIBITION, AND MODIFY SEIZURE-INDUCED INHIBITORY PLASTICITY IN ADULTHOOD

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Rationale: Febrile seizures frequently precede medically intractable temporal lobe epilepsy associated with hippocampal atrophy, which can be cured by resection of the medial temporal lobe. These clinical observations have suggested that seizures occurring during a critical period in early postnatal development may induce long-term alterations in hippocampal circuits, predisposing to episodes of neuronal synchronization and recurring seizures during adulthood. There is substantial evidence that an episode of seizures induced by kainic acid during the early postnatal period alters development of hippocampal circuitry and induces long-term alterations in hippocampal functional properties and behaviors that vary dramatically as a function of the postnatal age. To determine whether febrile seizures induce long-term alterations in hippocampal circuitry that might influence seizure susceptibility during adulthood, the effects of febrile seizures during postnatal days P4–10, P11–17, and P20–26 on development of kindling, paired-pulse inhibition (PPI), and seizure-induced alterations in inhibition were systematically assessed in adult rats at age P90. **Methods:** Rat pups experienced three febrile seizures evoked by exposure to hyperthermia (~40–41°C) every other day during one of the following postnatal periods: (a) P4–10, (b) P11–17, and (c) P20–26. At P90, these rats were evaluated for seizure susceptibility by assessing the rate of kindling evoked by electrical stimulation of the perforant path (twice daily 1-s trains of 62-Hz pulses). To assess the long-term effects of febrile seizures on functional properties and the balance of excitation and inhibition in hippocampal circuitry, PPI was measured in the dentate gyrus of hippocampal slices from rats with preceding febrile seizures during P4–10, P11–17, and P20–26. To assess the effect of febrile seizures on seizure-induced plasticity in adulthood, PPI was assessed after repeated seizures evoked by electrical kindling or 30 mg/kg, i.p., of pentylenetetrazol (PTZ) in P90 rats that experienced febrile seizures during P20–26, and was compared with the effects of kindling and PTZ in normal adult rats with no history of febrile seizures. **Results:** After febrile seizures occurring during P20–26, electrical kindling developed more rapidly (9.8 ± 1.7 ADs to first class V seizure) compared with normal adult controls (16.2 ± 1.5 ADs) and rats that experienced febrile seizures during P4–10 (14.7 ± 2.1 ADs) or P11–17 (21.0 ± 4.7 Ads; analysis of variance, $p < 0.05$). In normal adult rats, repeated seizures evoked by kindling induce an increase in PPI in the dentate gyrus. In rats that experienced febrile seizures during P20–26, PPI in adulthood was reduced in the dentate gyrus compared with normal controls, and failed to increase after repeated seizures evoked by kindling. **Conclusions:** The results demonstrate that febrile seizures during a critical period in early postnatal development increase susceptibility to seizures evoked by electrical or PTZ kindling in adulthood, decrease inhibition in the dentate gyrus, and induce alterations in responses to seizures during adulthood that would promote increased susceptibility to additional seizures and intractability. (Supported by the Epilepsy Foundation of America.)

1.065

MORPHOLOGY OF CEREBRAL LESIONS IN THE EKER RAT MODEL OF TUBEROUS SCLEROSIS

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Rationale: Tuberous sclerosis (TSC) is a multiorgan autosomal dominant disorder caused by mutations of either TSC1 or TSC2 genes.

In the brain, manifestations typical of TSC include cortical tubers (i.e., clusters of heterotopic neurons) and subependymal nodules or giant cell astrocytomas. These structural malformations are thought to cause neurologic dysfunctions, including epilepsy. The Eker rat, which carries a spontaneous germline mutation of the TSC2 gene, has been studied as an animal model of TSC. Although pathological analysis of Eker rat brain reveals subependymal and subcortical hamartomas, none of these animals develops cortical tubers with "giant" or "balloon" cells typical of TSC tubers. In the present study, we used postnatal irradiation as a "second hit," in an attempt to induce "loss of heterozygosity" in Eker TSC2 ± cells, and thus exacerbate cortical abnormalities that might be linked to seizures. **Methods:** Wild-type and Eker (TSC2 ±) rats were subjected to full-body irradiation within 3 days of birth. Twenty-one rats [five wild-type (WT) nonirradiated, eight WT irradiated, three Ekers non-irradiated, and five Ekers irradiated) were examined at postnatal age 3 months. All rats were tested for seizure susceptibility by measuring latencies to flurothyl-induced seizures. Rats were subsequently prepared for histologic/immunocytochemical processing, by using markers for neuronal and glial characterization. **Results:** Seizure-threshold testing revealed that for both WT and Eker rats, irradiation led to significantly shorter seizure latencies ($p = 0.004$ and $p < 0.001$, respectively). Whereas there was no latency difference between WT and Eker nonirradiated rats, irradiated Ekers showed slightly shorter latencies than irradiated WT rats ($p = 0.056$). Except for a reduction in the size of the dentate gyrus (seen in both groups), irradation generated no gross brain abnormalities and no aberrations in development. However, all of the irradiated Eker brains exhibited at least two abnormal histologic features in their morphology: (a) Subcortical/subependymal hamartoma-like aggregates of large, irregularly-shaped cells, which stain lightly with hematoxylin and eosin; cell bodies and their large processes show immunoreactivity for glial fibrillary acidic protein (GFAP) and γ-aminobutyric acid (GABA); and (b) Abnormal large cell bodies (cytomegalic neurons) with long extended processes in normal-appearing neocortical and subcortical regions; although usually seen as isolated cells, they sometimes appeared in clusters of two to six cells. None of these findings were seen in nonirradiated Ekers, or in irradiated or nonirradiated WT controls. **Conclusions:** Irradiation produces malformations in TSC2 ± (Eker) rats that resemble some features of TSC in humans, and which may contribute to greater seizure susceptibility. These results suggest that a "second hit" approach may provide insight into the generation of TSC-related brain abnormalities that are correlated with seizure activity. (Supported by NIH NS 18895.)

1.066
DOSE-DEPENDENT CORRELATION OF ATYPICAL ABSENCE SEIZURES AND STEROL CHANGES INDUCED BY AY-9944

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Rationale: Developmental treatment with AY-9944 (AY) leads to atypical absence seizures in waking adult rat and mice (Cortez MA, et al. *Neurology* 2001;56:341–9). AY-induced seizures appear to be related to AY-induced changes in brain sterols but persisted long after the sterols had return to normal after the last injection (Cortez MA, et al. *Epilepsia* 2002:43:3–8). Whether there is a dose-dependent correlation of atypical seizures and sterol changes induced by AY-9944 remains to be determined. **Methods:** Six groups of Neonatal Long–Evans Hooded rats ($n = 8$) received four subcutaneous AY-9944 (AY) injections at 2.5, 5.0, 7.5, 10, 15, and 22.5 mg/kg, respectively, or the equivalent volume of saline to controls ($n = 8$). AY or saline treatment was performed every 6 days from P2 to P20. Brain harvest was performed 24 h after each AY or saline injections. Sterol measurements were made with capillary gas chromatograms. Long-term electrodes were implanted from P40 to P50. Electrocorticogram recordings were made at P55, in AY-treated and controls. **Results:** There was a gradual increment in AY-SWD (mean seconds/hour ± SEM) from 300 ± 100 at 2.5 mg/kg to 680 ± 150 at 22.5 mg/kg. Brain cholesterol decreased from 12 mg/g at 2.5 mg/kg to 3.75 mg/g at the dose of 22.5 mg/kg. 7-Dehydrocholesterol increased from 1.75 mg/g at the lowest AY dose to 6 mg/g at the highest AY dose, compared with controls ($p < 0.05$; Student's *t* test). **Conclusions:** Length, severity of AY-induced seizures, and sterol changes increase with the AY dose. AY-induced atypical absence seizures appear to be closely related to the sterol effects of the drug. (Supported by Bloorview Childrens Hospital Foundation, The Hospital for Sick Children Pediatric Consultants, Dairy Farmers of Canada and The Canadian Institutes of Health Research.)

1.067
LONG-TERM INCREASE IN SEIZURE SUSCEPTIBILITY AFTER *N*-METHYL-D-ASPARTATE–INDUCED STATUS EPILEPTICUS DURING DEVELOPMENT

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Rationale: Despite the prominent role of *N*-methyl-D-aspartate (NMDA) receptors in the pathogenesis of epilepsy, few studies have used NMDA as a convulsant in whole animals. Velisek et al. (*Dev Brain Res* 1992;65:185; *Epilepsia* 1999;40:1357) showed that in developing rats, systemic NMDA induces seizures with a unique clinical phenotype ("emprosthotonic" or hyperflexion seizures) and electrographic pattern (electrodecrement). These features are not in kainic acid–induced seizures, suggesting that seizures activated by different glutamate receptors might cause different long-term consequences. Therefore, we investigated the effects of NMDA seizures during development on the susceptibility to seizures in adulthood. At the end of this activity, participants should be able to discuss how NMDA seizures during development alter seizure susceptibility in adulthood. **Methods:** Rat pups (P12–18) were injected with saline ($n = 36$) or NMDA ($n = 64$) at known convulsant doses (12–30 mg/kg, i.p.). Seizures were terminated 30 min later by ketamine (40 mg/kg, i.p.). On P90, rats were injected with pentylenetetrazol (PTZ, 50 mg/kg, i.p.); latencies to and durations of seizure stages were recorded. Cresyl violet–stained sections of cortex and hippocampus were then examined for major cell loss or gliosis. **Results:** A characteristic sequence of seizure activity was seen after NMDA injection: initially rats became hyperactive with increased locomotor activity and agitation, followed by emprosthotonus, and then generalized tonic–clonic activity. Ketamine terminated status epilepticus within minutes. At P90, there were significant differences in both the latency to class V PTZ seizures (con, 3.5 ± 0.3 min; NMDA, 1.3 ± 0.9 min; $p = 0.045$) and their duration (con, 8.3 ± 0.6 min; NMDA, 11.2 ± 0.7 min; $p = 0.004$). No obvious cell loss or gliosis was observed in either cerebral cortex or hippocampus. **Conclusions:** NMDA causes a unique seizure phenotype in the developing brain. Despite the lack of overt cell loss after NMDA-induced status epilepticus early in life, treated rats show a marked increase in susceptibility to PTZ seizures in adulthood. This study provides additional evidence for long-term seizure-induced alteration of neuronal excitability. [Supported by Parents Against Childhood Epilepsy (P.A.C.E.) and The Charlie Foundation.]

1.068
CORRELATION BETWEEN EXTRACELLULAR GLUCOSE CONCENTRATION AND SEIZURE SUSCEPTIBILITY IN IMMATURE AND ADULT RATS

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Rationale: In diabetic patients, periods of severe hypoglycemia may be associated with seizures. The purpose of this study was to determine the correlation between seizure susceptibility and extracellular glucose concentration in immature and adult rats. **Methods:** Adult male rats were injected with two doses of streptozocin (40 mg/kg, i.p.) on two consecutive days; controls either received vehicle or were not injected. After 2 weeks, blood glucose concentration was measured, and the rats

were challenged with the volatile convulsant flurothyl. Immature rats received either two or three doses of streptozocin (40 mg/kg) on postnatal days (PN) 9, 10, or 9–11, respectively, and were subjected to flurothyl testing on PN15. Thresholds for flurothyl-induced clonic and tonic–clonic seizures were determined. **Results:** In adult rats, low glucose concentrations were associated with high seizure thresholds (decreased seizure susceptibility), and high glucose concentrations, with low seizure thresholds (increased seizure susceptibility) in both clonic ($p = 0.0007$) and tonic–clonic ($p = 0.009$) flurothyl seizures. In contrast, in PN 15 rats, low blood glucose concentrations were associated with low seizure thresholds (increased seizure susceptibility) for clonic ($p = 0.031$) and tonic–clonic (0.035) seizures. **Conclusions:** Data indicate that in the immature brain, low glucose concentrations may be associated with proconvulsant effects, thus rendering juvenile diabetic patients more susceptible to develop seizures during periods of hypoglycemia. (Supported by Heffer Family Medical Foundation, NS-20253 from NINDS, and CURE Foundation.)

1.069

ELECTRON MICROSCOPIC ANALYSIS OF RECURRENT EXCITATORY CIRCUITRY IN DENTATE GRANULE CELLS OF p35 KNOCKOUT MICE: A MODEL OF CORTICAL DYSPLASIA AND EPILEPSY

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Rationale: Cortical dysplasia is a common cause of medically intractable epilepsy. To elucidate the relation between dysplasia and epilepsy, we have studied the p35 "knockout" (-/-) mouse. These animals develop severe defects in brain morphology as well as spontaneous seizures. The hippocampal dentate gyrus is particularly interesting in these animals, because it exhibits granule cell (GC) dispersion, mossy fiber (MF) sprouting, and GC basal dendrites—features typically seen in animal models and human patients with epileptic phenotypes. We hypothesize that these morphologic features are part of a recurrent excitatory network that contributes to the epileptic state. To begin to test this hypothesis, we examined the synaptic connections of dye-labeled GCs in p35 -/- hippocampus. **Methods:** Electron microscopic (EM) analyses were carried out on GCs that were electrophysiologically characterized and biocytin-labeled in hippocampal slices obtained from p35 (-/-) and wild-type mice (see accompanying poster by LS Patel et al.). Immunocytochemistry (ICC), EM, and 3D reconstruction were carried out on sprouted MF axons in the granule cell and molecular layers, and on basal GC dendrites localized within the hilus. Preembedding ICC EM for zinc transporter (ZnT3) was used to identify MF boutons, and postembedding ICC for glutamate and γ-aminobutyric acid (GABA) were used to characterize the postsynaptic targets of sprouted MF axons. **Results:** The dentate gyrus of p35 (-/-) mice exhibits GC dispersion into the molecular layer and hilus. Biocytin-labeled GCs in this tissue exhibit abnormal axonal and dendritic arbors. Four recurrent MF axon collaterals localized within granule cell and molecular layers were examined at the EM level, and axon segments reconstructed. The MF axon collaterals form periodic small varicosities (<2 μm in diameter), which synapse predominantly with dendritic spines (>85% of synapses) and dendritic shafts, and occasionally with GC somata. Only a few varicosities form synapses with dendritic shafts of interneurons (as confirmed by their morphologic features and/or GABA immunoreactivity). Two basal dendrites of GCs were examined and 3D-reconstructed; they exhibit typical features of GC dendrites (e.g., complex spines), and form numerous axospinous and axodendritic synapses with axonal varicosities and with MF boutons. **Conclusions:** Microscopic analyses of electrophysiologically identified GCs reveal a high degree of abnormality of GC morphology and synaptic connectivity, including sprouting of recurrent MF axon collaterals. EM reconstructions show that both abnormal axons and dendrites participate in excitatory synaptic interactions, and may thus contribute to a recurrent excitatory network in the dentate gyrus of p35 (-/-) mice. (Supported by NIH NS 18895 and GM 07108.)

1.070

SELECTIVE ALTERATION OF EXCITATORY AND INHIBITORY RECEPTORS AND TRANSPORTERS IN HIPPOCAMPAL DENTATE GRANULE CELLS AFTER SEIZURES IN THE DEVELOPING BRAIN

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Rationale: Seizures occur more frequently in infancy than at any other time in life. Prolonged seizures in early development result in significantly less structural damage than seizures in adult animals. Potential long-term subcellular and molecular effects of early life seizures, however, are not well elucidated. We examined the effects of status epilepticus (SE) at postnatal day 10 (P10) in rats on later seizure threshold and expression of excitatory and inhibitory neurotransmitter receptors and transporters in hippocampal neurons to better understand potential long-term consequences of early-life status epilepticus. **Methods:** On P10, rat pups were subjected to lithium-pilocarpine–induced SE. Occurrence of SE was confirmed by EEG and behavioral monitoring. At P90, antisense RNA amplification (aRNA) techniques were used to examine the expression of different γ-aminobutyric acid (GABA)(A) receptor (GABAR), *N*-methyl-D-aspartate (NMDA) receptor, AMPA receptor (GluR), glutamate (GluT), and GABA (GAT) transporter mRNAs in single hippocampal dentate granule cells (DGCs) from pilocarpine-treated and lithium-injected, identically handled littermate controls. Brains were subsequently examined for cell loss and synaptic reorganization using cresyl violet and Timm staining. Threshold for seizure induction by kainic acid (KA) tail-vein infusion at P90 was determined in a separate set of P10 pilocarpine-treated and lithium control animals. **Results:** Relative mRNA expression (compared with β-actin) of GABAR α1 subunit was increased threefold ($p < 0.001$), GABAR β1 subunit was increased 1.5-fold ($p < 0.01$), the neuronal GluT EAAC1 was increased sixfold ($p < 0.001$), and GAD67 was increased threefold ($p < 0.001$) in DGCs from adult rats subjected to pilocarpine-induced SE at P10 compared with DGCs from age-matched, sham-treated littermate control rats. Combined expression of all GluR subunit mRNAs was also increased 1.5-fold ($p < 0.05$), whereas total GAT mRNA expression (compared with β-actin) was decreased twofold ($p < 0.05$) in DGCs from pilocarpine-treated rats compared with controls. P10 pilocarpine-treated rats had a lower seizure threshold, requiring 50% less KA to induce first electrographic seizure (15.67 ± 1.6 mg/kg) compared with controls (7.96 ± 0.95 mg/kg, $p < 0.05$). Timm and cresyl violet staining did not show any evidence of synaptic reorganization or hippocampal cell loss in pilocarpine-treated rats. **Conclusions:** The data from this study demonstrate long-term molecular alterations in hippocampal neurons after early-life SE, which may contribute to a chronically lowered seizure threshold. (Supported by NIH NS38595 and Epilepsy Foundation of America to A.B.K.)

1.071

ATTENUATION OF NEURONAL EXCITABILITY AND EPILEPTIFORM ACTIVITY BY PROLONGED STIMULATION

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Rationale: We hypothesized that prolonged stimulation will reduce bicuculline-induced epileptiform activity (EA) by influencing neuronal/glial ionic currents leading to partial silencing of neural activity. **Methods:** Neuronal excitability (NE) in hippocampal neurons can be modulated and EA reduced by modifying ionic concentrations in the extracellular fluid. Specific patterns of stimulation might also be effective, but little is known about the effects of prolonged stimulation on NE and EA. Understanding mechanisms involved in prolonged stimulation has significance, especially with the increased use of pacemakers for neurostimulation. We used a rat hippocampal brain slice preparation

to study changes in NE and EA induced by prolonged stimulation. Slices were prepared from ~28- to 32-day-old rats (males) using standard methods (described previously). We stimulated (orthodromic) the Schaffer collaterals and recorded either excitatory postsynaptic potentials (EPSPs) or population spike (PS) responses in the CA1 subfield. The criteria for healthy slices was determined by using only those slices that had PS responses that showed ≥2 mV maximal amplitudes and that did not show multiple PSs under control and nontreated conditions. A baseline of 15 min (test pulse at 0.034 Hz) was followed to evaluate response stability at half-maximal intensity. Slices were then stimulated at either 1 or 100 Hz for either 1, 10, or 30 min. In some slices, 200 μ*M* bicuculline [γ-aminobutyric acid subtype A ($GABA_A$) antagonist] was applied after the establishment of baseline. After 10 min of drug treatment, slices were stimulated (same as earlier). At the end of the stimulation period, we followed up the responses for 20–30 min. We measured EPSP and PS responses (slope and amplitudes) and also evaluated potential spontaneous activity (between pulses) during baseline, drug treatment, stimulation, and poststimulation periods, unlike many investigators who evaluate responses only before and after stimulation. **Results:** We found that prolonged orthodromic stimulation (≥10–30 min) at either 1 or 100 Hz is effective at reducing normal PS activity. PS responses appear to be more affected by stimulation protocols than EPSPs. We also found that bicuculline-induced EA (PS multiple spiking) is diminished by prolonged stimulation (1 or 100 Hz), where 1 Hz appears most effective. In this case, the primary PS was reduced in amplitude, and in some cases, the additional PSs were either eliminated and/or reduced in size. **Conclusions:** We conclude that the hippocampal brain slice technique can be used to isolate the effects of prolonged stimulation on neuronal properties and that selected stimulation paradigms can reduce NE and EA. We believe the results have significant relevance for investigators and clinicians trying to understand mechanisms associated with deep brain stimulation (DBS). These results further support the idea that investigational applications of DBS for epilepsy and seizure activity are warranted. [Supported by Berkeley Citizens Commission/Bayer Pharmaceuticals (B.C.A.) and HL51614, NS43284, and NS38195 (D.J.).]

1.072
THE SMALL CONDUCTANCE K^+ CHANNEL SUBUNIT, SK2, IS A PROTEIN KINASE A SUBSTRATE

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Rationale: A Ca^{2+}-activated K^+ current causes an afterhyperpolarization (AHP), which follows single or multiple action potentials and plays an important role in regulating neuronal excitability by controlling firing-rate and spike-frequency adaptation. Adrenergic modulation of the AHP through activation of the cyclic adenosine monophosphate (AMP)-dependent protein kinase A (PKA) pathway is well established, but the mechanism underlying this effect is unclear. Evidence suggests that Ca^{2+}-activated, voltage-independent, small-conductance (SK) K^+ channels contribute to the AHP in hippocampal neurons. Three members of the SK class of K^+ channels, SK1-3, have been cloned. The hippocampally expressed SK1 and 2 subunits are of particular interest in the fields of plasticity and epilepsy. We hypothesize that PKA directly phosphorylates SK channel subunits and propose that this is a candidate mechanism of adrenergic modulation of the AHP. In the current studies, we determined whether the SK2 subunit is a PKA substrate. **Methods:** A glutathione-S-transferase (GST) fusion protein construct of the cytoplasmic terminal-SK2 (CT-SK2) domain was used in phosphorylation experiments in vitro. The GST-SK2-CT construct was incubated with PKA and [γ-^{32}P] ATP. Phosphate incorporation was determined using autoradiography. Reaction products were separated with sodium dodecylsulfate–polyacrylamide gel electrophoresis (SDS-PAGE). Phosphopeptide mapping was then performed using the GST-SK2-CT construct to determine the specific phosphorylated residues. Site-directed mutagenesis was used to define PKA phosphorylation sites further within the -CT domain. **Results:** We found [γ-^{32}P] incorporation into the GST-SK2-CT construct, indicating that the -CT region of SK2 was a PKA substrate, and phosphopeptide mapping identified one phosphorylated amino acid, corresponding to serine S465 within the SK2-CT cytoplasmic domain. However, additional studies using a site-directed mutant, S465A, demonstrated persistent [γ-^{32}P] incorporation in the SK2-CT construct, suggesting additional PKA phosphorylation sites. Studies are under way to characterize additional PKA sites within the SK2-CT cytoplasmic domain. Calmodulin, a Ca^{2+}-binding protein, is constitutively bound to SK subunits, which renders the SK channels Ca^{2+} sensitive. The amino acids R464 and K467 are necessary for calmodulin binding to the SK2-CT domain; therefore we are also evaluating the role of S465 phosphorylation in calmodulin binding to the -CT domain of SK2. **Conclusions:** These findings suggest that direct phosphorylation of SK2 may underlie PKA modulation of components of the AHP. (Supported by NINDS and NEF.)

1.073
PILOCARPINE AND KAINATE CHANGE SUBSTANTIA NIGRA PARS RETICULATA ACTIVITY OF γ-AMINOBUTYRIC ACID NEURONS

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Rationale: The substantia nigra pars reticulata (SNR) mediates seizure control. The study of the cellular substrates involved in the SNR-mediated seizure control would provide the knowledge to obtain new therapies that will allow the better management and control of seizures. However, in vitro models of SNR epileptiform activity that would help in the identification of these substrates have not been developed. In this study, we bath-applied two known convulsants with the purpose obtaining a workable in vitro model of SNR epileptiform activity to aid in the identification of these cellular substrates. **Methods:** Sagittal slices from PN14–17 male Sprague–Dawley rats were obtained by using a sucrose-based buffer and a vibratome and perfused in oxygenated (95% O_2/5% CO_2) artificial cerebrospinal fluid (aCSF) at room temperature. Visually guided recordings from SNR neurons were performed using the technique of whole-cell perforated patch-clamp recording with the cation-permeable ionophore gramicidin to avoid perturbations of intracellular chloride by the electrode. Pilocarpine (5 m*M*) and kainic acid (5 μ*M*) were dissolved in aCSF and bath-applied. **Results:** Bath application of both agents induced depolarization and increased firing rate of SNR γ-aminobutyric acid (GABA)ergic neurons within 2 min of application. The effect of pilocarpine was still present 1 h after washout of the drug. Washout of kainic acid led to restoration of normal firing rate after 30 min. However, membrane potential remained depolarized. **Conclusions:** Pilocarpine and kainic acid depolarize and increase the firing rate of SNR GABAergic neurons. With the concentrations used, the effect of pilocarpine was more persistent than the effect of kainic acid. Membrane potential remains depolarized after washout of pilocarpine or kainate, suggesting that neurons could be more susceptible to a subsequent excitatory stimulus. (Supported by NINDS NS 20253 and NS 36238. Dr. Olga I. Claudio is the recipient of the E. W. Lothman Award 2002 from the Epilepsy Foundation of America.)

1.074
SUPPRESSION OF EPILEPTIFORM ACTIVITY BY HIGH-FREQUENCY STIMULATION IN VITRO

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Rationale: High-frequency electrical stimulation of the deep structures of the brain (DBSs) has been effective at controllling abnormal neuronal activity in Parkinson patients and is now being applied for the treatment of pharmacologically intractable epilepsy. The mechanisms underlying the suppression of the abnormal neural activity with DBSs are not understood. Of particular interest is the response of neurons

around the electrodes to the high-frequency stimulation applied extracellularly. **Methods:** Experiments were carried using in vitro hippocampal slices. Two stimulation methods were applied: (a) Sinusoidal uniform electric fields were generated in the hippocampal slices with two large electrodes at a frequency of 50 Hz; and (b) Localized fields were applied with monopolar electrodes located in the stratum pyramidale with either a sinusoidal (50 Hz) or pulse waveforrm (140 Hz, 120 μs). Extracellular, intracellular recording electrodes as well as potassium-selective electrodes were used to measure the response of the tissue to the stimulation. Filtering was used to remove the large stimulation artifact.Three animal models of epielspy were used: high potassium (8.5 m*M*), low calcium (0.2 m*M*), and picrotoxin. **Results:** Using both uniform and localized fields, sinusoidal stimulation waveforms could completely suppress epileptiform activity in all three models of epilepsy tested (low calcium, high potassium, and picrotoxin). Suppression was associated with (a) an increase extracellular potassium concentration (~2.5 m*M*), and (b) a tonic (~19 mV) depolarization of individual CA1 neurons and a suppression of neuronal firing. The threshold for suppression was not affected by cell orientation relative to the applied field. Experiments carried out with monopolar electrodes using pulsed stimulation protocols closely related to those used clinically also showed that high-frequency stimulation can directly inhibit neuronal firing (n = 21). The threshold for local suppression using monopolar stimulation (~90 μA for sinusoidal, ~300 μA for pulsed) was significantly lower than for field stimulation (~1 mA). Using monopolar (but not uniform field) stimulation, suppresssion could be localized to the stimulation region. **Conclusions:** High-frequency stimulation can completely suppress neuronal firing in three different models of epilepsy. The mechanism of the suppression is most likely a depolarization block generated by an increased potassium concentration around neurons. The suppression is independent of the stimulation waveform, and sinusoidal as well as pulse waveform with low duty cycle can be used. The suppression by monopolar electrodes is independent of the orientation of the tissue and localized around the stimulation electrode. These experiments suggest a possible mechanism for DBS-mediated suppression of neuronal activity and role for high-frequency stimulation in epilepsy. (Supported by The Whitaker Foundation and by NIH grant R01 NS40785-01.)

1.075
PREICTAL REORGANIZATION OF HIPPOCAMPAL NETWORK ACTIVITY

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Rationale: Interictal epileptiform discharges (IEDs) in the human electroencephalogram (EEG) are an important diagnostic feature of temporal lobe epilepsy, although they have proven to be of little use in short-term seizure prediction. Seizures are preceded by increases in the extracellular potassium concentration, and in vitro studies have confirmed a corresponding preictal depolarization of the neuronal membrane potential. More recently, nonlinear time-series analyses of EEG activity have demonstrated reproducible changes in brain-wave activity minutes before a seizure. Together, these observations suggest that the operations of epileptic neural networks undergo predictable alterations for some time before a seizure. However, no clinically accessible and physiologically interpretable parameters can be used to address a fundamental question: what changes in the epileptic network lead to seizures? **Methods:** Dorsal transverse hippocampal slices 1-mm thick were prepared from Wistar rats at postnatal age P10–20, a stage of development at which seizure threshold is decreased in humans and rodents. Simultaneous extracellular field-potential recordings were made in the hippocampal slice preparation using arrays of tungsten microelectrodes placed in the granular cell layer of dentate gyrus, pyramidal cell layer of CA3a, b, and c, and proximal and distal CA1 areas. **Results:** The transition to seizures was characterized by (a) increase in IED afterdischarges; (b) increase in the velocity of IED propagation; and (c) shift in the IED initiation area from CA3a to CA3c-hilus. **Conclusions:** Here we demonstrate that both the site of initiation and the propagation velocity of IEDs are consistently altered preictally in the hippocampal CA3 network in vitro. These findings elucidate new targets for investigating the proximate causes of seizures, and provide a simple and robust new method for seizure prediction. Preictal alterations in IEDs can be detected with much greater computational efficiency than is currently possible with nonlinear techniques: by measuring the difference in population spike timing in CA3a and CA3c, seizure onset could be predicted ≤1 min in advance. (Supported by NIH.) (Disclosure: Grant: NIH.)

1.076
THE ROLE OF DEPOLARISATION BLOCK IN THE LOW-CALCIUM MODEL OF EPILEPSY

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Rationale: Low-calcium field bursts consist of a spontaneous 10- to 15-s negative shift in potential, superimposed on which are rhythmic, 20- to 50-Hz population spike discharges that are interrupted for variable periods during the burst; the purpose of the present investigation was to identify factors that contribute to the interruption of population spike discharges. **Methods:** Extracellular (population potentials) and intracellular recordings were made from the CA1 region of the rat hippocampal slice, maintained in an interface chamber. Slices were perfused with artificial CSF in which potassium concentration was increased to 5 m*M,* and calcium concentration reduced to 0.2 m*M.* **Results:** Field bursts were classified into types I–III, depending on whether population spikes were present for 90–100%, 10–90% or 0–10% of the event. A possible mechanism that could cause the interruption in population spike generation during the field bursts is desynchronisation of action potentials in individual neurons. To investigate this question, simultaneous field and intracellular recordings were made; our results showed that when population potentials were absent during an ictal burst, action-potential generation in individual neurons was interrupted rather than desynchronised. Moreover, intracellular recordings showed that, during type III bursts, although neurons produced action potentials only for brief periods at the beginning and end of the field burst, they were depolarised throughout the event. In a further group of experiments, current was passed through the intracellular electrode, hyperpolarising the neuron during the ictal event. The effect of this hyperpolarisation was to induce action potential firing, so that 20- to 50-Hz spikes could again be seen. **Conclusions:** The experiments demonstrate that depolarisation block has a role in blocking action-potential discharge in individual neurons and therefore in interrupting population spike discharges in the low-calcium model of epilepsy. Patients with focal epilepsy sometimes demonstrate a localised electrodecremental event before the onset of a seizure. These events are characterised by a reduction of background EEG activity accompanied or followed by a period of low-amplitude 20- to 50-Hz rhythmic sinusoidal activity, and we speculate that the depolarisation block, demonstrated in the present experiments, could play a role in generating these localised electrodecremental events in human epilepsy. [Supported by MRC (U.K.).]

1.077
EPILEPTIFORM ACTIVITY INDUCED BY 4-AMINOPYRIDINE IS ASSOCIATED WITH MITOGEN-ACTIVATED PROTEIN KINASE ERK ACTIVITY

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Rationale: Extracellular signal-regulated kinases, such as ERK1 (p44) and ERK2 (p42), are abundant in the CNS and are activated under various physiologic and pathologic conditions (e.g., brain ischemia and seizures). Application of the potassium channel blocker 4-aminopyridine (4-AP, 50 μ*M*) to rat hippocampal slices enhances synaptic transmission and makes epileptiform discharges appear.

Hence, it represents an in vitro model commonly used for investigating the pathophysiogenesis of seizures. Here we have studied the activation state of mitogen-activated protein kinase (MAPK) ERK1/2 in 4-AP–treated rat hippocampal slices. **Methods:** Hippocampal slices were processed for sodium dodecylsulfate (SDS)–polyacrylamide gel electrophoresis (PAGE) and immunoblot assays. Protein loading (10 μg) was monitored by staining filters with "Ponceau". Immunoreactivity was detected using the chemiluminescence system (ECL-Amersham) and autoradiography. Quantitation was carried out by densitometric analysis of the films (Fluor-S, Biorad). In all experiments, membranes were first processed to visualize the phosphorylated forms of proteins and then dehybridized (Restore Western blot stripping buffer, Pierce, U.S.A.) and successively reprobed with the antibody directed against total proteins for normalization. **Results:** We found that hippocampal slices superfused with 4-AP exhibit a marked activation (twofold vs. control) of MAP/ERK1/2 phosphorylation that peaks 90 min after treatment and remains above the basal level for ≥4 h. These effects are not accompanied by any change in the activation state of other members of the MAP kinase superfamily c-Jun N-terminal kinases (JNK, also named stress-activated protein kinase, SAPK). In addition, the total kinase content remains constant during 4-AP treatment, suggesting no change in the expression level of ERK proteins. We have also found that the 4-AP–induced ERKs phosphorylation is age dependent. Specifically, we observed (a) an increase in ERK protein expression with development (10-day-old vs. 21-day-old animals); and (b) a larger increment of the phosphorylation status in slices obtained from 10-day-old rats as compared with those prepared from 20-day-old animals. **Conclusions:** Our data indicate that activation of MAPK ERKs may play a role in the enhancement of synaptic transmission induced by 4-AP and thus in the implementation of epileptiform synchronization. (Supported by Canadian Institutes of Health Research and Savoy Foundation.)

1.078
CHARACTERIZATION OF ENDOPLASMIC RETICULUM Mg^{2+}/Ca^{2+} ADENOSINE TRIPHOSPHATASE–MEDIATED Ca^{2+} UPTAKE IN THE HIPPOCAMPAL NEURONAL CULTURE MODEL OF STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) is a serious condition characterized by prolonged seizure activity, significant neuronal damage, morbidity, and mortality. SE is also associated with loss of neuronal cytosolic Ca^{2+} homeostasis. It has been demonstrated in both animal and cell-culture models that SE significantly increased basal cytosolic Ca^{2+} and decreased the ability of neurons to restore resting Ca^{2+} homeostasis. One important mechanism for maintenance of Ca^{2+} homeostasis and low basal cytosolic Ca^{2+} is sequestration of Ca^{2+} into the endoplasmic reticulum (ER) via the Mg^{2+}/Ca^{2+} adenosine triphosphatase (ATPase). It has been shown in the rat pilocarpine model that SE resulted in significant inhibition of ER Mg^{2+}/Ca^{2+} ATPase–mediated Ca^{2+} uptake (*J Neurochem* 2000;75:1209–18) and that this inhibition persisted well after the establishment of epilepsy in this model (*J Neurochem* 2001;79:319–27). The objective of this study was to determine if SE caused inhibition of ER Mg^{2+}/Ca^{2+} ATPase–mediated Ca^{2+} uptake in the hippocampal neuronal culture model. **Methods:** Hippocampal tissue was dissected from 2-day-old postnatal rat pups. Primary, mixed neuronal cultures were plated and allowed to mature for 2 weeks. Hippocampal cultures were used for experiments after 14–28 days in culture. To induce SE, culture media were removed, and cultures were exposed to recording solution with the omission of Mg^{2+} for 3 h. Sham cultures were exposed to recording solution with normal, 1 m*M* Mg^{2+}. After exposure to recording solution, cultures were scraped into homogenization buffer, and utilized for $^{45}Ca^{2+}$ studies. **Results:** It was important to establish that Ca^{2+} uptake measured in the unfractionated homogenate was ER Mg^{2+}/Ca^{2+} ATPase mediated. There was no significant Ca^{2+} uptake in the absence of Mg^{2+}, ATP, or both. However, there was significant Ca^{2+} uptake in the presence of Mg^{2+} and ATP with a 37-fold increase in activity. Ca^{2+} uptake was also dependent on the ER-specific Ca^{2+}-precipitating anion oxalate. There was no significant Ca^{2+} uptake in the absence of oxalate. However, as the concentration of oxalate increased from 0 to 15 m*M,* Ca^{2+} uptake proportionately increased, with an 18-fold increase in activity. Ca^{2+} uptake was also inhibited by the ER Mg^{2+}/Ca^{2+} ATPase–specific inhibitor thapsigargin. As thapsigargin increased from 0 to 30 n*M,* Ca^{2+} uptake was proportionally inhibited reaching a maximum inhibition of 85% at 15 n*M.* Finally, Ca^{2+} uptake was compared in control and hippocampal neurons subjected to prolonged SE. SE resulted in a 45.1 ± 16.8% inhibition of ER Mg^{2+}/Ca^{2+} ATPase–mediated Ca^{2+} uptake as measured in unfractionated hippocampal cell culture homogenates. **Conclusions:** The data demonstrated that ER Mg^{2+}/Ca^{2+} ATPase–mediated Ca^{2+} uptake can be effectively measured in unfractionated hippocampal culture homogenates. The data also showed that prolonged SE caused inhibition of Ca^{2+} uptake in mixed hippocampal cultures. The results suggest that inhibition of ER Mg^{2+}/Ca^{2+} ATPase–mediated Ca^{2+} uptake may contribute to the loss of cytosolic Ca^{2+} homeostasis associated with SE in hippocampal neurons. [Supported by AES Training Fellowship (J.T.P.), RO1-NS39970, PO1-NS25630, and RO1-23350.]

1.079
NEUROSTEROIDS MODULATE EPILEPTIFORM ACTIVITY INDUCED BY 4-AMINOPYRIDINE AND PICROTOXIN IN THE RAT HIPPOCAMPAL SLICE

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Rationale: Neurosteroids have been implicated in the hormonal regulation of seizure susceptibility in catamenial epilepsy and stress. Allopregnanolone (3α,5α-THP), a powerful positive modulator of γ-aminobutyric acid (GABA)ergic neurotransmission, has anticonvulsant activity in animal models, whereas pregnenolone sulfate (PS), a $GABA_A$-receptor antagonist and positive modulator of *N*-methyl-D-aspartate (NMDA) receptors, is proconvulsant. Here we examined the modulatory effects of 3α,5α-THP (and its less active 5β isomer) and PS on seizure susceptibility in an vitro model system. **Methods:** Extracellular field recordings were carried out with glass micropipettes from the CA3 region of 500-μm rat hippocampal slices continuously perfused with oxygenated aCSF at 2.5–3.0 ml/min. Spontaneous epileptiform bursting was evoked by superfusion with 4-aminopyridine (4-AP; 55–75 μ*M*) or picrotoxin (PTX; 100 μ*M*). The rate of bursting was monitored for 1–2 h. Bursts were detected using Mini Analysis (Synaptsoft). **Results:** Superfusion with 4-AP evoked high-frequency discharges (≤50 per min). The frequency of discharges increased gradually to a constant level at ~40 min after the addition of 4-AP Washout led to a gradual disappearance of the discharges. Addition of 10 or 100 μ*M* PS 1 h after 4-AP did not alter the discharge frequency (six slices). However, 100 μ*M* PS alone did induce spontaneous discharges at a low rate (1 per min; five of six slices). Addition of 90 μ*M* (3α,5α-THP) 1 h after 4-AP led within 40 min to a cessation in epileptiform activity in all five slices tested. Removal of (3α,5α-THP) from the medium resulted in the reappearance of epileptiform discharges. Addition of 90 μ*M* (3α,5α-THP) simultaneous with 4-AP resulted in an 83% suppression of bursting (five slices). 3α,5α-THP also suppressed bursting by 83% (eight slices). PTX induced epileptiform discharges similar to those produced by 4-AP, but these occurred at a lower frequency (up to nine per minute). The PTX-induced activity began within 10 min of drug application and was maintained at a constant rate. 3α,5α-THP (90 μ*M*) perfused concurrent with PTX completely inhibited the epileptiform activity (three slices). In contrast, 3α,5α-THP (100 μ*M*) failed to affect the rate of discharge (three slices). **Conclusions:** The neurosteroid 3α,5α-THP suppresses 4-AP– and PTX-induced epileptiform bursting. However, there was no stereoselectivity of the THP isomers in the 4-AP model, suggesting that their activity does not occur through an interaction with $GABA_A$ receptors. (A similar lack of stereoselectivity is observed in the in vivo maximal electroshock model.) In contrast, the effect on PTX bursting showed stereoselectivity that matches the stereoselective effects of the steroids on $GABA_A$ receptors, as is the case for the in vivo pentylenetetrazol seizure model. Thus, neurosteroids can protect against seizures by effects on $GABA_A$ receptors and also by other mechanisms. PS

failed to affect epileptiform discharges induced by 4-AP but did itself weakly induce bursting, consistent with its proconvulsant activity in animals. (Supported by NIH.)

1.080

KAINIC ACID–INDUCED ALTERATIONS IN THE ENTORHINAL–HIPPOCAMPAL CIRCUIT

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Rationale: Despite recent advances in the treatment of epilepsy, a substantial patient population remains refractory to pharmacotherapy. The objective of this study was to determine if electrophysiological recordings from combined entorhinal cortex (EC)–hippocampal (HC) ventral brain slices obtained from kainic acid (KA)-treated animals would prove useful as a model system for the routine screening of novel anticonvulsant therapies for pharmacoresistant temporal lobe epilepsy (TLE). **Methods:** Male Sprague–Dawley rats were injected with either saline or multiple doses of KA [5 mg/kg, i.p., repeated to status epilepticus (SE)] (Hellier et al., 1998). Behavioral seizure activity was scored (Racine scale) for subsequent correlation with histologic and electrophysiologic results in control and KA-treated rats. Neuronal cell loss and mossy fiber sprouting were quantified 24 h, 1, 4, or 10 weeks after injections by cell counting and densitometric analysis of standard cresyl violet and Timm's stained horizontal sections (40 μm). Extracellular recordings from combined EC–HC horizontal brain slices (400 μm) were performed within 1 week of KA-induced SE. Differences in (a) baseline electrophysiologic properties in normal Ringer, (b) latency and extent of seizure-like activity in "hyperexcitable" Ringer (6 m*M* K^+), and (c) responsiveness to traditional (e.g., phenytoin, carbamazepine) and nontraditional (e.g., retigabine, levetiracetam) anticonvulsants (AEDs) were compared in slices from KA- and saline-treated rats. **Results:** All KA-lesioned rats demonstrated repeated stage 4/5 behavioral seizures at the time of KA administration. Significant cell loss was detected in layer III of mEC, the hilar region of the dentate gyrus, and the CA3 cell body region 24 h after KA-induced SE. This cell loss was not progressive, despite the gradual onset of spontaneous seizures in these animals. Analysis of extracellular field potential recordings demonstrated that in normal Ringer solution, multiple stimulus-linked population spikes and spontaneous burst activity could be observed in layer II of mEC, CA1, and CA3 of slices from KA-treated rats. Slices from saline-treated controls did not demonstrate any signs of baseline hyperexcitability. Increased extracellular [K^+] resulted in a shortened latency to onset of bursting and faster spontaneous burst rates in slices from KA-lesioned rats versus controls. Spontaneous bursting in CA1 and CA3 regions was attenuated by 50 μ*M* phenytoin and completely blocked by 10 μ*M* retigabine in slices from both KA- and saline-treated rats. However, neither carbamazepine nor levetiracetam significantly altered spontaneous bursting. **Conclusions:** These experiments suggest that KA-induced selective cell loss primes the ventral EC–HC circuit by markedly increasing slice hyperexcitability. Such KA-induced hyperexcitability may provide a fast and reliable model for the routine screening of novel AED treatments and may provide insight into the mechanisms underlying pharmacoresistant TLE. [Supported by NIH contract N01-NS-4-2311 (H.S.W.).]

1.081

NEUROPROTECTIVE EFFICACY OF CASPASE-9 INHIBITORS AGAINST DEPOLARIZATION INJURY TO CA1 PYRAMIDAL NEURONS IN RAT HIPPOCAMPAL SLICES

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Rationale: Seizure-induced neuronal damage appears to involve apoptosis. Caspase-9 is a key enzyme involved in apoptosis. Therefore, we assessed the neuroprotective effects of caspase-9 inhibitors against depolarization-induced CA1 neuronal injury in the hippocampal slice. Upon the conclusion of this presentation, participants should have an understanding of the neuroprotective effects of caspase-9 inhibitors against CA1 neuronal injury induced by depolarization. **Methods:** Using in vitro rat hippocampal slices, we monitored the CA1 orthodromic and antidromic population spike (PS) amplitude during hypoxia with and without caspase-9 inhibitor treatment. **Results:** Caspase-9 inhibitor II, a cell-permeable, reversible inhibitor, provided robust neuroprotection of CA1 PS amplitude in stimulated hippocampal slices subjected to depolarization-induced injury. At a caspase-9 inhibitor II concentration of 5 μ*M,* CA1 orthodromic and antidromic PS amplitude recovered to 92.0% ± 1.6 and 92.2% ± 1.7, compared with unmedicated slices, which recovered to 13.4% ± 1.7 and 13.5% ± 3.6, respectively. A potent, cell-permeable, irreversible inhibitor of caspase-9, caspase-9 inhibitor I also provided significant protection of CA1 PS amplitude in stimulated hippocampal slices subjected to depolarization-induced injury. At a caspase-9 inhibitor I concentration of 5 μ*M,* CA1 orthodromic and antidromic PS amplitude recovered to 89.5% ± 2.9 and 89.6% ± 3.2, compared with unmedicated slices, which recovered to 14.0% ± 0.7, and 14.6% ± 1.7, respectively. Similarly, caspase-9 inhibitor III provided excellent neuroprotection of CA1 PS amplitude in stimulated hippocampal slices subjected to depolarization-induced injury. At a caspase-9 inhibitor III concentration of 5 μ*M,* CA1 orthodromic and antidromic PS amplitude recovered to 92.7% ± 3.6 and 92.8% ± 2.1, compared with unmedicated slices, which recovered to 13.6% ± 1.6 and 14.3 % ± 2.4, respectively. **Conclusions:** These studies demonstrate that inhibitors of caspase-9 provide neuroprotection in an in vitro model of depolarization injury. In addition, these data suggest that the use of caspase-9 inhibitors may be a useful strategy in the prevention of brain injury during status epilepticus. (Supported by VA Research Service and UCLA Brain Injury Research Center.)

1.082

THE ROLE OF *N*-METHYL-D-ASPARTATE RECEPTOR SUBUNIT PHOSPHORYLATION IN EPILEPTIFORM ACTIVITY IN HIPPOCAMPUS

Carl Wang and Frances E. Jensen (Neurology, Children's Hospital and Harvard Medical School, Boston, MA)

Rationale: *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) function can be modulated by phosphorylation of the NR1 serine 897 site. Forskolin (FSK), an adenylate cyclase activator, increases NR1 phosphorylation through activation of the adenyl cyclase–protein kinase A (PKA) pathway, and we have reported that FSK enhances epileptiform activity in hippocampal slices. The goal of this study was to investigate whether the seizure-enhancing effects of FSK are mediated by NMDA receptors. We examined whether FSK increases phosphorylation level of NMDA-receptor NR1 subunit in postsynaptic density (PSD) fraction and whether the effect of FSK on tetanus-induced afterdischarge is affected by the NMDA-receptor antagonist 2-amino-5-phosphonovaleric acid (APV). **Methods:** Hippocampal slices were prepared from 15- to 22-day-old rats. Electrographic seizures were induced by a tetanus (2 s, 100 Hz) delivered by an electrode placed in area CA3. Field potentials were recorded in CA3 pyramidal cell body layer. FSK was administered alone or with APV by bath application 30 min before stimulation. Numbers of spikes and the duration of afterdischarges were measured to evaluate the effect of APV. To determine the phosphorylation level of NMDA receptor NR1 subunit, slices were taken 30 min after drug application. Triton X-100 insoluble membrane samples (PSD fraction) were prepared for Western blot analysis. Blots were first probed with an antibody against phosphoserine 897 (a PKA site) of NR1 and then reprobed with an antibody against NR1 C terminal. NR1 phosphorylation was calculated using the density ratio of these two signal bands. **Results:** Perfusion of hippocampal slices with FSK (50 μ*M,* 30 min) caused an increase in serine 897 phosphorylation of NR1 to 402% of the control level (FSK, 2.37 ± 0.39; control, 0.589 ± 0.09; $p = 0.004$, $n = 5$) in Triton X-100 insoluble membrane samples. The total amount of NR1 in the samples was not altered (102% of the control level). In comparison with the control group ($n = 14$), FSK-treated slices ($n = 8$) had significantly higher spike numbers (FSK, 223 ± 42; control, 53 ± 11; $p < 0.001$) and longer afterdischarge duration (FSK, 96 s ± 25; control , 22 s ± 2; $p < 0.001$). When slices ($n = 14$) were treated with APV (100 μ*M*) along with FSK, APV prevented the increase in spike numbers (57 ± 6, $p < 0.001$ vs. FSK, $p = 0.86$ vs. control) and afterdischarge duration (20 ± 2; $p < 0.001$ vs. FSK, $p = 0.915$ vs. control). **Conclusions:** FSK increases serine 897 phosphorylation of NR1 in the PSD fraction. The

NMDA-receptor antagonist APV attenuates FSK-enhanced ictal activity. The effects of FSK on ictal activity and NR1 phosphorylation occur within minutes. The results suggest that the phosphorylation state of the NMDAR NR1 serine 897 site may regulate seizure activity. Posttranslational modification of NMDARs may be an important early event in epileptogenesis. [Supported by NIH grant RO1 NS 31718-10 (F.E.J.).]

1.083
EFFECTS OF AN ANIMAL MODEL OF SOCIAL STRESS ON SEIZURE SUSCEPTIBILITY IN MALE AND FEMALE RATS

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Rationale: Isolation housing has been reported to act differentially as a stressor in female and male laboratory animals. As responses or adaptations to stress have been shown to influence brain excitability, we wanted to determine if mild chronic stress or brief acute stress would differentially affect seizure induction. Therefore, the objective of this study was to determine whether different stressors (chronic mild or acute) exerted sex-selective actions on seizure induction in male and female rats. **Methods:** The effect of stress was measured by seizure threshold (ST) determinations, a sensitive measure of seizure susceptibility. The chemoconvulsants bicuculline (BIC), 0.05 mg/ml, or pentylenetetrazol (PTZ), 5mg/ml, were slowly infused via a lateral tail vein, and STs were determined by recording the time to first twitch/body weight of the animal. Initially, we assayed the effects of a mild chronic stressor (10 days of individual vs. group housing) on STs. We compared the anticonvulsant effect of diazepam (DZP; 5 mg/kg) or ethanol (2.5 g/kg) on STs under these different chronic stress conditions. We also studied the effect of an additional brief restraint stress on STs of male and female rats under the two housing conditions. **Results:** We found that individual housing reduced BIC ST by ~10% in both male and female rats. In contrast, PTZ STs were similar between individual and group-housed male and female rats. The anticonvulsant effectiveness of DZP and ethanol were not altered by individual housing in either male and female rats. However, female rats displayed a greater response than male rats to both DZP and ethanol. For example, i.p. administration of ethanol increased PTZ seizure thresholds in individually housed animals from 30.8 ± 0.9 to 46.4 ± 2.3 mg/kg PTZ in male rats and from 31.3 ± 2.2 to 54.5 ± 3.1 mg/kg PTZ in female rats. Short-term administration of ethanol also increased BIC ST by 13 or 19% in female rats but only 8 or 9% in male rats (for group or individually housed animals, respectively). The addition of a brief, acute restraint stress decreased STs from 0.203 ± 0.012 to 0.183 ± 0.013 mg/kg BIC in individually housed male rats, without altering ST in group-housed male rats. Conversely, STs were reduced from 0.292 ± 0.012 to 0.254 ± 0.009 mg/kg BIC in group-housed female rats, with no effect on individually housed female rats. **Conclusions:** These data showed that both a chronic, mild stress as well as acute stress can influence seizure susceptibility in a laboratory animal model. Furthermore, there were interesting sex differences in responses to stressors as well as anticonvulsants. These data suggest that certain types of stressors, classified as social (modeled by housing conditions) or nonsocial (modeled by acute restraint stress) may differentially affect the risk for induction of seizures in men and women with epilepsy. (Supported by PHS AA11877.)

1.084
FUNCTIONAL MAGNETIC RESONANCE IMAGING AND CONCURRENT INTRACRANIAL EEG IN PENICILLIN-INDUCED FRONTAL LOBE SEIZURES IN SHEEP: EVIDENCE OF AMYGDALA INVOLVEMENT

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Rationale: Penicillin-induced seizures in animal models of epilepsy have been evaluated electrophysiologically in the past. Activation of subcortical structures such as the thalamus have been demonstrated in these studies. Whether other subcortical structures are routinely activated in cortical models of focal epilepsy is not known. We sought noninvasively to evaluate these structures by using functional magnetic resonance imaging (fMRI) techniques. **Methods:** Three adult merino sheep were used. Surgery was performed 1 week before the fMRI study to implant a custom-made penicillin infusion port and intracranial EEG electrode strips over both hemispheres. On the day of the experiment, animals were anesthetised with opiate and histamine anesthesia. This was previously shown to produce adequate anesthesia while preserving fMRI responses to penicillin-induced seizures. Epileptiform spike-and-wave activity as well as electrographic seizures were then generated by unilateral instillation of 8,000–10,000 IU of sodium penicillin into the right prefrontal cortex. Functional MRI was performed at 1.5 Tesla with concurrent bilateral intracranial EEG. Blood oxygen level–dependant (BOLD) weighted signals were measured. Subcortical structures were evaluated by five coronal slices with data points sampled every 10 s throughout the course of the experiment. **Results:** In all three animals, focal electrographic seizures were seen within 17 min after penicillin infusion. There was an average of 13 seizures per animal, each lasting ≤30 s. The BOLD fMRI signal intensity was evaluated during each of these seizures. Areas that showed large variance in subcortical sites were determined. In all three animals, dramatic signal BOLD signal increases occurred at a frequency consistent with the frequency of seizures in the amygdala ipsilateral to the site of penicillin injection. There was also a high signal change in the region of the ipsilateral hypothalamus, most consistent with the mamillary body. **Conclusions:** BOLD signals were seen in the ipsilateral amygdala and mamillary body during electrographic seizures in frontal lobe penicillin-induced seizures in sheep. No consistent activation was seen in the thalamus. These results suggest that the amygdala and mamillary body are key subcortical structures involved in maintenance or propagation of seizures in this experimental model. [Supported by National Health and Medical Research Council of Australia (Grant 135400), Brain Imaging Research Foundation, Canadian Institutes of Health Research, and Alberta Heritage Foundation for Medical Research.]

1.085
ELECTROBEHAVIORAL CHARACTERISTICS OF ADULT RATS DURING EPILEPTOGENESIS AND THE EPILEPTIC STATE AFTER PHOTOTHROMBOTIC BRAIN INFARCTION

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Rationale: Recently we demonstrated that large photothrombotic infarcts of the neocortex in adult rats were associated with the development of epileptic seizures. However, the number of animals that underwent photothrombosis was small, and continuous video-EEG recording was limited. We sought to evaluate more fully the latent period of epileptogenesis and the epileptic state by expanding our previous video-EEG recordings while eliminating or minimizing potentially influential variables such as toxicity of the photosensitive dye rose bengal and cortical irritation due to blood or indwelling intracranial electrodes. At the end of this activity, the participants should be able to discuss the photothrombotic model of poststroke epilepsy and the EEG and behavioral properties of animals during epileptogenesis and the epileptic state. **Methods:** Twenty 2-month-old male Sprague–Dawley rats were used in this study. Ten animals underwent photothrombotic brain infarction of the left sensorimotor cortex with the photosensitive dye rose bengal (30 mg/kg; femoral vein injection; 20 min photoactivation; lesioned animal). Three rats were injected with rose bengal but not photostimulated (sham-operated control). Seven animals were age matched and received no treatment (naive control). All animals had six skull screws placed for EEG recordings. Digital video-EEG monitoring was performed intermittently for each animal for 6 months. All video-EEG files were reviewed manually. Animals were anesthetized, killed by cardiac perfusion, and brains were sectioned and Nissl stained to evaluate infarct volumes and cortical cytoarchitecture. **Results:** All lesioned animals demonstrated intermittent rhythmic 4- to 6-Hz spike–wave discharges lasting 1–3 s over the lesioned hemisphere, variably maximal over frontal, frontocentral, or parietal areas. No clear behavioral changes occurred during these discharges. More prolonged ipsilateral spike wave or polyspike discharges were associated with motor arrest, prominent facial clonus, or mild multifocal body jerking. One lesioned

animal demonstrated frequent prolonged tonic–clonic seizures. All lesioned, sham-operated, and control animals demonstrated periods of solitary generalized spike discharges occurring every 1–1.5 s, variably associated with no movement, brief body jerks, or multifocal body clonus that could occur during locomotion. One naive control animal demonstrated frequent prolonged 7-Hz spike–wave absence seizures and multiple tonic–clonic seizures. Nissl-stained tissue sections from lesioned animals showed that the infarct was transformed into a vacant space with maximum extent to the cortical–subcortical interface. There were no observable abnormalities in cortical cytoarchitecture in sham-operated and naive control animals. **Conclusions:** These video-EEG results validate and expand our previous findings of the development of epileptic seizures after cortical photothrombosis and brain infarction. We propose that this model can be a useful tool for studying the molecular, cellular, and network properties associated with neocortical injury and mechanisms of secondary epileptogenesis. (Supported by American Heart Association Grant-in-Aid to K.M.K.)

1.086

EARLY POSTNATAL ADRENALECTOMY FOLLOWED BY REPEATED PERINATAL SEIZURES INJURE SELECTIVE THALAMIC NUCLEI AND CA3 PYRAMIDAL CELLS OF IMMATURE RATS

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Rationale: In adult rats, adrenalectomy (ADX) results in delayed and highly selective neurodegeneration of dentate granule cells but attenuates kainic acid (KA)–induced injury of hippocampal pyramidal cells. Prior seizures evoked by electroshock protect against the ADX-induced granule cell death, and ADX performed in P10 rats reduces behavioral inhibition. However, ADX has not been previously attempted during the first postnatal (P) week, and the effects of glucocorticosteroid (CORT) depletion on seizures and neuronal injury in this early neonatal period are unknown. Therefore, ADX was performed on P5–P6 pups, and sustained seizures with KA were induced 3 times on postnatal ages (P7, P10, and P13). **Methods:** Neonatal rat pups were anesthetized with low doses of ketamine, and the initial incision was made along the middle of the back. The surgery scope was exposed with expanders made from paper clips, and the adrenals were removed bilaterally with microsurgery instruments. All incisions were sutured with human hair. Sham control operations were performed but without removing the adrenal glands. KA (2 mg/kg) was used to induce seizures. CORT plasma levels by radioimmunoassay (RIA) and cell injury with classic histologic stains were assessed in controls and 48 h after ADX and the third KA seizure. **Results:** Approximately 95% of the animals survived the surgery. There were no changes in seizure onset or behavior after ADX and KA at the ages examined relative to controls. No detectable levels of plasma CORT were observed after ADX with RIA. Chromatin and silver stains 6–7 days after ADX or sham operation showed no histologic change in the hippocampus or other brain structures. In contrast, in ADX animals with three episodes of KA seizures, many thalamic nuclei, particularly those of the midline, showed eosinophilic or argyrophilic deposits within a large number of cell somata. Some injured cells were also revealed in the hippocampal CA3 region; the dentate gyrus was completely spared. **Conclusions:** These observations implicate age-dependent differences in the action of adrenal steroids on neuronal survival within limbic structures involved in seizure propagation.

1.087

NOREPINEPHRINE CONCENTRATIONS IN LOCUS CERULEUS COMPLEX AND AMYGDALA AS A FUNCTION OF GENDER AND KINDLED-SEIZURE SUSCEPTIBILITY

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Rationale: The objective was to compare norepinephrine (NE) concentrations in locus ceruleus complex (LC) and amygdala before, during, and after amygdala kindling as a function of gender and seizure susceptibility. **Methods:** Subjects were 16 preadolescent cats (<1 year, eight male and eight female). NE concentrations (5-min microdialysis samples at 2 μl/min infusion rate) were obtained over 2 consecutive days (6- to 8-h polygraphic recordings) before and 1 month after kindling as well as during a "1 day" kindling paradigm involving one per minute electrical stimulations evoking either focal afterdischarge (FAD) or generalized AD (GAD) for 1 h each. See Fig. 1. **Results:** When compared with females, males had lower NE concentrations (fmol/sample) at both collection sites before and 1 month after kindling but higher NE concentrations during FAD and GAD (Fig. 1). The most salient correlate of gender-specific findings during kindling was seizure severity, indexed by longer duration of FAD and GAD (seconds) as well as longer duration or increased number of behavioral seizure manifestations (not shown). One month after kindling, females showed more extreme fluctuation than males in NE concentrations and spontaneous seizure activity (shown). However, preliminary findings suggested that males continued to show higher and more persistent susceptibility to evoked and spontaneous seizures after dialysis was discontinued (not shown). **Conclusions:** Lower NE concentrations are more likely to predict increased susceptibility to onset and persistence of a severe seizure disorder in young males than in young females (Fig. 1). (Supported by Department of Veterans Affairs.)

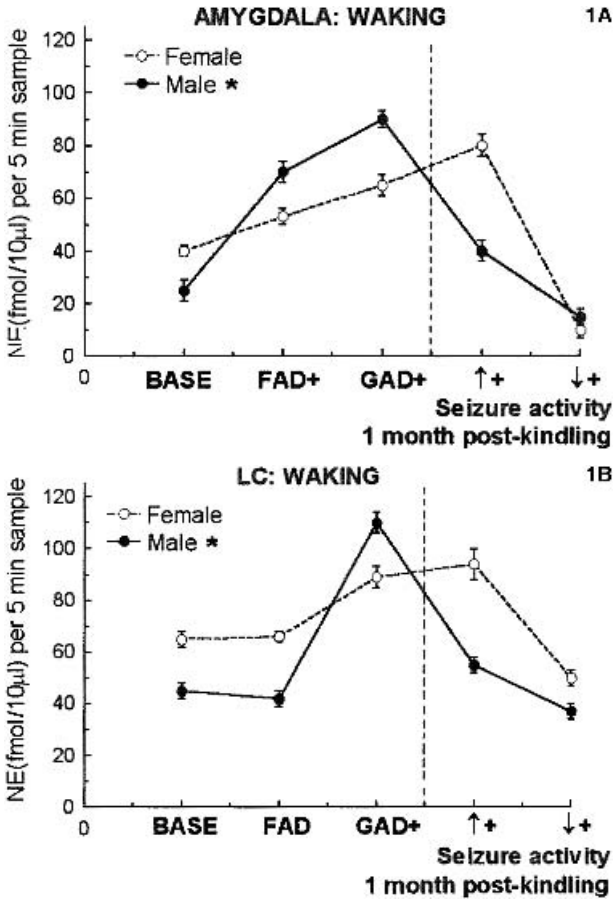

FIG. 1. A and B: Mean ± SD concentrations of NE over 5 consecutive conditions in 8 male and 8 female preadolescent cats. F and post-hoc t-tests = $p < .05$–$.01$: * = male different from females; + = change from base; ■ = LC higher than amygdala.

1.088

EFFICACY OF TOPIRAMATE IN BLOCKING EPILEPTOGENESIS AFTER LITHIUM–PILOCARPINE STATUS EPILEPTICUS DEPENDS ON TIME OF TREATMENT

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Rationale: An important goal of treatment of status epilepticus (SE), in addition to preventing mortality and stopping SE, is to improve long-term outcome. We studied short-term effects of topiramate (TPM) on SE and its ability to prevent epileptogenesis in relation to the time of administration. **Methods:** SE was induced in P28 rat pups by administration of lithium chloride (3 mEq/kg, i.p.) followed 20 h later by pilocarpine injection (60 mg/kg, s.c.). We observed latency of SE and duration of behavioral seizures. We injected TPM (10 mg/kg, i.p.) at three different intervals after pilocarpine administration (20, 40, and 70 min) together with atropine sulfate (10 mg/kg, i.p.). Controls received no treatment (C) or pilocarpine and atropine (no TPM). Three months later, we implanted skull electrodes under ketamine–xylazine anesthesia. After 1 week of recovery, animals were monitored by telemetry–videotape for 1 week, and we measured the number of recurrent spontaneous seizures per week, seizure frequency, mean seizure duration, and spike frequency. **Results:** Atropine alone given at 10 min after pilocarpine stopped SE, but at 20, 40, or 70 min. it failed to stop SE, demonstrating that self-sustaining SE had been set in motion. Mortality was much higher than in adults: 90% in no-TPM animals, 70% in the group treated with TPM at 70 min, 50% in the 40 min TPM group, and 40% in the TPM 20-min group. Seizure frequency was 1.7 ± 0.6 seizures per day in animals subjected to SE with no treatment; 2 ± 1.1 seizures per day in rats treated at 70 min with TPM; none had spontaneous recurrent seizures in the 40-min group, and one of five had one seizure per week in the 20-min TPM group. Spike frequency was 47.5 ± 10.9 spikes per hour in animals subjected to SE without treatment; 34.4 ± 9.9 spikes per hour in rats treated at 70 min with TPM; 4 ± 0.5 spikes per hour after TPM treatment at 40 min; and 2.4 ± 0.8 spikes per hour after TPM treatment at 20 min, which did not differ significantly from untreated controls (2.5 ± 0.5 spikes per hour). **Conclusions:** When treating experimental SE, timing of administration of TPM (10 mg/kg) is a crucial factor in the prevention of epileptogenesis. (Supported by VA Research Service, by research grant at NS13515 fom NINDS and by a grant from Johnson & Johnson, Pharmaceutical Research and Development.)

1.089

A KINDLING MODEL OF PHARMACORESISTANT TEMPORAL LOBE EPILEPSY IN SPRAGUE–DAWLEY RATS INDUCED BY CORIARIA LACTONE AND ITS POSSIBLE MECHANISM

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Rationale: The aim of this study was to develop a new animal kindling model of pharmacoresistant temporal lobe epilepsy (TLE) by intramuscular injection of coriaria lactone (CL), and explore the mechanisms that might be involved. **Methods:** Healthy male Sprague–Dawley rats (n = 160) were randomized into six groups: three groups (n = 50 for each group) received CL injection at subthreshold dosages (1.25 mg/kg, 1.5 mg/kg, and 1.75 mg/kg, respectively), and 10 received normal saline (NS) injection as control group. The maximal human adult dosage of carbamazepine (CBZ), valproate (VPA), and phenytoin (PHT) was administered as monotherapy to different groups of kindled rats for 1 month. Changes in EEG recording, seizure number, intensity, and duration, including spontaneous seizures during different interventions, were compared. The expression of P-170, a multiple drug resistance gene (MDR1) encoding P-glycoprotein, was measured in brain samples from different groups of experimental rats. **Results:** A total of 70 (46.7%) rats was fully kindled with a median of 15 CL (seven to 20) injections. Electrocorticography (EcoG) and ECG monitoring revealed the hippocampal origins of epileptiform potentials, which were consistent with the behavior changes observed. Spontaneous seizure occurred with similar frequency and diurnal pattern to those in human TLE. The antiepileptic drugs (AEDs) tested were ineffective for seizure control. The maximal P-170 expression was in the kindled rats with AED treatment; the next highest was in the kindled rats without AED intervention. Nonkindled SD rats with CL injection also had increased P-170 expression compared with control SD rats. **Conclusions:** The study provided a simple and stable animal TLE kindling model with pharmacoresistant properties. The pharmacoresistance to CBZ, VPA, and PHT observed in the kindled rats together with the increased P-170 expression was a distinct feature of this model. This model might be used in further investigations of the mechanisms involved in pharmacoresistant TLE and for developing new AEDs.

Clinical Neurophysiology (Human/Adult)

1.090

CLINICAL, ELECTROENCEPHALOGRAPHIC, AND NEURORADIOLOGIC CHARACTERISTICS OF SECONDARY BILATERAL SYNCHRONY IN LOCALIZATION-RELATED EPILEPSY

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Rationale: Secondary bilateral synchrony (SBS) was originally described by Jasper (1951) as "bilaterally synchronous discharges, which can be shown to arise from a unilateral cortical focus . . . " SBS would likely have significant impact on localization decisions based on scalp EEG, yet its incidence and other clinical features have been poorly defined. Therefore, we investigated the occurrence of SBS in a population of patients with intractable, localization-related epilepsy. **Methods:** Consecutive long-term, video-EEG evaluations were analyzed from May 1997 through March 2002. Patients were included if they demonstrated at least one generalized, nonlateralizing, or localizing epileptiform discharge during interictal recording and had at least one typical epileptic, localization-related seizure captured with video-EEG. Patients with primary or symptomatic generalized epilepsy were excluded. **Results:** A total of 1,079 patients was evaluated. Among the entire patient population, 448 (41%) were classified as having a localization-related epileptic syndrome. These patients were further classified into frontal epilepsy (12%), temporal epilepsy (41%), parietooccipital epilepsy (3%), and insufficient data to localize (44%). Sixteen patients met inclusion criteria for SBS, including 13 females and three males. This represented 2.9% of all patients with epilepsy and 3.6% with focal epilepsy. The mean age was 29.5 years (range, 18–56 years). A final assessment of localization was possible in 15 of 16 patients and were as follows: Frontal /frontoparietal, nine of 15 (60%); mesial/neocortical temporal, three of 15 (20%); parietooccipital, one of 15 (7%); temporooccipital, one of 15 (7%); and left hemisphere, one of 15 (7%). Ictal localization was obtained in 10 of 16 (63%): frontal/frontoparietal, four (40%); temporal, four (40%); temporoparietal, one (10%); and left hemisphere, one (10%). Interictally, three of 16 (19%) had exclusive generalized spike–slow wave discharges, six of 16 (38%) had localized frontal discharges, four of 16 (25%) had unilateral or bilaterally independent temporal discharges, two of 16 (12 %) had bilaterally independent frontotemporal discharges, and one of 16 (6%) had independent multifocal spike discharges. Magnetic resonance imaging results were available in 13 of 16 and showed extratemporal encephalomalacia in four of 13 (31%) (frontal in three), mesial temporal sclerosis in four of 13 (31%), and were normal in five of 13 (38%). **Conclusions:** SBS, as defined as generalized epileptiform discharges in patients with exclusive focal epilepsy, is a relatively infrequent interictal finding, occurring in ~4% of all intractable, localization-related patients undergoing video-EEG monitoring. Although less likely, the possibility of coexisting and unrecognized generalized epilepsy or an inherited generalized EEG trait cannot be absolutely excluded. The higher proportion of patients with likely fron-

tal lobe epilepsy and SBS (60%), in contrast with the overall incidence of frontal epilepsy in this population (12%), suggests an associated increased risk for extratemporal epilepsy.

1.091
COMPARATIVE EFFECTS OF LAMOTRIGINE VERSUS CARBAMAZEPINE ON CLINICAL EEG IN ADULTS
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Rationale: At the end of this activity, the participants should be able to discuss the differential effects of lamotrigine (LTG) and carbamazepine (CBZ) on clinical EEG. As newer antiepileptic medications (AEDs) have come into common use in the last decade, more patients treated with these new AEDs are undergoing EEG evaluation as part of their epilepsy management. Although the effects of standard AEDs, such as CBZ, have been recognized for some time, relatively little information is available with regard to the effects of the new AEDs on clinical EEG. This study looked at the effects of LTG and compares it with CBZ with regard to typical routine clinical EEG variables. **Methods:** Retrospective review of consecutive outpatient clinical EEGs over the last 2 years in the hospital-based outpatient laboratory was performed to identify those records that listed LTG (n = 14; mean age, 45 years) or CBZ (n = 28; mean age, 44 years) in the medication list as monotherapy. These patients were taking LTG or CBZ for the treatment of seizures. All EEGs were recorded with a Nicolet Voyageur or an XLTEK, Inc., digital clinical EEG system. Visual inspection and interpretation was performed by board-certified clinical neurophysiologists without knowledge that these studies were to be reviewed in the future for clinical data. **Results:** 79% of LTG, but only 54% of CBZ EEGs were interpreted as normal. The median alpha frequency was 9.5 Hz in both groups (range: LTG, 8–11; and CBZ, 8.5–11.5). The comparative abnormalities noted were as follows: Mild diffuse slowing: 7% LTG versus 21% CBZ; focal slowing: 0 LTG versus 14% CBZ; focal spikes: 0 LTG versus 14% CBZ; generalized spike–wave: 7% LTG versus 11% CBZ; seizure: 7% LTG versus 4% CBZ; and excessive beta: 7% LTG versus 0 CBZ. None of the records revealed moderate or severe focal or diffuse slowing. **Conclusions:** In this retrospective review of the differential effects of LTG versus CBZ on clinical EEG, care was taken to eliminate the role of concomitant AEDs, comorbidities, and to limit the role of concomitant CNS agents on the results. With that in mind, the main findings suggest that in the routine clinical setting, when compared with CBZ, LTG has relatively little effect on EEG background. Comparator clinical studies have revealed few differences between these medications in terms of efficacy of seizure control. However, the same studies suggest that LTG may be better tolerated, in terms of side-effect profile. The present finding that LTG has fewer effects on the EEG background seems to provide neurophysiologic support of that notion. This information is important to the neurologist who interprets EEGs of patients treated with these AEDs. A prospective evaluation, with the ability to randomize patients and control for variables such as dose and AED level, will likely provide more detailed information about the relation of these agents to the EEG. (Disclosure: Honoraria: GlaxoSmithKline Novartis.)

1.092
ELECTROENCEPHALOGRAPHIC PATTERNS IN UNRESPONSIVE ADULT AND PEDIATRIC PATIENTS
Syed Hosain, Erik J. Kobylarz, and Gail E. Solomon (Comprehensive Epilepsy Center, Department of Neurology, Weill-Cornell Medical College, New York, NY)

Rationale: Electroencephalograms (EEGs) are routinely requested for patients in unresponsive states. We studied the various EEG patterns occurring in unresponsive adult and pediatric patients to aid in their diagnostic evaluation. At the end of this activity, the participants should gain an understanding for EEG patterns in adult and pediatric patients in unconscious states and their potential etiologies. **Methods:** The EEG patterns of unresponsive patients between the ages of 1 day and 101 years were analyzed. The EEG studies were requested by intensivists and neurologists for patients admitted to intensive care units. The EEG interpreters were unaware of the patients' clinical diagnoses. EEG background patterns and epileptiform activity were determined. Patients in whom unresponsiveness could be attributed to pharmacologic agents were not included. All EEGs were performed by using the standard recommendations of the American EEG Society. **Results:** A total of 610 EEG studies (from 119 children and 491 adults) were analyzed over a 2-year period. The mean age of the patient population was 56.7 years. The following EEG patterns were observed: (a) 137 patients (23%) had EEG patterns consistent with nonconvulsive status epilepticus (NCSE). The incidence of NCSE was higher in the pediatric population (33%) compared with the adults (20%); (b) Of the patients with NCSE, 47 patients (8%) had generalized NCSE, and 90 patients (15%) had complex partial NCSE; (c) Of 119 children, 20 (17%) had generalized NCSE, and 19 (16%) had complex partial NCSE. Of 491 adults, 27 (6%) had generalized NCSE, and 71 (14%) had complex partial NCSE; (d) Of the 610 patients, 470 (77%) had only diffuse cerebral dysfunction, without evidence of NCSE; (e) Of the patients with diffuse cerebral dysfunction, 118 (25%) patients had interictal epileptiform activity; (f) In patients with diffuse cerebral dysfunction, 121 patients (26%) had triphasic waves, suggesting a metabolic encephalopathy. This was much more common in the adult population (24%) compared with the pediatric patients (4%); (g) In 22 patients (4%), alpha coma, theta coma, or burst suppression pattern was observed. **Conclusions: (a)** NCSE is a common EEG pattern in unresponsive patients, particularly in the pediatric population; (b) Generalized NCSE is more common in unresponsive pediatric patients compared with adults. However, the incidence of complex partial NCSE is not significantly different between these groups; (c) A moderate to severe disturbance in cortical function was seen in the majority of our patients in an unresponsive state; (d) The existence of triphasic waves, which could indicate an underlying metabolic encephalopathy, is not an uncommon finding in adult patients with diffuse cortical disturbance. In contrast, the EEGs from unresponsive children in our study rarely had triphasic waves; (e) Routine EEG is a valuable diagnostic tool for patients with unexplained unresponsiveness in all age groups. The difference in EEG findings in different age groups is not only an interesting neurophysiologic phenomenon, but also can aid in the clinical management of these patients.

1.093
DETERMINING RECURRENCE AND STABILITY OF FRONTALLY PREDOMINANT SUBCLINICAL SEIZURES
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Rationale: Recurrent subclinical seizures represent a problematic form of epilepsy. Their clinical significance is not always apparent, and when treatment is considered, clinicians lack details regarding stability of subclinical epileptiform discharges over time. Data regarding recurrence and potential for exacerbations can improve quality of care by identifying patients likely to benefit from extended follow-up and provide objective evidence of severity that clinicians can use in formulating treatment plans. The objective of this study was to examine serial EEGs from patients with frequent subclinical seizures and to track fluctuations in patterns of distribution and severity of discharges over time. **Methods:** We are conducting an ongoing study of short- and long-term effects of recurrent frontally predominant subclinical seizures on cognitive functions. Inclusion criteria for this study were (a) at least 2 consecutive years of follow-up with EEGs, and (b) frontal lobe involvement with electrographic seizures (i.e, events not accompanied by readily apparent clinical activity). Quantitative estimates of severity were obtained by determining the total amount of time/EEG with epileptiform discharges. Qualitative techniques were used to identify shared patterns of change because of small sample size and varying numbers of EEGs/patient. **Results:** Six patients met inclusion criteria. Follow-up covered 4–13 years (mean, 7 years). EEGs/patient ranged from eight to 25 (mean, 14). Five of six patients (83%) shared a primary ictal pattern of generalized 2- to 3-Hz frontotemporal (FT) pre-

dominant spike and slow wave discharges (SWDs); one of six patients (17%) had rhythmic sharp 5- to 6-Hz theta involving frontocentrotemporal regions bilaterally. Two of five patients (40%) with 2- to 3-Hz FT SWDs as their primary ictal pattern presented initially with a different pattern: 8- to 10-Hz SWDs or 1- to 4-Hz SWDs. With extended follow-up, four of six patients (67%) added patterns (e.g., 25- to 30-Hz polyspike waves). Most EEGs (76%) had epileptiform bursts from 1 to 50 s. Ictal activity varied greatly, ranging from 0 to 88% of time/EEG. Using burst duration as a marker, patients were stratified into two "tiers": five of five patients (100%) with bursts >2 s had large fluctuations in severity, whereas the patient with only 1- to 2-s duration bursts never exceeded 2% of time/EEG as nonconvulsive seizures. Three of six patients (50%) were treated for nonconvulsive status epilepticus (NCSE), and two of six patients had EEGs suggestive of NCSE, but cognitive deficits were not shown. The pattern of ≈3-Hz SWDs worsened by hyperventilation (resembling absence seizures) suggested treatment that suppresses T-calcium type channels might help. Valproic acid or lamotrigine in four of six patients (67%) with these discharges did reduce SWD severity. **Conclusions:** FT-predominant subclinical seizures, as 2- to 3-Hz SWDs, persist and often recur even after near-complete suppression. Extended follow-up with EEGs may capture changes in ictal patterns supporting specific treatment interventions. Prolonged exposure to FT-predominant subclinical seizures may be a risk factor for NCSE. Further studies on this issue are needed.

1.094

ELECTROENCEPHALOGRAPHIC DISCHARGES MIMICKING EPILEPTOGENIC ACTIVITY: ELECTROCLINICAL STUDY OF FOUR PATIENTS

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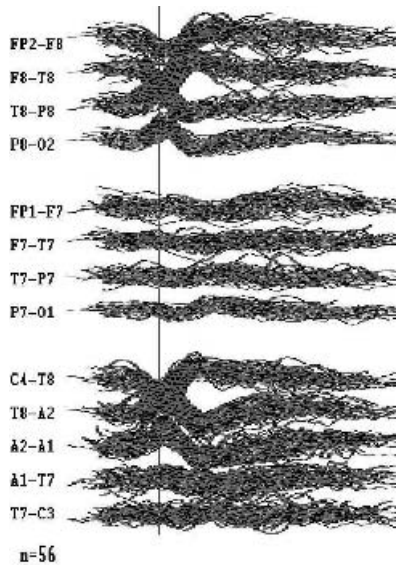
Rationale: Several type of repetitive EEG discharges without clinical significance have been reported. This is a rare nonepileptogenic epileptiform activity of unknown pathophysiology, which might be misdiagnosed as epilepsy. Different EEG patterns have been described according to frequency ranges, morphology, and distribution of the discharges. Here we report four additional patients considered as epileptic because of persistent epileptiform EEG activity. **Methods:** A diagnosis of absence seizures was made in the first case, at the age of 9 years, and treated with antiepileptic drug (AED) continued for 8 years. In the second case, status epilepticus was suspected after a typical syncope. In the third case, AED was given for 7 years after a single provoked convulsive seizure. In the last case, typical migrainous attacks was misdiagnosed as epilepsy. **Results:** In all four cases, rhythmic epileptiform discharges have been recorded on the EEG. These discharges consisted in frequent trains of rhythmic slow activity (range frequencies from 3 to 5 Hz) lasting 5–30 s, disappearing with eyes opening and during intermittent light stimulation. Such EEG abnormalities occurred without any clinical symptoms and predominated on the left temporooccipital region in the first case, the right temporooccipital region in the second patient, the right parietal region in the third, and left frontotemporal region in the last case. AEDs were finally interrupted. Further EEG recordings showed the same persistent epileptiform activity in all patients, without any clinical epileptic symptoms. **Conclusions:** These epileptiform discharges must be recognized as benign EEG variants without a relation to epilepsy. Our cases are probably a variant of subclinical rythmic EEG discharges of adults (SREDA).

1.095

THE PATIENT WITH COMPLEX PARTIAL EPILEPSY OF TEMPORAL LOBE ORIGIN REVEALS UNIQUE HEAD-SURFACE GEOMETRY OF BASAL TEMPORAL INTERICTAL EEG TRANSIENTS

Fumisuke Matsuo, Tawnya M. Constantino, and Lorie Blair (Department of Neurology, University of Utah School of Medicine, Salt Lake City, UT)

Rationale: Basal temporal interictal EEG transients (BTIETs) can reliably predict complex partial epilepsy, but their accuracy in localizing the epileptogenic neuronal matrix is questioned. A recent preliminary study suggested that BTIET geometry did not differentiate patients with mesial temporal sclerosis (MTS) from those without, as demonstrated by high-resolution magnetic resonance imaging (MRI). This study was designed to evaluate the range of variation in BTIET geometry within each patient and between patients. The material presented will enable the viewer to understand the principle of localization of EEG epileptiform discharges. **Methods:** Digital EEG data were available from a total of 20 patients, and all the BTIETs were identified. BTIETs were reformatted in polygraphic display in serial 10-20 bipolar derivations, consisting of anterior–posterior and basal chains [*J Clin Neurophysiol* 3(suppl 1):26–33]. Time series display gain was set to equalize the height of the primary BTIET peak. The time axis of BTIET display was graphically adjusted so that the primary BTIET peak and one immediately following it could be superposed. Geometric variation could be readily appreciated in display, superposing a varying number of BTIETs. **Results:** A total of 937 BTIETs was collected (individual patients contributing one to 426 BTIETs). Despite substantial variation in waveform among BTIETs, superposition indicated a unique localization of BTIET source in each patient. Superposed BTIETs could differentiate different patients, based on subtle but definite variation in voltage gradient over the head surface. Figure 1 illustrates a total of 56 BTIETs superposed from a patient. Instrumental phase reversal indicates middle temporal source localization (Fig. 1). **Conclusions:** Head-surface EEG geometry derived from 10-20 head-surface electrode placements differentiated source localization of BTIETs in this group of patients. Subregional localization of the epileptogenic matrix thus accomplished may offer a simple, noninvasive clinical tool for improved clinical neuroanatomic correlation. Further investigations are warranted to determine whether BTIET geometry can differentiate patients with MTS from those without and between primary and secondary BTIETs.



1.096

THE EFFECT OF PATHOLOGIC SUBSTRATE ON ICTAL EEG IN FOCAL EPILEPSY

Silvia B. Neme, Nancy R. Foldvary, George Klem, William Bingaman, and Hans O. Luders (Department of Neurology, The Cleveland Clinic Foundation, Cleveland, OH; Department of Neurosurgery, The Cleveland Clinic Foundation, Cleveland, OH)

Rationale: The purpose of this study was to analyze the effect of pathologic substrate on the ictal EEG in patients with medically refractory focal epilepsy. **Methods:** Ictal scalp EEGs from 30 patients with neocortical focal epilepsy due to neoplasm (n = 16) or malformation of cortical development (MCD; n = 14) who were classified as Engel class 1 after surgical resection involving one lobe were analyzed. Ictal-onset patterns were classified as generalized, lateralized, regional, or focal based on previously established criteria (Foldvary, et al. *Neurology* 2001). Ictal EEGs were classified as localized (focal or regional), lateralized, or generalized based on the earliest and most precise distribution of ictal activity during the entire event. **Results:** 275 seizures were analyzed (88 neoplasm and 187 MCD). Mean number of seizures recorded during VEEG was significantly greater for MCD (13.4) than for neoplasm (5.5) groups. Ictal-onset patterns (theta, delta, alpha, paroxysmal fast, repetitive spiking, suppression) did not differ significantly between groups. Lateralized ictal onsets were significantly more common in neoplasm (22.7% vs. 2.1%), and regional/focal onsets were more common in MCD (56.3% vs. 13.6%). Ictal EEGs were significantly more likely to be localized (regional/focal) in MCD than in neoplasm (67.1% vs. 34.1%). **Conclusions:** Ictal EEG patterns may vary depending on the underlying pathologic substrate. Although other factors such as location of the epileptogenic lesion may be operative, these differences may provide insight into the epileptogenicity of lesions seen in patients with refractory epilepsy.

1.097

THE ABSENCE OR PAUCITY OF SPIKES IN INTRACTABLE TEMPORAL LOBE EPILEPSY SUGGESTS A LESS SEVERE DISEASE

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Rationale: Temporal lobe epilepsy (TLE) patients usually have high incidence of interictal EEG tracings with frequent interictal spikes. Only 2% of TLE patients have no spike despite prolonged scalp EEG recordings (Ajmone-Marsan C, Zivin LS. *Epilepsia* 1970;11:361–81). The absence or paucity of spikes is more common in well-controlled or familial TLE. The objective of this study was to analyze clinical, EEG, and imaging characteristics of nonlesional intractable TLE patients with rare or absent spikes (oligospikers). **Methods:** Between 1990 and 2000, 31 patients (11 men; mean age, 34 years) with intractable TLE were prospectively selected on the basis of the absence or paucity of spikes (fewer than one/h). We compared the clinical and laboratory characteristics of these individuals with a group of 27 age-matched (10 men; mean age, 38 years) randomly selected nonlesional TLE patients who had frequent spikes. **Results:** Oligospikers showed a later age at seizure onset (19 vs. 10 years; $p = 0.004$), shorter disease duration (14 vs. 28 years; $p < 0.001$), lower incidence of secondarily generalized tonic–clonic (SGTC) seizures (10 vs. 81%; $p < 0.001$), and no status epilepticus (SE; 0 vs. 22%). Hippocampal atrophy (HA) was less commonly found in oligospikers (58 vs. 96%; $p = 0.001$). However, there were no differences between the two groups in the incidence of family history of epilepsy, risk factors, febrile convulsions, and type of medication. Excellent surgical outcome (Engel's class Ia) was found in 14 of 23 (61%) oligospikers and 17 of 25 (67%) TLE patients with frequent spikes. **Conclusions:** The striking lack of spikes in some patients with refractory TLE over a long interval led us to think that they represent a distinct TLE group with a more benign disease course. Oligospikers have less severe epilepsy, as suggested by a later age of seizure onset, shorter duration of epilepsy, rare SGTC seizures, and no SE. They also have a lower incidence of HA. The similarity of etiologic factors compared with patients with frequent spikes suggests that the rarity of spikes reflect a disease that is not really distinct, but less severe, particularly with respect to SGTC seizures and SE. Nevertheless, oligospikers also have frequent complex partial seizures, and their epilepsy may be severe enough to consider surgery.

1.098

COMPARISON OF BOUNDARY ELEMENT METHOD WITH 3-SPHERICAL SHELL MODEL BY USING ACTUAL SKULL CONDUCTIVITIES

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Rationale: Misspecification of skull conductivity and head geometry may lead to inaccurate source localization. **Methods:** Bulk conductivities of three live human skulls were measured using the four-electrode method in three patients undergoing neurosurgery. These values were 0.0112, 0.0093, and 0.0085 S/m. Somatosensory evoked electroencephalogram (EEG) data were obtained by stimulating the right median nerve of a normal subject. EEG source localizations were performed on these data using single equivalent moving current dipole model in a three-shell sphere and boundary element method (BEM) (CURRY) while varying the skull conductivity between the three measured values, and the results were compared with those obtained from the standard value of 0.0042 S/m. **Results:** The maximal variation of the absolute source location using the realistic skull conductivity values compared with the standard value was 6.6 mm using BEM and 12.7 mm using the three-shell sphere model. **Conclusions:** Applying actual skull conductivities along with realistic geometric head models will lead to less variation in EEG source localization compared with the three-spherical-shell model. (Supported by NIH grant NS20806.)

1.099

NONINVASIVE DC-EEG: DEVELOPMENT OF A BEDSIDE METHOD FOR CLINICAL PRACTICE

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Rationale: Animal studies, as well as invasive recordings from humans, have demonstrated prominent, very slow activity patterns (i.e., DC potential shifts) during epileptic activity, ischemia, and sleep. Due to previous methodologic difficulties, there are, however, only a few published noninvasive DC-EEG recordings on human patients with epilepsy or with any other clinical condition. We recently solved these issues and developed a DC-EEG technique that is capable of long-term, bedside recordings. We describe practical details of the DC-EEG technique used at our center, and we discuss the technical issues that are requisite for a reliable recordings from human scalp. **Methods:** We use a custom-made DC-EEG amplifier, and sintered Ag/AgCl electrodes, which are individually attached to skin (with collodion) by using custom-tailored plastic holders. Software for data acquisition and analysis was written under Labview. We examined the DC recording properties of several commonly used electrode materials (Ag/AgCl, silver, gold, tin, stainless steel, and platinum). We examined the characteristics, as well as the potential means of elimination of several biologic artefacts: skin potential, eye rotations (gaze shifts), tongue movements, respiration, and changes in intracranial pressure by Valsalva maneuver. Distribution of electric fields generated by eye and tongue movements were also evaluated with a 256-channel EEG device (Geodesic Inc., OR). **Results:** We show that our DC-EEG setup is capable of long-term ($\geq$24 h) stable recordings. We discuss the specific requirements of the amplifier, electrodes, and software. Comparison of different commercial electrode materials demonstrates that only Ag/AgCl gives a stable and reliable long-term recording. Skin potentials are easily short-circuited (i.e., eliminated) by scratching the skin; otherwise these long-term recordings would be severily contaminated with these millivolt-scale responses and baseline drifts. Tongue movements produce slow (up to many seconds) potentials effectively picked up by

mastoid electrodes, and with amplitudes comparable to those of very slow evoked responses (e.g., CNV). Tongue artefacts can be minimized by using termporal or vertex referencing. Eye rotations also cause electric potentials recordable over the whole head. Use of appropriate montages and eye channels makes it possible to exclude these artefacts. Respiration, by changing the end-tidal CO2, causes a very prominent DC potential shift with amplitudes ≤2 mV at vertex referred to mastoid. Finally, changes in intracranial pressure conditions by Valsalva maneuver results in a clear potential gradient between vertex and temporal/mastoid derivations, which implies that respiratory activity has to be carefully monitored during the recording periods of interest. **Conclusions:** Long-term bedside recordings are technically rather easy with very achievable modifications to routine clinical EEG methods. Presence of several noncortical sources of slow electric potentials requires attention. Our experience has shown, however, that with the precautions outlined, reliable DC-EEG recordings may be readily performed, providing a new insight into the mechanisms of epilepsy and other brain conditions (see abstracts by Thompson et al. and Miller et al., this meeting). (Supported by Finnish Academy, University of Washington Regional Epilepsy Center.)

1.100
EMERGENCY EEG: INDICATIONS AND DIAGNOSTIC YIELD

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Rationale: Emergency EEG (E-EEG) should be ordered if it is expected to have a major impact on patient diagnosis and management. Few published data suggest misuse of the test. Our objective was to identify why the test was ordered, and through correlation with the test results, determine its suitability for the clinical situation encountered. **Methods:** We retrospectively reviewed all E-EEGs (ordered to be performed within 1 h) during the last 2 years in our University Hospital. We collected the following data: demographics, reason of admission, service ordering the test, question to be answered, type of E-EEG (routine or prolonged), presence of suggestive clinical signs (SCSs) including involuntary movements or blank staring, previous history of seizures, antiepileptic medications (AEDs), and interpretation. Univariate and multivariate analyses were performed by using the $\chi 2$ test and logistic regression ($\alpha = 0.05$). **Results:** One hundred twenty-six E-EEGs were performed in 119 patients (62 M and 57 F; mean age, 56 years). Clinical history revealed mental status change (MS) in 28 (22.2%), cardiac or respiratory arrest or prolonged hypotension (CRAH) in 18 (14.3%), systemic primary disorder (SD) in 18 (14.3%), epilepsy in 16 (12.7%), stroke in 15 (11.9%), and tumor in 13 (10.3%) cases. Sixty-six (55%) E-EEGs were ordered by the neurology or neurosurgery and 32 (25.4%) by the Medical Intensive Care Unit (MICU) service. Status epilepticus (SE) had to be ruled out in 61% of cases, seizures in 18%, encephalopathy in 10%, and nonconvulsive status epilepticus (NCSE) in 8.7%. SCS before the E-EEG was observed in 62% of cases with question of SE and in 61% with seizure exclusion. SCS was observed in 36% of cases with NCSE exclusion. E-EEG was done to exclude SE in 83% of CRAH cases, in 69% of cases with epilepsy, and in 63% with MS changes. In only 11% of MS changes, E-EEG was done to exclude NCSE. Prolonged E-EEG was requested in only four cases (3.2%). Encephalopathy was confirmed by E-EEG when the test was done to rule it out (odds ratio, 5.4; 95% CI, 1.1–26; $p < 0.05$). No such association was found between reasoning for ordering the test and confirmation of the suspicion by E-EEG results for SE or NCSE. With recent SCS, SE or NCSE was found more often on E-EEG (5.6; 1.2–26; $p < 0.05$), but not epileptiform activity or electrographic seizure (EAES) or encephalopathy. In a logistic regression analysis, only CRAH was associated with SE or NCSE (5.3; 1.4–20; $p < 0.05$), tumor with EAES (5.9; 1.6–21.3; $p < 0.01$), and tumor or history of seizures with encephalopathy (0.08; 0.01–0.7; and 0.3; 0.1–0.9; $p < 0.05$, respectively). **Conclusions:** Our findings suggest that E-EEG is ordered more frequently in patients with MS changes, CARH, or SD, by neurologists or neurosurgeons, to rule out SE. SCSs were observed in only two thirds of cases when the test was ordered to exclude SE and in one third of cases to exclude NCSE, questioning the suspicion level of the ordering physician. Prolonged EEG, a more appropriate test according to the clinical situation and question asked, was ordered infrequently. E-EEG will most likely reveal SE or NCSE, if done after CRAH, and EAES in the presence of tumor. Encephalopathy is less likely to be found with a history of seizures or tumor.

1.101
COGNITIVE EVENT-RELATED POTENTIALS IN EPILEPSY PATIENTS

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Rationale: Epilepsy and antiepileptic drugs (AEDs) may be associated with cognitive dysfunction. P300 event-related potentials have been used to assess cognitive function. In this study we investigated the effects of epilepsy and AEDs on cognitive function in patients with epilepsy and evaluated the diagnostic value of P300 event-related potentials for cognitive dysfunction. **Methods:** P300 latency in event-related potentials was recorded during an auditory oddball paradigm in 29 patients, 10 with generalized epilepsy and 19 with partial epilepsy. The relations between epilepsy itself or AEDs and P300 latency prolongation were analyzed. **Results:** P300 latency was prolonged in nine (31%) of 29 patients with epilepsy. There were no significant relations between etiology of epilepsy, type of seizures, or type of AED and P300 latency prolongation. The number or serum level of AEDs and treatment duration were related to latency prolongation, but these relations were not significant. **Conclusions:** The prolongation of P300 latency in event-related potentials is not significantly related to epilepsy itself and AEDs. This findings suggests that P300 event-related potentials may not be a sensitive additional procedure to assess the cognitive status in patients with epilepsy. (Supported by a grant of Kosin University College of Medicine.)

1.102
INTERHEMISPHERIC DIFFERENCE IN MOTOR CORTEX INHIBITION BY TRANSCRANIAL MAGNETIC STIMULATION

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Rationale: To determine if there is an interhemispheric difference in motor cortex excitability that can be detected by transcranial magnetic stimulation (TMS). Many reports in the literature have suggested that epileptogenic discharges have a tendency to originate more frequently from the left hemisphere compared with the right (Dean et al., 1997; Foy et al., 1992). We hypothesized that the interhemispheric difference in epileptogenicity may be because the left hemisphere is physiologically predisposed to being more epileptogenic and that an interhemispheric difference in cortical excitability may be amenable to detection by TMS. **Methods:** Five right-handed normal volunteers were subjected to TMS of their two hemispheres separately. After determining the resting motor threshold (RMT), the cortical silent period (C-SP) was measured while recording from the appropriate abductor pollicis brevis. The C-SP obtained on right hemispheric stimulation was compared wtih the C-SP measured on left hemispheric stimulation by a paired *t* test. Informed consent was obtained from all the volunteers, and the study protocol was approved by the institutional review board of the Weill-Cornell Medical Center. **Results:** All the subjects had a longer C-SP on stimulation of their right hemisphere compared with that on stimulation of their left hemisphere. The mean interhemispheric difference in C-SP was 37.74 ± 8.09 ms. The difference was significant, with $p = 0.009$. **Conclusions:** In our study, although the sample size is small, we demonstrated a statistically significant difference in motor cortical inhibition between the two hemispheres with the inhibition being more pronounced on right hemispheric stimulation. This

suggests a physiologic asymmetry between the two hemispheres and is concordant with the data in the literature on increased left hemispheric epileptogenicity (Dean et al., 1997; Foy et al., 1992).

1.103
CLINICAL FEATURES OF NONEPILEPTIC SEIZURES: A VIDEO-EEG STUDY

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Rationale: Nonepileptic seizures (NESs) account for ~20% of all cases of intractable epilepsy. In the absence of early and definitive diagnosis, patients with NESs may be treated, often for an extended period, without benefit with expensive antiepileptic drugs (AEDs) with potentially serious adverse effects. We reviewed our experience to identify features that would be useful in differentiating NESs from epileptic seizures based mainly on semiology and clinical characteristics. **Methods:** All admissions to the Video-EEG Monitoring Unit at the Medical College of Ohio between 1997 and 2001 were reviewed after IRB approval of the protocol. All patients with NESs underwent extensive chart review to identify clinical features, semiology, comorbidity, and treatment. Data were analyzed by using independent samples *t* test and $\chi 2$ analysis. **Results:** One hundred thirteen patients with NESs were identified; 56 were excluded because of inadequate clinical data. Data from 57 patients with NESs were analyzed and compared with 24 randomly selected patients with complex partial seizures. In NESs group, the mean age was 33.61 years (range, 12–71 years); 31% of these were males. Mean duration of seizures in the NESs group before the diagnosis was 9.7 years (range, 1 month to 40 years). Mean number of AEDs used was 1.82 (range, 0–5), 61% of the patients with NESs had been exposed to two or more AEDs before their diagnosis. Aura was more likely in patients with complex partial seizures (70.8%) compared with the NESs group (28%; $p < 0.0001$). Clinical features seen only in patients with NESs included crying (15.7%), thrashing (15.7%), and pelvic thrusting (21%), while orofacial (50%) and limb automatisms (29%) as well as focal dystonia (13%) were seen only in patients with complex partial seizures. The mean seizure duration in the NESs group was 419.6 s versus 61.2 s in the complex partial seizure group, which was a statistically significant difference ($p < 0.0001$). Routine EEG was not very helpful in discriminating patients with NESs from epileptic seizures as EEG was abnormal in 55% of the patients with NESs. The most common abnormality was either generalized (45%) or focal slowing (45%). Interictal epileptiform discharges were noted in only 5% with NESs. In patients with complex partial seizures, routine EEG was abnormal in 88% of patients. The presence of epileptiform activity was more likely in the epilepsy (66%) cohort compared with the NES group (5%; $p < 0.001$). Head trauma was reported by 35.08%. Psychiatric comorbidity was noted in 47% of patients with NESs, including depression (29.8%), anxiety (8.8%), or personality disorder (8.8%). **Conclusions:** Patients with NESs are frequently misdiagnosed and receive prolonged AED therapy often with multiple agents. Although NESs may be more common in women, one third of the patients with NESs in our series were men. Clinical features suggestive of NESs include prolonged duration of episodes often associated with crying, thrashing, pelvic thrusting, and absence of aura, orofacial or limb automatisms. These clinical features, if elicited during initial evaluation, should alert physicians to consider early diagnositic video-EEG monitoring in these patients.

1.104
CONTINUOUS EEG MONITORING IN PATIENTS WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE

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Rationale: Continuous EEG monitoring (cEEG) in the intensive care unit (ICU) setting has documented frequent nonconvulsive seizures in patients with acute brain injury such as head trauma. However, the incidence of nonconvulsive seizures in patients with spontaneous (nontraumatic) intraparenchymal cerebral hemorrhage (ICH) is unknown. The purpose of this study was to review the utility of cEEG in these patients. **Methods:** Medical charts of neurologic ICU patients from 1998 to 2002 were reviewed. Patients were included in this study if they had spontaneous ICH and were monitored by cEEG. Patients were excluded if they had ICH resulting from trauma, hemorrhagic infarct, prior epilepsy, or primary subarachnoid hemorrhage; 34 patients met these criteria. **Results:** All 34 patients had abnormal mental status at some point. Seizures occurred in seven of 34 (21%) patients. Four of 34 (12%) had nonconvulsive seizures, which were diagnosed on the basis of cEEG monitoring alone. In all four patients, the seizures occurred despite initiation of prophylactic phenytoin on admission. Three of 14 (21%) patients with lobar ICH had nonconvulsive seizures on cEEG versus one of 20 (5%) patients with nonlobar (i.e., basal ganglia, cerebellar) ICH. Extension of ICH to the ventricles (IVH) was not associated with increased frequency of nonconvulsive seizures (two of 20 with IVH vs. two of 14 without IVH). Two of seven (29%) patients who underwent surgical evacuation had nonconvulsive seizures, whereas two of 27 (7%) patients who did not have surgical evacuation developed nonconvulsive seizures. None of these differences was statistically significant. **Conclusions:** Nonconvulsive seizures are not uncommon in patients with spontaneous ICH and abnormal mental status, especially lobar ICH. Continuous EEG monitoring may be indicated in these patients.

1.105
ICTAL EEG PATTERNS OF GENERALIZED-ONSET SEIZURES WITH PARTIAL ICTAL PROGRESSIONS

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Rationale: Secondarily generalized seizures are marked electrographically by spreading ictal patterns throughout the two cerebral hemispheres, unlike generalized-onset seizures in which such progression is believed not to occur. We describe two unusual cases of partial progression of generalized-onset seizures, mistakenly diagnosed as partial-onset seizures before long-term video-EEG monitoring (LTM). **Methods:** Five seizures were recorded from two young patients (ages 9 and 20 years) during inpatient LTM. Both patients had been previously diagnosed with partial-onset epilepsy based solely on observation by family members. Monopolar recordings were obtained by using the standard 10-20 electrode system supplemented with sphenoidal electrodes. Ictal recordings were reviewed utilizing sequential bipolar and referential montages. **Results:** Three seizures were recorded in the younger patient, each starting with sudden behavioral arrest and then lip-smacking. With seizure no. 2, she had right-sided posturing with forceful head deviation to the same side. With seizure no. 3, she had head and eye deviation to the left with a right-hand automatism. Ictal EEG revealed initial generalized 3-Hz spike–wave discharges for 2–3 s, followed by diffuse delta slowing for 5–6 s. The slow rhythm then progressed to lateralized spike–wave discharges (over the left temporal lobe with seizure 2, but over the right temporal lobe with seizure 3), which then generalized after 10 s. In the older patient, two seizures were recorded, each beginning with behavioral arrest and staring lasting 4–5 s. Seizure semiology did not reveal any lateralizing features. Ictal EEG was remarkable for an initial 1-s period of generalized low-voltage fast activity (GPFA), followed by left temporal spike–wave discharges lasting 3 s. **Conclusions:** Progression of generalized-onset seizures can at times resemble partial-onset seizures. Laterality of ictal semiology may sometimes lead to the misdiagnosis of partial-onset seizures, resulting in inappropriate medical treatment, unless LTM is used.

1.106
UTILITY OF CONTINUOUS VIDEO-EEG MONITORING IN A VETERAN POPULATION: REVIEW OF 144 CONSECUTIVE PATIENTS

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Rationale: Video-EEG monitoring (VEEG) is an established diagnostic technique for the evaluation of patients with epilepsy. We sought to determine the effectiveness of VEEG in the evaluation of veteran patients, a somewhat unique older population. **Methods:** We reviewed the results of 156 consecutive VEEG monitoring studies performed at the Houston Veterans Administration Medical Center on 144 patients. Reasons for referral included characterization of atypical spells, poor response to antiepileptic (AED) treatment, prior routine epilepsy evaluation that was unrevealing, and evaluation for possible seizure surgery. Mean age was 51 years. There were132 men (92%) and 12 women (8%). Average length of continuous VEEG monitoring was 85 h. In all cases, the entire record was reviewed by a clinical neurophysiologist (R.A.H., P.J.F.). **Results:** Our results revealed 46 patients (32%) with epileptiform activity (focal or generalized). Of these, 36 patients (78%) had focal temporal epileptiform abnormalities, as characterized by either interictal epileptiform activity or focal seizures. Review of the entire records revealed 18 of these patients had independent bilateral temporal epileptiform activity (50%). Extratemporal epilepsy accounted for only six patients, and generalized epileptiform activity was seen in four patients. Thirty-one patients had nonepileptic seizures (21%), and 26 patients (18%) had events attributable to other causes (e.g., syncope, posttussive syncope, panic attacks, REM sleep behavior disorder, obstructive sleep apnea). Multiple findings were present in 12 patients (8%), most often epileptogenic activity and nonepileptic seizures. **Conclusions:** Overall, the diagnostic utility of continuous VEEG monitoring was 67% for providing either a new diagnosis, confirming a prior diagnostic suspicion, or revealing the presence of multiple diagnoses. Furthermore, this study substantiates previous reports that temporal lobe epilepsy is often associated with bilateral epileptiform abnormalities and extends the observation that bitemporal spikes may go undetected on routine EEG and are more frequently seen with continuous VEEG monitoring and inspection of the entire record. (Supported by Houston Veterans Administration Medical Center.)

1.107
VIDEO-EEG TELEMETRY PROVES THE BEST CAN BE WRONG

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Rationale: To examine the usefulness of video-EEG telemetry for patients with spells of unclear etiology who were referred by a neurologist with experience in epilepsy or an epileptologist. At the end of this study, we were able to evaluate how frequently a patient's diagnosis changed after reviewing the video-EEG telemetry findings. **Methods:** We retrospectively reviewed the charts of 49 adult patients consecutively admitted to our epilepsy monitoring unit during the period of July 31, 2001, to April 14, 2002. We excluded patients who were admitted for epilepsy surgery monitoring. The charts were reviewed for demographic and clinical data that led to the initial referral for telemetry by a neurologist or epileptologist; this includes age at onset, interictal EEGs, and imaging studies (including magnetic resonance imaging). **Results:** Of the patients admitted for evaluation of spells of unclear etiology, a diagnosis of epileptic seizures was made in five of the patients who were initially thought to have nonepileptic seizures. The diagnosis of nonepileptic seizures was made in 11 patients who were initially thought to have epileptic seizures. Misclassification of epilepsy syndrome was found in three patients who were strongly thought to have epileptic seizures by the referring neurologist or epileptologist. Of those misclassified, two who were believed to have partial epilepsy, had generalized epilepsy, and one diagnosed as generalized epilepsy had partial epilepsy. Before video-EEG telemetry, six of the 11 patients with nonepileptic seizures were strongly believed to have epileptic seizures. Their histories were suggestive of epilepsy because of risk factors that would increase the likelihood of seizures, and/or abnormal interictal EEG. **Conclusions:** Video-EEG telemetry is crucial in establishing a diagnosis in patients with epilepsy. Without video-EEG telemetry, patients can be misclassified or receive ineffective treatment for epilepsy, even when being treated by the most experienced hands. With video-EEG telemetry, therapy can be improved to achieve the best possible results for our patients.

1.108
EFFECTS OF LEVETIRACETAM ON SLEEP IN EPILEPSY PATIENTS

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Rationale: Anticonvulsant drugs (AEDs) are known to have both detrimental and beneficial effects on sleep, which can have important implications for both seizure control and optimal daytime functioning of patients with epilepsy. Phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ) may all decrease REM sleep, and gabapentin (GBP) can increase slow-wave sleep. There is relatively little information, however, regarding potential effects of the newest anticonvulsants, including levetiracetam (LVT) on sleep. We performed overnight polysomnography on patients with intractable epilepsy who were taking LVT, and compared sleep with that of similar patients who were taking no AEDs. **Methods:** Consecutive patients with localization-related epilepsy (based on history, interictal and ictal recordings) admitted for video-EEG monitoring were included. Control patients were taking no AED. Patients taking LVT had to be taking $\geq$1,000 mg/day and have been taking the drug $\geq$24 h. If drugs were previously stopped, levels were less than half the minimal therapeutic dose (based on known half-life of the drug). Patients who had nonepileptic seizures or sleep disorders, were sleep-deprived, or were taking psychotropic drugs were excluded. Caffeine was not allowed. No patient had complex partial or secondarily generalized seizures during the recording or for $\geq$24 h before. Polysomnography was scored in 30-s epochs, according to standard technique, by reformatting digital EEG to polysomnographic channels and parameters. Sleep efficiency was calculated as percentage asleep from sleep onset until awakening. The initial night of recording was not used in the analysis; however, patients adhered to the sleep schedule on that night. All results were compared with control patients, using a *t* test. **Results:** Seven studies were performed in four patients taking LVT (one to two/patient). LVT dose was 1,000–2,750 mg/day (average, 1,792). Age was 20–37 years (mean, 26 years). A subset of control patients in the same age range was chosen (range, 25–36 years; mean, 31 years); this included 16 studies in 10 patients (one to two/patient). All results are LVT versus control, ±SEM. Total sleep time was similar (466 ± 11 vs. 443 ± 16 min). Stage 1 sleep was 7.7 ± 1.9 vs. 6.0 ± 1.1%. Slow-wave sleep was 14.7 ± 1.6 vs, 12.7 ± 1.1%. REM was 22.1 ± 1.1 vs. 18.8 ± 1.2%. Sleep efficiency was 97 ± 1 vs. 96 ± 1. REM latency was 88 ± 24 vs. 112 ± 17 min. None of these differences was statistically significant. **Conclusions:** In this study, there were no significant differences in sleep parameters between patients taking therapeutic doses of LVT in monotherapy when compared with similar patients taking no drug. Patients taking LVT showed slight increases in slow-wave sleep and REM sleep, and decreases in REM latency. Although the number of patients is small, this study has the advantage of examining effects in monotherapy and with confirmed absence of seizures, which are known to adversely affect sleep. The results suggest that LVT has no detrimental effects on sleep parameters in patients with epilepsy, and there may actually be improvements in essential sleep. These results will need to be confirmed in a larger group of patients. (Disclosure: Consulting: UCB Pharma, Pfizer, Novartis; Honoraria: UCB Pharma, Pfizer, Novartis.)

1.109
PREDICTORS OF OBSTRUCTIVE SLEEP APNEA IN EPILEPSY PATIENTS

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Rationale: Obstructive sleep apnea (OSA) is a common condition affecting $\leq$9% of women and 24% of men (Young et al. *N Engl J Med* 1993;328:1230–5). A higher prevalence, approaching 33%, has been reported in adults with epilepsy (Malow et al. *Neurology* 2000;55: 1002–7). Treatment of OSA may reduce seizure frequency and improve

daytime sleepiness in epilepsy patients (Malow et al. *Neurology* 1997; 48:1389–94). Therefore, identifying factors associated with OSA may contribute to improved management of these patients. We explored the relation between OSA, antiepileptic drugs (AEDs), and other factors in epilepsy patients. **Methods:** We reviewed the records of 156 adult epilepsy patients (ages 18–73; 56% men) who underwent polysomnography in our clinical Sleep Laboratory or in our General Clinical Research Center between 1995 and 2001. We determined the presence or absence of OSA, defined by an apnea–hypopnea index of ≥5 on polysomnography. Age, gender, body-mass index (BMI), and AED type and number at the time of polysomnography were recorded. To analyze the association between OSA and these variables, we performed $\chi 2$ (specific AEDs and gender) and independent-sample *t* tests (age, number of AEDs, BMI). A general linear model was also performed to include significant variables in the model. We limited our AED analysis to medications taken by ≥10 patients. Level of significance was set at $p < 0.05$. **Results:** The following AEDs were included in the analysis: phenytoin (PHT), carbamazepine, valproic acid, lamotrigine, topiramate, gabapentin, and barbiturates/benzodiazepines (phenobarbital, clonazepam, and primidone were combined into one category). A statistically significant association was seen between PHT use and OSA ($p = 0.03$); no other AEDs were associated with OSA. Other variables associated with OSA were older age ($p < 0.0001$), male gender ($p = 0.009$), and higher BMI ($p = 0.004$). In the general linear model, including age, gender, BMI, and PHT use, the only significant variables associated with OSAwere age ($p < 0.001$) and BMI ($p = 0.002$). Patients taking PHT as compared with those not taking PHT were older (40.6 ± 12.5 years vs. 36.5 ± 11.6 years, mean ± standard deviation; $p = 0.04$); this association between age and AED use was not seen with any other AED studied. The BMI was not significantly different in the PHT patients (29.9 ± 8.0 vs. 28.7 ± 6.3). **Conclusions:** In our sample, older age and BMI were independent risk factors for OSA. After adjusting for age and BMI, PHT use and male gender were not independent risk factors for OSA. Limitations were that sample size of individual AEDs was small so that the effects of specific AEDs on OSA may have been missed; in addition, several of the newer AEDs were not included. Additional study with larger numbers of patients will be needed to determine the relative contributions of specific AEDs and other variables to obstructive sleep apnea. [Supported by NINDS KO2 NS02099 (B.A.M.) and University of Michigan General Clinical Research Center grant M01-RR00042.]

1.110
HYPOTHALAMIC HAMARTOMAS: COMPARISON OF POLYSOMNOGRAPHY IN NONSYNDROMIC CASES VERSUS PALLISTER–HALL SYNDROME

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Rationale: To identify polysomnographic differences among patients with nonsyndromic hypothalamic hamartomas and seizures and patients with hypothalamic hamartomas associated with Pallister–Hall syndrome (PHS). The hypothalamus plays a key role in the regulation of sleep. Preliminary evidence suggests that sleep architecture, especially during rapid-eye-movement (REM) sleep, is altered in patients with nonsyndromic hypothalamic hamartomas. The mechanism by which this occurs is not clear. To better understand this process, we collected preliminary data on two groups of patients with hypothalamic hamartomas. Group one patients have nonsyndromic (sporadic) hypothalamic hamartomas, and group two patients have hypothalamic hamartomas associated with PHS, an autosomal dominant disease, associated with hypothalamic hamartomas, central polydactyly, pituitary dysplasia/hypopituitarism, bifid epiglottis, and visceral anomalies. **Methods:** Eight patients each underwent 2 nights of polysomnography (PSG). Ten nights of PSG data were available for the six patients with nonsyndromic hypothalamic hamartomas, and four nights of PSG data were available for the two patients who had hypothalamic hamartomas associated with PHS. PSG data were analyzed for latency to sleep onset, REM latency, percentage of time spent in each sleep stage, sleep efficiency, and presence of epileptiform discharges during the recording. **Results:** No significant differences were seen between the two groups with regard to sleep efficiency, latency to sleep onset, and percentage of time spent in non-REM sleep. However, a significant increase in REM latency and decrease in the percentage of time spent in REM sleep was seen in the nonsyndromic group (mean, 5.3%) when compared with the PHS group (mean, 20.2%), who had normal REM latencies and REM durations. In the nonsyndromic group, the characteristic bursts of rapid eye movement were more subtle, and REM sleep was less sustained than in the PHS group. All six patients with nonsyndromic hypothalamic hamartomas had a history of seizures and all had spike–wave discharges during PSG. There was a nonstatistically significant trend toward increased seizure frequency with decreased time spent in REM sleep. Neither of the PHS patients had a history of seizures, and no spike–wave discharges were seen during PSG. **Conclusions:** Sleep structure in the group with hypothalamic hamartoma associated with PHS was relatively preserved. However, the quality and quantity of REM sleep in the group of patients with nonsyndromic hypothalamic hamartomas was disrupted. The correlation of seizure frequency with amount of time spent in REM sleep requires further investigation. The presence of a hypothalamic hamartoma may not by itself account for disruption of REM sleep in individuals with nonsyndromic hypothalamic hamartomas. (Supported by NINDS Intramural Program.)

1.111
CHRONOBIOLOGIC VARIATION OF SPIKE-AND-WAVE DISCHARGE DURATION IN THE AY-9944 RAT MODEL OF ATYPICAL ABSENCE SEIZURES

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Rationale: Serotonergic mechanisms appear to be involved in experimental atypical absence seizures (Cortez et al. *Epilepsia* 2001;42: 81). We investigated the possibility of chronobiologic variations in spike-and-wave (SWD) duration in the AY-9944 (AY) model (Cortez et al. *Neurology* 2001;56:341–9). Diurnal and seasonal variations in cholesterol homeostasis are well documented (*Proc Natl Acad Sci U S A* 1996;93:9799–804). **Methods:** Electrocorticogram (EcoG) recordings in AY rats from postnatal day (P) 55, onward over a 24-h period. SWD quantification over 24 h ($n = 4$) and winter–summer comparisons of video-EEG and ECoG recordings ($n = 8$) in AY rats and control were made by two independent and blinded ECoG readers (R.S. and I.S.). All animals were kept under a controlled 12L/12D cycle, with lights on at 6 a.m. **Results:** The highest SWD duration (mean SWD ± SEM) was found at 03:00 and 15:00 h (229.9 ± 64.02), and the lowest at 05:00 h (16.87 ± 14.10) over a 24-h period ($F = 20.63$; two-tailed $p = 0.01$, unpaired *t* test). SWD in winter (495.33 ± 14.74) was greater than the SWD in summer (229.62 ± 45.27; mean difference, –265.71; $t = 5.58$; 14 *df*, $F = 9.42$; two-tailed $p = 0.001$), unpaired *t* test. **Conclusions:** Under controlled environmental conditions, there are diurnal and seasonal changes in AY-induced SWD duration. Whether there is any variation in levels of circulating 24-hydroxycholesterol and photoperiodic effects in the AY model remain to be determined. (Supported by The Hospital for Sick Children Pediatric Consultants.)

1.112
SLEEP STRUCTURE IN PATIENTS WITH NONEPILEPTIC VERSUS EPILEPTIC SEIZURES

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Rationale: Psychogenic nonepileptic seizures (PNESs) are a significant public health problem, representing ~25% of patients admitted to epilepsy monitoring units. The most accurate test to verify the presence of PNESs is video-EEG monitoring with recording of a typical spell;

however, this is not possible in all cases. Other clinical characteristics that distinguish these patients from those with epilepsy would be helpful from both clinical and scientific standpoints. We looked at sleep structure in patients with PNESs and compared this with patients with epileptic seizures. **Methods:** Patients admitted consecutively for diagnosis or surgical evaluation were included. Epileptic (ESs) and nonepileptic seizures were verified by video-EEG monitoring. No complex partial or secondarily generalized seizures occurred within 24 h of polysomnography or during recording. Patients were receiving no caffeine, anticonvulsant, or antidepressant medication, and patients with known or suspected sleep disorders were excluded. Subjects were not sleep deprived and were not allowed daytime naps. Polysomnography was performed by reformatting digital EEG to polysomnographic parameters. Rapid-eye-movement (REM) latency was measured as time from sleep onset until the start of the first REM period. Comparisons were made with Student's *t* test, with $p < 0.05$ considered significant. All patients with PNESs were evaluated by a psychiatrist. **Results:** Five patients with PNESs had a total of 10 polysomnograms (two per patient); all were women. Five female ES patients in the same age group (younger than 60 years) had at least two recordings; the first two recordings in each patient were used in the study. The average age of PNES patients was 31 years (range, 18–47 years); of epilepsy patients, the average age was 33 years (range, 27–45 years). Percentage REM sleep was significantly greater in patients with PNES (24 ± 1%) compared with patients with epilepsy (20 ± 2%). There were no significant differences in slow-wave sleep or sleep efficiency. REM latency was slightly less in PNES patients, although this difference was not statistically significant. Additionally, there were no differences for PNES versus epileptic seizure patients in stage 1 (6.6 ± 1.4% vs. 6.7 ± 0.9%), stage 2 (54.6 ± 2.1% vs. 47.5 ± 1.8%), or total sleep time (443 ± 22 min vs. 470 ± 16 min). **Conclusions:** The results show increased REM in patients with PNESs compared with ESs. All other parameters studied are similar. This could represent decreased REM in ESs or increased REM in PNESs. The study is important for three reasons. First, it suggests that patients with PNESs may suffer from major depression, which is known to be associated with increased REM sleep, even when not apparent on questioning. This finding would need to be confirmed in a larger group of patients, preferably using standardized depression inventories. Second, the study suggests that sleep patterns could help in distinguishing PNESs from ESs. At present this is not practical, but could be as automated staging improves. Perhaps in combination with other criteria such as normal EEG and magnetic resonance imaging, it might be possible to identify patients with a high likelihood of having PNESs when ictal recordings cannot be obtained. Finally, it further implicates the role of sleep (particularly REM) in psychiatric illness. This poorly understood area, although interesting, awaits further research.

1.113
INCREASED SYMPTOMS OF EXCESSIVE DAYTIME SLEEPINESS IN CHILDREN WITH EPILEPSY

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Rationale: Sleep problems in children with epilepsy have not been well characterized. Sleep problems and their impact on seizure frequency, the impact of epilepsy on sleep, the effects of anticonvulsants (AEDs) on sleep in children have not been well studied. Our studies aim is to quantify symptoms of sleep disorders in children with epilepsy compared with age-matched controls. At the end of this activity, participants should be able to discuss the incidence of sleep disorders in children with epilepsy. **Methods:** As part of larger study examining sleep disorders in children with neurologic problems, 39 children with epilepsy and 39 children matched for age, sex, and zip code were administered a 111-item questionnaire assessing bedtime behavior, nighttime behavior, arousals, parasomnias, seizures, morning behavior, and daytime functioning. From these questions, symptom scores were developed for sleep disordered breathing, excessive daytime sleepiness, insomnia, restless sleep, parasomnias, and narcolepsy. **Results:** Thirty-nine were epilepsy patients (26 boys, 13 girls) with a median age of 8 years. The closest obtainable matched control group consisted of 39 patients (25 boys, 14 girls) with a median age of 8 years. The epilepsy group obtained scores of 100, 232, 101, 248, 90, and 196 for sleep apnea, excessive daytime sleepiness, restlessness, narcolepsy, parasomnias, and insomnia, respectively. The control group obtained scores of 101, 71, 32, 80, and 55 for sleep apnea, excessive daytime sleepiness, restlessness, narcolepsy, parasomnias, and insomnia, respectively. Use of t statistics observing relations showed p values for the following disorders: sleep apnea, $p = 0.487757$; EDS, $p = 0.0000773$; RLS, $p = 0.005206$; narcolepsy, $p = 0.000103$; parasomnias, $p = 0.072913$; and insomnia, $p = 0.145796$. The overall added score of all sleep disorders gave the epilepsy group a total disorder score of 757 compared with the control group's 501 ($p = 0.003224$). **Conclusions:** Children with epilepsy have higher incidence of EDS and restlessness during sleep than normal controls. There is no difference in the incidence of parasomnias, apnea, or insomnia in the two groups. The difference in the narcolepsy score is related to symptoms of excessive daytime sleepiness only. Further characterization of these sleep symptoms is in progress to assess seizure type and therapy in a larger group.

1.114
VERY SLOW BRAIN ACTIVITY AND EPILEPTIC EVENTS: A HUMAN DC-EEG STUDY DURING SLEEP

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Rationale: In addition to the conventional EEG bandwidth (>0.5 Hz), experimental studies on sleep have indicated prominent brain activity at much lower frequencies, which is often called direct current (DC) potential shifts. Faithful detection of these patterns requires a genuine DC-coupled EEG amplifier and nonpolarizable electrodes. This study set out to characterize this very slow EEG activity during human sleep and to explore the possibility that interictal epileptic events could be associated with the sleep-related DC-potential shifts. **Methods:** We recorded bedside nonepilepsy and epilepsy patients ($n = 15$) during afternoon naps and overnight sleep. Recordings were performed with a custom-made 16-channel DC-EEG amplifier and Ag/AgCl electrodes (see Vanhatalo et al., this meeting). Because of the high global synchrony of slow activity, we used referential recording with calculated linked mastoid reference. Only non–rapid-eye-movement (REM) sleep was analyzed, and it was divided into two parts: non–slow wave sleep (phases I–II) and slow-wave sleep (phases III–IV). Visual and spectral analysis was performed. Interictal epileptiform events were identified from a simultaneously recorded conventional EEG, and their timing was compared with the phase of the very slow EEG oscillations (10–40 s per cycle). **Results:** Visual inspection revealed very prominent patterns of oscillating DC potential shifts with 10- to 40-s cycle. The cycle length was irregular and became shorter with gradual development of slow-wave sleep. Spectral analysis confirmed prominent activities at 0.02–0.5 Hz. On visual inspection, there was an impression that the conventional EEG activities (>0.5 Hz; K-complexes, delta frequency bursts, etc.) were unequally distributed in reference to the oscillating DC-potential shift, suggesting that the latter might have a functional significance in the brain mechanisms related to sleep. In addition, visual comparison of the interictal epileptiform activity and the phase of the oscillating DC-potential shifts showed that the vertex negative (referred to mastoid) phase of oscillating DC-potential shift was significantly less likely to involve epileptiform events than the other phases. **Conclusions:** Our findings demonstrate that human sleep involves very prominent EEG patterns at frequencies that are much lower than those recorded with conventional (AC) EEG. These can be recorded at bedside, and their temporal relation to physiologic EEG phenomena suggests a significance in sleep mechanisms. Furthermore, our findings of a temporal relation of interictal epileptiform activity to the phase of the oscillating DC-potential shifts may help in understanding the mechanisms of sleep–epilepsy interactions. (Supported by Finnish Academy, Finnish Cultural Foun-

dation, Arvo and Lea Ylppo Foundation, the University of Washington Regional Epilepsy Center.)

1.115
SLEEP DISORDERS IN PATIENTS WITH INTRACTABLE EPILEPSY: A POLYSOMNOGRAPHIC STUDY

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Rationale: Patients with epilepsy frequently have complaints of unsatisfying sleep. Sleep disorders are prevalent in the general population, but little is known regarding the prevalence of these disorders in patients with intractable epilepsy. Previous studies have shown that patients with epilepsy benefit from treatment of their sleep disorders. After the review of this poster, participants should have a greater sense of the pervasiveness of sleep disorders in patients with intractable epilepsy. **Methods:** We performed overnight polysomnography in 25 patients with intractable epilepsy who averaged over four seizures per month and did not express sleep complaints to their physician. In addition to the standard polysomnography parameters, we measured intranasal pressure and end-tidal CO_2. Studies were scored using Rechtschaffen and Kales criteria, and respiratory events were scored consistent with the Chicago Criteria. Correlation coefficients were determined for respiratory parameters ($p < 0.05$). **Results:** We found that 15 (60%) of our subjects had a respiratory disturbance index (RDI) greater than five events per hour, and nine (36%) of our subjects had RDI >10 events per hour. Yet we found 13 (52%) of our subjects had events of oxygen desaturation to ≤88%. We found significant correlations of degree of the oxygen desaturation and RDI and weight, but not age. We also found three (12%) individuals had a periodic limb movement (PLM) index >15 events per hour, and only one subject had a PLM arousal index greater than five events per hour. **Conclusions:** These findings suggest that patients with intractable epilepsy have a high prevalence of sleep disorders. Physicians should have an elevated index of suspicion for sleep disorders in patients with epilepsy. (Supported by Cyberonics Inc.) (Disclosure: Grant: Cyberonics, Glaxo Smith Kline, UCB, OrthoMcNeill, Cephalon; Consulting: Cyberonics; Honoraria: Cyberonics, Glaxo Smith Kline, Wyeth Ayerst, Searle, MER, Abbott.)

1.116
ON THE INFLUENCE OF NONSTATIONARITY OF THE EEG ON THE CAPABILITY OF NONLINEAR SURROGATE MEASURES TO CHARACTERIZE THE SPATIAL DISTRIBUTION OF THE EPILEPTOGENIC PROCESS

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Rationale: In a previous study we compared different techniques from linear and nonlinear time-series analysis in an application to intracranial EEG recordings of the seizure-free interval of patients with mesial temporal lobe epilepsy (MTLE; *Epilepsia* 2001;42(suppl 7):98). It was demonstrated that particularly nonlinear time-series analysis measures in combination with the method of surrogates (termed NST techniques) allowed a correct lateralization of the focal hemisphere in a high percentage of cases. However, NST techniques implicitly assume stationarity of the investigated dynamics, a prerequisite not fulfilled for neuronal dynamics. Consequently, many periods of EEG recordings exhibit nonstationary features, whereas other periods appear to be stationary. The aim of the present study was therefore to elucidate the influence of nonstationarity on the discriminative power of NST techniques for the focal hemisphere in MTLE patients. **Methods:** Our retrospective out-of-sample study was based on intracranial EEG recordings of the seizure-free interval of 38 patients with unilateral MTLE. Using a moving-window technique on average 116 min per patient were analyzed. In a first step, a criterion for weak stationarity was applied to separate the EEG into stationary and nonstationary segments. For all segments, a set of surrogate time series was generated using an iterative amplitude-adjusted technique. Three measures from nonlinear time-series analysis (coarse-grained flow average, prediction error, and an estimate of the correlation dimension) were calculated from both the original EEG time series and the corresponding set of surrogate time series. The differences between these values (EEG and the surrogates' mean values) were used as NST measures. The subsequent evaluation was carried for all segments and solely based on stationary segments. **Results:** Based on all segments, a correct localization could be established for 35 of 38 cases for the NST measures based on the coarse-grained flow average and the correlation dimension, and in 33 cases for the prediction error. For the individual patients, the portion of segments that were classified as nonstationary ranged from 15 to 40%. Nonetheless, based solely on the remaining stationary segments, 34 cases were correctly lateralized for the coarse-grained flow average and the correlation dimension, whereas the performance of the NST measure based on the prediction error did not change at all. **Conclusions:** In agreement with recent studies, our results indicate that NST measures can contribute valuable information to the lateralization of the focal hemisphere without the necessity of observing actual seizure activity. Furthermore, the discriminative power of NST techniques for the focal hemisphere is not related to the influence of nonstationarity of the EEG as tested here. (Supported by Deutsche Forschungsgemeinschaft.)

1.117
QUANTITATIVE INTERICTAL SUBDURAL EEG ANALYSES IN CHILDREN WITH NEOCORTICAL EPILEPSY

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Rationale: Cortical resection is an effective treatment for selected children with drug-resistant partial epilepsy of neocortical origin. Ictal EEG findings on subdural electrodes are currently used as the gold standard to define epileptogenic foci. Longer subdural EEG monitoring to capture habitual seizures, however, is expensive and increases the risk of complications such as infection. We studied the relation between quantitative interictal subdural EEG data and visually defined ictal subdural EEG findings and determined whether interictal EEG findings are predictive of ictal EEG onset zones. **Methods:** Thirteen children (aged 1.2–15.4 years) underwent prolonged intracranial EEG recording, using 48- to 120-channel subdural grid-electrodes. Three distinct 10-min segments of the continuous interictal EEG recording were selected for each patient, and the spike frequency for each channel was determined using an automatic spike-detection program. Subsequently, the average spike frequency of each electrode was compared with ictal assessment (seizure onset, seizure spread, and no early ictal involvement). In addition, 50 distinct regional interictal spikes were averaged for each patient, and the amplitude as well as latency after the leading spike (averaged spike showing the earliest peak) were measured for each electrode and analyzed with respect to ictal EEG findings. For each electrode in each patient, spike frequency and spike amplitude were normalized to the maximal value recorded, and these normalized values were further analyzed. **Results:** Reproducibility of the spike-frequency pattern derived from three 10-min segments was high (Kendall's W, 0.85 ± 0.08). Electrodes with the highest spike frequency were found to be a part of the seizure onset in all 13 cases. Seizure-onset electrodes showed higher spike frequency than spread electrodes (Mann–Whitney U test: $\chi2(13) = 101$; $p < 0.001$), and spread electrodes showed higher spike frequency than normal electrodes ($\chi2(13) = 288$; $p < 0.001$). A receiver operating characteristics analysis

showed that a cutoff threshold at 25% of the maximal spike frequency resulted in an accuracy of 0.87 for the detection of seizure-onset electrodes. Electrodes with the highest spike amplitude were found to be a part of the seizure-onset zone in 12 of 13 cases. The spike amplitude of seizure-onset electrodes was higher than that of seizure-spread electrodes ($\chi 2(13) = 93$; $p < 0.001$), and seizure-spread electrodes showed higher spike amplitudes than normal electrodes ($\chi 2(13) = 214$; $p < 0.001$). Furthermore, electrodes showing the leading spike were found to be a part of seizure-onset zone in 10 of 13 patients. **Conclusions:** Quantitative interictal subdural EEG may predict the ictal-onset zones in children with intractable neocortical epilepsy, and may potentially reduce intracranial EEG monitoring periods. Further correlation with surgical outcome is the logical next step to determine the clinical significance of quantitative interictal EEG analyses in pediatric epilepsy surgery. (Supported by NS34488, NS38324.)

1.118
SPECTRAL RELIABILITY OF VHS ARCHIVED EEG DATA IN PATIENTS WITH EPILEPSY

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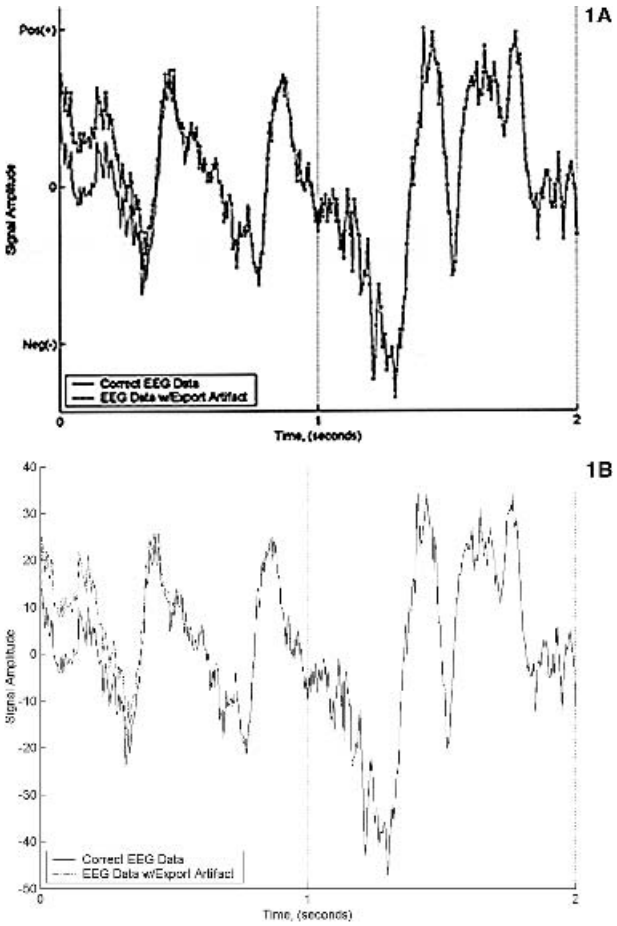
Rationale: Archiving EEG data on VHS tapes potentially introduces data artifacts. We performed a validation study to assess spectral differences between EEG data archived digitally and archived on VHS tapes. **Methods:** We retrospectively reviewed records in five patients whose EEG data were archived to both analog VHS (aEEG) and directly to digital media (dEEG). All EEG data were acquired by using the Telefactor Corp. Beehive-7, single-computer, integrated Beehive/SzAC system. The data were recorded at 200 samples/s and 12 bits/channel. Continuous 45-s segments were selected from each of the five patient EEG records. The aEEG data segments were redigitized and exported to European Data Format (EDF) files using Grass-Telefactor Twin Recording & Analysis Software (v. 2.5). The dEEG data segments were opened and exported to EDF files using the same Grass-Telefactor software. The EDF file pairs were imported into MATLAB (R12) and five 5-s data epochs were selected from each imported 45-s segment. The first 5-s epoch from each patient record was discarded due to artifact. Additionally, all epoch pairs (dEEG and aEEG) were shifted against each other and cropped appropriately to compensate for a lack of synchrony associated with the aEEG redigitization process. The power spectrum for each 5-s epoch was computed using the Fast Fourier Transform (FFT) in MATLAB. A Hanning window and a 512-point FFT were used in the transform. The raw power-spectrum data for each epoch were divided into standard frequency bands (δ: 0.75–4 Hz; θ: 4–8 Hz; α: 8–12.75; β: 12.75–31 Hz), and the total power contained in each band was summed. Each band's percentage of the total power (power within the total frequency range: 0.75–31 Hz) was also calculated. The difference in band percentage power between the aEEG and dEEG data was calculated. The mean and standard deviations of those differences over all epochs, patients, and channels were also calculated. **Results:** The data import/export process generated the majority of the notable artifacts. During the first 1–2 s of the EDF export process, the EEG was deflected, either positively or negatively, until it reached a reliable study-state (Fig. 1). There was also a lack of synchrony between the aEEG and dEEG data during the aEEG redigitization process. In general, the dEEG data lagged 1–200 samples behind the aEEG data. Additionally, the redigitization process introduced and sometimes deleted samples. The sample addition/deletion artifact was minimal and deemed notable, but insignificant. On average, the mean absolute value of the difference between the dEEG and aEEG band percentage of total power was 0.051% for the ™ band (STD = 0.854%), 0.027% for the θ band (STD = 0.620%), 0.052% for the β band (STD = 0.501%), and 0.026% for the ® band (STD = 0.781%). **Conclusions:** Although there were minor spectral differences between aEEG and dEEG data, the differences were insignificant. Thus, data archived on VHS tapes are acceptable for use in spectral EEG studies Figs. 1A and B).



1.119
ICTAL-ONSET PATTERNS DURING INVASIVE SUBDURAL RECORDINGS IN PATIENTS WITH REFRACTORY EXTRATEMPORAL EPILEPSY

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Rationale: The prolonged electrocorticogram obtained through implanted subdural electrodes is artifact free and represents an excellent tool for the study of the seizure's onset patterns in patients with extratemporal epilepsy who usually have poorly localizing scalp ictal EEG recordings. **Methods:** Sixteen patients with extratemporal epilepsy and normal or nonlocalizing magnetic resonance imaging (MRI) with extensive coverage of the brain convexity with subdural electrodes were included in the study. The patterns of seizure onset and the number of electrodes involved were studied. Mean follow-up time was 1.9 years. **Results:** Seizure onset included up to three electrodes in eight patients, four to six electrodes in four patients, and more than six electrodes in four patients. Seizure-onset patterns included low-amplitude fast activity evolving into a recruiting rhythm (n = 9), rhythmic theta activity (n = 4), and high-amplitude spiking (n = 3). A sentinel, more generalized spike was seen in six patients immediately before seizure onset. Overall, 81% of the patients have been rendered seizure free after surgery. There was no statistical difference in seizure outcome related to the pattern of seizure onset or to the number of electrodes involved at seizure onset. **Conclusions:** The main seizure-onset pattern

found in this study was fast activity evolving into a recruiting rhythm. Surgical outcome in relation to seizures was not different within the different subgroups, but patients with more widespread ictal zones were given considerably bigger cortical resections. The pathophysiologic significance of the sentinel spike seen in 37% of the patients remains unclear. (Supported by Sao Paulo Secretary of Health.)

***Abstract 1.120 has been withdrawn.**

1.121
SEIZURE PREDICTION BY DYNAMIC PHASE INFORMATION FROM THE EEG

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Rationale: We have shown in the past that mesial temporal lobe seizures are preceded by a preictal transition that evolves over minutes to hours (*J Comb Optim* 2001;5:9–26; *Epilepsia* 2001;42S7:41). The transition is detectable by monitoring the maximum Lyapunov exponents (STLmax) of critical cortical sites. In the present study, we present evidence that monitoring the convergence of the dynamic phase of corresponding critical cortical sites also can be used for seizure prediction. We report sensitivity and false-positive rate per hour of a seizure-warning algorithm based on dynamic phase monitoring (SWAP). **Methods:** Continuous 28- to 32-channel long-term intracranial EEG recordings previously obtained in patients with medically intractable partial seizures were used in this analysis. The method for the estimation of the dynamic phase profiles from the EEG is described (Iasemidis LD, et al. Phase entrainment and predictability of epileptic seizures. In: Pardalos PM, Principe J, eds. *Biocomputing.* Kluwer Academic Publishers, 2002:59–84). The phase profiles were estimated per electrode site. Then, instead of the STLmax profiles, the phase profiles were used as an entry to the SWA. Warnings were issued and evaluated, using the same criteria for convergence and length of the time horizon, respectively, as in the original SWA. **Results:** In four patients with a total of 49 seizures (range, seven to 20 seizures per patient) and 415 h of EEG (range, 70–140 h of continuous recordings per patient), the overall sensitivity of SWAP was 84.44%, the false-prediction rate was 0.205 false predictions per hour, and the average warning time per seizure and patient was 83 min. It is noteworthy that the range of warning time across patients was 78–99 min. The sensitivity of the method for subclinical seizures was approximately the same as that for clinical seizures, that is 83.33% versus 85.71%, respectively. These results compare well with those of the application of SWA on the same data sets from the same patients with the exception of a higher false-positive rate in the case of SWAP. However, in its present form, SWAP is computationally faster than SWA. **Conclusions:** The results of this study show that incorporation of the dynamic phase information of the EEG in a seizure-prediction scheme is promising. The speed of the new algorithm is an advantage for its real-time implementation as a monitoring and therapeutic tool (e.g., as part of a monitoring/stimulator/intervention device for epileptic seizures). Considering the results from both SWA and SWAP prediction algorithms, we may conclude that the dynamic progression from the interictal state to a seizure involves both changes in stability (STLmax) and synchronization (phase) of critical cortical sites. (Supported by NIH/NINDS NS039687 U.S. Veterans Affairs.)

1.122
QUANTITATIVE CONTINUOUS EEG ANALYSIS FOR THE DETECTION OF DELAYED CEREBRAL ISCHEMIA IN PATIENTS WITH POOR-GRADE SUBARACHNOID HEMORRHAGE

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Rationale: Delayed cerebral ischemia (DCI) due to vasospasm is often not detected by clinical examination in patients with poor-grade subarachnoid hemorrhage (SAH; Hunt–Hess grade 4–5). Continuous EEG (cEEG) monitoring may be useful to monitor brain function in comatose SAH patients. The objective of this study was to identify quantitative EEG (qEEG) parameters that are highly sensitive for DCI with reasonable specificity in poor-grade SAH patients. **Methods:** From a prospectively recruited cohort of 78 patients with Hunt–Hess grades 4–5 SAH admitted to the Columbia Neurological ICU between January 2000 and January 2002, 48 patients were eligible for enrollment in the study protocol, and cEEG was performed in 34. DCI was detected by clinical examination or computed tomography (CT), and corroborated with angiography and TCD. CEEG was performed from postoperative day 2 to 8. In each patient, 20 artifact-free, 1-min epochs of digital EEG directly after stimulation were analyzed: time 1, 10 epochs prior to DCI or on day 1 in patients without DCI; and time 2, 10 epochs during DCI or on day 4–6. After Fast-Fourier-Transform, 12 qEEG parameters were calculated (Magic Marker Insight, Persyst Inc., Arizona). These were averaged for individual patients for times 1 and 2. We calculated a ratio of change (time 2/time 1), and determined medians of these ratios for each patient. To incorporate four recording sites into one model, we used the generalized estimating equations method to compare ratios of change in qEEG parameters in patients with and without DCI. We calculated sensitivity and specificity for changes of qEEG parameters >5% and >10%. **Results:** Nine of 34 patients (26%) developed DCI, two with silent infarction. Among the investigated qEEG parameters, the alpha/delta ratio (alpha power/delta power; ADR) demonstrated the strongest association with developing DCI. The median decrease of ADR for patients with DCI was 24%, compared to a median increase of 3% for patients without DCI ($Z = 4.0$; $p < 0.0001$). Using an ADR cutoff of a >5% decrease, there was an 83% sensitivity and 66% specificity to detect DCI. Using a >10% cutoff, sensitivity was 77%, and specificity was 74%. Other parameters associated with DCI included increased delta, increased delta/total, decreased alpha/total, and decreased (alpha + beta)/delta power. **Conclusions:** A decrease in the alpha/delta ratio is a sensitive method of detecting DCI, with reasonable specificity. This poststimulation qEEG parameter may supplement the clinical examination in poor-grade SAH patients and may prove useful to detect ischemia from vasospasm.

1.123
A HYBRID MULTIFEATURE AND MULTICHANNEL ANALYSIS OF CONTINUOUS, PROLONGED INTRACRANIAL EEG DATA FOR SEIZURE PREDICTION

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Rationale: Based on retrospective studies, there is consensus that a preictal period of ≥20 min exists in mesial temporal lobe epilepsy. Given the heterogeneity of epilepsy, it is unlikely that a single quantitative measure will be useful in identifying this period in all patients. As a step toward practical implementation of seizure prediction in

humans, we present an individualized method for selecting EEG features and electrode locations for seizure prediction focused on precursors that occur within 10 min of electrographic seizure onset. **Methods:** Using a systematic approach to feature selection, classification, and validation, we analyzed a 94-h hospital stay, containing 17 seizures with this method. Four other patient analyses are in progress. The method was trained on 8-min data epochs leading to four seizures, 4 h of baseline EEG data, and then a set of features and electrodes were selected using a genetic algorithm and probabilistic neural network to optimize the method for individual patients. The trained system was then run on the rest of the patient stay, and its performance was assessed. **Results:** The complete method has been evaluated for one patient. In this patient, the best channel selected by the genetic algorithm was contralateral to the focus channel. The best feature using this channel was the "mean of the mean of the curve length," a derived measure related to signal complexity. Validation of this result demonstrated a sensitivity of 100%, with 0.71 false positives per hour (FPh) over the entire 94-h record. Average prediction time was 73.57 s with a standard deviation of 25.53 s. The results from all five patients, including algorithm outputs and receiver operating characteristic (ROC) curves, will be presented. **Conclusions:** The output of the probabilistic neural network (PNN) classifier for the first patient demonstrates that a system based on multiple features and electrode sites tailored to individual patients produces promising results for seizure prediction. That the electrode site selected as best for short-term prediction was contralateral to the focus channel may indicate the importance of brain outside of the ictal-onset zone in generating clinical seizures. This method requires further refinement and validation, but may provide one way of dealing with the heterogeneity of seizure types and individual patterns in seizure-prediction technology. It may also provide insight into brain mechanisms that underlie seizure generation. (Supported by funding from the Whitaker foundation, Epilepsy Foundation, American Epilepsy Society, University of Pennsylvania Research Foundation, and the National Institutes of Health grants R01NS041811-01 and MH-62298RO1.) [Disclosure: Stock: Drs. Echauz, Esteller, Litt, and Vachtsevanos have been awarded a small number of stock options (<0.25% of the company's total value) in NeuroPace Inc, resulting from licensure of patents to the company. These patents are all owned, singly.]

1.124
SEIZURE ANTICIPATION AND MARGINAL PREDICTABILITY IN MESIOBASAL TEMPORAL LOBE EPILEPSY

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Rationale: To design and use a nonlinear dynamic approach to reliably anticipate seizures in a cohort of patients with mesiobasal temporal lobe epilepsy (MBTLE). **Methods:** We compute a quantity called marginal predictability (MP) for time series of interictal and preictal (within 1 h of a seizure) scalp EEG. We compare results from one electrode proximate to the ictal-onset site to one remote ipsilateral, and to one homologous contralateral electrode. We performed this analysis for 24 seizures and 15 interictal epochs in seven patients with MBTLE. Statistical validation used Wilcoxon's sum of signed rank test, with sum of positive ranks (SPR) displayed as a function of time. **Results:** Interictally, SPRs indicate that MPs for electrodes adjacent to the site of ictal onset are significantly greater than for ipsilateral remote electrodes interictally and until 20–40 min before a seizure when they take on similar values. Metaphase space analyses suggest that tight clustering of points (implying autonomy) is correlated with higher MPs at adjacent electrodes. **Conclusions:** We suggest that this dynamic behavior adjacent to the site of ictal onset is an expression of tighter neuronal control that inhibits seizure development and that diminishes as time to clinical onset of a seizure approaches. (Supported by 1 RO1 NS36803-01A1.)

1.125
REAL-TIME SIMULATION OF A SEIZURE-DETECTION SYSTEM SUITABLE FOR AN IMPLANTABLE DEVICE

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Rationale: The advent of implantable devices for detection, termination, prediction, and prevention of seizures is becoming a reality. The goal of this study was to evaluate the NP seizure-onset detection system in a simulated on-line operation, under conditions resembling the clinical scenario that an implantable device for automated seizure detection/termination would face. **Methods:** Intracranial EEG (IEEG) signals available from recordings taken during the hospitalization of four patients under evaluation for resective surgery were analyzed in a prospective simulation with NP algorithm and an adaptive threshold classifier. All patients had medically intractable partial seizures of predominantly mesial or neocortical temporal origin. A total of 332.2 h spanning the full hospitalization stay were used in the simulation. An epilepsy expert properly marked electrographic onsets by following the UEO (unequivocal electrographic onset) definition of Litt B, et al. (1999). The system consists of four main blocks, the early detection block, the data collection, the parameter optimization, and the user-interface. Only the line-length tool (IEEE-EMBC 2001) from the tools available in the early detection block was evaluated at this point. The system is initialized by collecting a variety of IEEG segments and adjusting its parameters as a highly sensitive detector. After initialization, IEEG segments are collected in response to each detection. As expected in a real clinical situation after device implantation, initially every day, the physician accesses the system and labels collected data as seizure or baseline. Labeled IEEG segments are used by the parameter-optimization block to retune the adaptive threshold. It is expected that as the hospitalization time progresses, the adaptive threshold will be adjusted to decrease the false positives per hour (FPh) over time, so the threshold optimization is required less frequently. **Results:** All clinical and subclinical seizures were detected with the exception of two brief focal subclinical seizures. An overall rate of 0.054 FPh (worst case including postictal detections and flat artifact detections was 0.13 FPh), sensitivity of 92.6% (only two FNs, which corresponded to two subclinical focal seizures, 6-s duration, of 27 seizures), and an average UEO detection of 2.9 s with a range of –44.18 to 7.86 s were observed. The evolution of the FPh over time was assessed by comparing the FPh during the first 12 h for each patient with respect to the FPh in the last 12 h. The average reduction of the FPh for all patients was 91.6%, corresponding to an average of 0.25 FPh in the first 12 h and 0.021 FPh in the last 12 h. The FPs exhibit a clear tendency to decrease over time as the system "learns" the patient signals and is tuned to them. **Conclusions:** The adaptive classification scheme combined with the line-length tool tuned to each patient as data were collected demonstrated an outstanding performance in the prospective simulation conducted. Further evaluation is under way to validate this and the other NP tools. This study demonstrates the plausibility of an automated seizure-detection system for an implantable device under the causality constraint required for any real-world scenario and illustrates how the adaptation over time can lead to better performance. (Supported by NeuroPace, Inc.) [Disclosure: Salary: R. Esteller, J. Echauz, B. Pless, and T. Tcheng, are currently full-time employees of NeuroPace. Their salaries are confidential information; Stock: R. Esteller, J. Echauz, B. Pless, T. Tcheng, and B. Litt have been awarded stock options (each <0.25% of the company's total value) in NeuroPace Inc, resulting from licensure of patents to the company. These patents are all owned, singly.]

1.126
SEQUENTIAL MULTICHANNEL GABOR ATOM DENSITY FOR SEIZURE LOCALIZATION
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Rationale: Seizure localization is important in the evaluation of patients undergoing intensive video-EEG monitoring. Analysis of ictal EEG can determine the location of seizure onset; at times intracranial recordings are necessary when scalp recordings are indeterminate. We present application of the Gabor Atom Density (GAD) method, derived from the matching pursuit decomposition, as a means of seizure localization. **Methods:** The matching pursuit (MP) method developed by Mallat and Zhang (1993) allows for continuous time-frequency decomposition of rapidly changing signals without requiring linear or nonlinear assumptions. The GAD method (Jouny et al., 2001) is derived from the MP method and provides a value that represents the number of atoms necessary to represent the signal for each point in time. We applied GAD analyses sequentially to each channel of ictal activity recorded intracranially from 10 patients with mesial temporal onset complex-partial seizures, patients with well-defined electrographic seizure onsets. **Results:** The GAD analyses of partial seizures from each of the 10 patients revealed that at the time of ictal EEG onset, the earliest increases of GAD were seen at the area of seizure onset, based on visual analysis. The sequential multichannel GAD display also revealed the patterns and duration of ictal evolution and subsequential seizure propagation. **Conclusions:** These results demonstrate that the application of sequential multichannel GAD analysis reveals that the earliest elevations in GAD levels are seen in the channels near the seizure focus. These levels reflect changes in signal complexity that accompany the electrographic seizure onset. In addition, the GAD analyses reveal signal changes that reflect seizure propagation. Therefore, application of GAD analyses can provide a measure for seizure localization and onset potentially more consistent than visual analysis. (Supported by NIH grant NS 33732.)

1.127
POSTOPERATIVE EEG PREDICTS LONG-TERM SEIZURE OUTCOME
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Rationale: We investigated the correlation of sharp waves in routine EEG 6 and 24 months after epilepsy surgery with regard to long-term seizure outcome. **Methods:** In 148 patients [74% temporal lobe epilepsy (TLE), 26% extratemporal] EEG results [sharp waves (SWs) present or absent] were correlated with the postoperative outcome using the Engel classification 6 and 24 months after resection (PO1 and PO2, respectively). Self-evaluation was conducted 3 and 5 years after resection (PO3 and PO5, respectively). **Results:** Ninety-one patients (62%) were seizure free 5 years after resection; 88% of them showed no SWs in PO1; 28 patients (19%) displayed SWs in routine EEG 6 months after resection; 61% of them had recurrent seizures in PO5 ($p = 0.007$). No SWs in PO1 and PO2 correlate with a good outcome (73% seizure free); $p = 0.001$. Seizure-free patients (Engel I) and patients with a less favorable outcome (Engel III, IV) at PO1 and PO2 rarely changed the category of outcome during the following years; $p = 0.000$. Of the patients, 50% with a favorable seizure reduction (Engel II) changed to seizure free (Engel I) or to a worse outcome (Engel III, IV). SWs in PO1 were more predictive for a worse outcome in TLE than in extratemporal epilepsy ($p = 0.011$) and in FCD compared with other etiologies ($p = 0.077$). **Conclusions:** Postoperative routine EEG is a good prognostic instrument for the prediction of long-term seizure outcome, especially for TLE and FCD. It predicts the running up/down of fits in patients with rare seizures (Engel II).

1.128
SEIZURE ANTICIPATION THROUGH TIME-SERIES VISUALIZATION AND ANALYSIS
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Rationale: Extraction and subsequent analysis of time-series information form the foundation by which the behavior of systems, both physical and biologic, can be understood over time. An epileptic seizure may be considered as transient stabilization of quasi-periodic states within the dynamic repertoire of a population of hypersynchronized neurons (Perez Velazquez et al., 1999). We present a simple method, recursive peak time (RPT) analysis, based on peak detection, recursive plotting, and nonlinear mapping for time-series processing of electrophysiologic recordings. We demonstrate RPT as a tool for visualization and quantification of electrophysiologic signal changes relatable to quasi-periodicities. Analyses revealed characteristic signal changes that were interpreted to anticipate seizures. **Methods:** Hippocampal brain slice recordings were obtained from male Wistar rats (17–25 days old). Spontaneous seizure-like events (SLEs) were brought on by perfusing slices in 0.5 m*M* Mg^{2+}. Single or multichannel extracellular responses were recorded from CA1, CA3, and dentate granule (DG) regions of the hippocampus. Intracranial EEG recordings of seizures were obtained from implanted depth electrodes in three patients, with unilateral (mesial) and bilateral temporal lobe seizure disorders, undergoing presurgical EEG monitoring. Continuous, interictal, and ictal epochs of EEG were digitized at 200 Hz. Software was written to detect peaks and fast-transients using amplitude and width criteria. Recursive (return) maps were constructed from the interval data using appropriate delays. Resulting return plots were mapped onto an adjustable nonlinear surface that was used to unravel nontrivial temporal self-similarities in the time series. This allowed visualization and quantification of activity over time. **Results:** RPT analysis of slice and EEG recordings revealed common and characteristic temporal trends that were used to anticipate seizures. In slice recordings, signal changes were observed ~44 ± 33 s (average ± SD) in anticipation of the actual seizure-like event. Approximately 75% of detected anticipatory events occurred within 50 s of SLE onset. In the case of EEG, this analysis detected electrographic changes ~29 ± 13 s in anticipation of electrographic onset. Approximately 75% of detected anticipatory events occurred within 30 s of electrographic seizure onset. **Conclusions:** We present RPT analysis as a concise method suitable for the analysis of electrophysiologic recordings in the context of seizures. The analysis procedure and subsequent visualization tactics are able to extract meaningful information about temporal relations in time-series data. RPT is simple yet robust in quantitatively detecting electrographic signal changes, which make it useful for real-time implementation. This technique contributes to the investigation of dynamic mechanisms responsible for seizure onset by serving as a diagnostic tool, in conjunction with other available methods, for visualizing and quantifying electrophysiologic signal changes (Perez Velazquez et al. *Eur J Neurosci* 1999;11:2571–6). [Supported by research grants from Citizens United for Research in Epilepsy (CURE) and the Savoy Epilepsy Foundation.]

1.129
WAVELET-FREQUENCY ANALYSIS OF SEIZURES ON SUBDURAL EEG IN PATIENTS WITH FOCAL CORTICAL DYSPLASIA
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Rationale: Neuronal oscillations are recently the most remarkable topics in epilepsy. Wavelet-frequency analysis, one of the computational nonstationary analysis of EEG signals, has been used to investigate the synchronization property to cause intractable epilepsy. Focal cortical dysplasia (FCD) is known to be intrinsically epileptogenic. We applied wavelet-frequency analysis to evaluate the specific frequency patterns on ictal subdural EEG in patients with FCD. **Methods:** We reviewed five patients with FCD who underwent cortical excision after subdural EEG recording. For wavelet analysis, we selected paired subdural electrodes located to the center of the magnetic resonance imaging (MRI) lesion. We analyzed three phases (preictal, ictal onset, and periictal) in the most prominent EEG seizures with Gaussian wavelet analysis (1–12, 5–20, 10–35, and 30–60 Hz for 20 s). **Results:** We found various frequency patterns at each phase. Preictal phase showed wide-ranged (1–60 Hz) frequency activities associated with interictal spike discharges. During ictal-onset phase, two patients had brief high-intensity gamma activities, consisting of wide-ranged high-frequency (30–60 Hz) lasting >2 s. The other three patients did not have any explicit high-intensity activities. Periictal phase showed various prolonged high-intensity activities lasting >10 s, the gamma range (~50 Hz) in one, the beta range (~20 Hz) in one, and the alpha range (~10 Hz) in three patients. **Conclusions:** Wavelet-frequency analysis can differentiate the ictal transitional phases by dynamic changes of frequency. We found brief high-intensity gamma activities and prolonged high-intensity activities in various frequency during the ictal time course in patients with FCD. We need further investigation to understand neuronal oscillations in the intrinsically epileptogenic FCD.

1.130

COMPARISON OF TWO PHASE-SYNCHRONIZATION ANALYSES TECHNIQUES FOR INTERICTAL FOCUS LATERALIZATION IN MESIAL TEMPORAL LOBE EPILEPSY

Alexander Kraskov, Thomas Kreuz, Rodrigo Quian Quiroga, Peter Grassberger, Florian Mormann, Ralph G. Andrzejak, Christian E. Elger, and Klaus Lehnertz (John von Neumann Institute for Computing, Research Center Juelich, Juelcih, Germany; Department of Epileptology, University of Bonn, Bonn, Germany; Sloan-Swartz Center for Theoretical Neurobiology, Division of Biology, California Institute of Technology, Pasadena, CA)

Rationale: In a number of recent studies, the concept of phase synchronization has been applied to EEGs for description of spatio-temporal dynamics of the epileptic brain. We compared two different phase-synchronization analysis techniques on a theoretic basis. Subsequently the ability of both measures to lateralize the focal hemisphere in patients with mesial temporal lobe epilepsy (MTLE) was investigated. **Methods:** Fifty-five interictal artifact-free EEG recordings were selected from 23 MTLE patients. Data were recorded using permanently implanted intrahippocampal depth electrodes, each equipped with 10 contacts. We applied two phase-synchronization analysis techniques that are based on two different approaches for extraction of the instantaneous phase: the Hilbert and the wavelet transform. We calculated the wavelet transform using complex demeaned Morlet wavelet. For each time and scale, the instantaneous phase of the EEG was defined as the argument of the corresponding complex wavelet coefficient. Lateralization of the focal hemisphere was done by comparing the degree of synchronization for ipsi- and contralateral hemispheres after averaging over time and over all combinations of channels for the respective side. **Results:** Based on theoretic considerations, we show the close relation of the phases defined from Hilbert and wavelet transforms. These phases are identical if prefiltering of the EEG signal is applied before the calculation of the Hilbert transform. The filter characteristics should correspond to the wavelet mother function. Using the Hilbert phase synchronization, we could correctly lateralize the focal hemisphere in 18 of the 23 patients. A better discrimination was achieved by means of wavelet phase synchronization for the scales of the wavelet corresponding to the beta frequency range (20 correct cases). **Conclusions:** The comparison shows good performance of both phase-synchronization analysis techniques for focus lateralization in MTLE. The better discrimination achieved by the wavelet phase synchronization analysis technique can be explained by its ability to extract more specific information for different frequency ranges. The techniques described in this study might render additional information helpful for an improvement of the presurgical evaluation of MTLE patients. (Supported by Deutsche Forschungsgemeinschaft.)

1.131

SEIZURE PREDICTION: QUANTIFYING THE PERFORMANCE OF MEASURES IN DISTINGUISHING PREICTAL FROM INTERICTAL STATES

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Rationale: In the rapidly developing field of seizure prediction, more and more interest is directed toward the question of how to quantify the performance of measures applied to the EEG in seperating preictal from interictal states. In this study we compared two different concepts to address this point. Both evaluations are based on the extraction of characteristic features (e.g., positive and negative deviations from a given reference level) derived from time profiles of bivariate measures. Whereas the first approach attempts a statistical seperation of the preictal from the interictal states, the second one is an algorithmic approach defining alarms and evaluating their distribution relative to the times of seizure onset in terms of sensitivity and specificity. For the latter approach, a new way of weighting sensitivity and specificity to get one overall measure of performance is introduced. **Methods:** We analyzed continuous intracranial multichannel EEGs recorded from patients with unilateral mesial temporal lobe epilepsy (MTLE). In the first step, a number of bivariate measures (e.g., cross correlation) were calculated applying a moving window technique. Second, from the resulting time profiles, we extracted and parametrized characteristic features (e.g., positive and negative deviations from a given reference level). Using on the one hand a statistical and on the other hand an algorithmic approach, the performances of the different measures were evaluated automatically. **Results:** Within the statistical as well as within the algorithmic approach, the different bivariate measures yielded different degrees of performance in distinguishing preictal from interictal states. For the latter approach, different ways of weighting sensitivity and specificity to get one overall measure of performance were compared. As a solution to the problem of how to define sensitivity and specificity for continuous long-time recordings, we propose the use of the prediction horizon as a common time unit to get a proper normalized measure of performance (similar to the discrete case of diagnostic tests where the natural unit is the single patient). **Conclusions:** Whereas the statistical approach is free of parameters and therefore acts as an unbiased criterion for the distinguishability of the two different states, the algorithmic approach offers the possibility to adjust certain parameters. However, as with the parameters of the single measures, much care has to be taken to avoid in-sample optimization. For this approach a proper weighting of sensitivity and specificity seems to be of high importance for an unbiased judgment of the performance of any measure. (Supported by Deutsche Forschungsgemeinschaft.)

1.132

ANALYSIS OF THE PREICTAL EEG CHANGES DETECTED BY A NONLINEAR METHOD IN AN UNSELECTED POPULATION OF PATIENTS WITH FOCAL EPILEPSY

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Rationale: Nonlinear analysis of electroencephalographic (EEG) signals has been shown to detect dynamic changes before seizure onset. The similarity method has been used to measure preictal changes of EEG signals from selected patients with well-localized intractable focal epilepsies, originating from the mesial temporal lobe (Le Van Quyen et al. *Lancet* 2001;357:183–8) or from the neocortex (Navarro et al. *Brain* 2002;125:640–55). The efficiency of this method on unselected patients undergoing intracranial investigations needs to be evaluated. The nature of the dynamic changes detected before seizures needs to be defined. **Methods:** All patients (n = 7) undergoing an intracranial EEG investigation for medically intractable partial epilepsy at the Montreal Neurological Institute between December 2001 and April 2002 were included. A total of 51 seizures were studied, according to the following criteria: electroclinical or electrographic seizures, ≥1 h of EEG recording before each seizure and between two successive seizures. All EEG channels were analyzed by the similarity nonlinear method that compares the signal dynamics of successive windows with that of a 5-min long "reference" period, taken at the beginning of the recording. The presence of a preictal change was defined by a deviation of the similarity index of >5 standard deviations above that of the reference period. These changes should persist until the seizure, in at least three channels and for >1 min. To explain the nature of these dynamic changes, EEG recordings were then visually inspected, and video recordings were reviewed. **Results:** (a) Preictal changes were detected in a total of 31 of 51 seizures. Among these 31 seizures, visually detectable changes of the EEG may account for the preictal changes in 24 seizures, corresponding to moderate modifications of the background activity before two seizures, changes of sleep stages before seven seizures, changes of the epileptic interictal activity before 13 seizures, and concomitant artifacts before two seizures. No visually detectable change of the EEG could be related to the preictal changes before seven seizures. (b) In 14 seizures, changes of the similarity index were found, but did not meet our criterion. Among these 14 seizures, changes were found before nine seizures, but they included fewer than three channels. In five other seizures, the preictal changes could not be distinguished from postictal changes due to a previous seizure. (c) No preictal change was detected in six seizures. (d) Preictal changes were found in channels adjacent to the epileptogenic focus, as well as at a distance. **Conclusions:** The similarity nonlinear method was able to detect preictal changes in 60% of the analyzed seizures, in an unselected population of patients with various localizations and extensions of the epileptogenic area. Those changes could be related to visually undetectable dynamical modifications or to varied obvious modifications of the EEG. In the latter, preictal changes were sometimes difficult to distinguish from physiologic changes. (Supported by Canadian Institutes of Health Research grant FRN 10189 Fondation pour la Recherche Médicale.)

1.133
ANALYSIS OF ENTROPY DURING THE INTERICTAL AND ICTAL ELECTROCORTICOGRAM OF PATIENTS WITH REFRACTORY EPILEPSY INVESTIGATED WITH SUBDURAL GRIDS

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Rationale: Approximate entropy is a recently developed statistical measure of regularity and complexity. We applied the approximate entropy (ApEn) algorithm further to study and recognize epileptic seizures recorded in the prolonged electrocorticogram (ECoG) obtained through subdural electrode's grids. **Methods:** The interictal and ictal ECoG recordings of three patients with refractory epilepsy implanted with subdural electrode arrays were analyzed by applying ApEn. Interictal activity containing no spikes was used as control for each individual. ApEn was applied using a slide window with N = 300 (~1 s of ECoG), with overlap of d = 30 (samples), over a standard deviation (SD) of the signal. A filter r selected the frequency of presentation of vectors formed by two points, m = 2 (m is the vector's dimension). The vectors were compared one to the other, measuring the maximal distance between their scalar components. Thirty epochs (30-s duration) of epileptic activity were selected in each patient, and mean and SD values for ApEn were calculated. **Results:** We got better results with r = 1% or r = 2%. Low entropy (<0.50) was measured during the ictal onset and ensuing seizure in the three epilepsy patients. Ictal-onset entropy was 0.14 ± 0.026, 0.278 ± 0.022 and 0.136 ± 0.034 (mean ± SD) in each patient, respectively. Entropy levels >0.5 were never recorded during ictal activity. **Conclusions:** The ApEn algorithm is appropriate to evaluate nonstationary signals. It could detect modifications of complexity such as that seen during ictal onset. This is especially important while dealing with epileptic seizures in which long transients are difficult to obtain for spatial localization of epileptic foci. Additionally, it is conceivable that a decrease in entropy may precede the actual ictal discharge or clinical seizure and might be used in the future in the very early detection of seizures and triggering of drug release or stimulatory treatments. (Supported by Sao Paulo Secretary of Health.)

1.134
EVENT SYNCHRONIZATION: A VERY SIMPLE AND FAST MEASURE OF SYNCHRONIZATION AND TIME-DELAY PATTERNS

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Rationale: We propose a simple method to measure synchronization and time-delay patterns between EEG channels. **Methods:** The method is based on the relative timings of events in the time series, defined for example as local maxima. The degree of synchronization is obtained from the number of quasi-simultaneous appearances of events, and the delay is calculated from the precedence of events in one signal with respect to the other. Moreover, we can easily visualize the time evolution of the delay and synchronization level with an excellent resolution. **Results:** We show the application of the algorithm to intracranial human EEG recordings containing seizure activity, and we propose that it might be useful for the detection of the epileptic foci. **Conclusions:** Event synchronization gives an useful quantification of synchronicity and time-delay patterns between EEG channels. The method can be easily extended to other types of data, and it is very simple and fast, thus being suitable for on-line implementations. (Supported by Deutsche Forschungsgemeinschaft, SFB TR3. Sloan Swartz Foundation.)

1.135
THE INFLUENCE OF NONSTATIONARITY AND SEGMENTATION SIZE ON THE ANALYSIS OF INTRACRANIAL EEG RECORDINGS

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Rationale: Previous studies have demonstrated the relevance of a number of nonlinear time-series analysis techniques for the spatiotemporal characterization of the epileptogenic process. Almost all of these techniques require the system under investigation to be stationary. For the dynamic system brain, however, this is far from being the case. EEG recordings of several tens of seconds length, nevertheless are usually regarded as approximately stationary. On longer observation times (segmentation size) of the EEG, however, the statistical significance of an analysis technique should be improved almost always. We here investigate an enlarged observation time of EEG segments up to minutes. We compare the distribution and thus the significance of nonlinear measures of the EEG, covering different states for different observation times. Furthermore, we estimate the nonstationarity of the observed EEG segments and exclude all segments that are significantly nonstationary. **Methods:** EEG segments recorded intracranially in patients with focal epilepsies and covering different states (interictal, preictal, ictal, and postictal) were analyzed. The EEG segments were enlarged, starting with 23.6 s up to 94.4 s, corresponding to 4,096 data points and 16,384 data points, respectively. Short segments were included in longer ones. Analysis techniques comprised nonlinear measures for complexity, determinism, and nonlinearity, using iterative amplitude-adjusted surrogate data for each segment. Nonstationarity was quantified by measuring the loss of recurrence in reconstructed state space. **Results:** Some epochs within long nonstationary segments appear stationary. On the other hand, even segments that are nonstationary appear stationary when they are enlarged. For most measures, the distributions of the estimated values show a deviation between EEG segments from preictal and interictal states. This deviation enlarged with increasing observation time, particularly for measures employing surrogate data. **Conclusions:** Results suggest that most measures show an increased performance in characterizing and discriminating EEG time series under control of stationarity if the observation time was enlarged. Moreover, we hypothize that investigating nonstationarity at characteristic time scales might improve the understanding of the spatiotemporal ictogenic process. (Supported by Deutsche Forschungsgemeinschaft.)

1.136
DYNAMIC DEPENDENCE OF SEIZURE PREDICTION ON PRECEDING SEIZURES

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Rationale: There is accumulated evidence that mesial temporal lobe seizures are preceded by a preictal transition that evolves over minutes to hours. We have previously shown that preictal transitions are detectable through a nonlinear dynamic analysis of EEG signals (*Chaos in the Brain* 2000:112). These transitions can be characterized by convergence of the values of STLmax, a stability measure of EEG signals, among critical cortical sites. We have defined this phenomenon as dynamic entrainment. It would be possible to predict an impending seizure only if the critical cortical sites could be identified far in advance. The first automated seizure-warning algorithm (SWA), reported in *Epilepsia* (2001;42S7:41), predicts the occurrence of an impeding seizure based on the identification of critical sites from the preictal period of the preceding seizure. In the present study, we sought to investigate the null hypothesis that critical cortical sites identified from the preceding seizure (short system's memory) are more helpful in predicting the impending seizure than ones from more seizures in the past (long system's memory). **Methods:** Continuous 28- to 32-channel long-term (2.9 ~ 5.8 days) intracranial EEG recordings previously obtained in four patients with medically intractable partial seizures were used to test the hypothesis. Four methods for selecting the critical cortical sites were compared. Method 1: critical sites only from the preceding seizure; method 2: critical sites only from the first recorded seizure; method 3: n groups of critical sites from each of the preceding m seizures, $m = 2 \sim 5$; method 4: n groups of critical sites from preceding m seizures, $m = 2 \sim 5$, where n was the optimal setting for each patient. The sensitivity (percentage of seizures predicted) and the specificity (FPR; false-positive rate per hour) of the SWA for each of the four selection methods were estimated. **Results:** In four patients, the sensitivity and FPR for method 1 were 80.9% and 0.142 per hour, respectively. For method 2, they were 61.7% and 0.178 per hour. For method 3, the sensitivities were 87.2, 89.4, 89.4, and 93.6% for $m = 2, 3, 4, 5$, respectively, and the FPRs were 0.289, 0.407, 0.451, and 0.477 per hour. For method 4, the sensitivities were 66.0, 66.0, 68.1, and 68.1% for $m = 2, 3, 4, 5$, respectively, and the FPRs were 0.157, 0.181, 0.203, and 0.193 per hour. **Conclusions:** The results of this study show that the our seizure-warning algorithm SWA attains minimal FPR per hour at a sensitivity >80% when the critical cortical sites are identified from the preceding seizure. Including more seizures does not considerably increase the sensitivity but tremendously increase the FPR. The verification of our null hypothesis supports the selection we made in our previously reported SWA and demonstrates the similarity of the participating critical sites in the preictal transition state between closer than further apart seizures in time. (Supported by NIH/NIDS NS039687 U.S. Veterans Affairs.)

1.137
EVALUATION OF A METHOD FOR AUTOMATIC DETECTION OF EPILEPTIC SEIZURES FROM THE ELECTROENCEPHALOGRAM

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Rationale: We describe the implementation and evaluation of a method (Schindler et al. *Clin Neurophysiol* 2001;112:1006–17) for detection of spiking patterns in noninvasive scalp EEG registrations that are associated with epileptic seizures. **Methods:** Our detection method consists of a number of consecutive signal-processing stages. At the initial stage, each EEG signal is low pass filtered. The mean of all EEG channels is then computed and subtracted from each of the channels. The next signal-processing stage marks parts of the EEG signals where the slopes change from low to high values with a sequence of unit pulses. For that purpose, the absolute values of derivatives (slopes) are calculated for each DC-corrected EEG channel. Next, each of the derivatives is normalized using a continuously updated standard deviation of the slope computed from a prior interval of the same channel. In case the normalized slope exceeds a threshold, a unit pulse is created. In the third stage, the trains of unit pulses act as input for a leaky integrate-and-fire unit (LIFU). The LIFU is a classic simple cell model transforming input pulse trains ("action potentials") from the previous stage in a sequence of slower excitatory postsynaptic potentials (EPSPs) that sum up if they are spaced closely enough. Each time the summated EPSPs exceed a threshold, the LIFU emits a spike and resets the signals across all the internal circuits to zero. In the final stage, the output spikes of the LIFU are used to calculate a spiking rate (SR). If SR exceeds the given SR-threshold, a seizure onset is detected. We evaluated the method on 47 recordings obtained from 15 randomly selected patients with different types of drug-resistant epilepsy, who were evaluated for possible epilepsy surgery at the Inselspital in Bern. Recordings consisted of >11 h of EEG data and contained 47 seizures. All the patients signed an agreement that the EEG data might be used for research purposes. A standard 10-20 system of scalp electrodes and two FoV electrodes with four contacts each were used for EEG recording. The evaluation of the method was done for scalp electrodes only. Detection parameters were optimized for a training set of data and then

kept fixed. The actual evaluation was done in an independent test set of recordings. **Results:** Forty-one seizures (87%) were detected; six seizures (13%) were missed. There were 13 false detections during the evaluation. Sensitivity and positive predictive accuracy are 87 and 75%, respectively. The method is implemented and integrated in a clinical EEG software package (EEMAGINE Medical Imaging Solutions GmbH) within an environment providing a user-friendly interface with predefined analysis protocols, viewing facilities adapted to EEG signals and import facilities for a wide range of EEG data formats. **Conclusions:** We conclude that the performance of the method and its implementation are acceptable for off-line automatic detection of epileptic seizures in scalp EEG. The method is fast and therefore is applicable for on-line implementation. Our aims for the future are further improvement of the performance and on-line implementation of the method. Furthermore, recent results indicate that a slightly modified version of the method may be used to detect preseizure EEG changes. (Disclosure: Salary: M. Dümpelmann is employee at ANT Software and eemagine Medical Imaging Solutions. He receives salary from ANT Software. He was not involved in the evaluation of the method. eemagine Medical Imaging intends to exploit the presented method income.)

1.138
LATERALIZATION OF THE FOCAL HEMISPHERE IN MESIAL TEMPORAL EPILEPSY USING INDEPENDENT COMPONENT ANALYSIS

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Rationale: The EEG can be regarded as a mixture of electrical potentials that originate from distinct sources. Independent component analysis (ICA) is a recently developed method that allows decomposition of multivariate signals into their statistically most independent components. This preprocessing step might enhance features that are not available with other methods, by suppressing irrelevant components. We investigated the ability of this technique to improve focus localization in patients with mesial temporal lobe epilepsy (MTLE). **Methods:** We applied ICA on intracranial artifact-free EEG recordings of the seizure-free interval of 18 patients with unilaterial MTLE. Two different ICA algorithms were used to decompose the EEG. Subsequently, the mean phase coherence, a well-established measure of phase synchronization, was calculated for all channel combinations of both the original EEG and the independent components. Focus lateralization was done by comparing the degree of synchronization for the two hemispheres after averaging over time. **Results:** Higher values of the mean phase coherence were found predominantly for the focal hemisphere for both the original EEG and independent components.For a high percentage of patients, it was possible to get a correct lateralization of the focal hemisphere. Although in general, lower values of the mean phase coherence were found for the independent components, still a higher discriminative power for the focal hemisphere was obtained from this method. **Conclusions:** Lower values of the mean phase coherence found for the independent components indicate that ICA allows decrease of linear correlations that are known to increase values of synchronization measures. Furthermore, our results indicate that ICA can be helpful to further improve the capability of the mean phase coherence to lateralize the focal area. (Supported by Deutsche Physikalischegemeinschaft.)

1.139
ACTIVE OBSERVATION PARADIGMS FOR LATERALIZATION AND DETECTION OF IMMINENT SEIZURES IN TEMPORAL LOBE EPILEPSY

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Rationale: Forecasting seizure onset on the basis of analysis of running EEG signals is feasible in temporal lobe epilepsy (TLE). However, earlier work by our group (Lopes da Silva FH, et al. Rhythms of the brain: between randomness and determinism. In: Lehnertz K et al., ed. *Chaos in the brain?* Singapore: World Scientific, 2000:63–76.) has indicated that it might not always be possible to anticipate seizure onset in TLE even when the transition from the interictal to ictal activity proceeds according to the so-called attractor deformation scenario. We investigated whether we could reliably extend the horizon for forecasting seizures by probing for trends in local tissue excitability changes and signal modulation to external inputs in continuously sampled intracranial EEG in TLE. **Methods:** Informed consent was obtained from four pharamacoresistant TLE patients who were candidates for epilepsy surgery undergoing video/SEEG seizure monitoring for lateralization of ictal onset. A paired-pulse paradigm involving biphasic electrical stimulation and registration from adjacent intracerebral contacts in the pes hippocampi in either temporal lobe was carried out to determine local changes in tissue excitability over time. Patients received three paired pulses per minute, with interpulse intervals varying between 20 and 500 ms and current intensities between 0.5 and 1 mA for $\leq$12 h per recording session. Furthermore, 5-s trains of biphasic stimulation having a frequency and intensity related to the interstimulus distance of the paired-pulse paradigm were administered on the same contacts during the same sessions in addition to the paired-pulse paradigm in two of these patients. Amplitude ratios of the paired-pulse evoked responses and carrier signal modulation by tetanic stimulation were compared for purposes of seizure onset lateralization as well as for attempting to forecast seizure onset. **Results:** Correctly lateralizing interictal state paired-pulse suppression response in hippocampal signals was obtained in three patients but was bilaterally absent in the fourth one. When present, preictal loss of paired-pulse suppression response reliably coincided with extended periods of time when epileptic seizures did occur. Carrier signal modulation was more affected for signals obtained from the hippocampus of ictal onset than from the one in the other hemisphere in both patients tested with this active probing paradigm. **Conclusions:** Active probing for loss of carrier signal modulation in intracranial EEG signals correctly lateralizes the hippocampus of ictal onset in the interictal period. Measurement by the paired-pulse paradigm of changes in local tissue excitability thought to result from failure of local inhibitory factors leading to an ictal event may extend the horizon for reliable seizure forecasting in TLE patients. Reliable forecasting of seizures in such patients will ultimately lead to efficient closed-loop counterstimulation paradigms and effective seizure control. (Supported by SEIN Scientific Research, Heemstede, The Netherlands. The authors express their gratitude to the patients who consented to participate in this study and to the neurosurgeons of the *Dutch Collaborative Epilepsy Surgery Program* for implanting the intracranial electrodes used.)

1.140
EVIDENCE FOR SELF-ORGANIZED CRITICALITY IN HUMAN EPILEPTIC HIPPOCAMPUS

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Rationale: The neuronal mechanisms responsible for interictal epileptiform discharges are not well understood. Recently model networks of integrate-and-fire (IF0) neurons have been shown to exhibit self-organized criticality (SOC) (1,2), which describes the behavior of complex dynamical systems that evolve to a critical state from which large energy fluctuations can occur. **Methods:** We analyzed data from seven consecutive patients with mesial temporal lobe epilepsy who required monitoring with temporal lobe depth electrodes during evaluation for

epilepsy surgery. The patients had six-contact depth electrodes placed stereotaxically within each mesial temporal lobe. All intracranial electroencephalogram recordings (iEEG) were visually reviewed by an epileptologist to identify the seizure-onset zone. Continuous iEEG were collected using a digital, 64-channel, 12-bit Nicolet BMS-5000 epilepsy monitoring system. The referentially recorded iEEG was digitized with a 200-Hz sampling rate and bandpass filter of 0.1–100 Hz. The probability densities of interictal energy fluctuations within the seizure-onset zone were determined. **Results:** For the seven patients evaluated, the probability densities of anomalous large energy fluctuations in the ictal-onset zone on interictal iEEG were found to scale as $(\text{energy})^{-\delta}$, and the quiescent time between epileptiform energy fluctuations scaled as $(\delta t)^{-\gamma}$. Here δ and γ are patient-specific scaling constants that are determined by fitting the experimental data. The scaling relations were not found outside the ictal-onset zone. **Conclusions:** We demonstrate the primary features of SOC in the iEEG of seven patients with temporal lobe epilepsy. These findings in human temporal lobe epilepsy provide new insight into possible mechanisms underlying interictal epileptiform discharges and provide a connection to (IFO) network models. The results may also have utility in understanding the network mechanisms involved in seizure generation, and provide insight into how local electrical stimulation can prevent seizures. [Supported by a Mayo Foundation Scholar grant from the Mayo Clinic Foundation (G.A.W.). Dr. Cranstoun is funded by a National Science Foundation Graduate Research Fellowship and NIH grant T32-GM07517. Dr. Litt's research is funded by The Whitaker Foundation, The American Epilepsy Society, The Dana Foundation and National Institutes of Health grants RO1NS041811-01 and MH-62298RO1.]

1.141
EFFECTS OF ANTERIOR THALAMUS STIMULATION ON MOTOR CORTEX EXCITABILITY IN EPILEPSY

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Rationale: Many patients with medically intractable epilepsy are not candidates for traditional resective or transective surgeries. The anterior thalamus projects to medial frontal areas and may be involved in propagation of seizures. This thalamic involvement led to the use of DBS in the anterior thalamus in an attempt to abolish seizure propagation. Some patients had improved seizure control with anterior thalamic DBS. Antiepileptic drugs (AEDs) are known to change excitatory and inhibitory circuits in the motor cortex. The effects of anterior thalamic stimulation on motor cortex excitability is not known. The aim of the study is to examine motor cortex excitability in patients who have bilateral deep-brain stimulation (DBS) electrodes in the anterior thalamus for treatment of intractable epilepsy. **Methods:** Three patients [33 years (F), 48 years (F), 43 years (M)] with bilateral anterior thalamus DBS were studied. Three conditions were tested: stimulator switched off (Off state), continuous stimulation (Continuous state), and cycling stimulation (1 min on, 5 min off; Cycling state). Each state was tested in separate days in random order. The stimulator frequency was 100 Hz, and pulse width was 90?s. Transcranial magnetic stimulation (TMS) was applied over the hand area of left motor cortex, and electromyography (EMG) was recorded from the first dorsal interosseous muscle. The muscle was either at rest (Rest state) or active to 10% of its maximum (Active state). The Rest and Active motor thresholds were determined. Silent Period (SP) (duration of EMG suppression after TMS) was determined using suprathreshold single pulses during the Active state. Paired-pulse paradigms used to measure cortical facilitation and inhibition were short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), and long-interval intracortical inhibition (LICI). For SICI, a subthreshold conditioning pulse preceded the test pulse by 2 ms. For ICF, an interstimulus interval (ISI) of 10 ms was used. For LICI, suprathreshold conditioning and test pulses at ISIs of 50–200 ms were used. **Results:** Rest and Active motor thresholds and SP duration were significantly higher in patients than in controls for all three stimulator settings. Rest SICI was significantly reduced in the Continuous state compared with normal controls. Active SICI was significantly reduced in the Continuous and Cycling states compared with controls. Patients had reduced Rest ICF. Rest LICI at ISI of 50 ms was significantly reduced in patients. Patients had significantly increased Rest LICI (ISI 200) compared with normal controls. There were no differences among the three stimulator settings for motor threshold, SP, ICF, and LICI. **Conclusions:** These preliminary results suggest that anterior thalamic DBS may change some motor cortical circuits. Other changes in motor cortex excitability may be a result of the underlying disease or antiepileptic medications because DBS settings had no effect. At the end of this activity the participants should be able to discuss the effects of anterior thalamic stimulation on cortical excitability in patients with epilepsy. [Supported by Canadian Institutes of Health Research (G.F.M., R.C.), Canada Foundation for Innovation, Ontario Innovation Trust (R.C.), University Health Network Krembil Family Chair in Neurology (R.C.).] (Disclosure: Consulting: Drs. Lozano and Wennberg are consultants for Medtronic, Inc.)

1.142
MOTOR CORTEX EXCITABILITY CHANGES IN UNTREATED PATIENTS WITH EPILEPSY BEFORE AND AFTER SLEEP DEPRIVATION

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Rationale: Sleep deprivation (SD) before recording is a well-known method of activation of epileptic discharges. However, its physiologic mechanism is still not clear and might be connected with the changes of cortical excitability. Transcranial magnetic stimulation (TMS) can give information about the level of cortical excitability and inhibition. The aim of the study was to assess the influence of SD on the cortex motor threshold (MT) and cortical silent period (CSP) evoked by TMS in untreated patients with epilepsy. **Methods:** We studied seven patients (aged 17–39; five men, two women) with a history of at least two seizures. None of them had taken antiepileptic drugs (AEDs). TMS was performed using Magstim model 200. MT and CSP were estimated by applying single-pulse technique. The values of MT and CSP were assessed before and after sleep deprivation. The MT measures were compared with 30 normal control subjects. In all patients, routine EEG and EEG after SD immediately before TMS was performed. **Results:** Routine EEG examination revealed changes in six patients: bilateral groups of theta waves in frontotemporal or occipitotemporal areas in five patients with sharp waves in one case, and generalized spike–wave discharges in one patient. After SD in EEGs of two patients, focal sharp waves appeared, and in two other patients, the enhancement of preexisting discharges were observed. The mean MT values for the left and right hemisphere before SD (mean, 45.8 ± 8.8) and after SD (mean, 46.6 ± 10.3) did not change significantly ($p = 0.875$), and there were no significant differences in mean MT values in the epileptic group before and after SD compared with healthy controls (mean, 47.15; $p = 0.59$) The mean CSP duration increased after SD from 181.5 to 190.2 ms, but this difference was not significant ($p = 0.432$). Prolonged CSPs were found in all patients with activation of epileptic discharges after SD. **Conclusions:** In untreated epilepsy patients, MTs and CSPs values established with TMS did not change significantly after SD. However, CSPs duration were increased especially in patients with activation after SD. These preliminary observations should be confirmed in larger series and in relation to the specific epileptic syndrome. (Supported by National Committee of Research.)

1.143

LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR TREATMENT OF DRUG-RESISTANT EPILEPSY: INTERIM ANALYSIS OF A PLACEBO-CONTROLLED MULTICENTER STUDY

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Rationale: Low-frequency repetitive transcranial magnetic stimulation (rTMS) is known to induce long-lasting depression of cortical excitability. A previous open pilot study showed that low-frequency rTMS treatment can reduce seizure frequency in drug-resistant epilepsy patients (Tergau et al. *Lancet* 1999;353:2209). Currently we are performing a multicenter study to prove the antiepileptic efficacy of rTMS in a placebo-controlled single-blinded design. Results of an interim analysis are presented here. **Methods:** So far, 19 patients with drug-resistant epilepsy syndromes with on average at least two seizures per week were included, five patients dropped out, and nine patients finished the study. rTMS treatment consisted of 5 consecutive days with daily application of 1,000 pulses, 100% motor threshold intensity, using a Dantec MagPro magnetic stimulator with a round coil placed over the vertex. In each patient, we performed three different types of stimulation in randomized order: 0.3 Hz, 1.0 Hz, and as sham stimulation, 0.6 Hz. For sham stimulation, we used a special coil with ineffective magnetic output. Seizure frequency was recorded in diaries 4 weeks before and after stimulation. There was a minimum of 8 weeks between two treatment phases. **Results:** Overall results for periods of 4 weeks before and after rTMS showed a reduction in seizure frequency by on average 24.3 ± 24.7% and 38.0 ± 24.6% for 1 Hz and 0.3 Hz, respectively, whereas sham stimulation showed reduction only by 8.4 ± 26%. The effect was significant for 0.3 Hz versus Sham ($p = 0.037$) but failed significance for 1.0 Hz ($p = 0.333$). One patient did not respond to rTMS at all and showed increase by 20% after 1 Hz. In four patients, 0.3 Hz was superior to 1 Hz, whereas the reverse was true in two patients. Two patients did not show a difference between 0.3 and 1 Hz. The effect lasted for 1–4 weeks. In none of the subjects were side effects observed. **Conclusions:** The interim analysis apparently confirms the results of the pilot study and demonstrates the antiepileptic therapeutic potential of low-frequency rTMS in severe epilepsy syndromes; 0.3 Hz seems to be superior to 1 Hz, although there may be an interindividual difference in the optimal rTMS frequency. (Supported by Medtronic/Dantec Company, Duesseldorf, Germany.) (Disclosure: Materials: Magnetic Stimulators were provided by the Dantec-Medtronic Company, Duesseldorf, Germany; Royalties: Magnetic stimulators were provided by the Dantec-Medtronic Company, Duesseldorf, Germany.)

1.144

AN INTENSIVE CARE SYSTEM FOR CONTINUOUS NEUROPHYSIOLOGIC MONITORING WITH WEB-BASED REVIEW AND WIRELESS SIGNALING OF CHANGES IN CENTRAL NERVOUS SYSTEM FUNCTION

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Rationale: Patients admitted to the neurointensive care unit (NICU) are frequently postoperative neurosurgical or head trauma cases. Others commonly admitted to the NICU are patients in status epilepticus (SE). Patients may be in coma as a result of a complex combination of insults, or may have been rendered unconscious by the treatment (e.g., barbiturate coma to treat SE). An especially important parameter to follow in postoperative as well as SE patients is the level of anesthesia, as manifest by a burst-suppression EEG pattern. We developed a flexible research tool to study the feasibility and clinical usefulness of continuously recorded and processed neurophysiologic data in acutely ill patients at risk for, or undergoing treatment for, epileptic seizures and stroke. **Methods:** We have developed a NICU monitoring system that continuously applies a battery of EEG and evoked potential tests, selected and programmed by the physician. Routine physiologic parameters are also periodically obtained electronically from the bedside monitors. For each timed EEG epoch recording, the power spectral density is estimated from the averaged periodogram (squared Fourier spectrum). Power in the traditional EEG bands is calculated for each of the electrode derivations, typically eight channels. For each electrode, a count of the number of bursts is performed. The first step in the burst-detection algorithm is removal of baseline drift. Next, a 700-ms window is moved across the data in steps overlapping by 100 ms. Power in each window, computed from the average sum of squares of the sample voltages, is compared with the power in the preceding window. If the energy has increased more than sevenfold, the event is counted as a burst. Successive bursts must be separated by a nonburst interval of ≥100 ms. Trends are displayed continuously at the bedside and can also be accessed via the Worldwide Web (with appropriate security). Remote access to the main menu and control protocol is via simple HTML pages, and trend results are generated at the moment of access by CGI scripts written in Tcl/Tk. Because the monitoring system is connected to the network, automatic e-mail can be sent to the neurophysiologist attending to the patient, prompted by thresholds that have been exceeded or by error conditions. At our institution, the e-mail facility can also be used to automatically send a message to the physician's pager. The system has been initially tested by collecting data from one normal subject, and for a mean of 12 h in seven comatose NICU patients chosen because changes in their condition were anticipated. **Results:** The system was not hampered by the electrical noise in the NICU; however, detachment of electrodes was a frequent problem. Detection, processing, archiving, and display was activated by the technologists, and pager notifications were generated when changes occurred. **Conclusions:** Recording and processing of multimodality clinical neurophysiologic signals over extended periods have been successfully carried out. Identification of both normal and abnormal waveforms is satisfactory in our system, provided that the electrodes remain attached. The system can potentially detect changes in NICU patients as they occur. (Supported by CCF.)

1.145

PROPAGATION PATTERNS OF OCCIPITAL SEIZURES RECORDED SUBDURALLY

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Rationale: Based on EEG-video documentation of pentylenetetrazole-induced seizures in epilepsy patients, Ajmone Marsan and Ralston (1957) postulated that occipitally originating seizures could propagate either in a suprasylvian or infrasylvian direction, determined largely by origin above or below the calcarine fissure. We thus analyzed occipital seizure-propagation patterns. As clinical manifestations of occipitally originating seizures may reflect the propagated site, such documentation may have significant clinical implications. **Methods:** We visually analyzed subdurally recorded occipitally originating seizure-propagation characteristics among 16 patients undergoing bilateral subdural electrode coverage of the occipital, temporal, and parietal lobes. **Results:** All seizures propagated. Propagation direction did not correlate with seizure origin within the occipital lobe (mesial vs. lateral; supracalcarine vs. infracalcarine). Seizures propagated to both suprasylvian and infrasylvian regions in 10 patients, to infrasylvian only (temporal lobe) in six patients; exclusively suprasylvian spread never occurred. Seizures spread bilaterally in 10 patients, ipsilaterally in only six, but never only contralaterally. Seizures propagated within 5 s of origin in 12 patients and >5 s in four. **Conclusions:** Propagation to other lobes was a consistent feature of occipitally originating seizures. However, direction of propagation did not reflect the intraoccipital origin. Early propagation and contralateral propagation were common features. (Supported by Research Office, Faculty of Medicine and Dentistry, The University of Western Ontario, London, Ontario, Canada.)

1.146

THE IMPACT OF NEUROLOGIC PROGNOSTICATION BY CLINICAL EXAMINATION, EEG, AND CORTICAL EVOKED POTENTIALS ON WITHDRAWAL OF LIFE-SUSTAINING THERAPIES IN PATIENTS RESUSCITATED FROM CARDIAC ARREST

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Rationale: Neurologic prognostication in patients resuscitated from cardiac arrest (CA) is commonly sought by intensive care unit (ICU) physicians. We studied the impact of neurologic prognostication by clinical examination, cortical evoked potentials (CEPs), and EEG on the decision by ICU physicians and patients' families on the withdrawal of life-sustaining therapies (WLST) in patients after CA. **Methods:** All patients who were resuscitated from CA and referred for neurologic consultation at the Johns Hopkins Bayview Medical Center for a period of 3 years were included in the study. Serial evaluation by clinical examinations and Glasgow Coma Score (GCS) was undertaken. EEG and CEPs were performed during the first 72-h period after CA and prospectively graded as benign, uncertain, and malignant based on established protocols. Neurologic prognostication based on the clinical evaluation and tests was given to the ICU team. The desicion to WLST was made by the patient's family with the help of the ICU team. Clinical outcomes include alive at discharge (group A), brain or cardiac death (group D), and death from WLST (group W). Group W was further divided into subgroups by EEG/CEP grades and clinical condition at the time of WLST. The duration from EEG/CEP testing to WLST was compared between subgroups. **Results:** Forty-six patients were included in the study. Group A had seven (15%), group D had seven (15%), and group W had 32 (70%) patients. No significant difference in age range and place of CA was noted. For all groups, benign EEG was noted in 85% of A, none of D, and 18% of W. Benign CEPs were noted in 85% of A, 66% of D, and 42% of W. Focusing on the subgroups of group W and time from CEP/EEG testing to WLST, those with benign CEPs were provided aggressive life support and observed for 10.5 ± 2 days; those with uncertain CEPs were observed for 3.1 ± 1 days, and those with malignant CEPs had 1.1 ± 0.3 days to WLST. Good-grade CEPs correlated strongly with longer period of aggressive support and clinical observation to WLST (Spearman coefficient, 0.80; $p < 0.001$). EEG grade did not correlate with the period of observation to WLST. GCS (range, 3–4) was not significantly different for the subgroups of W immediately before the time of WLST. **Conclusions:** Neurologic prognostication based on grades of CEPs significantly correlated with the duration of observation before WLST. A benign CEP correlated with more days of aggressive support by the ICU team and families before deciding on WLST. Low GCS noted immediately before WLST may have also influenced the decision to WLST. [Supported in part (R.G.G.) by the Corporate Roundtable Clinical Research Training Fellowship Award of the American Academy of Neurology-Educational and Research Foundation.]

1.147

CLINICAL RELEVANCE OF TEMPORAL NEOCORTICAL PATHOLOGY IN TEMPORAL LOBE EPILEPSY

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Rationale: Pathological findings in temporal neocortex have not been extensively investigated in comparison with those of medial structures of the temporal lobe. The objective of this study was to investigate the clinical, imaging, electrophysiologic, and pathological findings and to determine the surgical strategy in the patients who showed positive findings in the neocortex of temporal lobectomy specimen **Methods:** We selected 90 patients who showed "epileptic pathology" from a cohort of >250 cases of temporal lobectomy performed between 1992 and 2000. Patients with brain tumor and vascular lesions were excluded. All the patients underwent temporal lobectomy after thorough evaluation according to preoperative investigation protocol. All the patients were followed up >12 months. Seizure outcome was classified according to Engel's classification. **Results:** Pathological examination showed epileptic tumor in six, Taylor-type cortical dysplasia (CD) in six, and occult CD in 78. However, hippocampal sclerosis (HS) was combined in 59 cases (66%). History revealed febrile convulsion in 21 (20%). Aura was revealed in 36 (40%), and the most common form was psychic aura (20%). Sixty-three patients (70%) showed the temporal lobe seizure patterns. Standard EEG showed unitemporal epileptiform disturbances in 41, bitemporal in 30, and multilobar abnormalities in 18. MRI findings were negative in eight, unilateral hippocampal atrophy (HA)/sclerosis in 44, bilateral HA/HS in 12, CD in seven, tumors in six, and others. Seizure outcome was graded as class 1 in 61 (69%), class 2 in nine (10%), class 3 in 10 (11%), and class 4 in nine (10%). **Conclusions:** CD was the most common finding in temporal neocortex in this study. HS was frequently associated with CD. These findings suggest that CD may contribute to the genesis and expression of temporal lobe epilepsy. (Supported by Honam Medical Center.)

1.148

UTILITY OF EEG IN ALZHEIMER DEMENTIA

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Rationale: Individuals with Alzheimer disease (AD) have an increased risk for seizures or epilepsy. Whereas tonic clonic and myoclonic seizures are identifiable in this group, complex partial seizures can be difficult to identify. Reactive seizures and other disorders may complicate the diagnosis. The objective of this study was to determine the utility of the EEG in identifying epileptiform activity or seizures in AD subjects suspected of having seizures. **Methods:** We reviewed the records of patients from the Epilepsy and Dementia Centers of Medical College of Pennsylvania Hospital to identify subjects with a diagnosis of dementia and who had an EEG between January 2000 and December 2001. Seventy-six patients met the selection criteria. Of these, only patients with probable AD, according to National Institute of Neurological and Communicative Disorders and Stroke/AD and Related Disorders Association criteria, were selected for the study. Subjects with strokes, structural lesions, epilepsy preceding dementia, and with reversible causes of dementia were excluded. Of the original 76 patients, only 11 remained after applying these exclusion criteria, and they formed the study cohort. Subjects were classified as having epilepsy, single seizure, possible seizure, or unlikely seizure. EEG findings were divided into normal, focal slowing, generalized slowing, focal spikes, or sharp waves. Subjects were divided into three groups depending on their Mini Mental State Examination (MMSE) scores: 20–30, 10–19, and <10. **Results:** The age range of the cohort was 60–91 years (mean, 73.4 years). Six of the subjects were women. EEGs were obtained in five subjects as part of the routine workup of dementia, and in six subjects to exclude seizures. Seven subjects had at least one EEG, two subjects had two, one subject had five, and one had a total of six EEGs. Of the 11 subjects, none was found to have epilepsy, one had a definite seizure (9.1%), one had a probable seizure (9.1%), and nine subjects were classified as unlikely to have had seizures (81.8%). Six of the 11subjects had normal EEGs (54.5%). Five had generalized slowing (45.4%), three had focal slowing (27.2%), two had focal sharp waves (18.1%), and none had focal spikes. Four subjects (36.3%) had MMSE scores between 20 and 30, 5 (45.4%) had MMSE scores between 10 and 19, and two (18.1%) had MMSE scores >10. The EEG was normal in all subjects with MMSE scores >20. Of the five with MMSE scores of 10–19, two (40%) had normal EEGs, three (60%) had focal and generalized slowing, and two (40%) also had sharp waves. The two subjects with sharp waves were those classified earlier as having definite and probable seizure, respectively. Both subjects with MMSE scores <10 had generalized slowing. **Conclusions:** Because we rigorously excluded patients with structural lesions and strokes, including lacunar infarcts, to study individuals with pure AD, our cohort sample size was relatively small. In our study, the incidence of epileptiform abnormalities in EEGs of patients with AD was 18%. This incidence is

higher than the incidence of epileptiform abnormalities seen in the general or in the geriatric population. This study also suggests that there may be a correlation between lower MMSE scores and slowing on the EEG. Our study shows that EEG is a useful tool in the evaluation of patients with AD.

1.149

INTRACRANIAL EEG IN TEMPORAL LOBE EPILEPSY: SPATIAL EXTENT OF SEIZURE ONSET IS RELATED TO DEGREE OF HIPPOCAMPAL PATHOLOGY

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Rationale: Faster frequency initial ictal discharges (IIDs) in scalp EEG correlate both with greater degrees of hippocampal pathology and with hippocampal seizure onsets in temporal lobe epilepsy (TLE) (Vossler et al. *Ann Neurol* 1998;43:756–62; Ebersole, Pacia. *Epilepsia* 1996;37:386–99). The goal of this study was to determine whether the site of seizure onset within the TL correlates with hippocampal pathology. After this presentation, participants should be able to discuss how hippocampal pathology may influence site of seizure onset in the temporal lobe. **Methods:** All consecutive patients with no hippocampal atrophy (HA) on magnetic resonance imaging (MRI) who had scalp EEG-video evidence of TLE (nonlesional TLE) were prospectively studied with intracranial electrodes to determine spatial extent of the IID in a protocol beginning in 1996. Twenty-six patients with either no HA, or slight HA (<3 SD below normal hippocampal absolute volumes and asymmetry index) were included. Twenty-three had longitudinal hippocampal depth electrodes and orbitofrontal and temporal subdural strip electrodes. Three had only strip electrodes for technical reasons. Three other patients with significant HA who required depth and strip electrodes for clinical purposes served as a comparison group. Electrode placement was verified using intraoperative x-ray or postoperative MRI. Hippocampal pathology was assessed by measurement of HA and by histopathologic grade of hippocampal sclerosis (HS). **Results:** A total of 29 patients was investigated. Twenty-three patients with depth electrodes had no, or mild, HA. The ictal EEG onsets in those 23 subjects showed simultaneous onsets in the hippocampus/amygdala, parahippocampal gyrus (PHG), and lateral neocortex in seven cases; IIDs in hippocampus and PHG in six patients; IIDs outside the hippocampus in eight individuals (three in PHG, three in lateral neocortex, and two in both PHG and lateral neocortex); a bilateral diffuse neocortical IID in one subject; and an IID confined to the hippocampus in only one case. The three patients with no depth electrodes and no HA all had IIDs involving the PHG and temporal neocortex simultaneously. The three patients with moderate-marked HA all had IIDs confined to the hippocampus. Moderate-marked HA significantly correlated ($\chi 2$, 18.65; $p = 0.001$; $n = 26$ depth electrode subjects) with IIDs restricted to the hippocampus. Fifteen patients had the degree of HS graded. high grade (3–5) HS also significantly ($\chi 2$, 6.24; $p = 0.012$) correlated with an IID limited to the hippocampus. **Conclusions:** Absence of HA and lower-grade HS both correlate with initial ictal electrographic discharges involving the hippocampus and medial (with or without lateral) temporal cortex or only the medial and/or lateral temporal neocortex. By contrast, substantial HA and high-grade HS both correlate with IIDs confined to the hippocampus/amygdala.

1.150

COMBINED SCALP–THALAMIC ICTAL EEG RECORDINGS IN PATIENTS TREATED WITH DEEP BRAIN STIMULATION FOR EPILEPSY

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Rationale: Deep brain stimulation (DBS) of the centromedian nucleus (CM) or anterior nucleus (AN) of the thalamus has been proposed as a treatment for medically refractory epilepsy. Hypothetically, thalamic stimulation may prevent generalization of seizures through interruption of thalamic recruitment during seizure propagation. Additional long-lasting beneficial changes in thalamocortical network sensitivity could result from prolonged stimulation. To address the extent to which the thalamus is indeed recruited in generalized seizures of presumed cortical onset, we performed combined scalp–thalamic EEG recordings in patients with intractable epilepsy after insertion of DBS electrodes, before internalization of the electrodes and pulse generators. **Methods:** In pilot studies of DBS for epilepsy performed at the Toronto Western Hospital, two patients have been treated with bilateral CM stimulation, and six patients, with bilateral AN stimulation. After implantation, continuous scalp–thalamic EEG recording was performed for 3–4 days before electrode internalization. Three patients had spontaneous seizures recorded: one CM patient with symptomatic generalized epilepsy, one AN patient with multifocal or symptomatic generalized epilepsy, and one AN patient with focal epilepsy and secondarily generalized convulsions. **Results:** One generalized tonic–clonic seizure was recorded in the CM patient: scalp EEG showed generalized low-amplitude slow-wave activity 2 s before clinical onset. Simultaneous CM recording showed, 500 ms before clinical onset, 1.5 s after the first scalp EEG changes, rhythmic ictal activity in the left CM and 1 s later in the right CM, persisting until seizure offset. Six sudden-onset drop attacks progressing to generalized tonic seizures were recorded in the second patient. A subtle generalized attenuation of the scalp background activity just before clinical onset was the only EEG finding: no rhythmic ictal activity was recorded from the scalp or AN electrodes. Thirty-one focal motor seizures with secondary generalization were recorded in the third patient. A generalized alteration in scalp background activity prededed by many seconds the first rhythmic ictal activity recorded from the right AN electrode, ultimately apparent synchronously in the scalp EEG over the right frontoparietal region before bilateral scalp/AN involvement during generalization. Scalp/AN coherence analysis of the right hemispheric ictal activity before generalization showed a 24-ms cortical lead with 98% coherence. **Conclusions:** Scalp–thalamic EEG showed early ictal recruitment of CM in a patient with symptomatic generalized epilepsy and of AN in a patient with focal-onset seizures. Coherence analysis in the latter patient demonstrated a consistent cortical lead to the synchronous scalp/thalamic ictal activity. These findings support the use of thalamic DBS for epilepsy. Unexpectedly, no rhythmic ictal activity was recorded from scalp or thalamic electrodes in a patient with drop attacks and tonic generalization, suggesting that these seizures may be generated below the level of the diencephalon. At the end of this activity, participants should be able to discuss the role of the thalamus in maintenance and propagation of seizures and the rationale for thalamic DBS as a treatment for epilepsy. [Supported by Bloorview Epilepsy Research Program (R.W.).] (Disclosure: Consulting: Drs. Wennberg and Lozano are consultants for Medtronic, Inc.)

Pediatric Epilepsy—Clinical

1.151

THE EFFECT OF LAMOTRIGINE ON EEG OF REFRACTORY PEDIATRIC EPILEPSIES

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Rationale: The objective of this study was to examine the effect of lamotrigine (LTG) therapy on epileptiform EEG patterns in children with refractory epilepsies. By the end of this presentation, the participants should be able to discuss the relation between LTG therapy and EEG abnormalities. **Methods:** Charts of 860 patients with epilepsy seen in Division of Epilepsy and Clinical Neurophysiology at Boston Children's Hospital between 1997 and 2000 were retrospectively reviewed. Only patients who had taken LTG during this period and had

≥2 years of follow-up after the commencement of LTG were included. Charts were reviewed for age at onset, seizure type, frequency, underlying possible etiology, neuroimaging studies, clinical response, side effects after starting LTG, concomitant AEDs, and other modes of therapy [vagal nerve stimulation (VNS), ketogenic diet, epilepsy surgery]. EEGs were examined for background activity (i.e., frequency of the reactive posterior rhythm), interictal epileptiform discharges (i.e., frequency and localization of spikes, sharp waves, and spike–waves). All the relevant demographic and clinical data during the two-year follow-up period were entered into a database and subsequently analyzed. **Results:** LTG was prescribed in 77 patients during the period studied; in 30 of these patients, EEGs before and after LTG were available for review (mean age, 11.9 years, with a range of 4 months to 25 years; mean age at seizure onset, 3.4 years, with a range of 1 month to 10 years). All patients had severe pharmacoresistant epilepsy. Mixed types of seizures were seen in 65%; generalized seizures in 23.8%; and complex partial seizures in 10.3% of the patients. Before LTG therapy, the baseline EEG was abnormal because of slow background activity in 17.2%; localized spikes or sharp waves in 27.5%; generalized spikes, sharp waves, or spike–waves in 24.1%, or both generalized and local epileptiform activity in 48.2%. EEG analysis during the 2 years of follow-up after starting LTG demonstrated improvement in the background pattern in 18.8% and increased background slowing in 2.2% of the patients. There was improvement in the interictal epileptiform pattern in 30% of the patients, with either elimination or reduction of spikes, sharp waves, or spike–waves, whereas interictal EEG spikes or sharp waves were increased or became generalized in 6.8% of the patients. To better understand the short-term effects of LTG on the EEG, we examined changes in the EEGs in a subset of patients who had repeated studies performed within 3 months of LTG initial therapy. In the first 3 months after LTG therapy, none of the patients showed a worsening pattern in background or epileptiform activity, whereas improvement was noted in 28.5%. During the 2-year follow-up period, 52% of the patients had a >50% reduction in seizures; 24% had a <50% reduction, and 24 % had no change in seizure frequency. Exacerbation of seizures did not occur in any patients. **Conclusions:** In this group of highly refractory pediatric patients with epilepsy, LTG therapy resulted in parallel improvements in interictal EEG background patterns and epileptiform activity and seizure control. Furthermore, our findings suggest that LTG does not acutely exacerbate EEG abnormalities. [Supported by a grant from Glaxo-Smith-Kline Pharmaceutical and a grant to G.L.H. from NINDS (NS27984).]

1.152
VAGAL NERVE STIMULATION IN YOUNG CHILDREN: PREDICTORS OF A RAPID RESPONSE

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Rationale: Whereas the anticonvulsant effect of intermittent vagal nerve stimulation (VNS) generally increases over time, a subset of children responds relatively rapidly. At the end of this activity, participants should be able to discuss factors that predict early success in the use of VNS in children. **Methods:** Ninety-two children (45 boys; 47 girls; average age at surgery, 10.2 ± 4.6 years; range, 2–20 years) were followed up for ≥24 months after VNS implantation. Ten children had Lennox–Gastaut syndrome, 33 had cryptogenic seizures, 48 had symptomatic seizures, and one had primary generalized seizures. VNS-stimulation parameters were adjusted according a standardized protocol. Seizure counts, as reported by the family, were recorded before surgery and at each follow-up visit. Patients were considered early responders if they had a sustained decrease in their seizure frequency of ≥75% by the 3-month visit. **Results:** The overall decrease in seizure frequency was 68 ± 30% at 12 months and 76 ± 29% at 18 months. Forty-six patients (50%) were classified as early responders. These patients were more likely to have a normal magnetic resonance imaging (MRI; 52 vs. 33%), were more likely to have a cryptogenic form of epilepsy (41 vs. 30%), and were less likely to have a symptomatic form of epilepsy (46 vs. 57%). There was no difference between the groups with respect to gender, age at onset of epilepsy, duration of epilepsy, or number of anticonvulsants (AEDs) used before VNS implantation. **Conclusions:** VNS is an efficacious anticonvulsant strategy for children, including young children, with a variety of types of epilepsy. Its efficacy is at least equal to that of currently available medications. Children with cryptogenic epilepsy with a normal MRI are more likely to respond rapidly to VNS therapy. (Disclosure: Honoraria: Cyberonics, Inc.)

1.153
ZONISAMIDE IN THE TREATMENT OF MYOCLONIC ASTATIC EPILEPSY (DOOSE SYNDROME)

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Rationale: To assess in an open pilot study the efficacy of zonisamide (ZNS) in the treatment of myoclonic astatic epilepsy (MAE), a syndrome that is relatively refractory to antiepileptic drugs (AEDs). **Methods:** Four consecutive patients were enrolled who met criteria for MAE and were treated with ZNS because they had not become seizure free with three to nine previous AEDs. **Results:** Patient 1: Age at onset of afebrile seizures, 5.5 years. Persistent myoclonic and astatic seizures despite treatment with valproate (VPA), clonazepam, and ethosuximide. VPA caused encephalopathy with generalized delta slowing on EEG. Lamotrigine (LTG) markedly reduced generalized tonic–clonic seizures (GTCSs). Age at introduction of ZNS, 6.1 years. ZNS ineffective. Subsequently no response to topiramate (TPM). Levetiracetam (LEV) reduced myoclonic and astatic seizures by ~50%. No astatic seizure for 2 months since vagus nerve stimulator (VNS) implant. Patient 2: Age at onset of afebrile seizures 4 years. Persistent GTCSs despite treatment with nine AEDs including VPA, LTG, TPM, and LEV. Methsuximide markedly reduced myoclonic and astatic seizures. Age at introduction of ZNS, 10 4/12 years. ZNS reduced GTCSs seizures by >50%. Patient scheduled for VNS implant. Patient 3: Age at onset of afebrile seizures, 2 5/12 years. Persistent GTCSs and astatic seizures despite treatment with VPA, TPM, and LTG. VPA caused encephalopathy with generalized delta slowing on EEG. Age at introduction of ZNS, 3 7/12 years. After introduction of ZNS, astatic seizures subsided within 1 day, GTCSs within 12 days. Patient now seizure free for 15 months. Patient 4: Age at onset of afebrile seizures, 3.5 years. Persistent daily astatic seizures despite treatment with PHT, VPA, lorazepam, and TPM. VPA caused encephalopathy with generalized delta slowing on EEG. TPM controlled the GTCSs. Age at introduction of ZNS, 4 years. After the introduction of ZNS, gradual reduction and then cessation of astatic seizures after 2.5 months. Patient now free of astatic seizures for 11 months. On monotherapy with ZNS for past 5 months. Two GTCSs during a febrile episode. **Conclusions:** Two of four consecutive patients with MAE and persistent myoclonic astatic and/or GTCSs refractory to three to nine AED trials became seizure free soon after the introduction of ZNS, and the most refractory of the four patients (nine AEDs) had a >50% reduction in GTCSs. The two patients who became seizure free were younger at the time of seizure onset (2 5/12 and 3.5 vs. 4 and 5.5 years) and of ZNS treatment (3 7/12 and 4 vs. 6 1/12 and 10 4/12 years). These results suggest selective efficacy of ZNS in this generally refractory syndrome. These results warrant further study of ZNS in the treatment of MAE. Three of these four patients with MAE developed an encephalopathic reaction to VPA. (Disclosure: Grant: Elan, Novartis, Ortho McNeil, Pfizer, UCB Pharma; Consulting: Abbott, Elan, Glaxo Wellcome, Novartis, Ortho McNeil, Pfiaer, Schwarz Pharma, Shire, UCB Pharma; Honoraria: Elan, Glaxo, Novartis, Ortho McNeil, Pfizer, UCB Pharma.)

1.154
NEUROPSYCHIATRIC COMPLICATIONS OF LEVETIRACETAM IN CHILDREN WITH EPILEPSY

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Rationale: To investigate the safety of levitiracetam (LEV) in children with epilepsy. At the end of this presentation participants should be able to identify children with comorbid conditions who would not be good candidates for treatment with LEV. **Methods:** We reviewed charts to identify children with epilepsy taking LEV. **Results:** Of 22 children, eight were taking LEV monotherapy. The rest were taking a combination therapy (zonisamide, divalproex sodium, topiramate, lamotrigine, clonazepam, oxcarbazepine, carbamazepine, phenytoin and ketogenic diet). Only four were taking three or more antiepileptic drugs (AEDs). The mean age was 12.5 years (SD, 4.2); range, 4–19 years. Eleven were boys, and 11 were girls. Thirteen had partial seizures, eight generalized seizures, and one benign rolandic epilepsy; 73% had attention deficit hyperactivity disorder (ADHD), developmental delay, cerebral palsy, mental retardation, learning disabilities, or oppositional defiant disorder. Mean dosage was 35 mg/kg/day (SD, 13); range, 11–55. Duration of treatment was 1 week to 25 months; mean, 9.8 (SD, 8.6); 68% had behavioral side effects including aggressive behavior, suicidal ideations, and depression, which required stopping the drug; 80% of them had prior psychiatric symptoms. Even in the absence of neuropsychiatric disorders, 50% of the children with epilepsy taking LEV developed behavioral changes.All abnormalities were reversible. **Conclusions:** LEV is associated with high incidence of psychiatric symptoms in children with epilepsy. Preselection of children to avoid comorbid neuropsychiatric disorders is important to the safe use of this drug.

1.155
OXCARBAZEPINE THERAPY OF EPILEPSY IN TUBEROUS SCLEROSIS

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Rationale: At the end of this activity, participants will be aware of the use of oxcarbazepine (OCBZ) for epilepsy in tuberous sclerosis patients. OCBZ is a novel anticonvulsant (AED) for partial epilepsy. It has a lower incidence of cognitive side effects than its parent compound carbamazepine (CBZ). Its primary side effect relates to the idiosyncratic development of hyponatremia, which is increased in individuals with preexisting renal disease. We present our clinical experience with the treatment of epilepsy in 28 individuals with tuberous sclerosis using OCBZ. **Methods:** The study group consisted of 15 men and 13 women. Genotype data were available for 16 patients; 15 had TSC 2 mutations, and one had TSC 1 mutation. OCBZ was instituted at 10 mg/kg/day divided b.i.d to t.i.d. Dose was escalated by 5–10 mg/kg at 3- to 7-day intervals until either seizure control was noted, clinical toxicity occurred, or dosage of 60 mg/kg/day was achieved without significant reduction in seizures. Patients who experienced a significant (>50%) reduction in seizures continued titration until optimal efficacy was achieved regardless of mg/kg dose. Monitoring included periodic determination of renal profile, hepatic profile, and complete blood count and differential. **Results:** Ten (36%) patients became seizure free, six (21%) experienced a >50% reduction (total responders, 16). Twelve (43%) did not respond, meaning a <50% reduction in seizure frequency. OCBZ was discontinued in one patient because of cognitive slowing greater than that previously noted with CBZ. Otherwise no clinically significant side effects or hyponatremia were noted. No clinically relevant laboratory abnormalities were noted. No individuals experienced an exacerbation of seizures. Responders and nonresponders did not vary significantly with regard to average tuber counts (13 vs. 14), autism (five vs. three), or history of infantile spasms (five in each group). However, eight responders had normal intelligence compared with two nonresponders. **Conclusions:** We conclude that OCBZ is a useful agent for the treatment of partial epilepsy associated with tuberous sclerosis, although apparently less effective than lamotrigine based on our previously published trial (Franz DN, et al. Lamotrigine therapy of epilepsy in tuberous sclerosis. *Epilepsia* 2001;42:935–40.) Its lower incidence of cognitive side effects and suitability for rapid dose escalation are valuable in this patient population. (Supported by Novartis Pharmaceuticals.) (Disclosure: Honoraria: Novartis Pharmaceuticals; Other: financial support for abstract preparation, Novartis Pharmaceuticals.)

1.156
USE OF LEVETIRACETAM (LEV) IN CHILDREN YOUNGER THAN 2 YEARS

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Rationale: Levetiracetam (LEV) was approved for use in patients aged 16 years and older as an adjunctive treatment for partial-onset seizures and launched in the United States in April 2000. Since then there has been little information regarding its use in children, particularly young children. The objective of this study is to better understand the use of LEV in children younger than 2 years. **Methods:** We reviewed our use of LEV in children younger than 2 years at Minnesota Epilepsy Group, PA. Patients who were younger than 2 years at the time they were started on LEV were identified. Their records were reviewed for starting dose (mg/kg), maximal dose (mg/kg), titration rate, tolerability, and efficacy. Seizure type/epilepsy syndrome were also documented. LEV levels, blood counts, and serum characteristics were not routinely drawn in all patients. **Results:** Twenty-two children younger than 2 years were identified. Ages ranged from 2 days to 21 months. There were four new-onset seizure disorders, the remainder having different epileptic syndromes (including infantile spasms). Initial dosages ranged from 10 mg/kg/day to 41 mg/kg/day (median 18.4-mg/kg). The maximum dosages ranged from 15 mg/kg/day to 144 mg/kg/day (median, 61.25 mg/kg) and was achieved after several days to 6 weeks. Four patients received LEV as their first anticonvulsant (AED). Six patients received LEV as their second AED. Six patients received LEV as monotherapy. Twelve of 20 patients continued LEV. Two patients were lost to follow-up. Six patients were reported to have side effects that included a slight increase in hyperactivity, becoming a "zombie," or fatigue (as described by caregivers). Side effects did not appear related to titration rate or maximal dose. Of the eight patients known to discontinue LEV, one discontinued because of side effects, seven, a lack of benefit. Of 20 patients, four patients were seizure free, six had a >90% reduction in seizures, and 11 patients had a >50% reduction in their seizures. Nine patients did not have a significant change **Conclusions:** LEV appears to be a safe, well-tolerated, and effective AED in young children. A faster titration rate and higher maximal dose were used in these children without an increase in significant side effects. Therefore, LEV may be considered as a first-line AED in neonates and children younger than 2 years. (Disclosure: Honoraria: Yes.)

1.157
TWO-YEAR LONG-TERM SAFETY AND EFFICACY DATA OF OXCARBAZEPINE IN CHILDREN WITH REFRACTORY PARTIAL EPILEPSY

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Rationale: To evaluate the 2-year long-term safety and efficacy of oxcarbazepine (OCBZ) during adjunctive therapy in children with inadequately controlled partial-onset seizures who had completed a double-blind, placebo-controlled phase. **Methods:** The randomized, double-blind, placebo-controlled, parallel-group trial consisted of a 56-day baseline phase during which patients (3–17 years) continued to receive treatment with one to two concomitant antiepileptic drugs (AEDs), a 112-day double-blind treatment phase during which patients were randomized to adjunctive therapy with OCBZ or placebo, and an

open-label extension phase. Patients received OCBZ at an initial dose of 10 mg/kg/day titrated over 14 days to a target dose of 30–46 mg/kg/day or their maximum tolerated dose. Dose adjustments were performed in a blinded manner. During the open-label extension phase, the dose of OCBZ was titrated to clinical response. We report the 2-year safety and efficacy results. **Results:** A total of 233 children (53% boys, 47% girls) with a mean age of 11.2 years entered the open-label extension phase, 128 (55%) of whom completed 2 years of open-label therapy. The reasons for exiting were unsatisfactory seizure control (25%), adverse events (7%), and other (13%). Compared to baseline, 53% of the patients experienced a >50% reduction in seizure frequency, and 4.7% were seizure free throughout 104 weeks of open-label therapy. Throughout the 2-year period, the most common adverse events (incidence >20%) reported were headache (37%), vomiting (36%), somnolence (33%), dizziness (32%), viral infection (27%), fever (24%), and upper respiratory infection (23%). Overall, the adverse events were mild and transient. **Conclusions:** The results indicate that OCBZ maintains its efficacy as adjunctive therapy during long-term management of children with partial seizures. (Supported by Novartis Pharmaceuticals.) (Disclosure: Salary: D'Souza, Novartis Pharmaceuticals; Grant: Glauser, Sachdeo, Bebin, Wheless, Novartis Pharmaceuticals; Consulting: Glauser, Sachdeo, Novartis Pharmaceuticals; Honoraria: Glauser, Sachdeo, Novartis Pharmaceuticals.)

1.158
TOPIRAMATE THERAPY IN RETT SYNDROME

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Rationale: At the end of this activity, the participants should be able to discuss topiramate (TPM) and its use in Rett syndrome. Rett syndrome, a neurodevelopmental disorder, manifests in the first few years of life with developmental arrest, stereotyped behaviors, and respiratory abnormalities. Seizures occur in 70–80% of patients, usually between ages 5 and 15 years. Epilepsy may become severe and intractable by school age but lessens in severity by adulthood. Clinical drug trials have not shown superiority of any specific antiepileptic drug (AED). **Methods:** We report our experience with TPM in seven patients with Rett syndrome. **Results:** Age at seizure onset varied from 1.5 to 9 years. The most common seizure type was complex partial seizures. TPM was initiated as monotherapy in four patients and as adjunctive therapy in three patients. The mean age at TPM initiation was 12.5 years (range, 4–31 years). In six patients, not only were seizures well controlled, but respiratory abnormalities improved by 50–75%. In one patient, TPM was discontinued 1 week after initiation because of canker sores and poor oral intake. There was no reported appetite change in the other six. In another patient, TPM was discontinued 3 months after initiation despite good seizure control because of maternal concern of possible side effects. **Conclusions:** In our cohort, six of seven patients showed benefit in seizure control and respiratory abnormalities with TPM. In general, TPM was well tolerated. TPM is a broad-spectrum drug, and its benefits may be due to its γ-aminobutyric acid (GABA)ergic and glutaminergic effects, both systems thought to be disordered in Rett syndrome.

1.159
TOPIRAMATE AS ADJUNCTIVE THERAPY: A PROSPECTIVE STUDY OF 500+ CHILDREN/ADOLESCENTS WITH REFRACTORY EPILEPSY

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Rationale: Topiramate (TPM) has been proven effective in double-blind, placebo-controlled trials in children with partial-onset seizures, seizures associated with Lennox–Gastaut syndrome, and primary generalized tonic–clonic seizures. Although such studies provide valuable information, study designs have limitations (e.g., fixed doses, relatively homogeneous populations, and short study durations) that are not present in clinical practice. Because clinicians also need information about a therapy's optimal/maintenance dose and performance in more heterogeneous populations, this study evaluated TPM as adjunctive therapy in children with inadequately controlled partial-onset or generalized seizures under conditions that more closely reflect clinical practice. The large population in this study allowed stratification of patient groups by age, seizure types, and weight percentile. **Methods:** Enrollment in this prospective, open-label study was open to children/adolescents (1–18 years) with partial-onset, generalized tonic–clonic, myoclonic, or absence seizures inadequately controlled with one or more antiepileptic drug (AED). Patients aged 3 years or older had to have a ≥1-year history of epilepsy; patients younger than 3 years had to have ≥6 months history. The starting dose was 25 mg/day TPM for patients weighing ≥25 kg (15 mg/day if <25 kg). TPM was titrated weekly in 15- or 25-mg increments to 100 mg/day, then increased weekly in 25- or 50-mg/day increments to the optimal/maximally tolerated dose (maximum, 24 mg/kg/day). Titration intervals, TPM doses, and concomitant AED doses could be adjusted according to individual response. Study duration was 6 months, although patients could continue in a study extension until TPM was approved for pediatric use. **Results:** The 556 patients (303, boys; 256, girls; mean age, 9 years) were enrolled. At baseline, 69% of patients had partial-onset seizures; 18% generalized tonic–clonic; 18% myoclonic; and 13% absence seizures. In preliminary data analyses, 66% of patients with partial-onset seizures and 58% of patients with generalized seizures had a clinically significant response (≥50% seizure reduction). The most common adverse events were loss of appetite, 25%; somnolence, 21%; fatigue, 10%; and weight loss, 10%. Cognitive/behavioral effects included nervousness, 8%; psychomotor slowing, 6%; and difficulty with attention/concentration, 5%; 9% discontinued because of adverse events; 6%, inadequate seizure control. **Conclusions:** Preliminary analyses of data from this large, in-practice study confirm the usefulness of TPM in the spectrum of seizures associated with childhood epilepsy. The low rate of discontinuations due to side effects and the low incidence of cognitive/behavioral effects underscore the tolerability of TPM in children/adolescents. Final data will be reported, including stratification of response by age and seizure type and analyses of weight changes by age-specific weight percentile. (Supported by Johnson & Johnson Pharmaceutical Research & Development.) (Disclosure: Grant: Ortho-McNeil Pharmaceutical Novartis.)

1.160
BEHAVIORAL AND EMOTIONAL EFFECTS OF LEVETIRACETAM IN CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: This objective of this study was to review and analyze the impact of levetiracetam (LEV) on the emotions and behaviors of children with intractable epilepsy. **Methods:** Medical records of 115 consecutive children aged 1–11 years who had been treated with LEV for intractable epilepsy were reviewed for (a) demographics, (b) history of behavior problems, (c) history of previous medications causing behavioral or emotional problems, and (d) changes in behavior or emotional status after treatment with LEV. **Results:** There were 63 children with a history of behavioral or emotional problems. After initiating treatment with LEV, parents reported that 18 (29%) had worsening of behavioral problems, 25 (40%) had no change, and 20 (31%) reported improvements in behavior. Sixty-five percent of this group had a history of behavioral problems caused by previous treatments. Of the 52 children with no history of behavioral or emotional problems, 42 (80.8%) were unchanged, five (9.6%) were reported as doing better, and five (9.6%) developed behavioral or emotional problems. Thirty percent of those developing problems in this group had a history of behavioral problems caused by previous treatments. The most common problems reported by both groups were aggressiveness, 20 (87%), and oppositional behaviors, 16 (70%). Emotional problems were worse in all children with exacerbations of behavior, and were isolated in three (2.6%) of the children. **Conclusions:** A history of behavioral and emo-

tional problems appears to predispose children to an exacerbation of these problems when treated with LEV. However, many parents of children in this group (31%) also reported improvements. The children whose behavior worsened were also more likely to have a history of previous treatments causing similar problems (65%). Ten percent of the group of children with no history of behavioral or emotional problems developed these side effects from treatment with LEV. (Disclosure: Honoraria: Yes.)

1.161
TOPIRAMATE, ZONISAMIDE, AND THE KETOGENIC DIET: INCIDENCE OF NEPHROLITHIASIS

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Rationale: Zonisamide (ZNS) and topiramate (TPM) are antiepileptic drugs (AEDs) with carbonic anhydrase inhibition as one of their mechanisms of action. Carbonic anhydrase inhibitors are associated with increased risk for renal calculi. The ketogenic diet (KD) is a high-fat, low-carbohydrate diet, used to treat uncontrolled epilepsy. Urolithiasis is a reported side effect of the KD. The purpose of this analysis is to evaluate the incidence of urinary symptoms in a large group of pediatric patients receiving these treatments in combination or alone. At the end of this activity, participants should have an appreciation of the risk of nephrolithiasis with selected new AEDs and the KD. **Methods:** Retrospective chart review was performed on all the pediatric patients seen in UCLA medical center for childhood epilepsy: 309 children receiving ZNS, TPM, or the KD in various combinations or alone were identified. Data regarding the duration of treatment, medication doses, and urinary side effect were collected and analyzed. **Results:** The patients' ages ranged between 2 month and 21 years; 198 (64%) were treated with TPM, 23 (7.4%) with ZNS, and 15 (4.8 %) were on the KD. Twenty-nine (9.4%) were treated with TPM and ZNS together, 32 (10%) with TPM and KD, seven (2.3%) with ZNS and KD, while five (1.6%) received TPM, ZNS, and KD concurrently. Seven (2.3%) of the patients had dysuria and gross hematuria during the treatment. A workup revealed three urinary tract infections (UTIs), one (0.3%) hypercalciuria, and three (0.97%) kidney stones or sludge as the cause. The hypercalciuric patient was taking TPM (8 mg/kg/day), ZNS (10 mg/kg/day), and KD concurrently. He did not develop nephrolithiasis at 1-year follow-up. Of the three patients with kidney stones, one had multiple medical problems and was admitted with dehydration; he was taking a minimal dose of TPM (1 mg/kg/day). The second patient was on the KD, had prolonged limited fluid intake, and was admitted with dehydration. After fluid intake was increased she remained borderline hypercalciuric without symptomatic stones. The third patient was taking TPM (10 mg/kg/day). No follow-up is available for him. **Conclusions:** Although ZNS, TPM, and the KD have been associated with increased risk of kidney stones, our analysis shows that the risk is minimal in the pediatric patient group . Only 1.3% of the patients had kidney stones or hypercalciuria, and 50% of them were severely ill and dehydrated. We conclude from our experience that it is safe to use these drugs/diet alone or in combination. Renal side effects can be reduced by increased fluid intake. (Supported by a Fellowship from the American Academy of Pediatrics to Shaunak Desai to undertake research with Dr. Sankar during the summer of 2001.) (Disclosure: Honoraria: Ortho-McNeil Pharmaceuticals, Elan Pharmaceuticals.)

1.162
TOPIRAMATE ADD-ON IN CHILDREN AND ADOLESCENTS WITH EPILEPSY

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Rationale: Children and adolescents with epilepsy have not been extensively studied in double-blind randomized controlled trials for new antiepileptic drugs (AEDs). Therefore, important data for daily practice are lacking. The objective of this observational study was to evaluate the efficacy and tolerability of topiramate (TPM) in children and adolescents, allowing flexible dosing. **Methods:** In this prospective multicenter open-label observational study patients aged 16 years or younger with a diagnosis of epilepsy were evaluated at baseline and 4, 8, 12, and 26 weeks thereafter. Doses of TPM and concomitant AEDs could be adjusted according to patient response. Seizure frequency and adverse events (AEs) were assessed at every visit. A total of 90 patients (51% boys; mean age, 8.4 years; mean duration of epilepsy, 5.4 years) were followed up for 189 ± 68 days. **Results:** Of the 90 patients, 62% had partial and one third had generalized epilepsy. Median baseline seizure frequency was 24/month. At end point, the mean TPM dosage was 4.6 mg/kg body weight. Mean seizure reduction was 80% ($p < 0.001$ vs. baseline). The responder rate (≥50% seizure reduction) was 78.7%, with 19.7% of these remaining seizure free for ≥3 months. Overall tolerability was rated very good or good by 69% of patients or relatives and 77% of the physicians. The most frequently reported adverse events were anorexia (20%), somnolence (17.8%), and aggressiveness (7.7%). Weight change from baseline to end point was +0.3 ± 2.8 kg. **Conclusions:** In children and adolescents aged 16 years or younger, TPM add-on proved to be effective and well tolerated in both partial and generalized seizures. (Supported by Janssen-Cilag Germany.) (Disclosure: Salary: Andreas Schreiner is a full-time employee of Janssen-Cilag Germany.)

1.163
BEHAVIORAL PROFILE OF LEVETIRACETAM IN CHILDREN

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Rationale: We previously reported on the excellent efficacy of levetiracetam (LEV) in children with intractable epilepsy (*Neurology* 2001;56(suppl 3):A46). Our preliminary observation of behavioral adverse experiences led us to retrospectively review the behavioral profile in 79 children with seizures treated with LEV as add-on therapy. **Methods:** We queried our clinical database (Filemaker) for all children treated with LEV at our institution over an 18-month period. A total of 79 children were identified (41 boys; 38 girls) with a mean age of 11 years (2–20 years). LEV was titrated to a maximal dose on a clinical basis. The average dose was 39.5 mg/kg/day (20–60 mg/kg/day). Seventy-seven children were taking concomitant antiepileptic drugs (AEDs). Office visits and phone records were reviewed to tabulate adverse experiences. Behavioral side effects were rated mild, moderate, or severe by a single investigator. **Results:** In 23 of 79 (30%) children, behavioral side effects were reported ranging from mild to severe. In these 23 children, behavioral symptoms included irritability/agitation, 15; aggression, nine; altered mood, seven; inattention/hyperactivity, five; anxiety/panic, two; hallucinations, one. One child had exacerbation of a previously established obsessive–compulsive disorder (OCD). Of 18 children who discontinued LEV, nine (12%) did so because of severe behavioral symptoms. In five of these nine children, parents opted to discontinue LEV despite good efficacy (seizure reduction, >50%). **Conclusions:** LEV, like most other AEDs, induces CNS-related side effects that are usually mild and transient. However, in our cohort of 79 children, we report adverse behavioral experiences in 23 (30%), which led to discontinuation of the LEV in nine (12%) children. This incidence of these behavioral effects appears to be more frequent than those reported in the adult phase III LEV clinical trials. These findings may be due to our relatively rapid rate of titration , premorbid behavioral substrate in predominantly intractable epilepsy patients, and polypharmacy. Ongoing randomized placebo-controlled clinical trials of LEV in children may clarify these unique issues in the pediatric population.

1.164
LEVETIRACETAM THERAPY OF EPILEPSY IN TUBEROUS SCLEROSIS
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Rationale: Tuberous sclerosis complex (TSC) is a neurocutaneous disorder that possesses two distinct genetic loci. The TSC 1 gene is on chromosome 9, with hamartin as its protein product. The TSC 2 gene is on chromosome 15 and produces the protein tuberin. The birth incidence of the disorder is estimated at one in 6,000–8,000. The gene exhibits highly variable clinical symptoms. Affected individuals have hamartomatous growths involving various organ systems; the brain, kidneys, heart, and skin are most often effected. Initially identified by the triad of intractable epilepsy, mental retardation, and facial angiofibromas, it is now known that this applies to no more than 30–40% of individuals with TS. As many as 90% of individuals with TSC experience seizures, a signficant number have infantile spasms, intractable epilepsy, or Lennox–Gastaut syndrome. Levetiracetam (LEV) is a novel anticonvulsant (AED) for partial epilepsy. Its specific mechanism of action is unknown. It has no known hematologic or hepatic toxicity. We present our experience with the clinical treatment of epilepsy in 17 individuals with TS using LEV. At the end of this activity, the participants should be able to discuss clinical situations in which LEV may be effective in treating epilepsy in patients with TS. **Methods:** We present our experience with LEV therapy of epilepsy in TS.The neurology records were reviewed for 17 patients with TS and epilepsy treated with LEV in an unrandomized, open-label study. Data gathered included change in seizure frequency and medication side effects while taking LEV. Additionally, tuber counts and diagnosis of autism were recorded. Assessments of efficacy were made at periodic follow-up visits or per telephone report from the parents. **Results:** The study group consisted of eight male and nine female subjects with partial epilepsy. None of the patients were experiencing infantile spasms during treatment with LEV. Eight individuals had TSC 2 mutations; one had TSC 1 mutation. Twleve cases were sporadic, and five were familial. LEV treatment was initiated at 10 mg/kg/day divided b.i.d. to t.i.d. and titrated upward until either a clinical response or intolerable side effects were observed. Two individuals became seizure free. These subjects were experiencing relatively fewer seizures, from once per month to once per week. Five individuals experienced a >50% reduction in seizure frequency. These individuals all had intractable epilepsy and had previously taken multiple seizure medications. Ten individuals did not respond, meaning a <50% reduction in seizure frequency or no change was observed. LEV was withdrawn owing to hyperkinesis and agitation in two individuals, one with >50% reduction in seizures and one nonresponder. Number or location of tubers did not predict response to LEV. Periodic monitoring of complete blood count, hepatic, and renal profiles were undertaken. No clinically significant laboratory abnormalities were observed. **Conclusions:** LEV is effective for the treatment of partial epilepsy and TS and may have particular application for individuals with refractory epilepsy.

1.165
LEVETIRACETAM LEVELS CORRELATING WITH SUCCESSFUL TREATMENT OF EPILEPSY, HEADACHES, COGNITIVE EFFECTS, AND ADVERSE REACTIONS IN PEDIATRIC AGE GROUP
Dwight Lindholm (Pediatric Neurology, University of Kansas School of Medicine, Wichita, KA)

Rationale: Levetiracetam (LEV) is a recently FDA-approved antiepileptic drug (AED) for use in people older than 16 years with complex partial seizures. Its mechanism of action is different from other AEDs. There has been little written, however, of its use in pediatrics and no reports correlating LEV levels with efficacy and side effects. This study was done to evaluate these aspects. **Methods:** Charts were reviewed and some parents interviewed for all the patients started on LEV from May 2000 and followed up through April 2002 for treatment of epilepsy and/or migraine headaches. Data collected included relevant demographic and clinical information. The age range was 5–19 years. **Results:** Of the 24 patients with intractable seizures, nine of these achieved 100% seizure control with LEV; eight achieved 75–99% improved control; five achieved 50–75% improved control; one achieved 39% improved control; and one had no improvement. Of the four children with Lennox–Gastaut epilepsy, one girl had 100% control of her epilepsy, one boy had 92% improved control of his seizures, one had 50% improvement, and one had no change. The reduction of seizure frequency in the autoimmune group was as follows: For the girl with continuous spike and slow wave of slow sleep, it was 93%. The Landau–Kleffner syndrome female had a 50% decrease. The two males with Rasmussen encephalitis had 85 and 39% decrease in seizure frequency. LEV levels associated with successful treatments of intractable epilepsy were as follows: Lennox–Gastaut, 7.8–33 μg/ml trough to peak range for >50% seizure control, using doses of 12.7–67 mg/kg. The intractable epilepsy group had levels of 6.4–60 μg/mg trough to peak, with doses of 41.38–84 mg/kg/day. Of the six patients with absence seizure disorder, three had 100% control with adding LEV (Keppra). Levels correlating with good control of absence seizures ranged from 16 to 21 μg/ml on 23–37.5 mg/kg/day. There were eight patients with complex partial seizure disorders and migraine headache problems. Seven of eight patients in this group responded 100% to seizure control with Keppra. The levels associated with success trough to peak ranged from 20 to 39 μg/ml. Doses ranged from 23.7 to 72.2 mg/kg. Bad behavior in the autistic or cerebral palsy patient correlated with doses of 47.5–68 mg/kg. Calmer behavior was at 13–15.8 mg/kg with levels of 4.2–8.9 μg/ml trough to peak. Nine of the 36 patients had significant cognitive improvement. **Conclusions:** About one third of the intractable epilepsies had full control with adding LEV. All the complex partial seizure disorder patients with a comorbid migraine headache component benefited significantly. The absence seizure disorder patients who had failed on other medications responded well with complete control in three of six. The adverse behavioral side effects of LEV are seen more often in patients with mental retardation and correlate with levels >16 mg/ml. Cognition was improved in one fourth of the patients and worsened in none. Further larger studies will elucidate the usefulness, optimal levels, and potential side effects in children. (Supported by Unrestricted Educational Grant.) (Disclosure: Grant: Unrestricted Educational Grant, UCB Pharma.)

1.166
LEVETIRACETAM (KEPPRA) HAS A POSITIVE RESPONSE IN REFRACTORY PEDIATRIC PARTIAL SEIZURE PATIENTS WITH VISUAL TRIGGERS
Marcia J. Litzinger and Annajill Hanny (Clinical Research, Epilepsy and Neurodevelopment, Inc., Salt Lake City, UT)

Rationale: There is some evidence to support the use of levetiracetam (LEV; Keppra) in pediatric patients, and even less evidence regarding LEV use in partial seizures associated with visual triggers. LEV offers potential benefits for pediatric patients, which include simple pharmacokinetics, lack of liver metabolism, and lack of drug interaction. The objective of our review was to determine the outcome of adding LEV to the regimens of nine refractory pediatric patients. **Methods:** A retrospective chart review of pediatric patients aged 12–16 years placed on LEV for the control of refractory partial seizures was done. Nine of the pediatric patients were placed on LEV in addition to their (one to more than three) other anticonvulsants (AEDs). All patients were queried during routine appointments about the presence of seizure triggers. These reports were compared to find common factors that might indicate which patients might respond to LEV as an add-on therapy for their partial seizures. Only patients who were verbal and able to report possible triggers were included in this analysis. Magnetic resonance imaging (MRI) and EEGs were also reviewed to see if a pattern emerged based on these tests. **Results:** Of the nine pediatric patient who received LEV, seven reported specific stimuli that seemed to be involved in making them "feel sick." Sunlight, flickering fluorescent lights, arcade, and mirror globe lights were the most common triggers reported in seven of these patients. One child had his epileptic

syncopal episodes on the playground only on sunny days. Three reported problems while riding in the car. Nighttime oncoming car headlights were especially remarked about. Finally, a migraine-quality headache was seen in all of these patients, suggesting occipital lobe involvement in their seizures. None of these of these children showed an epileptic response to photic activation during the EEG. Three patients had what appeared to be a generalized seizure pattern on EEG. Six patients showed normal MRIs. Four patients had a normal EEG. No real pattern seemed to emerge using either EEG or MRI data. **Conclusions:** LEV (Keppra) was shown during phase II trials to be effective in patients who had photoparoxysmal EEG responses. Our chart review shows that true EEG-positive photoparoxysmal response did not predict which children responded to this medication. Instead, clinical verbal reports suggesting activation of early seizure symptoms with visual stimuli such as sunlight, the window of a moving vehicle, problems looking at the headlights of oncoming traffic at night, fluorescent and arcade lights, and flashing globes activated seizures in this group of patients. Additionally, reports of migraine headache, known to involve the occipital lobe, should be included as an indicator of potential positive response to Keppra. At the end of this activity, readers should be able to discuss which pediatric partial-seizure patients might improve with the addition of LEV to their seizure medication regimen. LEV in currently approved for use in patients aged 16 years or older. (Supported in part by UCB pharmaceuticals.) (Disclosure: Grant: Multiple UCB pediatric drug studies; Consulting: Consultant to UCB.)

1.167

CLINICAL APPLICATION OF STABLE ISOTOPE-LABELED PHENYTOIN AND PHENOBARBITAL TO STUDY DISPOSITION IN NEONATES

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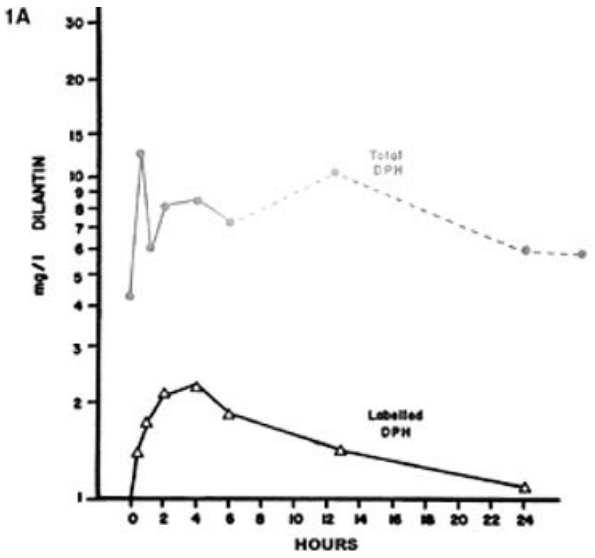
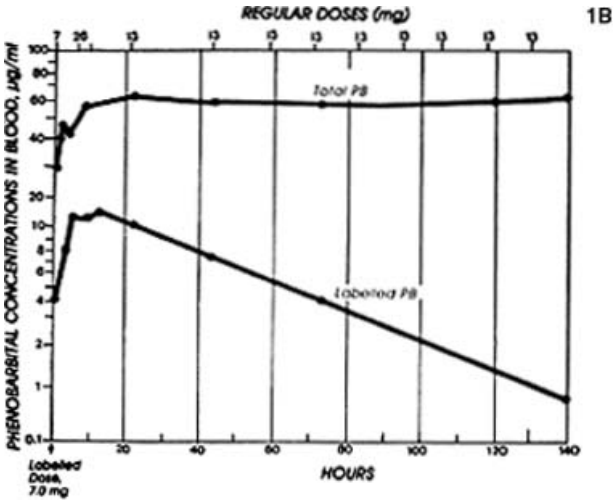
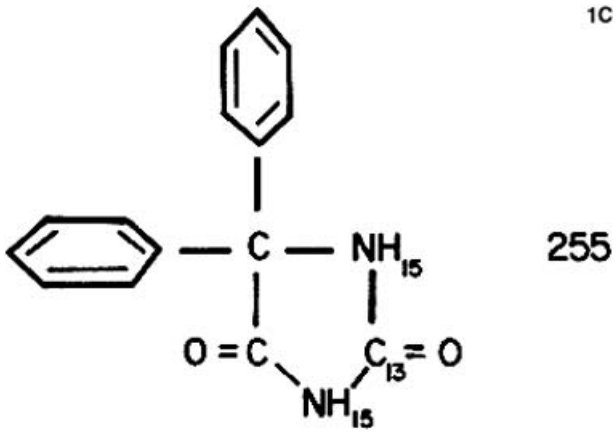
Rationale: At the end of this activity, the participant will understand the rationale of pharmacokinetic dynamics in neonates and will be able to apply this understanding toward use of either phenobarbital (PB) or phenytoin (PHT) in neonatal seizures **Methods:** PB, PHT, and methyl PB were obtained from Sigma Chemical Corporation (St. Louis, Mo, U.S.A.). Isotopically labeled PB [2-^{15}N,^{13}C-phenobarbital] and isotopically labeled PHT [2-^{13}C-1,3^{15}N-phenytoin]. **Results:** Based on calculations obtained from the labeled analogue only, peak plasma levels of labeled PHT appeared 4–6 h after oral administration and varied from 1.4 to 3.7 mg/L. For the purpose of illustration, one representative plot from a patient who received labeled PHT is shown. Using a semilogrithmic scale, the $t_{1/2}$ of labeled PHT was calculated as the







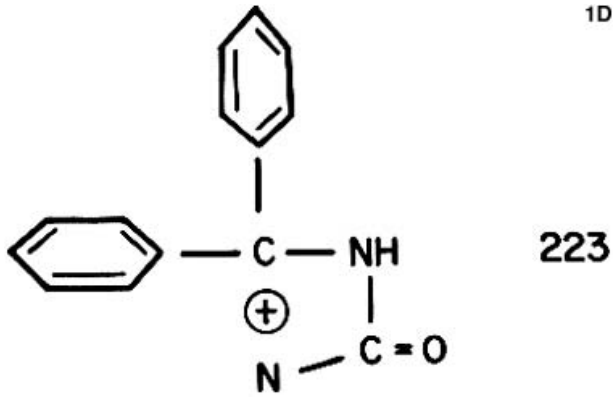


TABLE 1. *Metabolism of isotopically labeled phenytoin in neonates*

Subject	Age	Weight (kg)	Dose	Serum albumin	t ½ (h)	Ke	Ka
1	40 weeks	4.84	10.6 mg	1.8	11	0.063	0.38
2	40 weeks	3.15	7.5	2.3	16	0.042	0.61
3	25 weeks	0.76	1.75	1.3	12.6	0.055	1.11
4	40 weeks	3.88	9.30	2.5	16.2	0.048	0.43

Ka, rate constant for absorption; Ke, elimination constant.

time required for change in drug concentration by 50%. Similar methods were used to calculate the $t_{1/2}$ in patients receiving maintenance PB. **Conclusions:** In this study we were able to enroll nine neonates between 25 and 40 weeks gestational age. Four neonates received one half of the calculated 24-h maintenance dose of unlabeled PHT intravenously along with one half of the maintenance dose orally as labeled PHT. This constituted between 12 and 23% peak enrichment of the PHT body pool with labeled analogue. Of the four patients in this study at these doses, variability in $t_{1/2}$ (11–16 h) was much narrower than that reported in previous literature as 3–140 h (8–11). Five neonates received an oral labeled PB dose. Conventional pharmacokinetic approaches to obtain these data would have demanded achievement of steady-state, single-dose administration, or cessation of therapy. These data were obtained without altering the medically indicated therapeutic regimen or assuming the presence of steady state.

1.168
PYRIDOXINE AMELIORATES ADVERSE BEHAVIORAL EFFECTS OF LEVETIRACETAM IN CHILDREN
G. Steve Miller (Child Neurology, Childrens Medical Center, Tulsa, OK)

Rationale: At the end of this activity, the participants should be aware that pyridoxine may alleviate many or all of the levetiracetam (LEV)-induced behavioral side effects seen in young children, allowing continued use of LEV. LEV is a newly approved drug for adjunctive treatment of partial epilepsy. LEV use is associated with the occurrence of CNS adverse events classified as somnolence and fatigue, coordination difficulties, and behavioral abnormalities. Behavioral adverse events in children include insomnia, agitation, anxiety, emotional lability, and a hyperactive state. In rare instances, hallucinations or psychosis have been induced. These adverse events often necessitate discontinuation of LEV. A 2-year-old child with partial seizures, secondary generalized, had simultaneous initiation of pyridoxine (150 mg/day) and LEV (250 mg/day). When the pyridoxine was discontinued 2 months later, hyperactivity and associated symptoms developed within 1 week. Within several days of reinstituting the pyridoxine, the child's behavior became normal. **Methods:** Six patients, ages 2–10 years, five with partial or partial secondarily generalized seizures and one child with migraine had behavioral adverse events to LEV, severe enough to necessitate discontinuation. LEV dosage averaged 21 mg/kg. Each child was treated with pyridoxine at an average dose of 7 mg/kg. **Results:** Within 1 week, behavioral side effects had resolved in five patients, or in one patient were minimal and acceptable to parents. All of the patients were neurologically and developmentally normal and seizure free. **Conclusions:** Pyridoxine appears to ameliorate behavioral adverse effects of LEV in some children, especially normal children, thus allowing continued use of LEV. (Disclosure: Grant: KEEPER Trial, UCB; Consulting: UCB; Honoraria: Speakers Bureau, UCB.)

1.169
LEVETIRACETAM MONOTHERAPY IN PEDIATRIC PATIENTS
Mark Mintz, Carol Ann Graner, Susan Blumenfeld, and Lisa Alberts (Center for Children and Families, Bancroft NeuroHealth, Cherry Hill, NJ)

Rationale: Levetiracetam (LEV) received United States Food and Drug Administration approval in 1999 for adjunctive therapy for partial-onset seizures in adults. There have been reports concerning the efficacy of LEV in children with epilepsy. However, there is a paucity of data concerning the use of LEV as a monotherapeutic agent in pediatric patients. **Methods:** Medical records of 51 patients receiving LEV were retrospectively reviewed to identify patients who were seizure free with LEV prescribed as initial, or conversion to, monotherapy. **Results:** Six pediatric patients (8–19 years; two boys, four girls), were seizure free with LEV monotherapy. Age at seizure onset ranged from 2.5 to 18 years. Five patients had complex partial seizures, and one experienced two convulsions of unclear seizure type; this patient had a family history of epilepsy, whereas the other patients did not. All children had normal clinical neurologic examinations; only one had a previous diagnosis of neurodevelopmental delay. One patient had mesial temporal sclerosis on magnetic resonance imaging (MRI); the other five patients had normal MRIs. EEGs were variable, ranging from frontal spikes in one patient, focal spikes in two (left temporal and left central spikes), and three patients with normal EEGs. Two patients were seizure free after beginning LEV as initial monotherapy. Four patients had failed one to three antiepileptic drugs (AEDs) before LEVas add-on therapy; these patients were successfully converted to LEV monotherapy. Effective doses of LEV ranged from 750 to 2,250 mg/day, given in two divided doses. Patients were seizure free from 6 to 22 months. None of the patients reported any adverse effects. **Conclusions:** Two children became seizure free with LEV initial monotherapy. Four children became seizure free with LEV add-on therapy with successful conversion to monotherapy. LEV was well tolerated. LEV may be a beneficial and well-tolerated monotherapeutic AED in selected pediatric patients. Further research is necessary to define the efficacy and sustainability of LEV as a monotherapeutic AED for pediatric epilepsy. (Supported by UCB Pharma.) (Disclosure: Grant: Participate as a site for UCB Pharma clinical trials of LEV in children: Study N159 and N157; Consulting: UCB Pharma; Honoraria: UCB Pharma.)

1.170
INTRAVENOUS VALPROATE EXPERIENCE IN PEDIATRIC PATIENTS
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Rationale: Intravenous valproate (i.v. VPA) was approved in April 1997 as temporary substitution for oral dosing. It is recommended that it be given over 1 h, at a rate not to exceed 20 mg/min. Despite these recommendations, optimal clinical care often requires a wider range of dosing schedules. Pediatric studies outside of approved indications are limited. At the end of this activity, the particpants should be able to discuss safety and uses of i.v. VPA outside of indicated use and with a variety of dosing schedules in pediatric patients. **Methods:** Pharmacy records were reviewed to identify pediatric patients who received i.v. VPA from January 1998 to March 2002 at the Virginia Commonwealth University Health System. These patient charts were reviewed for age, gender, dosage, underlying medical condition(s), and concomitant therapies, including other anticonvulsants (AEDs). Additionally, side effects, complications of infusion, obtained serum levels, and other surveillance laboratory values were recorded. When available, infusion rates were recorded. Data from a pilot study of 10 pediatric patients using rapid infusion were included in the analysis. **Results:** Fifty-three patients with a total of 75 admissions were identified. The patients received 881 doses as loading and maintenance doses. Loading doses ranged from 11.2 to 66 mg/kg. Maintenance doses ranged from 4.1 to 25 mg/kg. One patient received 347 mg/kg/day. One patient received 108 doses. Ages ranged from 10 days to 16 years (13 younger than 1 year; 35 from 1 to 5 years; 27 older than 5 years). Indications for i.v. infusion were status epilepticus (SE), 16 patients (pts); acute or intermittent seizures, 42 pts; substitution for oral dosing, 17 pts. Two patients had transient mild decreases in blood pressure after i.v. VPA began. One patient had transient elevation of AST/ALT while receiving i.v. VPA. A second patient had elevated liver function tests before i.v. VPA; liver functions remained stable during i.v. VPA treatment. Two patients died while receiving i.v. VPA, thought to be secondary to underlying etiology (encephalitis, hypoxia/SE, respectively). One patient complained of burning on infusion, not present on subsequent doses. No infusion rate or site complications, cardiac arrhythmias, respiratory failure, or hepatic failure occurred. No infusion-site tenderness, swelling, or redness was noted. Levels of 34–183 mg/L were achieved. All patients could be maintained at target levels with dose adjustments. When available, infusion rates of 1.5–11 mg/kg/min were reported. One loading-dose i.v. push was reported. **Conclusions:** Intravenous VPA may be administered safely across all age ranges in children, with a wide range of infusion rates and dosages, including

very high dosages. Pediatric patients can achieve and maintain target concentrations after i.v. VPA administration.

1.171
EXTREMELY HIGH DOSE REQUIRMENTS OF INTRAVENOUS VALPROIC ACID IN TWO PEDIATRIC PATIENTS WITH STATUS EPILEPTICUS

Kathryn A. O'Hara, Lawrence D. Morton, William R. Garnett, and John M. Pellock (Neurology, Virginia Commonwealth University Health System, Richmond, VA; Pharmacy, Virginia Commonwealth University Health System, Richmond, VA)

Rationale: Traditionally, the maximal recommended dose of valproic acid (VPA) is 60 mg/kg/day, and an intravenous dose is given over 60 min at a rate not to exceed 20 mg/min. At the end of this activity participants should be able to discuss the requirements for extremely high doses of intravenous VPZ and continuous infusions in extraordinary clinical situations. **Methods:** Pharmacy records were reviewed at Virginia Commonwealth University Health Systems (VCUHS) for pediatric i.v. VPA use. Two patients were identified who required high doses of i.v. VPA for the control of status epilepticus (SE), and both required continuous infusions. **Results:** Patient 1, a 3-year 4-month-old boy with a weight of 11.4 kg, was transferred to VCUHS from an outlying hospital after 51 days of intractable seizures. On transfer, medications were topiramate (TPM), lamotrigine, lorazepam, VPA, ranitidine, L-carnitine, amoxicillin, albuterol, beclomethasone, dipropionate, and ipratrapium bromide. VPA levels were <25 mg/L with doses of 25 mg/kg every 6 h. Additional bolus doses of i.v. VPA ranged from 90 to 263 mg/kg/day with levels, ranging from 26 to 104 mg/L, and seizure activity continued. A continuous infusion of i.v. VPA was begun at 50 mg/h, and seizure activity ceased. VPA levels remained consistent at 71 mg/L. Patient 2, a 3-month-old boy with a weight of 8.3 kg, was admitted via VCUHS ER in SE. Admission medications were phenobarbital and famotidine. When i.v. VPA was started, medications included metoclopramide, chloral hydrate, glycopyrrolate, nitrofurantoin, TPM, tiagabine, ferrous sulfate, famotidine, and midazolam. I.v. VPA was started at 25 mg/kg with an additional bolus given 2 h later. VPA level was 49 mg/L. Additional bolus doses of i.v. VPA ranging from 36 to 217 mg/kg/day were given. To maintain consistent therapeutic levels, dosing intervals were shortened, and total daily doses were increased. For patient-care reasons, continuous infusion was substituted when bolus dosing reached every 2 h. Infusion rates of 120 mg/h (347 mg/kg), which resulted in concentrations of 134–160 mg/L were needed to stop the SE. In both patients, there were no significant changes in blood pressure, liver enzymes, or platelet count. **Conclusions:** In some cases, patients high doses of i.v. VPA are indicated. We report two cases where doses ≤347 mg/kg/day given by continuous infusion were needed to stop SE. These pediatric patients reinforce the need to monitor the therapeutic response in determining the most appropriate dose and rate of infusion. However, appropriate surveillance laboratory tests should be followed up.

1.172
LOW RISK OF DEVELOPING RENAL STONES OR NEPHROCALCINOSIS IN PEDIATRIC PATIENTS ON TOPIRAMATE: 6 AND 12 MONTHS' FOLLOW-UP

Hian-Tat Ong, Wei-Ling Lee, Wei-Kin Gong, and Poh-Sim Low (Pediatrics, National University Hospital, Singapore, Singapore, Singapore)

Rationale: This is a prospective study to assess the risk of developing renal stones or nephrocalcinosis in pediatric patients given topiramate (TPM) for the treatment of epilepsy. **Methods:** Patients younger than 16 years, for whom TPM was to be added in the treatment of poorly controlled epilepsy, were enrolled. The parents were informed of the risk of renal stones of 1.5% in adults using TPM [*Epilepsia* 1996;37(suppl 4):S74]. Renal ultrasound recordings of the longitudinal and transverse sections of both kidneys were obtained just before starting TPM, at 6 months, and at 12 months for patients who were still taking it, using the Diasonics Ultrasound Multisync M500 or GE Ultrasound System RT2800. Frank renal stones were first looked for in the kidneys and bladder. In the absence of stones, the renal sonogram was further classified based on the nephrocalcinosis grading scale. Grade 0 is used when there are no abnormalities in the medullary pyramids, grade I when there is mild increase in echogenicity around the border of the medullary pyramids, grade II being mild diffuse increase in echogenicity of the entire medullary pyramids, and grade III being homogeneous increase in echogenicity of the entire medullary pyramids. **Results:** Twenty-two patients (11 boys and 11 girls) with the mean age of 7 years 9 months were included in the study. Ten patients were taking one antiepileptic drug (AED), eight were taking two AEDs, and four were taking three AEDS before starting TPM. These various AEDs included carbamazepine, valproic acid, phenytoin, phenobarbitone, lamotrigine, vigabatrin, nitrazepam, clobazam, and clonazepam. None was taking acetazolamide, zonisamide, or ketogenic diet. The average dose of TPM 6 months after starting treatment was 8.96 mg/kg/day, with the range from 1.58 to 22.73 mg/kg/day. Twenty patients were taking doses >6 mg/kg/day, based on the minimal effective dose suggested for TPM in children (*Can J Neurol Sci* 1998;25:S8–12). On follow-up 6 months later, all 22 patients had normal renal sonograms, with no evidence of frank renal stones or nephrocalcinosis. Twelve patients continued to be treated with TPM. At 12 months, their average dose of TPM was 7.92 mg/kg/day, with the range from 0.92 to 11.50 mg/kg/day. Nine of the 12 patients were taking a TPM dose >6 mg/kg/day. Their renal sonograms at 12 months were all normal. **Conclusions:** This study suggests low risk of developing renal stones or nephrocalcinosis in pediatric patients using TPM after 6 months to a year. (Supported by Department of Pediatrics, National University Hospital, Singapore.)

1.173
SUSTAINED-RELEASE SODIUM DIVALPROEX FOR THE TREATMENT OF PRIMARY GENERALIZED EPILEPSIES IN CHILDREN

Phillip S. Riback (Upstate Clinical Research, Upstate Neurology Consultants, Albany, NY)

Rationale: Advances in medication-release systems have improved ease of medication administration, decreased side effects, and improved compliance with medication regimens. Since it has been available, an extended-release preparation of sodium divalproex (VPA ER) has been replacing delayed-release sodium divalproex (VPA DR) in this office for the treatment of epilepsy. There are limited data on the use of this preparation in children with epilepsy. At the end of this activity, participants should be aware of the potential for improved compliance and tolerability with VPA ER for children with epilepsy. **Methods:** The charts of all children with primary generalized epilepsies were reviewed to ascertain if the patient had received VPA ER for epilepsy treatment and the specifics of each case reviewed. **Results:** Nine children aged 10.2–20.1 years (mean, 14.3 ± 3.4 years) received treatment with VPA ER. Epilepsy syndromes included juvenile myoclonic epilepsy (JME; four), juvenile absence epilepsy (two), reflex epilepsies (two), and childhood absence epilepsy with generalized tonic–clonic seizures on awakening (1). Before changing VPA preparations, all children had complete seizure control except for the four with JME, two of whom only experienced seizures with medication noncompliance. Reasons for medication change were noncompliance (four), convenience of once-daily dosing (two), peak/trough effects of VPA DR (two), and nausea with VPA DR (one). The one child nauseated with VPA DR experienced no improvement with VPA ER, discontinued it after 2 weeks, and continued to experience morning myoclonus. This was the only adverse event. Patients were on VPA DR for 25 ± 37 months (range, 1–120 months) and remained on VPA ER for 11.1 ± 5.5 months (range, 0.5–17 months). One child with JME experienced resolution of morning myoclonus and of EEG generalized spike–wave discharges on changing medication formulations. The previously noncompliant subjects experienced complete seizure control on VPA ER. All other patients continued to experience complete clinical and electrographic control of their epilepsy. Two children continued to require concurrent treatment to maintain seizure control, one with VPA DR 125 mg qAM and one with levetiracetam. Dosage substitutions

ranged between equivalent (375:500) and matching (500:500) depending on dose and availability. **Conclusions:** In this preliminary, retrospective study, VPA ER was effective and well tolerated by children and adolescents for the treatment of primary generalized epilepsies. The only patient was been unable to tolerate multiple medications. All of the patients who had been seizure free before transition to VPA ER remained so, two JME patients with compliance-related seizures became seizure free and the one JME patient with uncontrolled morning myoclonus improved clinically and electrographically. If controlled, prospective studies confirm these results, VPA ER may improve compliance, seizure control and tolerability. (Supported by a grant from Abbott Laboratories.) (Disclosure: Grant: Research grant to support the review of records and abstraction of clinical data from the records; Consulting: Elan, Novartis, UCB-Pharma; Honoraria: Abbott, AstraZeneca, Elan, Glaxo-Smith-Kline, Merck, Pfizer.)

1.174

DIFFERENTIAL EFFICACY OF OXCARBAZEPINE AND CARBAMAZEPINE DURING ADJUNCTIVE THERAPY IN CHILDREN WITH REFRACTORY PARTIAL EPILEPSY

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Rationale: To evaluate the efficacy of oxcarbazepine (OCBZ) during adjunctive therapy with or without carbamazepine (CBZ) in children with inadequately controlled partial-onset seizures. **Methods:** During the baseline phase of this randomized, double-blind, placebo-controlled, parallel-group study, patients (aged 3–17 years) were maintained on their stable dose of concomitant antiepileptic drugs (AEDs). During the double-blind treatment phase, patients were randomized to adjunctive therapy with OCBZ (initial dose, 10 mg/kg/day titrated over 14 days to a target dose 30–46 mg/kg/day) or placebo. Patients unable to achieve the target dose range were titrated to maximal tolerated dose. All dose adjustments were performed in a blinded manner. Median percentage change from baseline in partial-seizure frequency/28 days during the double-blind phase was compared in patients who received CBZ as a concomitant AED versus those who did not receive CBZ as a concomitant AED. **Results:** A total of 267 patients was randomized (138 received OCBZ: 61 OCBZ/no CBZ, 77 OCBZ/CBZ; 129 received placebo: 74 placebo/no CBZ, 55 with placebo/CBZ). Median baseline seizure frequency per 28 days for the OCBZ/no CBZ group was 15.0 compared with 14.8 for the placebo/no CBZ group, and was 11.9 for the OCBZ/CBZ group compared with 10.9 for the placebo/CBZ group. When compared with placebo, both OCBZ/CBZ (33.7%, $p = 0.0001$) and OCBZ/no CBZ (39.5%, $p = 0.0044$) demonstrated significant reductions in median partial-seizure frequency/28 days during the double-blind phase relative to baseline. **Conclusions:** Adjunctive therapy with OCBZ was equally efficacious in children with partial seizures whether added to CBZ or to other AEDs. (Supported by Novartis Pharmaceuticals.) (Disclosure: Salary: D'Souza, Novartis Pharmaceuticals; Grant: Sachdeo, Glauser, Wheless, Bebin, Beydoun, Novartis Pharmaceuticals; Consulting: Sachdeo, Glauser, Beydoun, Novartis Pharmaceuticals; Honoraria: Sachdeo, Glauser, Beydoun, Novartis Pharmaceuticals.)

1.175

DOES PARTIAL SLEEP DEPRIVATION INCREASE THE INCIDENCE OF RECORDING SLEEP DURING A ROUTINE EEG?

Mary A. Bare and Donald Gilbert (Neurology, Cincinnati Childrens Hospital, Cincinnati, OH)

Rationale: It has been reported that recording sleep during an EEG increases the incidence of epileptiform discharges. The benefits of sedation may not outweigh the risks in children. A sleep-deprivation protocol restricting the child to <4 h of sleep may not be reasonable for all children. Partial sleep deprivation (PSD) may improve compliance yet increase the likelihood of recording sleep. This study was done to see if there was an association between sleep-deprivation protocols and EEG results. **Methods:** Patients having outpatient EEGs for evaluation of seizures were entered into the study. Two months of baseline data were collected. During the 2-month test period, instructions for PSD were given unless the child had a sleep-deprived EEG ordered. Data were collected from three EEG protocols: total sleep deprivation, partial sleep deprivation, and no sleep deprivation. Clinical predictor variables were included in a multivariate logistic model. **Results:** Data were analyzed using SPSS. Eight hundred nineteen EEG reports were reviewed. The ages of the children ranged from birth to 18 years. In the multivariate model, the adjusted odds of epileptiform discharges were significantly greater in older children and in children taking antiepileptic drugs (AEDs; $p < 0.001$ for both). Neither sleep protocol nor the presence of stage II sleep appeared to be associated with epileptiform discharges. **Conclusions:** Based on this study, there is no evidence that sleep deprivation is useful in increasing the likelihood of seeing epileptiform discharges on EEGs in children being evaluated for seizures. At the conclusion of this activity, participants should be able to discuss the association between sleep deprivation and increased incidence of epileptiform discharges on EEGs in children.

1.176

NEONATAL EEG WITH DIGITAL TECHNOLOGY: COMPARISON OF A REDUCED ELECTRODE MONTAGE AND FULL 10/20 MONTAGE FOR SEIZURE DETECTION

Hasan Tekgul, Ann M. Bergin, Kimberlee Gauvreau, and Blaise F.D. Bourgeois (Department of Neurology, Children's Hospital, Boston, MA)

Rationale: EEG is an important tool in identification of neonatal seizures. Seizures in newborns are topographically restricted, and it is known that extremely reduced montages may fail to identify such seizures. Current guidelines recommend either a full 10/20 montage (16 electrodes) or a reduced montage (RM; nine electrodes) for recording EEG activity, with additional channels devoted to polygraphic variables. A comparison of these two montages for detection of neonatal seizures has not been reported. With digital technology, it is now possible to remontage previously recorded EEGs for such a comparison. **Methods:** One hundred fifty-one neonatal EEG records were obtained from the master database of the Clinical Neurophysiology Laboratory at Children's Hospital, Boston. EEGs were given a study number, and identifying markings were removed. All EEGs were first analyzed by two independent, blinded readers using an RM. The number, location, and duration of seizures was recorded. All EEGs were then reanalyzed, by the same blinded readers, using a full montage (FM), and seizure data again recorded. Results of these analyses were compared to evaluate the sensitivity and specificity of the RM compared with the FM for the detection of electrographic seizures. **Results:** Electrographic seizures were identified in 31 of the 151 records analyzed. A total of 187 electrographic seizures were identified in these 31 records when the FM was used for display. Using the RM, 166 electrographic seizures were identified in 30 records. RM therefore failed to identify the single seizure occurring in one record. The RM was 97% sensitive and 100% specific for identification of electrographic seizures when compared with the FM. In two records with multiple seizures, >50% were missed when reading with RM. In one record, a single prolonged seizure was misread by both readers as representing four separate short seizures when using the RM display, thus overestimating seizure number in this instance. Excluding this case, the rate of underestimation of seizure number was <14% for the RM in this study, and seizure activity was missed altogether in only one record. Interreader agreement was 100% for identification of ictal records when using either RM or FM. With respect to the number of seizures identified in the ictal records, interreader agreement was 74%. **Conclusions:** The potential advantages of using an RM for detection of neonatal seizures are shorter electrode application time, decreased handling of vulnerable infants, and in-

creased scalp space for performance of cranial ultrasound and intravenous access. This study illustrates the modest potential for both underestimation and overestimation of neonatal seizure number when using an RM compared with an FM. Despite this, the RM has a high sensitivity and specificity for seizure detection when compared with the FM, and may be adequate for diagnosis and managment of neonatal seizures in these ill infants. At the end of this activity, the participants should be able to discuss the advantages and disadvantages of using a reduced electrode montage rather than a full montage in detection of electrographic seizures in neonates. [Supported by (H.T.) a grant from the NATO Science Fellowship Program, under the auspices of The Scientific and Technical Research Council of Turkey (TUBITAK).]

1.177

ANALYSIS OF EEG FEATURES IN CHILDREN WITH BENIGN EPILEPSY WITH CENTROTEMPORAL SPIKES AND CORRELATION WITH COGNITIVE DEVELOPMENT

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Rationale: This study sought to examine the relation between the amount of epileptiform activity in children with benign epilepsy with centrotemporal spikes (BECTS) and parental reports of cognitive and language difficulties to determine the incidence of EEG features: spike location, lateralization, discharge frequency, and focal slowing during wakefulness and sleep in a cohort of children with BECTS; to determine by systematic telephone interview any difficulties in cognitive development (learning, problem-solving, memory, language), behavior, and school performance; and to correlate these data with EEG features. **Methods:** Patients were recruited from the EEG laboratories by identification of the typical EEG feature of BECTS. Syndrome was confirmed by telephone interview. In each record, the duration of wakefulness, drowsiness, and sleep was reviewed. Spike location was defined by maximum negativity in 10-20 electrode system; two or more nonhomotopic regions were defined as multiple. A laterality index was computed by determining spike frequency over time in either hemisphere, expressing this as a ratio. **Results:** Twenty children (12 boys, eight girls) aged 4–14 years (mean, 9.4 years) were studied. A central (e.g., C4, T4, or Cz) focus was identified in 40% of the children, and 60% had multiple spike foci. In 35% of children, the spike foci were lateralized to one hemisphere. The discharge frequency in wakefulness varied between 1 and 46 spikes/min. There were frequent long runs of discharges in wakefulness in 12 children, and in six, these occupied $\geq$10% of the recording in wakefulness. Eight children had focal slowing independent of spikes. The increase in spike frequency with sleep was 0.3 to 23 times the wakeful baseline record. In four children, spikes occupied $\geq$85% of the sleep record. Eight children were identified as having cognitive problems by interview, of these four had language problems, in two these preceded first seizure. Seven had behavior problems, and seven had difficulties in school performance. Seven children did not have problems identified by parents. Children with reported cognitive, school difficulties, or behavioral problems had higher spike frequency in wakefulness. This was significant (means, 20/min vs. nine/min; $p = 0.04$) only for behavior. There was no correlation between the presence of cognitive, school, or behavioral problems and the presence of multiple foci, laterality, or sleep activation of spikes. **Conclusions:** Multiple foci, continuous spike activity in sleep, and focal slowing were common in this cohort of BECTS with infrequent seizures. Reports of cognitive, behavioral, and school difficulties were present in more than half of the cohort. However, we did not find significant correlations between measures of discharge location, lateralization, or frequency in wake or sleep and reports of cognitive or school problems. The clinical significance and origin of the relation between behavioral problems and spike frequency will be tested further as recruitment continues and formal neuropsychological assessments are completed. (Supported by NHMRC, Australia.)

1.178

L-CARNOSINE THERAPY FOR INTRACTABLE EPILEPSY IN CHILDHOOD: EFFECT ON EEG

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Rationale: L-Carnosine is an amino acid dipeptide (histidine and alanine) that may indirectly affect spike and wave discharges by altering γ-aminobutyric acid (GABA) bioavailability or affecting copper and zinc influx at the cellular level. Magnetic resonance imaging (MRI) spectroscopy has recently demonstrated that brain homocarnosine levels may correlate with seizure control. We hypothesized that if dietary carnosine could be ingested to create homocarnosine in the brain, then spike-and-wave activity would decrease, and seizure control should improve. We gave L-carnosine to four patients as add-on therapy for intractable spike–wave discharge and documented changes in both clinical (overt seizures) and physiologic (EEG) status. **Methods:** Seven children (three girls, four boys; age range, 2–12 years) met inclusion criteria. All had intractable seizures for $\geq$2 years, had failed at least three anticonvulsants, had documented, abnormal generalized or secondarily generalized spike–wave, atypical absence, or Lennox–Gastaut syndrome. All families signed written consent from an IRB-approved protocol. All children were evaluated with a baseline EEG on the same day they were started on 400 mg b.i.d. of L-carnosine. Posttreatment EEG was undertaken after 10 weeks of L-carnosine therapy. No other concurrent medications were changed. **Results:** After 10 weeks of carnosine therapy at 400 mg p.o. b.i.d., five of these seven children had documented improved EEG findings. Changes included decreased frequency of polyspikes (two children), improved secondarily generalized spike–wave activity (one child), and improved background and decreased EEG slow-spike and wave activity (two children). No significant EEG changes occurred in two children. Seizure frequency improved in all seven patients. Although not evaluated formally, improvement in the domains of global cognition, behavior, and language function was reported in all seven patients. Those domains were not predicted to react to carnosine and were elicited spontaneously via blinded therapists and family members who noted gains in areas not typically associated with the GABA-ergic system. **Conclusions:** L-Carnosine may be a useful add-on medication for intractable seizure disorders with encephalopathic EEG changes or generalized epileptiform activity. Although the exact mechanism is unknown, L-carnosine is believed to bind with GABA to form homocarnosine, and may also modulate copper and zinc influx into the neurons, decreasing the afterdischarges of spike–wave discharges. Further investigation of the effects and exact mechanisms of L-carnosine is warranted.

1.179

CHARACTERISTICS OF PROLONGED AFTERDISCHARGE: CHILDREN WITH MALFORMATIONS OF CORTICAL DEVELOPMENT

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Rationale: To clarify aberrant cortical excitability of malformations of cortical development (MCDs), we evaluated characteristics of extraoperative afterdischarges (ADs) and motor responses (MRs) using subdural electrodes. **Methods:** This study evaluated 23 pediatric epilepsy patients (aged 4–18 years). We reviewed amperage thresholds, distribution and propagation of AD, and MR for 13 patients with MCDs and 10 patients with non-MCD pathologies (normal or gliosis). We collected and analyzed ADs lasting $\geq$6 s, with or without seizures. **Results:** We saw no differences in age, gender, preoperative seizure frequency, and distribution of epileptic regions between groups. We recorded ADs in 12 of 13 MCDs and six of 10 non-MCD patients. We successfully mapped primary motor functions in all 23 patients. MR

thresholds were higher in MCD patients than in non-MCD patients. Closely-related MR and AD thresholds inversely correlated with age in 12 MCD patients ($p < 0.01$). Age-dependent AD thresholds declined abruptly in MCD so that AD thresholds in eight MCD patients older than 11 years (mean ± SD; 5.0 ± 1.6 mA) were lower than those of three non-MCD patients (8.7 ± 3.0 mA; $p < 0.05$). Nine MCD patients showed ADs in remote sites compared with two non-MCD patients. **Conclusions:** Closely related and higher MR and AD thresholds indicate a less excitable and immature cortex in MCDs before adolescence. In adolescents with MCDs, low AD thresholds correlate to local hyperexcitability in the malformed dysplastic cortex. Remote ADs in the epileptic dysplastic cortex suggest the aberrant cellular excitability or excitatory circuits of epileptogenesis in MCD.

1.180
ELECTROENCEPHALOGRAPHIC SUBGROUPS IN BENIGN ROLANDIC EPILEPSY

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Rationale: To describe the distribution of the spikes in patients with benign rolandic epilepsy (BRE) and to try to distinguish differences in seizure manifestation such as described by Legarda et al. (*Epilepsia* 1994;35:1125–9). **Methods:** We have studied 28 patients (18 boys, 10 girls) with BRE aged 7–15 years. Awake and sleep EEG recordings were performed using closely spaced electrodes (10/10 system) over the perisylvian area. The maximum electronegative region was analyzed by reference montages. Feet, hand percussion, and protrusion of the tongue were performed. **Results:** Maximum electronegativity was observed in the following regions: low central (C5/C6) in 18 patients (64.3%); high central (C3/C4) in seven (25%); temporal (T3/T4) in two (7.1%); and finally in centroparietal in one (3.6%). Seizure manifestation in the low-central group consisted of oromotor symptoms in 83.3% (15 of 18) and generalized tonic–clonic seizures (GTCSs) in 16.7% (three of 18) patients. Hand involvement or hemiconvulsion occurred in 42.9% (three of seven), GTCSs in 28.6% (two of seven), and oromotor symptoms in 85.7% (six of seven) patients in the high-central group. The two patients with temporal spike predominance presented hand (one of two) and oromotor (one of two) involvement; finally one patient with centroparietal discharge accentuation had GTCSs. Protrusion of the tongue suppressed the discharges in six patients; feet and hand percussion did not evoked spikes in any patient. **Conclusions:** The subgroups described by Legarda et al. (1994) in BRE can be identified and have some clinical correlation. Although oromotor symptoms occurred in both low- (C5/C6) and high-central (C3/C4) subgroups, hand involvement was more observed in the latter.

1.181
FREQUENCY OF OVERNIGHT EEG ABNORMALITIES IN SIBLINGS OF CHILDREN WITH AUTISTIC SPECTRUM DISORDERS

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Rationale: The presence of spike or other epileptiform activity in sleep has been described even in the absence of clinical seizures in patients with autistic spectrum disorders (ASDs). Overnight ambulatory or video-EEG results show 20–60% of these children have epileptiform EEG abnormalities, yet the frequency in normal age-matched controls is unknown. In addition, genetic factors may play a significant role in the frequency of epilepsy. Therefore, we studied overnight ambulatory EEG in nonepileptic, nonautistic children aged between 2 and 6 years who had a sibling with ASDs and an abnormal 24-h EEG. We hypothesized that the normal siblings would not have the types of EEG abnormalities seen in their autistic siblings. **Methods:** Twelve siblings without ASDs (average age, 5.5 years, six boys/six girls) were selected for study by digital 24-h EEG monitoring. All children had siblings with ASDs and an abnormal EEG (seven boys, five girls; average sibling age, 4.6 years). EEG studies were coded by number and read independently by two board-certified pediatric epileptologists blinded to the identity of the patients. Interpretations of the EEGs were compared for agreement between the readers. Frequency and type of EEG abnormalities were described. All subjects were paid for participation, and the study was approved by the Lake Forest Hospital IRB. **Results:** Independent readings were exactly the same for both epileptologists. Two of the 12 siblings showed evidence of epileptiform discharges. One was read as borderline abnormal, and the nine others had normal studies. The abnormal EEGs showed one patient with triphasic benign focal epilepsy–type discharge, and one patient with generalized polyspike–wave discharges. **Conclusions:** The lack of similarity between sibling EEGs suggests that genetics alone does not explain the higher frequency of EEG abnormalities reported in ASDs. Of the abnormal EEG findings, one showed benign focal epilepsy of childhood, and the other abnormal EEG showed a suspected primary generalized epileptiform potential. Because these findings may be seen fairly commonly in childhood, and occurrence in our study population was infrequent and lower than the spike incidence in the ASD patients, we conclude that siblings have less frequent epileptiform activity than seen in the ASDs population. It remains to be studied whether or not the general childhood population exhibits the same frequency of typicality in routine or prolonged EEG.

1.182
EEG SAILBOATS IN CHILDREN WITH ATTENTION DEFICIT–HYPERACTIVITY DISORDER AND SEIZURES

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Rationale: Early EEG investigators described posterior slow waves in children with behavior problems. More recently it has been noted that this occipital slowing consists of several patterns, some of which may be age-related and state-related normal variants. This abstract should bring to the attention of readers one of the possibly significant EEG findings in children with ADHD and seizures. **Methods:** We evaluated the EEGs of 63 children (age range, 4–15 years) seen between 1992 and 2000. Forty-four had ADHD, and 21 had seizures (Sz) and not ADHD. EEG sailboats are randomly occurring, single, asymmetric, surface-negative occipital slow waves (150–250 ms in duration), 1.5 to 2.5 times the amplitude of background alpha rhythm. Although usually bilateral, sailboats can predominate on one side or the other; the higher amplitude can shift from side to side in one recording. Sailboats do tend to disappear during sleep. **Results:** The average age of children with sailboats (9.2 years) did not differ significantly from that of children without sailboats (9.6 years). Sailboats were found in 9.5% of patients with Sz and not ADD, 5% of children with ADHD and not Sz, and in 50% of children with both ADD and Sz. This association is statistically significant ($p = 0.012$). Partitioning of the $\chi 2$ showed that this was due to the association between EEG sailboats and ADHD+Sz. **Conclusions:** Although nonspecific, the occurrence of sailboats may be a marker for the occurrence of both ADHD and Sz.

1.183
THE USE OF EEG DIPOLE ANALYSIS TO EVALUATE EPILEPTIC FOCI IN INTRACTABLE PEDIATRIC EPILEPSY

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Rationale: Equivalent current dipole analysis can be used to visualize the source of epileptic discharges three-dimensionally in children

with focal epilepsies. A prolonged video-EEG is necessary in children with intractable epilepsy to define the ictal-onset zone. There are often multiple foci recognized from the interictal spike zone and the ictal-onset zone. We studied the dipole localizations of these interictal discharges to evaluate and compare epileptic foci with other neuroimaging studies. **Methods:** We studied 18 pediatric patients with intractable epilepsy, who underwent prolonged video-EEGs (19 scalp electrodes; sampling rate, 200 Hz). We performed EEG dipole analysis of interictal epileptiform discharges using single moving dipole modeling. We compared EEG dipoles with the interictal spike zone, ictal-onset zone detected by video EEG, magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography, and magnetoencephalography (MEG). **Results:** In four of 18 patients, a cluster of dipoles was localized to one region corresponding to interictal spike zone, ictal-onset zone, and neuroimaging data. In six of 18 patients, dipoles and interictal spike zones were localized diffusely in one hemisphere. Two of the six patients had the ictal-onset zone in one region, whereas the other four patients had unlocalized hemispheric onset. Four of the six patients had diffuse hemispheric MRI lesions. These lesions consisted of cortical dysplasia in two patients, porencephalic cyst in one patient, and diffuse hemispheric atrophy in another. MEG spike sources were concordant to MRI lesions in these four patients. The PET showed hemispheric hypometabolism in one patient and diffuse hypermetabolism in another. One of the six patients had right occipital tumor, and MEG spike sources were localized anterior to the tumor. In the remaining one patient, MRI and PET were normal. In three of 18 patients, dipoles, interictal spike zones, and ictal-onset zones were localized to the bilateral homologous regions. MRIs were normal in all three patients, and neither MEG nor PET could lateralize the epileptic region. In the remaining five of 18 patients, dipoles were localized to two or more regions in both hemispheres, which were concordant with multifocal interictal spike zones. Four patients had diffuse hemispheric ictal onset, whereas one patient had bilateral independent onset. One patient with left parietooccipital cortical dysplasia had consistent lateralization among the ictal-onset zone, MRI, PET, and MEG, whereas the other four had inconsistent localization. **Conclusions:** EEG dipole analysis from focal or hemispheric interictal epileptiform discharges can localize the zone of epileptogenesis. EEG dipole analysis from multifocal interictal discharges can predict inconsistent epileptic foci in other neuroimaging studies. Higher spatiotemporal resolution is necessary to evaluate the homologous epileptic discharges to define the primary epileptic focus. (Supported by KATANO Award from Kansai Medical University, Osaka, Japan.

1.184
HIGH-DOSE DIAZEPAM PROTOCOL FOR LENNOX–GASTAUT AND LANDAU–KLEFFNER SYNDROMES

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Rationale: Childhood epilepsy syndromes have poor clinical outcome if EEG abnormalities remain intractable and clinical seizures persist. Prior studies have described the use of diazepam (DZP) for treatment of continuous spike–wave activity in sleep (CSWS). We detail our experience with a modified DZP protocol for treating CSWS. In the current study, we performed the intervention on an outpatient basis in conjunction with simultaneous EEG recording in children with Lennox–Gastaut syndrome (LGS) or Landau–Kleffner syndrome (LKS). We hypothesized that improvements in both EEG and control of epileptic seizures would be apparent if the DZP protocol were successful. **Methods: T**o be included in the study, all children had failed at least two seizure medications (AEDs) including valproic acid (VPA) and steroids. All children had pulse-oximetry and vitals checked during the DZP ingestion on day 1. Nine children (seven LGS, two LKS; nine girls/three boys; age range, 2–10 years) were administered rectal or oral DZP (1- to 1.5-mg/kg doses given during day 1 of protocol), followed by a 0.5- to 0.75-mg/kg daily DZP dosing for 2–3 additional weeks. EEG studies were performed on days 1, 2, and 21 or 28 of the protocol. **Results:** When sustained EEG improvement occurred, it was readily observable on the Digitrace within 30–90 min after high-dose DZP ingestion. These improvements were notable in four of seven LGS and two of two LKS patients. Follow-up on day 21 or 28 revealed EEG in three of four initial responders with LGS and two of two with LKS showed significant changes. Clinical correlation for these six patients revealed continued improvement of overt seizures. No complications occurred other than irritability or intoxication during the first 24 h in six of seven patients, and prolonged irritability in three of seven patients. The symptoms of mood change resolved with tapering DZP over several weeks. **Conclusions:** Severe childhood seizure syndromes such as LGS or LKS typically have limited pharmacologic responses. Steroids, high-dose VPA, or poly-AED therapy are often implemented without benefit. High-dose DZP short-term protocols may offer an alternative to these more prolonged therapies with only transient side effects. Future studies should evaluate the long-term efficacy of this short-term intervention.

1.185
THE RELATION BETWEEN BEHAVIORAL AND EMOTIONAL DISTURBANCES AND SLEEP DISORDERS IN CHILDREN WITH EPILEPSY

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Rationale: Higher rates of sleep problems are reported in children with epilepsy compared with healthy children or children with other chronic illnesses. Emotional and behavior problems are also more common in these children. Interestingly, studies suggest that emotional or behavioral disturbances can result from childhood sleep disorders. The purpose of the current study was to examine the relation between sleep disorders and epilepsy, and to explore the behavioral and emotional consequences that may result in children with these comorbid diagnoses. At the end of this activity, the participants should be able to discuss the relations between seizure variables, sleep disturbance, and behavioral and emotional problems in children with epilepsy. **Methods:** Study participants consisted of 23 children [12 boys; 11 girls; mean age, 10.0 years (±2.1 years)] diagnosed with epilepsy, with reports of possible sleep disturbances. The presence of sleep-disordered complaints was first assessed with a parental questionnaire focusing on the child's behavior during sleep and wakefulness (Chervin et al., 2000). Further quantification of sleep problems was obtained from an overnight polysomnograph, and included measures of sleep efficiency, rapid eye movement (REM) latency, a respiratory arousal index, a periodic limb-movement arousal index, and the length of apnea events. Evidence of behavioral and emotional disturbances was assessed using parent rating questionnaires and child symptom self-report measures. **Results:** Nineteen of the 23 children were found to have abnormal polysomnographs with evidence of obstructive hypopneas or apneas with associated sleep disruption and mild hypoxemia. Regression analyses found that seizure frequency had a significant effect on length of apnea ($\beta = 0.557$; $p < 0.007$). Analyses also confirmed that children with higher scores on measures of hyperactive–impulsive/inattentive behavior experienced delayed REM onset ($\beta = 0.532$; $p < 0.017$). Children with higher scores on a depression measure displayed an increased length in their apnea events ($\beta = 0.475$; $p < 0.021$). Published normative data for each behavioral/emotional measure was then used to reclassify the entire sample into clinical and nonclinical groups on each measure. Unpaired *t* tests found that children who fell into the clinical ranges on the parent report and child symptom report behavioral measures took a significantly longer time to go into REM sleep. Type of seizure disorder (generalized vs. partial) and the presence or absence of current seizures did not affect these findings. **Conclusions:** The present research supports the hypothesis that sleep disruption is associated with increased behaviors such as hyperactive–impulsive/inattentiveness and depression in children with epilepsy. This research is relevant to clinical care because it may aid clinicians in the recognition and treatment of sleep disorders, thus potentially reducing sei-

zure frequency and improving quality of life for children with epilepsy. (Supported by University of Florida, Division of Sponsored Research.)

1.186
VAGUS NERVE STIMULATION: IMPROVED BEHAVIOR BUT NOT COGNITION IN CHILDREN

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Rationale: Prolonged intermittent left vagal nerve stimulation (VNS) has been shown to be an effective adjunct treatment that suppresses the occurrence of seizures in children. There is evidence for improvements on subjective ratings scales, but few studies have utilized quantitative measures to investigate the influence of VNS on cognition, mood, and behavior. A recent study (Hoppe et al.) suggested that VNS does not affect cognitive functioning in adults over time. A similar study in children with Lennox–Gastaut syndrome (Aldenkamp et al.) showed no significant change across tests measuring mental age, language, attention, cognitive style, behavior, and mood. This study examined a group of children with intractable epilepsy treated with VNS for 12 months with a battery of cognitive and behavioral measures. The goal of this investigation was to better understand the long-term cognitive and behavioral effects of VNS treatment in a cohort of children. **Methods:** Ten children (aged 6–18 years) with intractible epilepsy were examined before implantation with the Cyberonics Inc. Vagus Nerve Stimulator on standardized measures assessing cognition and behavior. Six participants were available for examination at 12 months after implantation. The cognitive test battery consisted of three domains that assessed overall intelligence (Wechsler Abbreviated Intelligence Scale), attention (Digit Span/Finger Windows), and learning/memory (California Verbal Learning Test/Visual Learning from WRAML). The behavioral outcome battery consisted of parent ratings on the Behavior Parent Rating Scale (BASC Behavioral Symptoms Composite) and the Vineland Adaptive Rating Scale (Communication, Daily Living Skills, Socializaton, and Adaptive Behavior). The percentage change in seizure frequency was also collected. Intergroup comparisons of changes in standardized scores (based on normative data) on the measures were conducted across time intervals utilizing individual Mann–Whitney *U* tests. The relation between cognitive performance, behavior ratings, and seizure reduction was examined utilizing Spearman's rank correlations. **Results:** Five of six patients experienced a positive seizure reduction at 12 months after implantation. The results of Mann–Whitney *U* tests comparing baseline and 12-month follow-up revealed no significant change on the cognitive domains of attention ($p = 0.91$), learning/memory ($p = 0.60$), and overall intelligence ($p = 0.95$). The results from the parent ratings indicated a significant decrease in behavioral symptoms ($p = 0.04$). Although no significant changes were noted on the Vineland scales, there was a trend noted for improvement in parent ratings of adaptive skills ($p = 0.10$). There were no significant correlations between seizure attenuation and changes in cognitive scores and behavior ratings. **Conclusions:** These findings provide further support for the notion that treatment with VNS does not result in a measurable increase in cognitive functioning. However, it suggests that it is associated with improvement in behavioral functioning and adaptive skills. Our findings confirm beneficial effects of long-term VNS with respect to overall quality of life.

1.187
NEUROPSYCHOLOGICAL FINDINGS AT FIRST RECOGNIZED SEIZURE: COMPARISON OF CHILDREN WITH AND WITHOUT ABNORMAL MAGNETIC RESONANCE IMAGING

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Rationale: Previous studies have suggested that neuropsychological deficits may be present very early in the course of childhood epilepsy (Fastenau et al., 1999; Powrozek et al., 2000). Attention, psychomotor speed, receptive language, and memory were most affected, although not all children with newly recognized seizures demonstrated such deficits. This study of 75 children with newly recognized seizures compared those with abnormal findings on magnetic resonance imaging (MRI) of the brain with those with normal MRIs in terms of neurospychological functioning. At the end of this activity, participants should be able to discuss the relation between brain-imaging abnormalities and neuropsychological functioning in children with newly recognized seizures. **Methods:** Children and adolescents were recruited for this study within 6 months of their first recognized seizure. The sample ranged in age from 6 to 15 years (mean age, 9.27 years; SD, 2.29 years). Forty-nine percent of the children were girls. The majority of the children were white (87%), with African-American (9%), multiethnic (3%), and Hispanic (1%) children making up the remainder of the sample. Children underwent MRI an average of 1.3 months after the first recognized seizure. They underwent neuropsychological evaluation an average of 2.5 months after the first recognized seizure. The evaluation consisted of a 3-h battery of tests measuring intellectual ability, academic achievement, language, memory, psychomotor speed, attention, and executive function. **Results:** Eight of the 75 children (11%) with newly recognized seizures had MRI abnormalities that were judged to be significant and possibly related to their seizures. These included gray matter heterotopia, cortical dysplasia, leukomalacia, and volume loss. There were no mass lesions. Another 19 children (25%) had MRI abnormalities that were judged to be insignificant and unlikely related to their seizures such as Chiari I malformation and dilated perivascular spaces. Multivariate analysis of variance comparing those children with and without significant MRI abnormality on neuropsychological testing showed marginally significant differences on verbal memory ($p = 0.095$) and psychomotor speed ($p = 0.096$). There were no differences in other neuropsychological domains, including intelligence, academic achievement, language, attention, or executive function. **Conclusions:** These findings suggest that the variability in neuropsychological functioning in children with newly recognized seizures may be due to underlying brain abnormalities. The group with significant MRI abnormalities was very small ($n = 8$), however, and therefore the findings should be viewed with caution. Memory and psychomotor speed are likely to be most impaired in children who demonstrate deficit early in the course of epilepsy, consistent with previous research. (Supported by NIH grant NS 22416 to J.K. Austin.) [Disclosure: Grant: NS 22416 (NIH) J.K. Austin, Principal Investigator.]

1.188
HIGHER-LEVEL LINGUISTIC SKILLS AFTER PEDIATRIC HEMISPHERECTOMY

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Rationale: Lovett et al. (1986) described poor organization of narrative with overuse of unclear/ambiguous pronouns for reference after left hemispherectomy, but well-organized narrative and appropriate reference use after right hemispherectomy. Evidence from normal adults (Caplan and Dapretto, 2001) and unilateral brain-damage patients (Brownell et al., 1992) suggests that the left hemisphere is involved in understanding the reasoning and the right hemisphere in topic maintenance during conversation. This study examined how children

who underwent hemispherectomy for intractable epilepsy used language to formulate their thoughts during conversation. We predicted that before and after surgery, children with a left or right hemispherectomy would differ in their discourse profiles with impaired reasoning and use of lexical ties (i.e., cohesion) after left hemispherectomy, but impaired topic maintenance after right hemispherectomy. We posited that these deficits would relate to postsurgical seizure control and type of underlying pathology. **Methods:** Reliable and valid reasoning, topic maintenance, and cohesion measures were coded from transcriptions of the Story Game (Caplan et al., 1989, 1992) of 19 children (eight boys, 11 girls), aged 10.7 years (SD, 3.84 years), before and 15.3 (SD, 18.97) months after hemispherectomy (13 left, six right). These scores were compared with those of 314 normal children, aged 5–18 years. Nine patients had cortical dysplasia and 10 had Rasmussen encephalitis. Thirteen patients had seizure control at their last postoperative visit. **Results:** After correcting for age, a repeated-measures analysis of variance demonstrated that, irrespective of the side of surgery, the patients had significantly more illogical thinking ($p < 0.005$), more loose associations ($p < 0.08$), and fewer utterances ($p < 0.0001$) before and after surgery compared with the normal children. They also made significantly fewer cohesive ties using conjunctions ($p < 0.002$), referential cohesion ($p < 0.008$), lexical cohesion ($p < 0.004$), unclear/ambiguous reference ($p < 0.001$), and substitution ($p < 0.004$) than the normal children. The children with an isolated right hemisphere, however, were significantly more impaired in using conjunctions ($p < 0.02$), referential cohesion ($p < 0.03$), and lexical cohesion ($p < 0.03$) than those with an isolated left hemisphere. There was a significant decrease in illogical thinking ($p < 0.01$) and substitution ($p < 0.04$) at the first postsurgical visit, but no subsequent improvement. Loose associations ($p < 0.02$), but none of the cohesion measures improved over time. The Rasmussen patients had significantly more topic maintenance and cohesion deficits than the cortical dysplasia patients. Postsurgical seizure control was unrelated to the findings. **Conclusions:** These findings imply plasticity, albeit limited, in both left and right hemispheres for higher-level linguistic skills involving organization of thoughts and use of linguistic ties that connect ideas across sentences during conversation. Continued deficits after surgery suggest more limited plasticity in the isolated right hemisphere for cohesion. In children with cortical dysplasia, the isolated hemisphere might have more plasticity for higher-level linguistic skills than in Rasmussen encephalitis. (Supported by PO1 NS28383 and R01 NS39505.)

1.189
ARE SLEEP DISRUPTION AND BEHAVIORAL PROBLEMS RELATED IN CHILDREN WITH EPILEPSY?

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Rationale: Children with epilepsy have more behavioral problems and more sleep disturbances than children in the general population. Previous studies have shown changes in sleep architecture, excessive daytime sleepiness, poor-quality sleep, and parasomnias in children with epilepsy. The purpose of this study was to assess the association between behavioral problems and sleep disorders in children with epilepsy. **Methods:** We identified 174 children with chronic seizures currently taking antiepileptic drugs (AEDs). The children were aged 9–14 years and had seizures for a mean duration of 5.2 years (SD, 3.9 years). Problems with sleep were determined using the six questions concerning sleep (nightmares, overtired, sleeps less than most kids, sleeps more than most kids, talks or walks in sleep, trouble sleeping) on the Child Behavior Checklist (CBCL). Behavior was assessed using the CBCL, Child Depression Inventory, and Piers–Harris Self-concept Scale. Differences in behavioral scores were compared for children with and without sleep disturbance by using *t* tests. **Results:** Compared with children without sleep problems, the mean scores for CBCL Total Behavior, Internalizing, and Externalizing scales were significantly higher for children with each of the six sleep problems ($p < 0.001$ for five of six Total Behavior mean scores, six of six Internalizing mean scores, and three of six Externalizing mean scores; $p < 0.05$ for one of six Total Behavior mean scores and three of six Externalizing mean scores). Children with nightmares and trouble sleeping had more depression (nightmares, $p < 0.002$; trouble sleeping, $p < 0.02$) and poorer self-concepts (nightmares, $p < 0.002$; trouble sleeping, $p < 0.04$) than those without sleep disturbances. **Conclusions:** There is a significant association between behavioral problems and sleep disturbance in children with epilepsy. The presence of behavioral problems should trigger assessment of sleep in children with seizures. (Supported by NR04836.)

1.190
NEUROCOGNITIVE FUNCTIONING IN 23 CHILDREN WITHOUT NEUROLOGIC SYMPTOMS OTHER THAN EPILEPSY

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Rationale: The aim of this study was to evaluate cognitive and neuropsychological functioning in children with epilepsy only (i.e., without additional neuroimpairments or significant learning disabilities) and to evaluate the possible role of various epilepsy-related factors in this respect. **Methods:** The study group consisted of of 23 children aged 7–15 years with idiopathic or cryptogenic, generalized or localization-related epilepsy. All children attended mainstream school at age-appropriate level and did not have any other neurologic diagnoses or therapies except antiepileptic drug (AED) treatment. Medical data including demographic factors, duration of epilepsy, seizure type, seizure control, EEG, magnetic resonance imaging (MRI), current AEDs, and most recent AED levels were analyzed through medical charts and records. All children attended two test sessions for general cognitive abilities (WISC-R) and neuropsychological functioning (developmental neuropsychological assesment battery, NEPSY; Korkman et al., 1998). **Results:** The study group consisted of six boys and 17 girls with a mean age of 12.5 years and mean duration of epilepsy of 4.1 years at time of the study. Type of epilepsy was localization-related in 17 children and generalized in six. Seizure control was good (>1-year remission) in 11 children and partial (seizures randomly but fewer than one/month) in 12. The general cognitive performance (WISC-R) of the study group did not differ from normative data (full scale IQ, 102; verbal IQ, 100; performance IQ, 104). The study group performed significantly ($p < 0.05$) worse compared with norms only in one WISC-R subtest (coding) and significantly better in three subtests (arithmetic, picture arrangement, and block design). Neuropsychological sumvariables showed significantly worse performance in the study group in visual short-term memory but significantly better performance in design copying, picture recognition, and sentence repetition. Children with localization-related epilepsy performed significantly worse in narrative memory and list learning and the partial control group in two WISC-R subtests (digit span and coding) and in three neuropsychological subtests (auditive attention, list learning, and picture memorizing). Polytherapy group performed significantly worse in verbal fluency. Demographic factors, age at onset of epilepsy, duration of epilepsy, AED currently in use, or recent AED serum levels did not show any statistical correlation with the neuropsychological or cognitive test results. **Conclusions:** Some specific neuropsychological problems do exist in school-aged children with normal general cognitive ability and epilepsy. In detailed neuropsychological assesment, they seem to perform significantly worse (e.g., in visual short-term memory). The problems in memory, learning, and attention seem to be most prevalent in children with only partial seizure control, but also localization-related epilepsy and/or polytherapy seem to increase this risk. Seizures, EEG abnormalities, and AED treatment have an complex—possibly cumulative—effect on cognitive performance and neuropsychological functioning. (Supported by A. & L. Ylppö Foundation.)

1.191

NEUROPSYCHOLOGICAL FUNCTIONING AT FIRST RECOGNIZED SEIZURE: COMPARISONS WITH SIBLING CONTROLS AND EFFECTS OF PRIOR UNRECOGNIZED SEIZURES

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Rationale: A prior study suggested that neuropsychological (NP) deficits are present near onset of epilepsy in children (Fastenau et al., 1999), especially in children who have had prior unrecognized seizures (PURSs). Attention, psychomotor speed, receptive language, and memory were most affected. Children with PURSs showed greater NP deficits than those without PURSs (Powrozek et al., 2000), similar to the effect of PURSs on behavior problems (Austin et al., 2001). However, those NP studies were limited by small sample size, and time between onset and testing was prolonged for many children. The present study compared children with first-recognized seizures (FRSs) with sibling controls on NP functioning in a larger sample and closer to onset of the FRSs. In addition, children with PURSs were compared to those without PURSs. At the end of this activity, participants should be able to discuss the effects of prior untreated seizures on NP functioning. **Methods:** Children were tested within 6 months (M = 2.5) of their FRS. Children with a FRS (n = 105) ranged in age from 6 to 15 (M = 9.4, SD = 2.4); 49% were girls, and 7% were left-handed. A healthy sibling closest in age to the child was recruited as a control; not all children with FRS had an eligible sibling, resulting in a smaller control group (n = 67). Controls ranged in age from 5 to 16 (M = 10.1, SD = 2.8); 49% were girls. There was no difference ($p > 0.10$) on IQ between affected children (M = 100.2, SD = 16.2) and controls (M = 101.1, SD = 12.5). During a detailed interview at the time of enrollment into the study, 60% of children with FRS reported having had a PURS. All children completed a 3-h battery of NP tests measuring processing speed, attention, memory, language, executive processing, spatial skills, and academic achievement. **Results:** Multivariate analysis of covariance (MANCOVA; covarying on site) comparing affected children to their matched sibling controls using patient–sibling difference scores on NP variables (organized by a priori constructs) revealed no differences between the groups ($p > 0.10$). MANCOVA comparing children with PURSs to those without PURSs revealed three trends, all in the predicted direction; the PURSs group performed worse on attention ($p = 0.06$), processing speed ($p = 0.09$), and visuospatial skills ($p = 0.09$). **Conclusions:** Although these data are preliminary, there was some support for our hypothesis; trends were observed showing possible adverse effects of prior unrecognized, untreated seizures. Because NP evaluation was conducted soon after the FRS, the cognitive inefficiencies among children with FRSs are not likely to be due to medication effects. Our other hypothesis was not supported; we failed to find differences between children with a FRS and their siblings. Because the present analyses are based on baseline data after the FRS, it is not yet known which of these children will experience a second unprovoked seizure (i.e., be diagnosed with epilepsy); consequently, these results likely underestimate the effects of seizures at the onset of epilepsy. (Supported by NIH/NINDS NS 22416.)

1.192

BENEFICIAL EFFECTS OF ENRICHED ENVIRONMENT AFTER STATUS EPILEPTICUS IN IMMATURE RATS

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Rationale: Status epilepticus (SE) has a high mortality and morbidity rate in children. In children who survive SE, disturbances in learning and memory are frequent sequelae. There is increasing evidence that enriching the environment can improve cognitive and motor deficits after a variety of brain injuries. The goal of this study was to determine whether the environment in which animals are raised influences cognitive function after SE. **Methods:** Rats underwent lithium–pilocarpine-induced SE at postnatal (P) day 20. After SE, animals were randomly assigned to either an enriched environment or standard vivarium care for 28 days. Assessments of neurogenesis using bromodeoxyuridine (BrdU) analysis and pCREB immunostaining were made at 2 times during the enriched-environment phase of the study: P29 when the rats had been exposed to the enriched or nonenriched environment for 9 days; and P49, the last day in the environment. The animals were tested in the water maze from P50 to P55. BrdU analysis and pCREB immunostaining were made at 2 times during the water-maze testing: P51 after 1 day of testing; and P55, after completion of the probe test. **Results:** Whereas both the enriched and nonenriched showed reductions in escape latencies over 4 days of testing [$F(3, 46) = 6.007$; $p = 0.002$], the enriched group performed significantly better than the nonenriched group in the water maze [$F(1, 20) = 5.5203$; $p = 0.029$]. In addition, the enriched group spent more time in the target quadrant during the probe test than the controls ($t = 2.751$; $p = 0.012$). No differences were noted in the swimming speed in the two groups ($t = 0.445$, $p = 0.660$). There was a significantly increased number of BrdU-labeled cells in the animals raised in the enriched environment at P29 ($t = 3.041$; $p = 0.038$), but not at the other time points. To determine the identity of the BrdU-labeled cells, sections from both enriched and nonenriched killed at P29 underwent fluorescence double-label immunohistochemistry. In both the enriched and nonenriched groups, the majority of BrdU-labeled nuclei in the dentate granule cell layer exhibited colocalization with NeuN [enriched 233 of 332 (70.2%); nonenriched 169 of 211 (80.1%); $\chi 2 = 0.474$, $p = 0.491$]. A significant increase in pCREB-immunostained cells was found in animals exposed to the enriched environment at P29 ($t = 3.315$; $p = 0.030$); P49 ($t = 3.834$; $p = 0.018$), and P51 ($t = 4.060$; $p = 0.015$) but not at P55 ($p > 0.05$). **Conclusions:** This study demonstrates that exposure to an enriched environment after SE in weanling rats significantly improves cognitive function. The increased neurogenesis and activation of transcription factors associated with the enriched environment likely contributes to this enhanced visual–spatial memory. At the end of this presentation, participants should be able to understand the importance of environmental stimulation after status epilepticus. [Supported by A Mental Retardation Research Center grant from NIH (2P30HD18655) and a grant from the NINDS (NS27984) to G.L.H.]

1.193

INTEGRATED APPROACH TO EPILEPSY IN HEMIMEGALENCEPHALY

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Rationale: Hemimegalencephaly (HME) is a rare asymmetric hamartomatous brain malformation. Epilepsy is usually severe and begins early. We attempt to establish diagnostic criteria integrating clinical, imaging, and neuropathological parameters and correlations with epilepsy. **Methods:** We studied 12 children with HME, confirmed by imaging: five boys and seven girls, aged 3 days to 2.5 years when first seen. All patients had seizures with onset before 1 year in 11, with four newborns. The epilepsy was partial in 10 patients, tonic and infantile spasms in one patient, and one had epilepsia partialies continua. All were studied with computed tomography (CT), magnetic resonance imaging (MRI) and EEG. Three patients underwent hemispherectomy for intractable seizures, and one died during the procedure. We performed neuropathologic investigations in these three, including immunocytochemistry for neuronal and glial maturation. **Results:** Six cases of HME were isolated, and six were syndromic, associated with epidermal nevus; two presented with hemifacial lipoma. Of the 12 patients, five exhibited hemiparesis, four had generalized hypotonia, and three had no overt motor deficit. The clinical and imaging features corresponded to moderate or severe HME; none of our cases was mild.

EEG studies showed asymmetric paroxysmal activity in all. MRI showed colpocephaly in five patients, reduced ventricles in one, and asymmetric cortical dysplasia in 11. The "occipital sign" (displacement of the occipital lobe to the opposite side) was observed in six. Neuropathologic studies using synaptophysin demonstrated that single heterotopic neurons in white matter are not "isolated" as they appear histologically, but are connected with grey matter neurons by axonal projections and synapses with afferent axons. These heterotopic connected neurons included some, but not all, balloon cells. Many cells were of mixed lineage, coexpressing both neuronal and glial proteins. **Conclusions:** Epilepsy affected all of our patients with HME. Clinical, EEG, and imaging data are essential for the selection of patients for hemispherectomy. Neuropathologic examination with immunocytochemistry provides new information in the pathogenesis of HME and insight into epileptogenesis. Heterotopic individual neurons and balloon cells and others with mixed lineage in white matter may contribute to epilepsy because they are not synaptically isolated. No pathological studies of mild cases are available.

1.194

DEGREE OF SLEEP ATTAINED DURING EEG AS A MODERATER OF THE RELATION BETWEEN SPIKE–WAVE DISCHARGES AND NEUROPSYCHOLOGICAL PERFORMANCE

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Rationale: In adults, neuropsychological functioning was correlated with spike–wave discharges (SW), but in a recent study with children, this relation was not observed (Koop et al., 2000). The lack of a correlation in children may be due to more subtle SWs that were undetected. Sleep deprivation before an EEG increases sensitivity to SWs (Liamsuwan et al., 2000). Thus, it was hypothesized that the degree of sleep attained during EEG recording would moderate the relation between SW discharges and neuropsychological performance. At the conclusion of this presentation, the participant will better understand the relation between sleep, SWs, and neuropsychological functioning. **Methods:** Memory and attention scores on standardized tests were obtained in 70 children with epilepsy (age M = 10.8, SD = 2.7; 34.3% recent onset, 65.7% chronic). Clinical reports of the most recent EEG recording were reviewed and coded for degree of sleep attained (none, drowsy, stage 2). **Results:** As a manipulation check, the relation between sleep and SWs was examined; although not significant in this small sample ($\chi 2 = 2.96$, $p > 0.05$), higher proportions of children showed SWs with stage 2 sleep (73%) than did those who did not attain stage 2 sleep (53%). In a 2 × 3 (Presence of SW × Level of sleep) analysis of variance on memory, there was no main effect for sleep, $F(2, 67) = 0.45$, $p > 0.05$, or for SW, $F(1, 69) = 0.55$, $p > 0.05$, nor was the interaction term significant, $F(2, 69) = 0.89$, $p > 0.05$. In a 2 × 3 (Presence of SW × Level of sleep) ANOVA on attention, there was no main effect for sleep, $F(2, 67) = 0.48$, $p > 0.05$, or for SW, $F(1, 69) = 0.15$, $p > 0.05$, nor was the interaction term significant, $F(2, 69) = 1.37$, $p > 0.05$. However, the pattern of means for the six groups generally followed the pattern hypothesized (worse memory and attention with presence of SWs, but only when sleep was attained). This pattern was even more evident in the chronic subsample. **Conclusions:** The degree of sleep attained during EEG did not moderate the relation between SWs and neuropsychological performance. However, the pattern of subgroup means supported the hypothesis, even though the differences did not reach the prescribed level of significance. Similarly, the relation between SW detection and levels of sleep followed the predicted pattern, without reaching significance in this sample. Part of the reason for this may lie in the constitution of the sample. Although the sample size was reasonable, approximately one third of this sample had recent onset of seizures; consequently, limited variability in SWs and/or in neuropsychological functioning may have attenuated the effect sizes. Future studies should examine the potential moderating relation in a larger sample of children with chronic epilepsy. (Supported by Epilepsy Foundation, NIH/NINDS NS22416, and NIH/NINR NR04836.)

1.195

LAMOTRIGINE ADJUNCTIVE THERAPY IMPROVES BEHAVIOR IN ADOLESCENTS WITH MENTAL RETARDATION AND REFRACTORY EPILEPSY

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Rationale: Epilepsy and behavioral disorders are frequent comorbid conditions in persons with mental retardation (MR). In a trial evaluating the efficacy of lamotrigine (LTG) in persons with epilepsy and MR (*Neurology* 2000;54(suppl 3):A192), behavioral assessments (Aberrant Behavior Checklist, ABC; Habilitative Improvement Scale, HIS) were used to address this issue. **Methods:** Persons (12 years or older) taking one to three antiepileptic drugs (AEDs) but still having seizures, entered an 8-week baseline with doses of concurrent AEDs kept constant. LTG (Lamictal) was titrated over the next 8 weeks, and then during an 8-week maintenance, doses of AEDs were held constant. During the next 12 weeks of optimization, the number/doses of AEDs were adjusted as needed for optimal response. Outcome measurements were changes from baseline to week 36. **Results:** For the adolescent subgroup (older than 12 and 20 years or younger), n = 22, 50% female, with mean age of 17 years. Level of MR was 18% mild, 18% moderate, 23% severe, and 41% profound. Patients were in private families (68%), institutions (27%), and group homes (5%). Most common seizures types were complex partial (36%), partial with secondary generalization (23%), primary generalized (45% tonic–clonic, 23% myoclonic, 18% absence). The mean LTG dose during optimization was 193 mg/day with valproate (VPA), 375 mg/day without VPA. Of all adolescent patients, 15% became seizure free, and 40% experienced a 75% decrease in seizures. Mean HIS score improvement (8.7–16.2) was significant ($p < 0.01$). All five ABC dimensions showed improvement, with mean scores improving significantly ($p < 0.05$) for Lethargy (7.7–3.7), for Hyperactivity (6.8–4.5), and stereotypic behavior (2.7–1.7). **Conclusions:** LTG decreased both seizure frequency and maladaptive behavior, improving social behavior and habilitation potential in adolescents with epilepsy and MR. (Supported by GlaxoSmithKline.) (Disclosure: Salary: Vuong, Hammer, Messenheimer; Grant: McKee, Messenheimer; Stock: Vuong, Messenheimer.)

1.196

PSYCHOPATHOLOGY IN CHILDREN UNDERGOING TEMPORAL LOBECTOMY FOR INTRACTABLE EPILEPSY: A PRE- AND POSTOPERATIVE ASSESSMENT

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Rationale: Children with epilepsy are at increased risk of mental health problems, but the psychiatric outcome of childhood epilepsy surgery has not been examined. The aim of this study is to establish the spectrum of psychiatric illness in children before and after temporal lobectomy. **Methods:** The case notes for all children who underwent temporal lobectomy at Great Ormond Street Hospital, London, between 1992 and 1998 were reviewed independently by two professionals (a child psychiatrist and a paediatric neurologist), and a clinical rating scale was applied both pre- and postoperatively to establish DSM-IV criteria psychiatric diagnoses. Relevant clinical information including postoperative outcome was obtained, and EEG and neuroimaging were reviewed. Children with progressive pathology were excluded. **Results:** Sixty children [35 boys (58%); 32 left-sided lesions (53%)] fulfilled the study criteria and had undergone a total of 71 procedures with a mean age at first operation of 10.6 years. Mean age at seizure onset was 3.43 years. A DSM-IV psychiatric diagnosis was established

in 50 of 60 (83%) of these children at some point. Forty-three of 60 (72%) had a DSM-IV mental health disorder diagnosis preoperatively and 41 of 57 (72%) postoperatively (mean length of postoperative follow-up, 5.1 years; three were lost to follow-up). Pervasive developmental disorders (PDDs) were present in 23 of 60 children (38%), disruptive behaviour disorder (DBD) in 36 of 60 (60%), attention deficit–hyperactivity disorder (ADHD) in 16 of 60 (27%), oppositional defiant disorder/conduct disorder (ODD/CD) in 16 of 60 (27%), and emotional disorders in 15 of 50 (25%). There were two children each with eating disorders and conversion disorders and one child with psychosis. Children with PDDs had a younger age at seizure onset (1.74 years; $p \leq 0.05$) compared with children without PDDs. PDDs were significantly associated with right-sided temporal lobe lesions and male sex. There was no relation between type of pathology or seizure frequency and PDD. Increased epileptiform discharges during sleep and disturbed sleep architecture on EEG were associated with PDD. ADHD (39 vs. 19%) and DBD (83 vs. 46%) were more common among the children with PDDs compared with those without, but emotional disorders were less frequent (9 vs. 35%). There was improvement in PDDs postoperatively in 13 of 23 (57%) and deterioration in the disorder in three of 23 (13%). ADHD and DBDs were both more common amongst boys ($p \leq 0.05$). Emotional disorders were most common amongst children with normal IQ (13 of 15) and evolved postoperatively in 67% (10 of 15) cases. There was no relation between the evolution of a new disorder or any change in the severity of psychiatric disorders and seizure outcome. **Conclusions:** Mental health problems are very common amongst children undergoing temporal lobectomy for intractable epilepsy and are present in 83% in this study. There is a chance of emotional and behavioural improvement after surgery unrelated to seizure control. However, parents and patients should be counseled about the possibility of the emergence of new mental health disorders or a deterioration in existing psychopathology postoperatively, which may actually be part of the natural history of the disorder rather than the result of surgery itself.

1.197
ANXIETY AND DEPRESSIVE SYMPTOMS IN PEDIATRIC EPILEPSY PATIENTS

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Rationale: Existing studies in children and adults report an overrepresentation of anxiety and depression in epilepsy patients. Still the characterization of such symptoms has eluded specific description, and particularly in pediatric epilepsy, fewer studies exist overall. At the end of this activity, participants will better understand the nature of anxiety and depressive symptoms present in chronic pediatric epilepsy patients. **Methods:** Thirty-five chronic epilepsy patients (18 boys, 17 girls) were consecutively recruited to participate. Ages ranged from 8 to 16 years (average, 11.7 years), estimated IQ was >70, and estimated reading ability was at least fair. None had received psychiatric treatment or assessment in the past. Patients completed standardized questionnaires including the Multidimensional Anxiety Scale for Children (MASC) and the Children's Depression Inventory (CDI). The MASC is a 39-item questionnaire that asks for one of four symptom-severity ratings per item. MASC profiles include overall scores as well as subscale scores for specific anxiety symptoms including physical symptoms (tense/restless, somatic/autonomic), harm avoidance (perfectionism, anxious/coping), social anxiety (humiliation/rejection, performance fears), and separation/panic. The CDI contains 27 items and asks for one of three symptom-severity ratings per item. CDI profiles include overall scores and subscores of negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem. Overall scores and subscores were tabulated for each measure. Cinically significant levels were defined as t scores of $\geq$65, reflecting levels $\geq$1.5 standard deviations above the normative mean for the measures. **Results:** Ten (28.6%) of 35 had overall significant scores on the MASC. Additionally, 60% (21 of 35) had at least one significant subscore elevation on the MASC. Significant symptom subcategories included 37.1% (13 of 35) with separation/panic, 22.9% (eight of 35) with somatic/autonomic, 17.1% (six of 35) with humiliation/rejection, 14.3% (five of 35) with tense/restless, 14.3% (five of 35) with performance fears, two of 35 (5.7%) with anxious/coping, and one of 35 (2.9%) with perfectionism. Two of 35 (5.7%) had overall significant scores on the CDI, and six of 35 (17.1%) had at least one significant subscore elevation. No CDI subcategory had more than two of 35 respondents indicating significant symptoms. **Conclusions:** Anxiety symptoms were very common in this sample of pediatric epilepsy patients who had not previously been referred to psychiatry. The majority of patients had at least one elevated anxiety subscore. The subcategory of separation/panic was particularly common, and notable well beyond the next most common subcategory elevation of somatic/autonomic symptoms. Symptoms of harm avoidance (perfectionism, anxious/coping) were notable for their lack of prominence. The preferential anxiety symptom profile may have some specific relevance to epilepsy patients. Depressive symptoms were neither prominent in overall scores nor in subcategory scores. It is possible that such patients were already referred to psychiatry and thus not a part of the sample. Further study is important to appropriately provide comprehensive care and reduce potential morbidity among pediatric epilepsy patients. (Supported by Children's Research Institute, Children's National Medical Center, Washington, DC.)

1.198
SEX DIFFERENCES IN MEMORY IN CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: Of the many potential risk factors for memory impairment in children with epilepsy, one that has not received much attention is that of sex, although sex differences in memory have been reported in the general population. The objective of the present study was to determine whether the child's sex has a differential impact on performance on verbal and visual memory tasks. **Methods:** The participants included 51 children and adolescents (26 boys, 25 girls) with intractable epilepsy, ranging in age from 7 to 18 years (mean, 13.1). Four standardized tests of memory were administered. The verbal memory measures included a task requiring the learning and recall of a list of words presented over five trials, and a task requiring the recall of the content of a short story. Visual memory was assessed by asking the children to recognize, from among distracters, photographs of faces they had briefly viewed, and through the recall of a complex geometric design. **Results:** Analyses were conducted using age and IQ as covariates to control for within-group variability. Girls obtained higher scores on all verbal memory tasks, with the differences reaching significance on the measures of word-list learning, and immediate and delayed recall of the story. No sex differences were found on the visual memory tasks. **Conclusions:** As is true in the general population, children with intractable epilepsy show sex differences in verbal memory, with girls having an advantage over boys. These differences appeared to be more pronounced in this group than in children without epilepsy. These results suggest that in understanding the impact of epilepsy on memory, the child's sex should be considered. Because of their more pronounced verbal learning and memory deficits, boys with intractable epilepsy may be at greater risk than girls for difficulty and failure in school. At the end of this presentation, participants should be aware that girls with intractable epilepsy have better verbal learning and memory abilities than do boys. (Supported by The Ontario Mental Health Foundation.)

1.199
THE IMPACT OF ATTENTION AND OTHER NEUROPSYCHOLOGICAL SKILLS ON MEMORY TEST PERFORMANCE IN CHILDREN WITH EPILEPSY

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Rationale: Memory tests play an important role in the neuropsychological evaluation of children with epilepsy. However, our understand-

ing of how memory test performance can be affected by deficits of other abilities such as attention is limited. We studied several measures of attention and other neuropsychological skills in relation to memory task performance to understand how measures of attention and other skills are related to memory test performance in childhood epilepsy. **Methods:** Thirty-five children from a tertiary pediatric epilepsy center with a mean age of 12.5 ± 2.1 years and a mean seizure onset of 6.3 ± 3.8 years were studied. Neuropsychological testing included the WISC-III, which yielded a mean Full-Scale IQ (FSIQ) of 84.6 ± 16.8, as well as the indices of Verbal Comprehension (VC) and Perceptual Organization (PO) from the WISC-III. Memory indices were generated from the Children's Memory Scale (CMS) and the California Verbal Learning Test–Children's Revision. Attention measures included the Freedom from Distractibility (FD) and Processing Speed (PS) indices of the WISC-III, a focal attention index from the Cognitive Assessment System (CASFA), and a sustained attention index, the reaction time standard error of the Conners Continuous Performance Test (CPTSE). **Results:** Pearson correlations indicated that general verbal and visual memory indices were both associated with FSIQ, VC, and PO. General verbal memory was more strongly associated with VC than with other abilities. All indices of attention except CPTSE were moderately but nonspecifically correlated with general verbal and visual memory. Individual CMS memory subtest correlations revealed a stronger relation between Story Memory scores and VC than between Story Memory and other indices of ability and attention. In contrast, Word Pairs correlated in a nonspecific manner with all indices of ability and attention except CPTSE. The Facial and Dot Memory tasks yielded generally weaker and nonspecific correlations with measures of ability and attention. CPTSE failed to correlate significantly with any of the memory indices. In regression analyses, only VC contributed uniquely to general verbal memory and Story Memory performance, and only PS to general visual memory. **Conclusions:** Our results suggest that deficits of abilities such as attention and verbal working memory should be regarded with caution as factors that can account for poor memory task performance. Though they correlated with memory indices, their associations tended to be modest and nonspecific. These findings enhance our understanding of factors related to clinical memory test performance and will enable us to better interpret the neuropsychological test results of children with epilepsy. For example, the strong association between narrative memory performance and general verbal ability suggests that narrative memory tasks may be more useful than rote verbal learning procedures in localizing the neural substrate of verbal memory compromise in children with epilepsy. Improved neuropsychological assessment techniques should also allow us to better identify patterns of performance that are indicative of specific epilepsy syndromes. (Supported by internal funding.)

1.200

DURATION, NOT AGE, DETERMINES THE EFFICACY OF DIAZEPAM IN TERMINATING SECONDARILY GENERALIZED STATUS EPILEPTICUS

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Rationale: There is ample evidence from both clinical and animal studies that the efficacy of benzodiazepine (BZD) intervention in the adult is inversely related to seizure duration. This relation has not been well studied in children. The objective of this study is to investigate the relation between age and success of BZD treatment in the lithium–pilocarpine (Li-Pilo) model of secondarily generalized seizures in the rat using three age groups, roughly corresponding to the human ages of infancy, adolescence, and adult. At the end of this activity, the participants should be able to discuss the relation between seizure duration, age, and treatment of prolonged seizures. **Methods:** Male Sprague–Dawley rats had left frontal and parietal epidural electrodes implanted on P8, P12, P18, and P58. Status epilepticus (SE) was induced through pretreatment with intraperitoneal lithium (3 mEq/kg) followed ~20 h later by subcutaneous pilocarpine on P10 (100 mg/kg), P15 (60 mg/kg), P20 (30 mg/kg), and P60 or later (30 mg/kg). Electrographic onset of SE was defined as the onset of continuous, rhythmic epileptiform discharges lasting ≥30 s. Before pilocarpine injection, animals were randomized to time of diazepam (DZP) injection: 5, 15, 30, 60, and 120 min after seizure onset. DZP was administered intraperitoneally. The dosage of DZP in each age group (n = 3) was determined in pilot studies as the minimal dose required to consistently terminate seizures of 5 min in duration. Seizure termination was defined as the absence of continuous or periodic seizure activity as well as the absence of spikes 15 min after the administration of DZP. **Results:** Behavioral changes were observed within 3 min of pilocarpine injection in all age groups. The electrographic onset of SE typically occurred 15–30 min after the injection of pilocarpine and, in the majority of animals, corresponded to or was observed just before the onset of forelimb clonus. Of interest, while behavioral changes such as shivering were observed in the P10 rat, forelimb clonus was never observed, and continuous surface EEG recording for ≤2 h after pilocarpine injection failed to reveal continuous, rhythmic epileptiform discharges. Therefore, the P10 age group was not used in the assessment of DZP efficacy. Based on the design of this experiment, DZP was effective in terminating all seizures of 5 min in duration in all age groups. However, the DZP dose was less effective in terminating seizures of longer duration in the two younger age groups (P15 and P20) as well as in the adults. This decline in efficacy was present as early as 15 min after seizure onset in all age groups. **Conclusions:** These findings demonstrate that DZP efficacy in the Li-Pilo model of secondarily generalized SE is inversely related to seizure duration in these age groups and provide further evidence that intervention for SE should commence early. (Supported by The National Epifellows, NIH grant 32NS07473, and NINDS NS27984.)

1.201

REFRACTORY STATUS EPILEPTICUS IN CHILDREN

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Rationale: Refractory status epilepticus (SE) in children has been confirmed to carry a high morbidity and mortality. Low numbers of cases plus the confounding variables of age and etiology make prognostication as well as valid comparisons of treatment difficult. This study assessed age, etiology, and outcome in a larger number of prospective cases of SE in children between the ages of 1 month and 16 years who had seizure duration >60 min requiring three or more standard anticonvulsants (AEDs) for treatment. At the end of this activity, participants should be able to discuss the potential outcomes of refractive SE in children with some of the prognostic factors. **Methods:** Data were obtained from the NIH Greater Richmond Metropolitan Area database to identify cases of SE in children betweeen 1 month and 16 years of age who required three or more standard AEDs and who had seizure duration >60 min. Data were analyzed for treatments, seizure duration, mortality, morbidity (including pre- and postevent clinical status), age, and etiology. Long-term follow-up of the survivors is in progress. **Results:** Seventy-two pediatric patients older than 1 month were identified with refractory SE. Many of these were treated at local hospitals and transferred to VCU, and many were treated en route by rescue squad personnel. Although only nine of 72 patients required midazolam or high-dose barbiturates (none received propofol), mortality remained high: 13.9% acutely (death during admission for status) and 19.4% overall; 40.3% of patients were thought to be at baseline at discharge. The outcome for 36.1% could not be determined. When patients with significant morbidity were added to the percentage who died, bad outcomes occurred in 23.6%. In a subset of patients where long-term follow-up was available, six of seven were in regular classrooms without chronic seizures, and one with chronic seizures was off medications since 2000. In another subset of patients with more detailed data, 10 of 51 had seizure duration >5 h: four of 10 died, three of 10 had marked worsening of neurologic deficits, and two of 10 had unknown outcomes although they survived. **Conclusions:** Refractory SE in children has high mortality and morbidity. Although etiology helps in prognostication (children with brain tumors, prolonged hypoxia, cardiac transplant), several children who died had evidence of infectious disease and normal premorbid status—a presentation similar

to those with excellent long-term outcomes. Children with SE >5 h had almost uniformly poor outcomes. Long-term follow-up and more detailed clinical analysis of this patient group is ongoing, with the purpose of identifying prognostic factors and providing a database to assess treatment efficacy. (Supported by NIH P50NS25630.)

1.202
ATTENTION IN CHILDREN WITH EPILEPSY

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Rationale: Children with epilepsy without associated neurologic disorders generally do less well than classmates in school. Impaired attention/concentration has been implicated as contributory to their academic difficulties and has been variably ascribed to different factors that include seizure type, drug effects, comorbid attention deficits, and psychosocial adjustment. To determine the nature of attentional difficulties of children with epilepsy, their performance on multiple tests of attention was compared with the performance of normal children and with those with diagnosed attention deficit–hyperactivity disorder (ADHD). **Methods:** Seventy children (aged 6–12 years) seen for research or clinical purposes were administered tests of immediate attention (auditory and visual span) and sustained attention (Conners' CPT) as part of neuropsychological assessment. Their parents completed the ADHD Behavior Checklist and Child Behavior Checklist (CBCL). Clinical groups consisted of 20 children with ADHD and 30 children with medically controlled seizures (15 partial, 15 primary generalized). Focus for partial seizures was frontal, temporal, or occipital. There were 20 normal controls. Groups did not differ in age, gender, or intellectual functioning. Children with ADHD were unmedicated at the time of assessment. Children with seizures differed in number (focal > generalized) and type of AED [primarily carbamazepine (CBZ) vs. valproate (VPA)]. **Results:** Data were analyzed by single-factor analysis of variance (ANOVA) or repeated-measures ANOVA. Significant differences were found between clinical groups and controls for CBCL School Competence (0.05), Social Problems (0.0001), and Attention (0.0001). DSM-IV symptoms of inattention varied in frequency (ADHD > Epilepsy > Controls), as did performance for CPT accuracy and consistency (Controls > ADHD/Epilepsy). Children with epilepsy did not differ from children with ADHD for sustained attention. No differences were found for immeidate attention, but children with generalized seizures did poorer than those with partial seizures on the CPT and were rated as less competent by parents (0.04). Children with generalized seizures also showed slower processing speed (0.01) than the other groups. **Conclusions:** Children with medically controlled epielspy have significant problems with school competence and sustained attention but have fewer symptoms of inattention than do children with ADHD. Children with generalized seizures have greater attentional difficulties than do children with partial seizures, as well as slower processing speed. The specific causes/neural substrates of the attention problems of children with epilepsy (partial vs. generalized) require further study, as does the difference in attention problems between children with epilepsy and ADHD. Polytherapy may be contributory to the attention problems in epilepsy, but drug type likely is not. At the end of reading this poster, the participant should be able to discuss the attention problems of children with epilepsy and the relation of these problems to lower academic achievement.

1.203
THE IMPACT OF CONVULSIVE STATUS EPILEPTICUS ON THE RISK OF DEATH VARIES BY AGE

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Rationale: Animal models, population-based epidemiologic studies, and clinical series have suggested that status epilepticus (SE) contributes to brain injury and increases the risk of death. Using data from a very large sample of inpatients from United States community hospitals, we recently demonstrated that SE increases the risk of death after controlling for multiple comorbid conditions. At the end of this activity, the participant will be able to discuss how the risk of death among inpatients with SE differs by age. **Methods:** The National Inpatient Sample of the Healthcare Cost and Utilization Project (1988–1995) is a very large population-representative 20% sample of U.S. hospital discharges, which contains >50 million discharge records with data available at the patient level while protecting privacy. We extracted all discharge records with a diagnosis of SE (ICD-9 codes 345.2, 345.3, 345.7), and then obtained a random sample (stratified by year) of discharge records without a diagnosis of SE for a case/control ratio of 1:3. Discharge records with only a diagnosis of nonconvulsive SE and discharge records of neonates (younger than 1 month) were excluded from this analysis. Descriptive analyses were performed, and unadjusted odds ratios (OR) were caclulated using convulsive SE as the primary exposure and death as the primary outcome variable. Step-wise multiple logistic regression models were developed for all ages together as well as multiple age groups, with SE as the primary exposure variable and inpatient death as the outcome. Comorbid conditions and other potential confounding variables were examined and considered for the logistic regression model; final regression models were developed based on the best model fit. **Results:** The 39,649 inpatient records with a diagnosis of SE and 118,383 discharge records without a diagnosis of SE were ascertained. The inpatient mortality was 10.4% among those with SE and was 2.9% among those without SE. The unadjusted and adjusted (after multiple logistic regression) OR are shown in Table 1. **Conclusions:** The increased risk of death associated with SE among inpatients varies by age. Children younger than 1 year appear to be the most vulnerable. Children aged 1–4 years and adults have significant increased risk of death, and schoolage children and younger teenagers do not appear to have significant increased risk of death associated with SE in our study population. [Supported by 1 RO3 HS11453-01 (ET) from the Agency for Healthcare Research and Quality.]

TABLE 1. *Age-specific risk of death associated with status epilepticus*

Age group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All ages[a]	3.93 (3.75, 4.11)	2.04 (1.96, 2.11)
1–12 months	10.77 (7.79, 14.9)	4.63 (2.65, 8.09)
1–4 years	3.17 (1.66, 6.05)	3.10 (1.36, 7.02)
5–10 years	1.75 (0.87, 3.15)	0.747 (0.32, 1.77)
11–16 years	3.04 (1.59, 5.89)	0.65 (0.24, 1.74)
17–25 years	13.43 (8.97, 20.11)	1.86 (1.42, 2.44)
26–55 years	6.79 (6.02, 7.65)	2.53 (2.16, 2.97)
56–65 years	4.72 (4.14, 5.38)	2.17 (1.84, 2.55)
66+ years	3.63 (3.42, 3.86)	2.02 (1.86, 2.20)

[a] Excludes neonates.

1.204
NEUROIMAGING IN CHILDREN DURING THE IMMEDIATE EVALUATION OF NEW-ONSET SEIZURES

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Rationale: The utility of computed tomography (CT) and magnetic resonance imaging (MRI) in children with new-onset seizures is debated. Neuroimaging is advocated to determine seizure etiology and prognosis and plan therapy. CT or MRI has been considered mandatory in patients with partial seizures, focal neurologic examination, or focal alterations on EEG. Rational utilization of neuroimaging during the evaluation of children in the emergency department with a first seizure

is discussed in this presentation. Correlation among clinical findings, EEG, and neuroimaging is presented for patients with new-onset partial seizures. **Methods:** We prospectively evaluated 191 patients diagnosed with new-onset seizures over 11 months at Children's National Medical Center as part of a clinical care pathway. CT was mandatory as part of the evaluation. MRI was done based on clinical considerations. **Results:** A total of 189 patients (99%) had CT, and 58 (30%) had MRI. CT scans were abnormal in 48 patients (25%), with six acute findings (tumor, hemorrhage, infarct) and 42 chronic findings. MRI was performed for: abnormal CT in 14 (24%), focal neurologic examinations (15), focal EEG [30 including hypsarrhythmia (three)]. Twenty-eight MRIs (48%) were abnormal: dysplasia (13), remote symptomaric (five), metabolic (two), acute processes (three), tumors (four), and mesial temporal sclerosis (MTS; one). Abnormal MRI was found in 14 patients (7%) with normal CT: brainstem lesions (two), atrophy (two), ventricular/lobular asymmetries (three), metabolic disease (two), periventricular leukomalacia (one), MTS (one), and migrational disorders (three). Twelve of 14 (85%) of these patients had partial seizures; 109 patients (57%) had partial seizures; 27 (25%) had abnormal neurologic examination, and 27 (25%) had abnormal CT including three patients with acute pathology (two ischemia, one hemorrhage), and 11 patients with chronic changes [periventricular leukomalacia (PVL), old infarct, migrational disorders]. Seventeen (16%) had abnormal MRI, and 12 (70%) of these patients had previous normal CT. **Conclusions:** Seizure etiology that will change short-term medical managemant can be identified mostly with CT. MRI provides additional information regarding etiology and may provide long-term prognostic information, especially in the presence of partial seizures, even with normal CT.

1.205

MAGNETIC SOURCE IMAGING AND NEUROPATHOLOGY IN CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: We correlated the spatial distribution of epileptic discharges recorded by magnetic source imaging/magnetoencephalography (MSI/MEG) with the pathology of epileptogenic lesions for the possible differentiation of lesions by location of MEG spikes. **Methods:** We reviewed the records of all patients for intractable localization-related epilepsy who underwent examination by MSI between April 1993 and October 2001 and subsequent surgery. Twenty-four of these subjects satisfied additional selection criteria for this study: (a) neuropathology results of epileptogenic lesions, (b) preoperative MSI, and (c) preoperative magnetic resonance imaging (MRI) with abnormalities. Two neuroradiologists and one epileptologist retrospectively reviewed preoperative MRI and MSI for each of these patients simultaneously. The spatial distribution of epileptic spike sources was evaluated by consensus. Epileptic spike sources were classified into clusters of more than five spikes, or those without a clustered configuration. Spikes were further categorized into three groups, according to their spatial relation to epileptogenic lesions: (a) those within and extending from the lesion, (b) those along the marginal zone, defined as $\leq$2 cm from the lesion, and (c) those in an ipsilateral extramarginal area, defined as >2cm from the lesion. **Results:** Demographic data for the 24 subjects was as follows: mean age at time of MSI study, 10.8 ± 4.2 years (mean ± SD; range, 4.6–17.4), and F/M ratio, 9:15. Preoperatively, all patients had partial epilepsy, with complex partial type in 11 (45.8%). Secondarily generalized epilepsy occurred in 12 (50.0%). Neuropathology of epileptogenic lesions consisted of: cortical dysplasia (CD) in 14 (58.3%), tumor (low-grade astrocytoma or dysembryoplastic neuroepithelial tumor (DNET)) in seven (29.2%), and infarct or porencephalic cyst in four (16.7%). One of the patients had a combination of DNET and CD. Spikes located within lesions, whether clustered or not clustered, were noted in 13 (92.9%) of the subjects with CD. Clustered epileptic spike sources originating within lesions were only present in patients with CD. Two patients (28.6%) in the tumor category displayed spikes within their lesions (Fisher's test, $p < 0.01$), and histology revealed DNET in both, with one having the mixed pathology (DNET and CD) noted above. None of the patients with infarcts displayed spikes within their lesions. Ipsilateral marginal spikes were present in six (85.7%) of the patients with tumors, two (50.0%) with infarcts, and six (42.9%) with CD. Ipsilateral extramarginal spikes were present in six (85.7%) of the patients with tumors, one (25.0%) with infarct, and six (42.9%) with CDs. **Conclusions:** The spatial distribution of epileptic spikes sources on MSI/MEG of children with localization-related epilepsy is helpful in distinguishing CD from other epileptogenic lesions. Spikes, especially clustered ones, originating from within epileptogenic lesions are significantly more associated with CD, whereas marginal spike sources are more indicative of tumor. This information can also assist in the trajectory and the extent of resection during epilepsy surgery.

1.206

SURGERY FOR INTRACTABLE INFANTILE SPASMS: THE ROLE OF α[^{11}C]METHYL-L-TRYPTOPHAN POSITRON EMISSION TOMOGRAPHY SCANNING

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Rationale: Positron emission tomography (PET) with 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) can detect focal cortical abnormalities in children with cryptogenic infantile spasms, although many show bilateral, multifocal hypometabolism. Recently the new PET tracer α[^{11}C]methyl-L-tryptophan (AMT) was reported to differentiate between epileptogenic and nonepileptogenic lesions in children with tuberous sclerosis. Increased uptake of AMT on PET occurs in epileptogenic cortical regions in 40–60% of patients with intractable partial epilepsy. In the present study, AMT PET was applied to children with intractable infantile spasms not associated with tuberous sclerosis to determine if this imaging modality can further identify the epileptic focus. **Methods:** Eighteen children [11 boys and seven girls, aged 9 months to 8 years; mean age, 3.0 years; 15 with nonfocal magnetic resonance imaging (MRI) and three with cortical developmental malformation] with intractable infantile spasms underwent AMT PET scans. Focal cortical areas of increased AMT uptake were recorded and compared with FDG-PET and EEG findings. **Results:** Seven patients (39%) had a single focus of increased AMT uptake, and these children were significantly older (mean age, 4.4 years) than the remaining 11 without focal AMT PET abnormalities (mean age, 2.2 years; $p = 0.038$). There was only one child (a 17-month-old girl) younger than 2 years (of seven) who had an AMT focus. Age at onset of spasms did not differ significantly between AMT-positive and AMT-negative patients ($p = 0.19$). Of the 11 children whose EEGs revealed an epileptic focus, four showed increased AMT uptake, and these areas were concordant with the EEG findings. One of two children with lateralizing but nonlocalizing ictal EEG showed increased AMT uptake in the left temporal lobe, which was later verified as the site of seizure onset by intracranial EEG. Five patients had nonfocal ictal EEG findings, and one of these showed increased AMT uptake in the right temporal lobe. FDG-PET showed unilateral hypometabolism in eight children (44.4%), and three of these had increased AMT uptake ipsilaterally involving a smaller area than the corresponding FDG abnormality. Of 10 patients with multifocal FDG-PET hypometabolism, four showed a single focal area of increased AMT uptake. Seizure onset was identified by intracranial EEG monitoring in three cases, and it was always concordant with the location of the AMT PET findings. **Conclusions:** AMT PET can reveal focal epileptogenic cortical regions in ~40% of children with intractable infantile spasms. This sensitivity of AMT PET appears to be similar to that in older patients with partial epilepsy, especially in

children older than 2 years. Focal increase of AMT uptake can occur in children with infantile spasms whose FDG-PET is nonlocalizing, and these AMT abnormalities are concordant with ictal intracranial EEG findings. Thus, FDG and AMT PET can be used as complementary imaging methods to identify focal epileptogenic cortical regions for surgical resection in infantile spasms. (Supported by NS 34488, NS/RR 38324.) (Disclosure: Grant: NS 34488, NS/RR 38324.)

1.207

MAGNETOENCEPHALOGRAPHIC FEATURES ASSOCIATED WITH CORTICAL MIGRATION DISORDER

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Rationale: Magnetoencephalography (MEG) is a novel noninvasive technique for presurgical localization of the epileptogenic zone in patients with epilepsy. The presence of interictal epileptogenic bursting activity on the electroencephalography (EEG) is marker of the underlying pathology in intractable epilepsy associated with cortical migration disorder. The present study was designed to investigate the significance and localization accuracy of epileptogenic bursting activity detected by MEG in 20 patients with cortical migration disorders (focal cortical dysplasia, tuberous sclerosis, hemimegalencephaly, and schizencephaly). **Methods:** We reviewed 20 patients (focal cortical dysplasia, seven; tuberous sclerosis, seven; hemimegalencephaly, four; and schizencephaly, three). Equivalent single dipole modeling was applied to interictal epileptogenic bursting activity, easily distinguished from background activity, more easily with MEG than EEG. **Results:** Interictal epileptogenic activities were seen in four (57%) patients with focal cortical dysplasia, five (71%) with tuberous sclerosis, four (100%) with hemimegalencephaly, and three (100%) with schizencephaly. In focal cortical dysplasia, the localization of these activities corresponded with the electrocorticography. In tuberous sclerosis, interictal epileptogenic bursting activities were frequently bisynchronous when cortical tubers were seen in the frontal lobes. In such cases, dipole localization could hardly be detected. Hemimegalencephaly patients' cortical malformation was maximal in the posterior part of the hemisphere, and the dipole localization corresponded with the magnetic resonance imaging (MRI) findings. In schizencephaly patients, one had dipole localization around the open cleft; however, the other two patients showed dipoles originating from the temporal lobe ipsilateral to the lesion. **Conclusions:** Existence of interictal epileptogenic bursting activity on MEG confirms that cortical migration abnormalities are highly epileptogenic. In children with tuberous sclerosis and schizencephaly, further assessment may be needed before epilepsy surgery. (Supported by NIH grant R01 NS37941 to Dr. Andrew C. Papanicolaou.)

1.208

MAXIMAL REDUCTION OF *N*-ACETYLASPARTATE IN METABOLIC BORDER ZONE OF FLUORODEOXYGLUCOSE–POSITRON EMISSION TOMOGRAPHY IN NONLESIONAL EXTRATEMPORAL LOBE EPILEPSY

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Rationale: Decreased *N*-acetyl aspartate (NAA) measured by proton magnetic resonance spectroscopy (^{1}H-MRS) has been reported in epileptogenic brain regions. This finding is commonly interpreted as a sign of neuronal loss or dysfunction. In our previous study (*Ann Neurol* 2000;48:88–96), 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) positron emission tomography (PET), a technique widely used to define epileptogenic regions, showed that the cortical region bordering hypometabolic cortex corresponded to the site of seizure onset measured by intracranial EEG, rather than cortex within the hypometabolic area. In the present study, we measured NAA concentrations within and bordering hypometabolic regions on FDG-PET by using ^{1}H-MRS imaging (^{1}H-MRSI), and compared these values to NAA concentrations measured in surrounding gray and underlying white matter. **Methods:** Multivoxel ^{1}H-MRSI (chemical-shift imaging) and FDG-PET scans were performed in six children (four boys and two girls; mean age, 6.8 ± 4.2 years) with medically intractable nonlesional extratemporal lobe epilepsy. The extent of glucose hypometabolism on PET was identified objectively by marking cortical regions with >10% hypometabolism compared with the contralateral homologous cortex. FDG-PET images with "marked" hypometabolic cortex were coregistered to the MRI. After coregistration, voxels on MRSI were classified as corresponding to the hypometabolic zone, metabolic borderzone (voxels located at the border of marked hypometabolic cortex), surrounding gray matter (voxels outside the borderzone), and underlying white matter. NAA concentrations in contralateral homologous voxels were also measured to calculate an asymmetry index (AI) of NAA for each group of voxels. **Results:** Fifteen hypometabolic areas were detected in the six children. All 15 metabolic borderzone regions showed lower NAA than the homologous contralateral region (>10% asymmetry). In contrast, only two hypometabolic zone regions showed decreased NAA. Four surrounding gray matter regions and one underlying white matter region also showed decreased NAA. The mean NAA concentration was significantly reduced in the metabolic borderzone (mean AI, –18.75%) as compared to the hypometabolic zone (mean AI, –5.84%), surrounding gray matter (mean AI, –6.69%) and underlying white matter (mean AI, –4.68%; $p < 0.0001$; analysis of variance). Mean NAA concentrations in the latter three regions did not differ significantly from each other. **Conclusions:** In nonlesional extratemporal lobe epilepsy patients with focal FDG hypometabolism, ^{1}H-MRSI showed greatest reduction of NAA in voxels bordering the hypometabolic brain region. Such metabolic borderzone areas were found to be most epileptogenic in our previous studies. The results suggest that FDG-PET hypometabolism and decreased NAA reflect different physiologic processes and provide complementary information regarding the extent of cortical dysfunction in neocortical epilepsy. ^{1}H-MRSI may assist to delineate the epileptogenic zone for successful epilepsy surgery in conjunction with other localization techniques. (Supported in part by NIH grant NS 34488.)

1.209

MAGNETIC RESONANCE IMAGING DETECTION OF MESIAL TEMPORAL SCLEROSIS IN CHILDREN

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Rationale: To study the incidence and clinical characteristics of children with mesial temporal sclerosis (MTS) as diagnosed by magnetic resonance imaging (MRI). MTS has not been well studied in children. In children, it is believed to be an uncommon finding and not a major cause of epilepsy. No studies have been performed specifically on the MRI diagnosis and incidence of MTS in children. We reviewed all pediatric brain MRI reports and studied the incidence and clinical features of those with MTS in detail. **Methods:** All brain MRI reports on children younger than 14 years over a 52-month period (January 1997 to April 2002) were reviewed. All reports with the diagnosis of definite or possible MTS were noted. These patients' MRI scans were then reviewed by two board-qualified pediatric neurologists to confirm the MRI diagnostic criteria of MTS. The charts of the patients who satisfied these criteria were then reviewed in detail to study their clinical details. **Results:** Three hundred ninety brain MRI reports were reviewed; 14 reports of MTS were found. Twelve of the 14 MRI films satisfied the criteria of MTS by MRI after the films were reviewed. The incidence of MTS among all pediatric brain MRI studies was 3.1%. The 12 children consisted of six boys. The average age was 6.4 years (range, 2–12 years) at time of initial MRI diagnosis of MTS. Six

patients had left MTS, five had right MTS, and one patient had bilateral MTS. Eleven of the 12 patients had been imaged by using a specific epilepsy protocol. Five patients had other MRI pathology, including dysgenesis of the corpus callosum, periventricular leukomalacia (PVL), and gliosis. All 12 children presented with seizures (i.e., there were no "incidental" findings of MTS). The patients' seizure types consisted of complex partial (n = 9), typical absence (n = 1), generalized tonic–clonic (n = 1), and both complex partial and generalized tonic–clonic (n = 1). Only one patient had a history of febrile seizures. At the latest follow-up, histopathology results were available on six patients, all of whom had undergone temporal lobectomy as a treatment for refractory, complex partial seizures. This showed MTS and surrounding gliosis and/or dysplasia in four patients, isolated MTS in another, and gliosis in the sixth. Only one patient had a likely cause of his MTS (bilateral) due to encephalitis 3 years before MRI diagnosis of MTS. Of the nine available perinatal histories, seven were normal, and two were abnormal only for prematurity and threatened abortion (patient with PVL). Associated comorbidities were seen in five patients and included developmental delay, behavioral problems, cerebral palsy, and Gorlin syndrome. **Conclusions:** MTS is an uncommon finding in children. Asymptomatic MTS or MTS not presenting as seizures did not occur in our series. Febrile seizures occurred in only one of the 12 children, so unlike MTS in adults, this may be a very low association. Histopathology in six children confirmed MTS in five, and there was associated gliosis and/or dysplasia in four. In children, MTS often occurs in the setting of dual pathology and has associated comorbidities and seizure types other than complex partial.

1.210
CROSSED CEREBELLAR DIASCHISIS ON SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY MAY PREDICT SEIZURE LATERALITY IN CHILDREN WITH REFRACTORY EPILEPSY

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Rationale: We examined crossed cerebellar diaschisis (CCD) on single-photon emission computed tomography (SPECT) as a possible predictor of laterality of seizure foci in pediatric patients with refractory epilepsy. Participants should be able to discuss the possible implications of CCD seen on SPECT in this patient population. **Methods:** As part of a presurgical evaluation for epilepsy surgery, 22 patients with refractory epilepsy underwent SPECT studies using 99m-Tc. These were patients in whom clinical localization by history and/or magnetic resonance imaging (MRI) and/or EEG suggested a focal onset of epilepsy. All patients had interictal SPECT performed, and eight patients had both ictal and interictal studies. Other patients who had SPECT studies performed but who did not have historic, MRI, or EEG evidence of focality were not included in this analysis. CCD was characterized by ictal crossed cerebellar hyperperfusion or interictal crossed cerebellar hypoperfusion. The SPECT studies were evaluated visually for CCD, and cross-sectional histograms across the cerebellar hemispheres were used to establish asymmetry indices. Asymmetry indices of $\geq$10% were considered positive. We evaluated whether CCD corresponded to the clinical localization as well as to the laterality seen on SPECT in the cortices of the patients. **Results:** CCD was observed, with asymmetry indices of $\geq$10%, in 10 of the 22 patients (45%). In eight of these 10 patients (80%), CCD correctly corresponded to clinical and cortical SPECT lateralization of seizure foci. Examining the interictal SPECT studies alone, nine of the 22 patients (41%) had CCD. Among the nine, there were seven (78%) in whom CCD corresponded to clinical localization and therefore correctly predicted laterality. Ictal SPECT was performed in seven of these 22 patients. Only two (29%) had CCD. In one case, the ictal crossed cerebellar hyperperfusion corresponded to interictal crossed cerebellar hypoperfusion. However, in the other case, the ictal CCD was contralateral to the interictal CCD. Of the five patients with ictal SPECTs negative for CCD, three also had interictal SPECTs negative for CCD, one had interictal SPECT positive for CCD that corresponded to clinical localization, and one had interictal SPECT positive for CCD that did not correspond to clinical localization. The patients included had temporal and extratemporal foci in the left and right hemispheres by MRI and EEG. The predictability of CCD did not correlate with either hemisphere or any particular location in the cortex. **Conclusions:** CCD on interictal and ictal SPECT may be used in conjunction with clinical data to predict lateralization of seizure foci in patients with refractory epilepsy. When present, CCD on interictal SPECT was more closely associated with clinical localization and cortical SPECT abnormalities and may be more predictive as well as easier to obtain than ictal studies. Our study suggests that the cerebellum and its connections may have a role in the pathophysiology of epilepsy that is yet to be elucidated.

1.211
HIPPOCAMPAL ABNORMALITIES REMOTE FROM THE SEIZURE FOCUS IN CHILDREN WITH PARTIAL EPILEPSY: A MAGNETIC RESONANCE T_2 RELAXATION STUDY

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Rationale: From this work, participants should appreciate the extent to which hippocampal damage can result from remote seizure activity. Hippocampal T_2 (HT2) relaxometry has been shown to be useful in presurgical assessment of adults with mesial temporal sclerosis (MTS) and is correlated with side of seizure onset and histologic severity. A long period of active epilepsy has been negatively correlated with hippocampal volume, generating the hypothesis that ongoing epilepsy causes damage to the hippocampus, possibly including those that are not the primary epileptogenic focus. Histologic data suggest that the latter hippocampal abnormalities are subtle. The aim of this study was to examine hippocampi in children with partial epilepsy using HT2 relaxometry, with the aim of comparing the findings from patients in whom the hippocampus is the primary seizure focus with those from patients with seizures arising from elsewhere. This may provide insight into the cause of hippocampal abnormalities in children with active partial epilepsy. **Methods:** Ninety-five consecutive children with partial epilepsy and 22 age-matched controls underwent magnetic resonance (MR) imaging, including HT2 relaxometry using a modified CPMG sequence. Visual analysis of structural scans was carried out to identify lesions associated with partial epilepsy. Abnormal quantitative HT2 was defined as >2 SD from the control mean after adjustment for age. Right-to-left asymmetry was investigated by comparing ratios of higher to lower HT2 using a Mann–Whitney *U* test. Group abnormalities were investigated with multiple linear regression. **Results:** HT2 was dependent on age in the age range investigated (33–233 months, $p = 0.001$). Patients were divided, on the basis of clinical, EEG, and visual MRI assessment, into three groups; those with temporal lobe epilepsy (TLE) and MTS (MTS-TLE), lesional TLE (l-TLE), or extratemporal epilepsy (ETE). Patients with MTS-TLE had asymmetry of HT2 ($p < 0.001$); 29 of 35 (84%) had abnormal HT2, and in 9%, the abnormality was bilateral. On group analysis, HT2 in the sclerotic hippocampus was prolonged by a mean of 19 ms (95% CI, 15–22 ms; $p < 0.001$). In the nonsclerotic hippocampus, HT2 was prolonged by a mean of 3.4 ms (95%CI, 1–6 ms; $p = 0.01$) when compared with controls. Ten of 32 (32%) patients with l-TLE and nine of 29 (23%) of those with ETE had an abnormal HT2 in at least one hippocampus. On group analysis, patients with l-TLE had prolongation of HT2 by a mean of 4.4 ms (95% CI, 2–7ms; $p = 0.001$), and those with ETE had prolongation of HT2 by a mean of 3.8 ms (95% CI, 1–7 ms; $p = 0.006$) when compared with controls, after adjustment for age. **Conclusions:** As in adults, HT2 is shown to be useful in the presurgical assessment of children with MTS. In addition, the extent of prolongation of HT2 in hippocampi that are not primary epileptogenic foci was found to be similar in all three patient groups studied. The wide variety of structural associations and varied sites of epileptogenic foci suggest that the abnormalities are likely to be caused by ongoing seizure activity rather

than by underlying aetiology or site of epileptogenic focus. (Supported by The Wellcome Trust.)

1.212
VOLUMETRIC ANALYSIS OF THE THALAMUS IN PEDIATRIC PATIENTS WITH MEDICALLY INTRACTABLE EPILEPSY

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Rationale: With prolonged status epilepticus, neuronal loss and gliosis has been reported in multiple subcortical structures including the hippocampus. The thalamus relays information in various sensory modalities, as well as from the basal ganglia and cerebellum. Significant neuronal loss in the thalamus would be expected to affect learning and higher motor and cognitive functions, and therefore be linked with long-term disabilities associated with chronic medically intractable epilepsy. At the end of this activity, the participants are expected to be able to discuss volume changes of the thalamus on magnetic resonance imaging (MRI) in pediatric patients with intractable epilepsy. **Methods:** Eleven patients were studied (three male, eight female subjects) with partial epilepsy, defined both on clinical and EEG grounds. The age at onset of seizures was 1.5–14 years (mean, 6.1 ± 4.1), and the age at evaluation was 2–22 years (mean, 11.6 ± 6.3 years). All patients had more than one seizure per week on average for the 3 months preceding evaluation, and had failed three or more antiepileptic drugs (AEDs). Coronal IR-Prepped FAST-SPGR T_1-weighted images of 124 contiguous 1.5-mm coronal slices were obtained and analyzed with a custom-made software CARDVIEWS (Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA) for volumetric measurements. Each image was segmented into various substructures of the brain including the thalami, cerebral cortex, and basal ganglia according to semiautomatic signal intensity with manual corrections. Volume of the substructures was calculated based on the number of voxels included (Caviness et al. *J Cog Neurosci* 1996;8:566–88). **Results:** On EEG video-telemetry, six patients had left-sided predominance of the epileptiform activity (ictal EEG in five, one had only interictal EEG recordings), and five patients had right-sided predominance (all had ictal EEG). No change in thalamic volume was detected when comparing left versus right, in patients with both predominantly left-sided and right-sided EEG activity (surface monitoring, ictal EEG in 10 of 11, only interictal EEG in one of 11). **Conclusions:** Volumetric MRI studies provides a sensitive tool to closely monitor subtle changes in brain volume in patients with epilepsy. No asymmetries in thalamic volumes were detected in patients with either predominantly left-sided or right-sided epileptiform activity. Despite frequent seizures, we found no evidence for thalamic volume loss in this selected group of patients. These results suggest that the thalamus is a low risk for injury with recurrent seizures. [Supported by The National Epifellows Foundation (Research Grant) and the Epilepsy Foundation (Research Clinical Fellowship, with support from Pfizer).]

1.213
MAGNETOENCEPHALOGRAPHY ASSISTS IN FINDING SUBTLE CORTICAL DYSPLASIA

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Rationale: Focal cortical dysplasia (FCD), a neuronal migration disorder, was originally described by Taylor et al. Searching for subtle FCD on magnetic resonance imaging (MRI) is challenging. Patients with a normal MR often need invasive EEG recordings. The intrinsic epileptogenic nature of FCD allows precise localization by magnetoencephalography (MEG) if sufficient epileptic discharges are available. The purpose of the present study was to investigate whether MEG increases the detection of subtle FCD as part of an epilepsy surgery evaluation. **Methods:** Among 20y medically intractable epilepsy patients with migational disorders and MEG recording, three patients had normal MRIs and histologic findings of FCD. Their ages were 6, 3, and 15 years. Spontaneous MEG recordings were performed on a whole-head MEG system (Magnes WH2500, 4-D Neuroimaging, San Diego, CA). The intracranial locations of electromagnetic events were modeled as equivalent current dipoles (ECDs). The dipoles were overlaid on 3D-SPGR MRIs. Their MRIs were evaluated in a standard way and reevaluated with special inspection in limited regions guided by MEG spike localization. **Results:** Interictal epileptogenic discharges on EEG and MEG were found in all three patients. Clusters of focal interictal epileptic discharges were localized to frontal (two of three) and central (one of three) areas after overlay on MRIs. In two patients we found tiny focal abnormalities including slightly increased cortical thickness and blurred gray–white matter junction at the locations of interictal events after reevaluation of the MRIs. FCD was confirmed histologically in all patients. All patients are seizure free after surgery. **Conclusions:** MEG can assist in the detection of FCD. MR images might be reevaluated after MEG recording if they appear normal during standard evaluation. (Supported by NIH grant R01 NS37941 to A.C. P.)

1.214
KRABBE LEUKODYSTROPY PRESENTING WITH INTRACTABLE SEIZURES AND RAPID NEUROLOGIC DECLINE

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Rationale: Krabbe disease is a progressive neurologic disorder. We descibe two infants with severely abnormal electroencephalograms (EEG), and clinically demonstrated rapid neurologic decline and death. **Methods:** The infants, a boy and girl, presented in the neonatal period with seizure activity. Each had multiple EEGs and biochemical analysis of serum, urine, and skin fibroblasts. Each also had histochemical and structural analysis of skin and muscle biopsy material. Both patients underwent computed tomography (CT) and magnetic resonance imaging (MRI) scans of the brain. Final diagnosis of Krabbe disease was based on β-galactocerebrosidase activity in cultured skin fibroblasts. **Results:** The girl had seizure activity at birth, described as eye deviation with tonic stiffening of the limbs. She had multiple seizures per day uncontrolled by medication. The inital EEG, at 1 month of life, showed multifocal independent spikes (MSID) as well as EEG seizures. At 2 months of life, a second EEG showed the same MSID, but with a more regular background. The boy had rhythmic arm jerking during the first weeks of life, followed by tonic stiffening in his limbs, and staring with behavioral arrest at age 3 months. EEGs performed at 3 and 4 months of life and showed generalized slowing with infrequent MSID and subsequently with more frequent MSID, both without EEG seizures. A repeat EEG at age 7 months showed hypsarrhythmia with no clinical manifestations of epileptic spasms. A final EEG performed at age 8 months showed generalized slowing of the background and regional right occipital and temporal spikes. Both patients developed irritatability and multiple gastrointestinal problems of vomiting and feeding difficulties within the first month of life. The boy's CT scan (at 3 months) showed bilateral basal ganglion calcifications. The girl's, performed at about the same time, was normal. Subsequent brain MRI (5 months) of the boy, showed T_2 hyperintensities within the thalami and posterior limbs of internal capsule and along cortical spinal tracts. The girl's MRI (4 months) only showed mild global atrophy. The boy's skin biopsy showed mitochondria containing crystalloid. Both had muscle fiber–type disproportion. The girl had

5–10% β-galactocerebrosidase activity, whereas the boy had no detected enzyme activity. The girl died at 6 months, and the boy died at 8 months. **Conclusions:** Unlike those in other published reports, our patients showed generalized background slowing and MISD with initial EEG recordings, presumably during the early stages of the disease. The evolving frequency of spikes and amplitude between 100 and 200 μV suggests the MSID syndrome. The boy evolved into a frank hypsarrhythmia pattern in the later stages of the disease and then, with adrenocorticotropic hormone treatment, into a more focal EEG discharge pattern with background slowing. The girl only had EEGs performed during the early stages. The severely abnormal EEG having frequent epileptiform discharges may be related to the low to zero detected enzyme activity, the rapid neurologic decline, and early death.

1.215

UTILITY OF VIDEO-EEG TO EVALUATE EPILEPTIFORM DISCHARGES AND SEIZURES IN CHILDREN WITH AUTISTIC SPECTRUM DISORDER

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Rationale: Children with autistic spectrum disorder (ASD) are often evaluated with prolonged video-EEG (VEEG) recordings to determine if specific behavioral manifestations are seizures. VEEG is also done to evaluate the presence of interictal epileptiform activity, in the absence of clinical seizures. The significance of this interictal abnormality, as a possible contributing factor for abnormal behavior or poor language development, is not fully understood. We studied the relationship between the incidence of interictal epileptiform discharges and seizures in children with ASD. **Methods:** We reviewed 55 patients, diagnosed with ASD (ages ranging between 2.5 and 10 years, mean 5.9 years, 46 boys and nine girls) who underwent overnight or prolonged VEEG for 16–72 h. ASD was diagnosed using the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria. The data were analyzed for clinical spells with EEG changes. Other EEG abnormalities noted included frequency of epileptiform activity, spatial distribution of discharges, and other nonspecific abnormal findings (i.e., frontal arousal rhythm, focal slow waves). **Results:** Frequent epileptiform discharges were seen in 20 of 55 individuals (36.3%), nine (16.4%) had infrequent or rare discharges, and 26 (47.3%) had no epileptiform discharges. Thirteen of the 20 children (65%) with frequent discharges had a history of epilepsy, and 10 of the 13 had clinical events with EEG correlates during VEEG monitoring. Thirty-five had rare or no epileptiform discharges. Four of these 35 children (11%) had a history of seizures, and two had captured electroclinical events during VEEG. The incidence of epileptiform discharges correlated with seizures ($p < 0.01$). Electrical status epilepticus during sleep (ESES) was captured in two children (3%), who had no clinical events during VEEG. Epileptiform discharges were recorded over the frontal, central, and/or temporal regions in 25 children. Three of the 25 children also had parietal or occipital discharges, and one child had occipital discharges only. Other EEG findings did not correlate with seizure history. **Conclusions:** There was a significant correlation between a high incidence of epileptiform discharges and seizures in ASD patients. Most focal epileptiform discharges were localized in the perirolandic and perisylvian regions. There have been conflicting reports about the frequency or significance of epileptiform activity seen in ASD children. In our study of objectively defined ASD children, during overnight or more prolonged VEEG recordings, frequent epileptiform activity was seen in a minority of children without a seizure history. None of those children had electroclinical seizures during monitoring.

1.216

DO EPILEPTIFORM DISCHARGES SHOW HEMISPHERIC FAVORING IN CHILDREN?

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Rationale: Although adult EEG studies demonstrate left hemispheric favoring of epileptiform discharges (EDs), little is known about when such asymmetries first become evident. We studied if, where, and when similar EDs favoring occurs in children. **Methods:** Thirteen months of consecutive EEG reports were retrospectively examined from Seattle's Children's Hospital. Electroencephalographers were blind to study objectives. Recorded data included age in months, if it was a first EEG study, general findings, location of EDs (left or right), and interpreting electroencephalographer. Standard age-associated normal findings were not recorded. EDs were defined as interictal spikes, interictal sharp waves, ictal activity, or periodic lateralized epileptiform discharges. Age-appropriate neonatal sharp waves were not considered epileptiform. Both premature and term infants were considered 1 month old until they entered their second month of life. Bilateral independent EDs were coded as predominantly left or right; if the encephalographer did not specify, they were tallied as "bilateral EDs." Data were entered into a computerized database, and statistical analysis performed. **Results:** The 1,327 reports were reviewed by two board-certified electroencephalographers and two board-eligible, recent Epilepsy fellowship graduates. All used digital montages according to their preference. Mean age was 78 months. Focal EDs were seen in 258 records with right in 159 and left in 99 ($p < 0.01$ $\chi 2$). Mean ages of those with EDS showed right 71 months, left 83 months; 727 (55%) results were first EEG (FEEG) studies; in this group, mean ages of those with EDs on the right were 45 months, left 76 months. FEEG results showed the right hemisphere displayed EDs more often in the first 54 months ($n = 37$ right, 21 left), but between 55 and 78 months, EDS occured symmetrically ($n = 10$), and after 79 months, left-sided EDs predominated (12 right, 19 left). Comparing EDs by side with two age cohorts, <54 and >54 months, showed this age-related shift to be significant ($p = 0.023$, Fisher's Exact). This suggests no reading bias for right-sided EDs. Furthermore, hemispheric favoring of EDs seems age influenced. This age-associated shift in FEEG records may help explain the discordant left-favoring EDs data from adults and the right-sided findings in this study. Our FEEG findings parallel several normal parameters of childhood development: infantile blood flows show right-sided hemispheric favoring up to age 3 years, and transition to the left therafter; additionally, left hemispheric growth lags that of the right in infancy, yet undergoes a marked growth spurt between ages 3 and 6 years that ultimately outpaces the right. These shifts correspond temporally with developing handedness and language. It may be that mechanisms of normal lateralizations such as handedness and language similarly influence abnormal EDs-prone regions. Clarifying these influences in other cohorts may suggest age-associated factors that alter susceptibilities to focal EDs. **Conclusions:** Focal EDs in our pediatric cohort appear more commonly over the right hemisphere. In first EEG evaluations, this finding is age dependent: in infancy, EDs favor the right side, at 54 months they occur symmetrically, and after 79 months, they favor the left side.

1.217

VAGUS NERVE STIMULATION FOR REFRACTORY ABSENCE SEIZURES

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Rationale: Vagus nerve stimulation (VNS) has been shown to be effective treatment for partial-onset seizures. Several case studies in the literature have shown its efficacy in symptomatic generalized epilepsy, mostly Lennox–Gastaut syndrome. Its effectiveness in primary generalized epilepsy, especially absence seizures, has not been reported. The aim of this study was to report the effectiveness and tolerability of VNS in patients with refractory absence seizures. **Methods:** A retrospective

chart review of three patients with refractory absence seizures implanted with VNS was carried out. IRB approval for the study was obtained. They had failed treatment with three or more antiepileptic drugs (AEDs) known to be effective in absence seizures. Patients had several routine EEG recordings; two of the three subjects also had prolonged EEG-video monitoring. All patients showed the typical generalized 3-Hz spike–wave complexes. Magnetic resonance imaging (MRI) scans were of all three patients were normal. Doses of concurrent AEDs were not altered after VNS implantation. Postoperative follow-up ranged from 5 months to 2 years (mean, 15.7 months). **Results:** Patients ranged in age from 10 to 17 years (mean, 14.3 years). Their seizures began between ages 5 and 11 years (mean, 8.3 years). Seizures occurred between 20 and 50 times a day in all subjects. All had failed standard therapy for absence seizures including valproic acid, ethosuximide, lamotrigine, and topiramate used to maximally tolerated levels. One patient also failed zonisamide. Two of the three patients also had generalized tonic–clonic seizures. Their neurologic examinations were normal and they had normal IQs. Two patients experienced a >75% reduction, and the third patient had a 90% seizure reduction in absence seizures. A similar reduction was also noted for generalized tonic–clonic seizures. Side effects consisting of hoarseness and throat discomfort were mild in all three and were minimal by 3 months. **Conclusions:** In our three subjects with refractory absence seizures, VNS produced >75% seizure reduction in all three patients. During the follow-up period, we did not observe any loss of efficacy or significant side effects. VNS is a promising therapy for refractory absence seizures.

1.218

CHRONIC PERIODIC LATERALIZED EPILEPTIFORM DISCHARGES IN CHILDREN WITH MALFORMATIONS OF CORTICAL DEVELOPMENT

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Rationale: Periodic lateralized epileptiform discharges (PLEDs) are an EEG finding seen in patients with acute stroke, infections, or hypoxic encephalopathy. However, in most case series on PLEDs, there were a group of patients who had chronic intractable epilepsy with no acute deterioration and persistent PLEDs on EEG. The etiology of PLEDs in this group of patients with chronic epilepsy without any acute deterioration is not known. We studied the etiology, clinical and neuroimaging findings, and outcome of children with chronic epilepsy and PLEDs on EEG but without any acute clinical deterioration. At the end of this activity, the participant should be able to recognize the causes of chronic PLEDs in children younger than 2 years. **Methods:** The EEG database at the Cleveland Clinic from 1990 to 2000 was searched for children younger than 2 years with EEG diagnosis of PLEDs. Their medical charts, neuroimaging, and EEG records were then retrospectively reviewed. **Results:** Nineteen patients, 6 days to 23 months in age, were identified with EEG diagnosis of PLEDs. Seven had acute neurologic illness, and 12 patients had chronic epilepsy with no acute deterioration. All patients in the chronic group had brain magnetic resonance imaging (MRI). Malformations of cortical development (MCDs) were seen in seven; three had PLEDs after functional hemispherectomy (two hemimegalencephaly, one Sturge–Weber); and two patients had metabolic diseases with basal ganglia lesions in one, and normal brain MRI in the other. Of the seven patients with MCD, two had unilateral frontoparietal cortical dysplasia, two had hemimegalencephaly, one had tuberous sclerosis with bilateral cortical tubers, one had lissencephaly, and one patient had bilateral diffuse CD. Eleven of the 12 patients with chronic PLEDs had a long-term follow-up (5 months to 9 years). The two with metabolic diseases died, and nine remained stable with persistent PLEDs on EEGs. **Conclusions:** PLEDs may be seen in the children younger than 2 years who have chronic intractable epilepsy due to MCD and metabolic diseases. PLEDs may not always represent an acute neurologic illness.

1.219

A COMPARISON OF DIFFERENT EEG TECHNIQUES IN THE EVALUATION OF AUTISTIC CHILDREN WITHOUT SEIZURES

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Rationale: In addition to its role in evaluating autistic spectrum children for seizures, different EEG techniques are being used increasingly commonly in the evaluation of autistic children for underlying epileptic disorders, such as the Landau–Kleffner syndrome or epileptic aphasia. By retrospective review, we set out to determine the relative rates that epileptiform activity was discovered according to which EEG technique was used: awake only EEG, awake/asleep EEG, and 24-h ambulatory EEG telemetry. **Methods:** We performed a computer search of the medical records of children with the diagnosis of autism, pervasive developmental disorder, or Asperger syndrome at the Floating Hospital for Children at Tufts-New England Medical Center, for patients seen between March 2000 and March 2002. Medical records were reviewed, and all children in whom a standard EEG or 24-h ambulatory EEG had been obtained were included; children in whom such studies were obtained to evaluate possible or definite seizures were excluded, however. Each EEG study was classified as to whether epileptiform activity was identified. **Results:** Sixty-five children with autism spectrum disorders and without suspicion of seizures in whom at least one EEG study had been done were identified. None of the 12 awake-only EEGs exhibited epileptiform activity (mean age, 4.5 years). Among EEGs in which both wakefulness and sleep were recorded, five (12%) of 42 showed epileptiform activity (mean age, 3.9 years). Among 11 ambulatory EEG recordings of ≥24 h duration, none exhibited epileptiform activity (mean age, 4.3 years). Thus, the rate at which epileptiform activity on EEG was found among children in whom sleep was recorded was relatively low, five (9%) of 53 children. **Conclusions:** Routine EEGs including sleep appeared fairly good at picking up epileptiform activity in such children. Ambulatory telemetry, which should be a more "thorough" technique, did not pick up any cases although deeper and longer duration sleep was recorded. We intend to carry out a larger study to ascertain the frequency of epileptiform activity in children with autistic spectrum disorders comparing the yields of these two techniques.

1.220

ANTICARDIOLIPIN ANTIBODY IN WEST SYNDROME AND OTHER CHILDHOOD EPILEPSIES

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Rationale: Anticardiolipin antibody (aCL) is reported to be positive in patients with antiphospholipid syndrome. However, aCL has been reported in patients with various CNS disorders. We examined the frequency of aCL in patients with various kind of epilepsy to clarify whether aCL is involved in the pathogenesis of childhood epilepsy. **Methods:** Serum samples from 175 epilepsy patients and 71 nonepilepsy patients were obtained after informed consent. The aCL immunoglobulin G (IgG) was measured using an enzyme-linked immunosorbent assay (ELISA) kit purchased from MBL (Nagoya, Japan). The 175 epilepsy patients included nine with idiopathic generalized epilepsy (IGE), 46 with symptomatic generalized epilepsy (SGE) including 21 with West syndrome, 73 with cryptogenic or symptomatic localization-related epilepsy (C/SLE), 29 with idiopathic localization-related epilepsy, and 18 with unclassified epilepsy. **Results:** Although the normal range of this kit is set as <10 U/ml in adults, we tentatively set the normal range as <15 U/ml. Consequently, 24% of epilepsy patients and 15% of nonepilepsy patients were positive for aCL. There was no significant difference between the two groups. Among epilepsy patients, SGE patients were positive significantly more often than C/SLE patients ($p = 0.014$). When epilepsy patients were divided into aCL-positive (42 patients) and aCL-negative (133 patients) groups, there were no significant differences between the two groups in terms

of sex, polypharmacy, antinuclear antibody, anti-DNA antibody, and drugs used for treatment. However, SGE and age younger than 1 year were significantly more frequent in the aCL-positive group ($p = 0.014$ and <0.0001, respectively). Patients whose seizure type was epileptic spasm including West syndrome were significantly more frequent in the aCL-positive group ($p = 0.0001$). **Conclusions:** We found that aCL was present in some pediatric patients with epilepsy and other nonepileptic disorders. In all of our cases, CT and MRI showed no evidence of vascular lesions. This suggests that there is a direct cross reaction between aCL and the CNS. There was a significant relation between aCL and those who had SGE and whose seizure type was epileptic spasm, suggesting that aCL was involved in the pathogenesis of particular type of epilepsy including West syndrome. (Supported by Grant-in-Aid from the Ministry of Education, Culture, Science, Technology of Japan.)

1.221

INCREASED PREVALENCE OF UNPROVOKED SEIZURES IN PATIENTS WITH 22Q11.2 DELETION

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Rationale: Clinical findings in patients with a deletion of chromosome 22q11.2 (Digeorge syndrome, velocardiofacial syndrome) have been well described, including cardiac anomalies, palatal abnormalities, immune deficiencies, and characteristic facial features. However, beyond descriptions of a wide range of nonspecific structural brain abnormalities, typical neurologic features have not been well established. Recently there have been several reports of recurrent, unprovoked seizures, characterized as idiopathic partial and atypical absence epilepsy, in patients with this deletion. The large database of patients with chromosome 22q11.2 deletion syndrome evaluated at the Children's Hospital of Philadelphia provided the opportunity to assess the prevalence of idiopathic epilepsy in a population of almost 400 patients with the deletion. We hypothesized that the prevalence would be increased compared with that of the general population. Participants should be able to discuss the relation of chromosome 22q11.2 deletions and idiopathic epilepsies, and its potential influence on their clinical practice or genetic research. **Methods:** The clinical records of 376 patients were reviewed for documentation of seizure activity; potential triggers such as hypocalcemia, fever, and recent surgery; as well as magnetic resonance imaging (MRI) and EEG findings to aid in seizure classification. Head circumference, neuropsychological test results, family history, and cardiac and palatal abnormalities were also noted. Phone follow-up was performed to clarify details. **Results:** Of 344 patients whose histories were adequately detailed, 83 (24%) had seizures; 24 (29%) of those patients with seizures had associated hypocalcemia; 19 (23%) patients' seizures occurred in the postoperative period, and 15 (18%) occurred with fever; 25 (30%) patients had unprovoked seizures, comprising 7% of the total population analyzed. **Conclusions:** The lifetime prevalence of unprovoked seizures in the general population has been estimated to be 0.84–1.5%. The prevalence of unprovoked seizures in patients with 22q11.2 deletion evaluated at our institution is much greater. Further definition of seizure phenotypes will determine whether this increased risk represents a secondary manifestation of features of chromosome 22q11.2 deletions or a primary process. These results have implications for consideration of a chromosome 22q11.2 deletion syndrome in patients seen primarily for epilepsy, and for the identification of potential genetic loci responsible for idiopathic epilepsy. (Supported by grant number DC02027.) (Disclosure: Grant: Grant number DC02027.)

1.222

TIZANADINE HYDROCHLORIDE IS AN EFFECTIVE HYPNOTIC FOR ROUTINE ELECTROENCEPHALOGRAPHY

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Rationale: To report the novel use of tizanadine hydrochloride (TH) as an hypnotic for children undergoing outpatient EEG. The comprehensive evaluation of seizures requires EEG recordings in both awake and asleep states. Sleep deprivation is often insufficient for producing sleep onset. Hypnotics such as chloral hydrate can cause EEG artifact and irritability in children as they wear off. TH is a centrally acting $\alpha 2$ agonist that is indicated for the reduction of spasticity of central origin. Because of its sedative side effects and safety profile, we hypothesized that TH could be an effective hypnotic agent for routine EEG. **Methods:** All consecutive patients seen at our office older than 2 years who did not achieve sleep within the first 20 min of the study were eligible for study inclusion.TH was administered based on body weight per manufacturer's indications. A second dose was given after 30 min if the first dose was ineffective (maximum, 10 mg). No additional sedatives were given. Oxygen saturations and pulse rate were monitored. Technicians observed and rated sleep onset and ease of awakening. Computerized EEG recordings were subsequently analyzed by nonblinded observer for presence of sleep patterns (theta slowing, vertex waves) as well as medication artifacts. **Results:** Thirty-eight children (mean age, 8.7 years; range, 2–18 years; 24 boys/14 girls) were administered TH. Most patients had been sleep deprived. Average dose was 4.0 mg (range, 2–10 mg). Sleep was achieved in 35 of 38 patients (92%). Mean time to sleep after TH administration was 33 min (range, 6–110 min). All patients maintained normal saturation levels and cardiac rates, and readily awoke at the end of the procedure. No adverse side effects were noted. **Conclusions:** TH is an effective, safe agent for inducing sleep in children undergoing outpatient EEG. It does not cause EEG artifact. Prospective trials are required to further assess its role in other pediatric procedures that require short-term sedation.

1.223

CONFLICTS BETWEEN LABORATORY AND CLINIC ON THE PUTATIVE INJURIOUS EFFECTS OF NEONATAL SEIZURES

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Rationale: Conflicting views exist between laboratory and clinic on whether seizures (szs) in newborns (NBs) are injurious to the immature brain. Most neuroscientists' research concludes that they are, and may be epileptogenetic. Most clinical investigations conclude that NBs szs, if systemic complications are controlled, are not injurious and that there is no evidence for their epileptogenicity. Pertinent to such conflict, I summarize here data obtained from a prolonged follow-up of a large cohort of seizing NBs. **Methods:** The neurologic status of 190 unselected full-term (FT) NBs, after a time span of 8–20 years, composes the nucleus of this investigation. Thirty-two died before 2 years (16%). Of the surviving 158 NBs, reliable data could be obtained in 95 (60%) when adolescent or adult. Data on their motor, developmental status, and on the occurrence of epilepsy at any time of their life were obtained by direct contacts or by questionnaires sent to them, their families and, for many, schools or workplaces. **Results:** Forty-three (46%) did not have szs since they were neonates, and were free of neurodevelopmental deficits. Fifty-two (48%) had either motor or neurodevelopmental abnormalities. Twenty-three (25%) persisted having szs or had developed ex novo epileptic syndromes, the majority being those with worst phenotypes. Almost all with epilepsy had motor and/or developmental deficits, but the converse was uncommon. Review of early biographies: of the 23 with epilepsy revealed that the etiologic factors inducing NB szs were the most severe in 20 (88%); only three (12%) were cryptogenic or had transient metabolic disorders ($p < 0.01$). In contrast, of the 43 free of sequelae, in 34 (80%), their szs had been triggered by benign etiologies. Only nine were shown or suspected to harbor CNS pathologies ($p < 0.03$) **Conclusions:** To my knowledge this is the first very prolonged study of outcomes in a large cohort of NBs with szs. Main conclusions are (a) long-term sequelae of NBs szs correlate best with etiologies characteristic for this age; (b) the majority of NBs szs are either symptomatic markers of preexisting CNS pathologies or reactive to metabolic derangements; (c) there is no clinical evidence to support laboratory conclusions that NBs szs are, per se, epileptogenetic, although many of their etiologies are; (d) prolonged antiepileptic therapies fail to prevent or ameliorate sequelae, even when the NBs szs stop

early. Hence the results of these clinical studies appear to be in conflict with the conclusions arising from much experimental research. Whether or not an "inevitable energy failure" or the "excitotoxic effects" or the "aberrant circuitries following neurogenesis" described in the laboratory also occur in human NBs, their long-term functional effects are still obscure. From the optics of a clinician, further research could be focused more on the "protective" compensatory mechanisms existing in the CNS that prevent or ameliorate the putative injurious consequences of ictal phenomenology in the immature brains.

1.224
EVALUATION OF AN EDUCATIONAL PACKAGE FOR FAMILIES IN BRITISH COLUMBIA WHOSE CHILDREN HAVE BEEN RECENTLY DIAGNOSED WITH EPILEPSY

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Rationale: Epilepsy is a chronic condition with an associated stigma and often leaves families whose child is newly diagnosed, with a sense of feeling out of control and unaware of information and supports available to them. To address these issues, an Epilepsy Education Package was created. This package was designed using the Evaluating Printed Education Materials (EPEM) model (Bernier, 1993) to guide its development. This descriptive study was designed to invite parents to evaluate the usefulness of the Epilepsy Education Package they received when their child was diagnosed with epilepsy. There were no evaluation tools looking at the usefulness of printed educational materials for families, so an evaluation tool was created by adapting the Client Satisfaction Questionnaire (CSQ) developed by Daniel Larsen et al. (1979). **Methods:** The population of interest was families from the inpatient neurosciences unit and outpatient neurology clinic at British Columbia's Children's Hospital as well as from the Epilepsy Society of British Columbia who received the Epilepsy Education Package when their child was diagnosed with epilepsy. Evaluation tools were mailed to 93 families. The evaluation tool contains 39 questions in which 13 use a Likert scale, 15 closed-ended questions, and 11 open-ended questions as well as a demographic tool containing 10 questions. Telephone follow-up and interviews were done with 48 of these families. Analysis of the data was done descriptively. The percentages for each Likert-scaled response and closed-ended question were calculated. The open-ended questions and telephone data were analyzed using content analysis. Patterns or common themes were identified and responses categorized into these themes. **Results:** Data was obtained from 45 of the 93 families. Of that number, 35 (78%) found it useful. The package was read an average of 3 times. Results found the resource package informed the families of safety issues and allowed them to have these discussions with others. It also informed them about the medications their child was taking and the common side effects associated with those medications. Of the respondents, 68% felt they received enough information; 77% felt the package helped them inform others about their child's diagnosis; 59% felt it helped in their interactions with health professionals and teachers; 60% felt it helped clarify other's misconceptions about epilepsy; 76% felt the information in the package was new; and 95% felt it was relevant and up to date. **Conclusions:** The study findings indicate that most parents read and found the Epilepsy Education Package useful. Recommendations were given as to how the package could be improved. The recommendations included adding extra suggestions for resources and supports for families, such as information for siblings, websites, and an annotated bibliography or reference list for extra reading. Implications for clinical practice and education as well as research are included. As a result of this study, the importance of written educational materials for families whose child has epilepsy will be clear as well as the importance of evaluating such material.

1.225
FAMILIAL DYSAUTONOMIA (RILEY–DAY SYNDROME) MAY BE ASSOCIATED WITH EPILEPSY

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Rationale: The participants should be aware of the possibility of a relation between Riley–Day syndrome and epilepsy and exclude seizures in similar patients with autonomic dysfunction. Familial dysautonomia (FD) is a rare autosomal recessively inherited disorder affecting nervous system development, principally autonomic and sensory neurons. The disorder affects mainly Ashkenazi Jews and to my knowledge, it has never been reported to be associated with seizures. It usually presents in infancy, with failure to thrive due to swallowing difficulties, aspiration, and diarrhea. Recurrent pneumonias are frequent, with a high incidence of scoliosis. Mortality is high during the early years of life. The dysautonomic crisis, commonly induced by stress, does not become a prominent feature until after age 3 years. These crises, of severe vomiting and retching, occur with varying severity and frequency, and they may involve impairment of consciousness. They are associated with hypertension, tachycardia, sweating, erythematous blotching of the skin, gastric distention, and irritability. Peripheral pain sensation is diminished, but visceral and peritoneal pain sensation is intact. Diagnosis is usually confirmed by absence of flare response to intradermal histamine. Although it involves neurologic dysfunction, those patients are not typically managed by neurologists, and seizures may be overlooked. **Methods:** I report a family of three children, two of whom are monozygotic twins, with genetic confirmation of familial dysautonomia and atypical absence epilepsy. The seizures were analyzed using video-EEG. The history, physical examination, and diagnostic workup are analyzed as well as the EEG findings. **Results:** All three patients had a history of slow development. The monozygotic twins have atypical absence seizures associated with identical EEG features characterized by central rhythmic high-voltage theta preceding generalized irregular 3-H spike-and-wave discharges lasting several seconds and frequently followed by diffuse central high-voltage theta. The older sibling has a history of similar clinical and EEG seizure pattern, now having only frequent brief generalized discharges associated with subtle behavior changes. One of the twins and the older brother have history of febrile seizures. Initially the seizures were triggered by breath holding and occurred between ages 19 months and 4.5 years. The seizures were characterized by sinking slowly to the floor and not losing consciousness. Now after treatment, the seizures are characterized by brief staring with upward gaze and blinking lasting 1–2 s. They are currently treated with topiramate and ethosuximide, which has improved the seizure frequency without side effects. They had typical clinical signs of familial dysautonomia and tested positive for the intradermal histamine test. **Conclusions:** The presence of similar seizures and febrile convulsions in this family suggests a possible genetic association between familial dysautonomia and epilepsy. Autonomic crisis may mask the presence of absence seizure; therefore I suggest screening those patients with EEG and neurologic consult. Video-EEG is useful to correlate subtle behavior with EEG abnormalities.

1.226
SAFETY AND EFFICACY OF LAMOTRIGINE IN INFANTS AGED 1–24 MONTHS WITH PARTIAL SEIZURES: INTERIM OPEN-LABEL RESULTS

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Rationale: Refractory partial seizures are common in infants, and there are few proven treatment options. The safety and efficacy of lamotrigine (LTG) in this age group are currently being studied in a double-blind, placebo-controlled, responder-enriched trial. In this study, LTG is added to an ongoing antiepileptic drug (AED) regimen and titrated to an individually optimized dose. The titration and optimization phase of this study is open-label (OLP). Patients who "respond" to therapy with a $\geq$40% and $\leq$80% seizure reduction are then

eligible for randomization into a double-blind LTG continuation or withdrawal phase. The open-label titration and optimization phase provides a preliminary view of the profile of LTG in this population. **Methods:** Infants with partial seizures, aged 1–24 months, are entered into the study, and LTG (Lamictal) is gradually titrated to optimal effect consistent with product label (slower rate and lower final dose in the absence of enzyme-inducing AEDs (EIAEDs). The maximal allowed dose of LTG was 15.6 mg/kg/day (concurrent EIAEDs) or 5.1 mg/kg/day (no concurrent EIAEDs). The open-label phase of the study lasted ≤27 weeks. **Results:** Seventy-four patients have completed or prematurely discontinued the OLP. The mean age is 13.5 months (SD, 6.8; range, 1–24). The mean weight is 9.7 kg (SD, 3 kg). There are 38 boys and 36 girls. The mean duration of epilepsy was 9.2 months (SD, 6). Presenting seizure types were partial seizures (81%, primarily noted as complex), secondarily generalized seizures (41%), and generalized seizures (31%). Data were available for efficacy analysis of 43 patients taking EIAEDs and 18 patients taking non-EIAEDs. After titration and dose optimization, the mean total daily dose of LTG was 10.5 mg/kg/day (concurrent EIAEDs) and 3.4 mg/kg/day (non-EIAEDs), with ranges of 1.2–15.6 and 0.2–5.1, respectively. During the last 28 days of OLP, the median percentage reduction from baseline seizure frequency was 35% for the EIAED group and 80% for the non-EIAED group. Forty-two percent of the patients taking EIAEDs had a >50% reduction from baseline seizure frequency compared with 67% of the patients taking non-EIAEDs. Eleven patients (18%) were seizure free during the last 4 weeks of the OLP. There were 10 dermatologic reactions, three of which were attributable to concurrent infection; six were attributed to the medication. Rash was the cause of study drug discontinuation in three (4%) patients. There were no cases of Stevens–Johnson syndrome or serious rash. Serious adverse events were systemic in nature or related to poor seizure control and in keeping with the overall ill nature of the patient population. **Conclusions:** In this interim analysis, the data indicate that LTG is an effective and well-tolerated drug for patients with refractory partial seizures in the 1- to 24-month age range. This study is ongoing. (Supported by GlaxoSmithKline.) (Disclosure: Salary: Glaxo SmithKline for: Womble, Caldwell, Onks, Morrison, Messenheimer, Blum; Consulting: J. Eric Pina-Garza, M.D., consultant for Glaxo-Smith-Kline; Honoraria: J. Eric Pina-Garza, M.D., speaker for Glaxo-Smith-Kline.)

1.227
OUTCOME OF NEONATAL SEIZURES

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Rationale: Neonatal seizures are classified as undetermined epilepsies with both generalized and focal seizures. The aim of our study was to evaluate how many and which of our newborns with neonatal seizures developed subsequent epilepsy and the type of epilepsy they had. **Methods:** We reviewed the data of 2,207 newborns consecutively admitted to the Neonatal Intensive Care Unit of University of Parma during the last 7 years. Fifty-six patients were selected according to the following criteria: repetitive neonatal seizures treated with antiepileptic drugs (AEDs), more than one EEG performed during the neonatal period, at least one imaging examination [cerebral ultrasounds and/or cerebral magnetic resonance imaging (MRI)] and neurologic follow-up ≥6 months. The neonatal seizure type and the epilepsies were identified according to the Classification of the International League Against Epilepsy (1981–1989). **Results:** The average of the seizures onset was for the preterms 6.2 days, and for the newborns at term, 5.8 days, whereas their gestational age ranged from 25 to 42 weeks. Etiologic factors were hypoxic–ischemic insult in 17 of 56, intracranial hemorrhage in 19 of 56, cerebral malformation in six of 56, metabolic disorders in seven of 56, sepsis in three of 56, and four of 56 with fetal chronic distress. The outcome of the 47 patients (nine lost during the follow-up) has been normal in 22 of 47; neurologic impairment without epilepsy in six of 47; epileptic encephalopathy in 14 of 47, death in five of 47. All the 56 patients had partial seizures; three of them had both partial and generalized seizures. The most frequent seizure type was clonic unifocal and multifocal; however, tonic seizures were present in nine of 14 newborns who had epileptic encephalopathy and in the five who died. The three newborns with both types of seizures presented, as causative factors, inborn error of metabolism (two) and holoprosencephaly. Today, among the epilepsy patients: nine of 14 developed symptomatic localization-related epilepsy with motor partial seizure and with secondary generalization in six of 14; three of them developed a transient West syndrome; four of 14 present a generalized symptomatic epilepsy such as West syndrome (three) and Aicardì syndrome (one); one died at 3 months of life. All of them (14 of 14) had an abnormal background EEG activity since birth together with more specific epileptic abnormalities. **Conclusions:** The tonic seizures represent a negative prognostic factors. Furthermore, most of the patients with cerebral lesions and neonatal seizures may develop symptomatic localization-related epilepsy, sometimes throughout a transient West syndrome.

1.228
POSTTRANSPLANT SEIZURES IN INFANTS WITH HYPOPLASTIC LEFT HEART SYNDROME

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Rationale: Posttransplant seizures are common in infants undergoing cardiac transplant and are usually attributed to hyperperfusion. However, the number of variables potentially contributing to posttransplant seizures is multiple. Identification of these variables may allow treatment to prevent or more effectively treat these seizures. The aim of this study was to determine specific variables associated with the occurrence and severity of posttransplant seizures in infants with hypoplastic left heart syndrome (HLHS). **Methods:** We reviewed medical records from the pediatric cardiac transplant database, spanning an 11-year period (January 1989 to December 2000). Of 127 HLHS infants, 27 (21%), aged 9–175 days, had posttransplant seizures. Patients with pretransplant seizures were excluded. The control group consisted of 27 age-matched infants without seizures. We compared multiple pre-, intra-, and acute posttransplant variables including birth and growth parameters, time at HLHS diagnosis, maternal variables, circulatory and bypass parameters, laboratory data, neuroimaging, EEG and neurologic examination findings, and occurrence of infections or other perioperative complications. We determined which variables were associated with the occurrence and severity of posttransplant seizures. **Results:** Occurrence of posttransplant seizures was associated with the total cardiopulmonary bypass time (CPB; $p = 0.004$), and to a lesser extent the duration of cooling ($p = 0.056$). None of the other variables was significant; 40% of the patients with seizures required ongoing antiepileptic drug treatment (AED) after discharge. Of those patients with seizures, circulatory arrest time ($p = 0.04$) inversely correlated with the continued need for postdischarge AED use. Pretransplant EEG abnormalities, higher preictal heart rates, and the presence of posttransplant arrhythmias were associated with the need for postdischarge AEDs ($p = 0.052$, 0.078, and 0.072, respectively), but this did not reach statistical significance. Posttransplant EEGs were not associated with the need for continued AEDs ($p = 0.696$). **Conclusions:** Patients with longer CPB times, especially those with a longer duration of cooling, are at higher risk for the development of posttransplant seizures. Shorter circulatory arrest times are associated with the need for ongoing AEDs. Pretransplant EEG abnormalities, higher preictal heart rates, and the presence of posttransplant arrhythmias are likely to be predictive of the need for continued AEDs. Our data suggest that certain variables are associated with an increased risk for posttransplant seizures in HLHS infants. This may allow early inter-

vention to prevent seizures or suggest early aggressive AED treatments. Future studies on modification of transplant techniques to reduce risk variables and to minimize or decrease the severity of posttransplant seizures are also warranted.

1.229
VAGUS NERVE STIMULATION IN A PEDIATRIC POPULATION: OUTCOME OF PATIENTS IN PRIVATE-PRACTICE SETTING

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Rationale: At the end of this activity, the participants should be able to discuss the outcome of vagus nerve stimulation (VNS) therapy among pediatric patients in a private-practice setting. Many of the data on the outcome of VNS therapy describe patients treated in clinical trials or at epilepsy centers. This report describes pediatric patients followed up in a private-practice setting. **Methods:** Demographic and seizure syndrome information was compiled for patients aged 17 years and younger who received VNS therapy. Changes in seizure frequency were tracked after 3 and 12 months of VNS therapy and physician-assessed changes in quality of life were noted after 12 months. **Results:** Of the 35 VNS patients aged 17 years or younger, 18 were boys. Median age at implant was 12 years (range, 2–17 years). Median age at seizure onset was 1.5 years (range, 0–9 years), and median duration of epilepsy was 7.9 years (range, 0–17 years). Epilepsy syndrome was listed as localized for 12 (34.3%) patients, generalized for 16 (45.7%), Lennox–Gastaut for six (17.1%), and juvenile myoclonic epilepsy (JME) for one (2.9%). All 35 patients have not been implanted for 12 months; therefore data on changes in seizure frequency and quality of life are provided for 24 patients after 3 months of VNS therapy and for 14 patients after 12 months. Median seizure reduction after 3 months was 72.52% (range, –100 to 90.91) with 19 (79%) patients reporting reductions of ≥50%, 11 (46%) of ≥75%, and three (13%) reporting no seizures. Median seizure reduction after 12 months was 70% (range, –100 to 100) with 10 (71%) patients reporting reductions of ≥50%, five (36%) of ≥75%, and one (7%) reporting no seizures. Quality-of-life measures had improved for 64% of the patients in alertness; for 50% in verbal communication, mood, and postictal period; and for 36% in memory, achievement at work or school, and seizure clustering at 12 months. **Conclusions:** Median seizure-frequency reductions among this private-practice pediatric cohort are somewhat greater than the clinical trial experience. Although reasons for the difference are not clear, further comparisons of device-setting parameters and concomitant antiepileptic drugs may yield further insight into achieving greater seizure-frequency reductions through VNS therapy. VNS is a practical treatment alternative for the private-practice pediatric epilepsy clinic. (Disclosure: Honoraria: Cyberonics, Inc.)

1.230
HYPOTHALAMIC HAMARTOMA-RELATED SEIZURES TREATED WITH GAMMA KNIFE RADIOSURGERY: REPORT OF THREE CASES

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Rationale: Hypothalamic hamartoma is often associated with gelastic epilepsy. Due to the delicate site in which the tumor is located, surgery is associated with considerable risks. Stereotactic radiosurgery is a noninvasive procedure that effectively treats patients with vascular malformations and brain tumors. While preliminary results are promising, data concerning its efficacy for gelastic epilepsy is limited. **Methods:** In the three cases presented, gamma knife radiosurgery was applied as a safe and noninvasive alternative to microsurgery in an attempt to obtain seizure control. Three patients, a 13-year-old girl, a 6-year-old girl, and a 5-year-old boy, had medically intractable gelastic epilepsy. Abnormal behavior and cognitive impairment were also evident. Magnetic resonance (MR) imaging revealed hypothalamic hamartomas in all of them. Radiosurgical treatment was performed with the Gamma Knife model C system in Marseille (October 2001 for the first two and February 2002 for the third). The procedures were performed under general anesthesia. A complex multiisocentric highly conformal dose planning was performed, relying on stereotactic imaging [MR and computed tomography (CT)]. Two small lesions in the third ventricles were treated with 17 gy at the margin. The third lesion (larger in and under the floor of the ventricle) was treated with 14 gy. **Results:** Follow-up evaluations revealed a marked improvement in seizure frequency and global functioning. Patients are currently able to attend public school. There were no significant complications from the radiosurgical therapy. **Conclusions:** Our findings suggest that gamma knife surgery is a potentially safe and valuable treatment modality for children with hypothalamic hamartomas and drug-resistant gelastic epilepsy.

1.231
EPILEPSY IN CHILDREN WITH CEREBRAL PALSY

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Rationale: To study the spectrum of epilepsy in children with cerebral palsy (CP) and to find out whether there is any significant difference between those children with CP who have epilepsy versus those who do not. **Methods:** One hundred five consecutive children with CP and active epilepsy, between ages 1 and 14 years, were studied prospectively. A cross-sectional study of 452 consecutive registered cases of CP was also done to find the incidence of seizures. Detailed history and examination including neurodevelopmental assessment, an EEG and computed tomography (CT) scan were done in all cases. The social quotient (SQ) was assessed using the Vineland Social Maturity Scale. A control group of age-matched children with CP but no epilepsy was also studied for comparison of SQ. Epilepsy was classified according to the International League Against Epilepsy (ILAE) classification. Descriptive statistics, $\chi 2$, and Student's t test were used for subgroup differences. Correlation and multiple regression analysis were used to compare variables of subtypes of CP and find the relation between IQ and other variables. **Results:** Of the 452 children, 160 (35.4%) had epilepsy. The maximal incidence of 66% was seen in children with spastic hemiplegia (SHP) followed by quadriplegia (SPQ; 42.6%) and diplegia (SPD; 15.8%). Seizures were less common in dystonic (DYS), hypotonic (HYPO), and mixed (MIX) CP. Of the 105 children, 65 were boys, and 45 were girls; 40 (38%) had a history of birth asphyxia. The mean age at onset of seizures was 18.9 months; 64 (60.95%) had seizure onset before 1 year of age. Children with myoclonic seizures ($p < 0.05$) and infantile spasms ($p < 0.01$) had seizure onset significantly early in life as compared with those with generalized tonic–clonic seizures. Types of seizures in different types of CP are shown in Table 1. Seizures were controlled in 45 (58.1%) children, polytherapy was required in 40; of these, 65% had CT abnormalities. Seizure control was achieved in 74% patients with normal to borderline SQ as compared with 48.7% with SQ <70. SQ values had a positive correlation

TABLE 1. *Seizure types in subtypes of CP*

Seizure type	SPQ (n–58)	SPD (n–24)	SPH (n–21)	DYS (n–5)	HYPO (n–3)	MIX (n–2)	Overall (n–105)
GTC	19 (35.1%)	9 (45%)	7 (35%)	1 (20%)	3 (100%)	1 (50%)	38.1%
SP	3 (5.5%)	3 (15%)	1 (5%)	1 (20%)	0	1 (50%)	8.5%
CP	6 (11.1%)	1 (5%)	6 (30%)	0	0	0	12.3%
P–G	7 (13%)	3 (15%)	3 (15%)	0	0	0	12.3%
MJ	9 (16.7%)	3 (15%)	1 (5%)	2 (40%)	0	0	14.3%
IS	14 (25%)	5 (25%)	3 (15%)	1 (20%)	0	0	22.8%
Others	0	1 (5%)	0	0	0	0	1%

GTC, generalized tonic clonic; SP, simple partial; CP, complex partial; P–G, partial with secondary generalization; MJ, myoclonic jerks; IS, infantile spasms.

with age at onset of seizures ($p < 0.01$) and with better control of seizures ($p < 0.01$). **Conclusions:** Epilepsy occurs in more than a third of patients with CP and is commonest in spastic hemiplegia and quadriplegia. Seizure onset is mostly in infancy. While generalized tonic–clonic seizures are most common, myoclonic jerks are seen in about one fourth of cases. Seizures are more common and more difficult to control in children with low intelligence.

1.232
SUBJECT RETENTION IN A LONG-TERM STUDY OF EPILEPSY

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Rationale: Questions about the long-term prognosis of epilepsy require rigorously designed prospective studies. The key to the validity of these studies is a high follow-up rate. We describe some of the techniques and approaches currently being used in the Connecticut Study of Epilepsy. Our methods are based on recognition of the uniqueness of each family and sensitivity to and consideration of each of them. **Methods:** 1. Establish relationship with family: The study was introduced to families by treating physicians at the time of an office visit or in a personally addressed letter. Families were interviewed at their convenience in their homes. During subsequent follow-up calls, interviewers take the time to allow parents to relay information and concerns (e.g., life-cycle events, concerns about schooling). The interviewer notes such conversations and, when appropriate, inquires about the event during a subsequent follow-up call. 2. Logistics of maintaining contact: Follow-up calls are made every 3–4 months. Telephone numbers of friends and family of participants were requested at the intiial interview and periodically are reviewed with participants. Self-addressed postage-paid change-of-address and telephone postcards are sent to families who plan to move or to those whose telephone numbers are found to be no longer in service. 3. The study as a resource: Initially a book on epilepsy in children was given to each family for participating in the study. Information for contacting relevant agencies and institutions is made available on request. The study sends mailings from the local Epilepsy Foundation about their summer camp and other programs that may be beneficial to study participants. 4. Being unobtrusive, flexible, and supportive: The researchers are sensitive to stressors such as illnesses, deaths, divorces, changes in employment, and moving that may affect families. Taking the time to listen to participants and being sensitive to their needs and flexible about conducting the follow-up calls lessens the imposition posed by the study on their time. Some participants prefer e-mail communication rather than phone calls. Others have preferences about when and where they are called (home/work, weekday/weekend). Respecting these preferences helps minimize the interruption to the family. 5. Age of majority: When study subjects attain majority, they are invited to continue their participation in the study as adults, and appropriate informed consent and authorizations are obtained. Their preferences as to whether we continue to communicate with their parents, with them, or with either are determined. 6. Ongoing acknowledgement, appreciation, and support: During follow-up calls, we acknowledge their continued participation and remind them of how valuable their contribution is to the study. Periodically families are sent reprints of articles published about the study. **Results:** Over a period of 5–9 years (median, 7), only 29 (4.7%) families have been lost to follow-up, and 11 (1.8%) refused to continue follow-up after study entry. **Conclusions:** Behind the mechanics of a successful follow-up study are numerous personal and interpersonal factors that turn study subjects into active interested participants in a research project. (Supported by NIH-NINDS grant R01-NS 31146.)

1.233
EEG STUDIES IN CHILDREN WITH AUTISM AND RELATED DISORDERS

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Rationale: To define the value and results of EEG studies in children with autism and related disorders at this hospital. To compare the incidence and type of abnormal EEGs in patients with target disorders (autism, Landau–Kleffner syndrome, language regression, pervasive developmental disorder, and autistic specturm disorder) to our EEG results on all patients studied over 3 consecutive years. **Methods:** EEG and videotelemetry reports from 1999, 2000, and 2001 were reviewed, selected abnormal studies were reviewed. Only patients whose EEG requests indicated the presence of autism were included. Because many EEG requests provide little or no information, some patients were surely omitted. **Results:** The 262 studies were attempted over the 3-year period in 203 patients; 19 EEGs could not be done because of agitation; 193 EEGs and 50 videotelemetry studies were done, of 4,456 total EEGs and 540 video studies done here over 3 years. Sixty-nine of 103 waking EEGs were normal; 15 showed epileptiform discharges (EDs). Twenty of 22 sedated sleep (barbiturate, chloral hydrate) EEGs were normal, two showed Eds; 40 of 68 waking and sleep EEGs were normal; 15 had EDs. Clinical or EEG seizures were recorded in six patients (vs. 6.1% of all outpatient EEGs), one of whom, with primary generalized seizures, had marked and sustained improvement with AED treatment. The incidence of abnormal EEGs and videotelemetry studies (VTs) was higher in very handicapped and nonverbal patients; VTs were more often abnormal than EEGs but represented a different and more selected patient group. Sleep was obtained in nine of 10 ambulatory video studies and all overnight or longer studies. The commonest VT abnormality was slow or disorganized background. Sixteen VTs showed at least three EDs. Seven of these had nonepileptic staring spells plus EDs. Three of seven improved when AEDs were reduced or stopped. Three patients without EDs had events that were nonepileptic and had been presumed by parents and some physicians to be seizures. Five patients had grossly abnormal VTs, three with long portions of continuous spike–wave discharges. Two of these patients had marked and sustained improvement with vigorous AED therapy. Of 44 patients with EDs, 11 had a previously normal waking and sleep EEGs; 54% had focal epileptiform discharges. Many patients were taking AEDs (38%) at the time of the study. Of the 10 patients with recorded seizures or near status epilepticus VTs, four had no clinical history of seizures. The others were taking AEDs. Most of our patients were low functioning and could be classified as mentally retarded; 95% came from in the state. Fewer than 10 patients received steroids or adrenocorticotropic hormone. **Conclusions:** The incidence of EDs in autistic and related conditions was similar to that of all EEG studies in our hospital. Sedated sleep studies had very low yield. Natural sleep recordings yielded the highest incidence of EDs. Only three patients had major sustained functional improvement after very epileptiform EEGs were found and treated. A significant number of patients had nonepileptic staring spells being treated with AEDs. Some of these patients improved when AEDs were decreased or stopped. (Supported by divisional funds.)

1.234
IMPACT OF A PHARMACY EDUCATIONAL PROGRAM ON PEDIATRIC PATIENTS WITH SEIZURES

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Rationale: Concern about the preventability of adverse drug events (ADEs) and medication errors, especially in the pediatric population, is increasing. Programs targeting the most common classes of ADEs are needed. A retrospective review at our institution of all ADEs spontaneously reported that between 1997 and 2000, anticonvulsants (AEDs) accounted for 10.4% of ADEs, of which 39.7% were considered preventable because of a lack of consistent parent/patient education. **Methods:** We designed a study to evaluate the parents' knowledge at baseline and after a comprehensive educational program provided by a pharmacist regarding their child's AEDs with respect to dose, adverse effects, and storage. Parents were also surveyed at baseline and after education regarding their satisfaction with the information provided by all healthcare professionals as well as the amount of information the parent knew about proper seizure first aid and precautions. All new and returning parents of seizure patients were included in the study. **Results:** Seventy parents' knowledge improved after the educational program provided by a pharmacist. Knowledge of AED adverse effects, AE management, seizure first aid, medication storage, and seizure pre-

caution for before versus after pharmacist consultation improved from 0.134 to 0.926 ($p < 0.001$), 0.478 to 1.00 ($p < 0.001$), 0.217 to 1.00 ($p < 0.001$), 0.550 to 0.986 ($p < 0.001$), and 0.289 to 0.957 ($p < 0.001$), respectively. All parents were also highly satisfied with the role of the pharmacist [1.97–3.69 ($p < 0.0001$)]. **Conclusions:** The pharmacist is perceived by the parents to be a valuable medication-education resource. Pharmacists can play an important role in the multidisciplinary approach to the management of pediatric patients with seizures.

1.235
NEUROPHYSIOLOGICAL EVALUATION IN PEDIATRIC PATIENTS WITH HEREDITARY METABOLIC DISORDERS

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Rationale: At the end of this activity, the participants will be able to discuss the neurophysiological data as an additional tool to clinical workup and neuroimaging studies in patients with hereditary metabolic disorders (HMDs). EEG is of limited help in specific diagnosis of patients with HMDs. However, it can provide complementary functional information in the clinical workup of patients with HMDs. **Methods:** We present 83 patients with 18 different types of clearly documented metabolic disorders. Female/male ratio was 37:46. Age at the time of evaluation ranged between 1 month and 17 years (mean, 4 years 9 months), age at the time of diagnosis ranged between 1 month and 16 years (mean, 1.5 years). Parents were relatives in 62 patients. Routine EEG was obtained in all patients. VEP was done in 65 patients, and BAEP in 66. Forty-six patients underwent psychometric evaluation, and 38 patients had neuroimaging studies [cranial ultrasonography, computed tomography (CT), and/or magnetic resonance imaging (MRI)]. **Results:** Forty-eight patients initially presented with seizures, yet at the time of evaluation, 34 had associated seizure disorder. Sixty patients (72%) had an abnormal EEG. The most common abnormality was background slowing, seen in 42 patients (50.4%). Epileptiform abnormality was seen in 27 patients (32.4%); asymmetry was present in 18 (21.6%). Patients with no obvious seizures had an abnormal EEG in 60%, and 14% showed epileptiform activity. EEG abnormalities were most common in patients with dihydropteridine reductase deficiency, urea cycle disorders, maple syrup urine disease (MSUD), and glutaric aciduria. Epileptiform activity was most common in MSUD, whereas background slowing was predominant in dihydropteridine reductase deficiency, and asymmetry in urea cycle disorders. Of 65 patients who had a VEP study, 50% were abnormal, with bilateral delayed P1 latencies being the most common abnormality. BAEP was obtained in 66 patients, and 47% had abnormal results. Bilateral prolonged I-V interpeak latencies were seen in a majority of cases. Psychometric evaluation was performed in 46 patients; three had severe mental retardation (MR), eight had moderate MR, and 11 had mild MR. Twenty-six of 38 patients had abnormal neuroimaging findings; white matter involvement was the leading abnormal feature on MRI. **Conclusions:** EEG is recommended in evaluation and follow-up of patients with HMDs. EEG may detect cerebral dysfunction and show epileptiform abnormality in the absence of severe cognitive deficits and seizure disorder. Background slowing on EEG and prolonged latencies in evoked potentials are supportive of white matter disease. Neurophysiological studies may help early detection or improvement in patients with HMDs as an additional tool to clinical features and neuroimaging studies.

1.236
CORRELATION OF COPPER LEVELS AND EEG ABNORMALITIES IN PATIENTS WITH MENKES DISEASE

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Rationale: The correlation between the severity of the EEG findings and copper levels in Menkes disease has not been well described. This retrospective study was undertaken to better define such a correlation. At the end of this activity, the participants should be able to discuss the correlation between copper levels and EEG abnormalities in patients with Menkes disease. **Methods:** The records of children treated with Menkes disease at St. Christopher's Hospital for children (Philadelphia, PA) from 1973 to present were reviewed. Nineteen patients with Menkes disease were identified during the period of the study. Sixteen patients had copper levels available, and six of these patients had both copper levels and EEG data available at the time of analysis. Patient demographics, EEG data, copper levels, and mortality were recorded. EEG data were stratified using a scoring system. Abnormalities including background slowing, focal slowing/asymmetry, disorganized background, generalized epileptiform, focal epileptiform, multifocal epileptiform, very low amplitude, very high amplitude, or the presence of a seizure during the EEG were given 1 point each. Points were summed as a measure of severity of the EEG. Maximal score was seven, as two of the abnormalities were exclusive with other characteristics. The EEG severity scores and the copper levels were plotted against age, in each patient. **Results:** The nineteen children ranged in age from birth to 22 months at the time of the diagnosis (average, 8.5 months). All but one had seizure disorder and severe developmental delay. Of the total sample, 10 children are dead at the present, with an average age at death of 7.7 years (range, 3 months to 17 years). A total of 400 copper levels was available for the six patients of the analysis. An average of 10 EEG data per patient were available for these six patients. Most of the patients showed a negative correlation between the copper levels and the severity of the EEG. The lower the copper levels, the more abnormalities noted on the EEG. The effect was shown both individually and when comparing between patients. **Conclusions:** Our study shows that it is possible to correlate EEG data and copper levels in patients with Menkes disease. We found a negative correlation, with lower copper levels having more abnormalities on the EEG. This study suggests that keeping copper levels toward normal limits in patients with Menkes disease may help to control EEG abnormalities in this group of patients, although not necessarily modify the course of the disease.

1.237
SEIZURES IN THE POSTENCEPHALITIC/ENCEPHALOPATHIC SETTING IN CHILDREN

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Rationale: To evaluate characteristics and predictors of persistent seizures in children with an encephalitic/encephalopathic illness. At the end of this activity the participants should be able to discuss the development of seizures, characterize seizure type, and describe the common EEG abnormalities in children admitted with encephalitis/encephalopathy. **Methods:** A retrospective review of the medical records of patients admitted with encephalitis/encephalopathy from December 1989 to Decenber 2001 was performed. Data abstracted included age, gender, presenting features, laboratories, neuroimaging, EEG, and neuropsychologic testing. Time course was categorized as: prodromal (day –30 to admission), early (days 0–7), middle (days 8–30), and late (beyond day 30). **Results:** Ninety-one patients were included (60% boys); mean age, 5.1 years (1 week to 13 years). Early seizures were present in 66%: 34% partial, 25% generalized, 7% status epilepticus. Late seizures occurred in 32%: 19% partial, 9% generalized, 2% myoclonic, with the clinical seizure type often evolving over time. EEG was abnormal early in 54 of 65 patients (83%), with diffuse slowing/disorganization in 29%, focal slowing in 20%, focal epileptiform discharges on a normal background in 14%, epileptiform discharges on a slow background in 9%, generalized epileptiform discharges in 5%, and multifocal discharges in 6%. Late EEG abnormalities were found in 74% (25 of 34 patients who had EEG), with diffuse slowing/disorganization present in the majority (35%). Predictors of late seizures included middle seizure ($r = 0.822$, $p < 0.001$) and early abnormal EEG (40% vs. no patients with late seizures who had an initial normal EEG; $p < 0.001$). Age, gender, and CSF WBC did not correlate with late seizure. Neither focal nor bilateral/diffuse neuroimaging abnormality correlated with seizure, either early or late. **Conclu-**

sions: In the setting of an acute encephalitis/encephalopathy, children with seizures persisting beyond the first week of hospitalization were more likely to develop a chronic seizure disorder. Serum/CSF laboratory values and neuroimaging findings were not predictive of outcome regarding seizures. EEG abnormalities correlated with the development of late seizures.

Human Imaging—Adult

1.238
CONTINUOUS FUNCTIONAL MAGNETIC RESONANCE IMAGING ACQUISITION WITH SIMULTANEOUS EEG RECORDING IN FOCAL EPILEPSY

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Rationale: Spike-triggered functional MRI (fMRI) has been used to study interictal epileptic discharges (IEDs) in patients with epilepsy. Recently, continuous fMRI acquisition with simultaneous EEG recording and off-line EEG processing has become available. This method is easier to implement and provides a stronger statistical analysis. We present the results on a large group of patients with focal epilepsy investigated using this new technique. **Methods:** The only inclusion criterion was the presence of focal intractable epilepsy and frequent IEDs. EEG was recorded simultaneously during BOLD-fMRI acquisition. Each session lasted ~80 min. The IEDs were identified off-line after removal of the artifact from fMRI scanning. IED timing was used to perform statistical analysis of the fMRI data. For those patients with an activated area, the volume of activation was calculated. The study population was divided into two groups according to the presence or absence of fMRI activation. The two groups were compared in terms of their clinical and electrophysiologic variables. **Results:** A total of 32 studies were performed on 28 patients. Nine studies were not included in the analysis: seven in which the patients had no IEDs during the scanning period and two in which some data were lost. Activation was obtained in 12 of the remaining 23 studies (52%). The average volume of activation was 5.1 cc (SD, 7 cc). In 11 of these 12 studies, there was at least one region of activation concordant with the EEG (same lobe). In two studies, there were also regions of activation at a distance from the EEG focus. In one study, the activation was contralateral to the EEG focus. Patients who had bursts of IEDs were more likely to have fMRI activation than patients with isolated spikes ($p < 0.05$). The number of spikes per study did not influence the presence of activation, nor did the existence of a lesion. A set of other electrophysiological and clinical variables was also examined, and none was correlated to the presence of activation. **Conclusions:** Continuous acquisition of fMRI with simultaneous EEG recording is feasible and yields regions of activation that are concordant with EEG activity. However, activation was only found in ~50% of studies, and no clear explanation could be found for this result, with the exception of presence or absence of bursts of IEDs. The significance of regions of activation outside the expected EEG focus remains to be investigated. This technique will require further validation and some technical improvements before its routine use in presurgical evaluation of epilepsy patients. (Supported by Canadian Institutes of Health Research under grand MOP-38079.)

1.239
VISUALIZATION OF INTERICTAL SPIKES AS MEASURED WITH SUBDURAL EEG ELECTRODES USING FUNCTIONAL MAGNETIC IMAGING

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Rationale: Functional magnetic resonance imaging (fMRI) using echo-planar imaging (EPI) and the BOLD effect can detect regional activation during interictal spikes in focal epilepsy. We investigated whether interictal activity as documented by subdural EEG electrodes but not detected by concomitant surface EEG electrodes can elicit regional blood oxygen level–dependent activation. **Methods:** Three patients with temporal lobe epilepsies were investigated before resective epilepsy surgery. All patients had subdural electrodes covering the temporal lobe of seizure onset and additional surface electrodes. EEG was recorded using the "EMR" EEG amplifier (Schwarzer GmbH, Munich, Germany) and BrainLab software (OSG, Rumst, Belgium). EEG artefacts due to MRI acquisition were eliminated based on MATLAB software (Math Works, Inc., Natick, MA, U.S.A.). MRI was performed using a 1.5-T whole-body MR system (Vision; Siemens, Erlangen, Germany). Images were obtained during "baseline" (without interictal temporal spikes recorded on subdural or surface electrodes) and during interictal spiking as documented by subdural EEG. The interictal activity was not detected at the surface electrodes in all patients. The localization and frequency of interictal spikes before and during MRI acquisition was registered using offline artefact elimination and analysis. Only episodes without additional spiking during MRI acquisition periods were used for further analysis using the Analysis of Functional NeuroImages (AFNI) software. **Results:** Activation maps revealed significant regional hyperperfusion of 8% corresponding to the localization of the temporal lobe spikes in two of the three patients. **Conclusions:** We demonstrate that interictal epileptiform discharges recorded with subdural EEG electrodes but not detected by concomitant surface electrodes are sufficient to elicit regional fMRI activation.

1.240
INTERICTAL SPIKE-TRIGGERED FUNCTIONAL MAGNETIC RESONANCE IMAGING IN CORTICAL DYSPLASIA AND HIPPOCAMPAL SCLEROSIS

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Rationale: Partial epilepsy is the most common form of epilepsy and can frequently become medically refractory. Interictal spike-triggered functional MRI (fMRI) can be a useful investigative tool to aid in the surgical planning of these patients. However, no studies have systematically investigated two common causes of refractory partial epilepsy, hippocampal sclerosis and cortical dysplasia. **Methods:** Four patients with cortical dysplasia and three patients with hippocampal sclerosis with intractable seizures and frequent interictal discharges (more than one discharge per minute) were recruited from our video-EEG telemetry unit. All patients had anatomic MRI, and most also had positron emission tomography (PET) and single-photon emission computed tomography (SPECT) to facilitate seizure localization. Patients were studied 2–8 weeks after discharge from hospital. Echo-planar fMRI was performed at 3.0 Tesla with concurrent EEG. Blood oxygen level–dependent (BOLD) weighted signals were measured. Whole-brain fMRIs (20–22 axial slices, 4 ± 1-mm thick, TE/TR 40/3,000 ms) were acquired immediately after interictal discharges (spike) or when ±15 s has passed without a discharge (rest). The images were then analyzed using the Student's *t* test to compare spike and baseline datasets to generate a statistical map of spike-related BOLD activation. **Results:** The patient profiles are shown in Table 1. Studies were attempted on an additional four patients with cortical dysplasia. However, the interictal discharges subsided in these patients between the time of discharge from hospital and the day of the study. Patients with cortical dysplasia and hippocampal sclerosis had seven to 25 and four to 10 spike-triggered fMRI acquisitions, respectively. BOLD activation was seen in only two patients, both with cortical dysplasia. Notably, these patients had the most spike-triggered fMRI acquisitions in the study (20 and 25, see Table 1). The BOLD activation was centered on the dysplastic lesion in both cases. **Conclusions:** Spike-triggered fMRI shows BOLD activation in patients with cortical dysplasia, but only if a large number of discharges are captured. In patients with hippocampal sclerosis, ≤ 10 interictal discharges were not sufficient to produce BOLD activation. These results highlight the need for careful patient selection and timing

of experiments when employing spike-triggered fMRI in these groups of patients. [Supported by National Health and Medical Research Council of Australia (grant 135400), Brain Imaging Research Foundation, Canadian Institutes of Health Research, and Alberta Heritage Foundation for Medical Research.]

TABLE 1. *Patient characteristics*

Lesion	Lobe (or side)	Interictal discharges	Activation
Dysplasia	Frontal	25	Yes
Dysplasia	Frontal	20	Yes
Dysplasia	Frontal	7	No
Dysplasia	Occipital	14	No
Hippocampal sclerosis	Left	10	No
Hippocampal sclerosis	Left	8	No
Hippocampal sclerosis	Left	4	No

1.241

USING PATIENT-SPECIFIC HEMODYNAMIC RESPONSE FUNCTION IN THE ANALYSIS OF COMBINED EEG-FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES IN EPILEPSY

Joong Koo Kang, Christian-G. Bénar, Abdullah Al-Asmi, Bruce Pike, François Dubeau, and Jean Gotman (Montréal Neurological Institute, McGill University, Montréal, Québec, Canada)

Rationale: With combined EEG-fMRI studies, it is possible to find brain regions activated as a result of epileptic spikes. A standard hemodynamic response function (HRF) is commonly used in fMRI activation studies (Glover, 1999), but there are several reports showing variability in the shape of HRFs across subjects in sensorimotor activation studies. In addition, little is known about the HRF to epileptic spikes. The use of the patient-specific HRF may help identify areas activated by epileptic spikes. The objective of this study is to compare the activated areas obtained by using the Glover HRF and the patient-specific HRF. **Methods:** The HRF can be modeled as the sum of two gamma density functions (positive response and undershoot). We detected activated areas by comparing the fMRI signal at each point in the brain with a model based on the Glover HRF. For each activated area, we computed the actual HRF by averaging the BOLD signal around the time of the discharges. For these patient-specific HRFs, the positive responses are usually similar to the Glover HRF, but we found longer undershoot latencies and a variable ratio between the peak amplitudes of the positive response and the undershoot. We analyzed again the fMRI data using the patient-specific HRFs and compared the activated areas and *t* statistical scores to those obtained with the Glover HRF. **Results:** Six patients with intractable focal epilepsy were studied, and all showed activation in the same areas with both methods, but the *t* statistical scores were always higher with patient-specific HRF. The activated areas obtained with the patient-specific HRF were always wider. Additional activated areas were seen in three patients, two of them showing a significantly delayed undershoot. The first had bilateral subependymal heterotopia in the occipital horn and EEG spikes over the left temporooccipital area. The Glover HRF showed activation in the left temporooccipital junction only. With the patient's HRF, the activation included also the left subependymal heterotopia. The second had normal MRI and bifrontal spikes with clear right predominance. Activation was in the right frontal region with the Glover HRF but bifrontal with the patient's HRF. The third had right hemispheric atrophy maximum over the temporal region and bifrontal spikes. The Glover HRF showed several areas of activation in the left frontal lobe. An additional activation was seen over the right temporal lobe using the patient's HRF. **Conclusions:** The patient-specific HRF yields wider activation areas and higher *t* statistical values compared to Glover HRF in BOLD-fMRI studies of epileptiform discharges. Furthermore, new activation sites may be seen, and these are concordant with what is known of the epileptogenic region in these patients. Using the patient-specific HRF brings new information in the analysis of EEG-fMRI studies of epileptic spikes. (Supported by the Canadian Institutes of Health Research under grant MOP-38079.)

1.242

ASSESSING HIPPOCAMPUS FUNCTION IN PARTICIPANTS WITH EPILEPSY OR SCHIZOPHRENIA USING FUNCTIONAL MAGNETIC RESONANCE IMAGING DURING A VIRTUAL MORRIS WATER TASK

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Rationale: Various types of neuropathology are associated with the hippocampus (HPC) in both temporal lobe epilepsy and schizophrenia. Moreover, it has been hypothesized that there are often changes in HPC connectivity or function without concomitant neuroanatomic changes evident from structural imaging. It is known from a variety of converging data sources that the HPC is critical for spatial memory. One memory task particularly sensitive to HPC function is the Morris water task. In this task, the animal must use the spatial relations in a room to remember and navigate to a hidden goal location within a pool of opaque water. Virtual versions of this task have been used successfully to assess spatial memory in humans and to elicit HPC activation during fMRI in normals (Astur and Constable, 2002). The goal of this study was to reveal how fMRI can be used during performance of a virtual navigation task to assess the functioning of the HPC in participants with epilepsy or schizophrenia. **Methods:** Ten participants with temporal lobe epilepsy, 10 participants with schizophrenia, and 10 controls performed a virtual Morris water task in a block-design fMRI paradigm. Participants were placed in a virtual round pool that had four balls floating in the water. In the activation condition, the platform was always in the same location, the balls were identical, and participants had to use the spatial cues to navigate to the ball that floated above the goal platform. In the baseline condition, the platform changed locations from trial to trial, one unique ball floated above the platform, and participants navigated to the platform by swimming to the unique ball among three identical balls. **Results:** Behaviorally, all groups are able to learn this task in a spatial manner and hence should be utilizing HPC resources. All activation maps are the result of a subtraction of the Activation condition (i.e., Spatial memory) minus the Baseline condition (i.e., Cue memory). We found that for the control subjects, there were selective bilateral deactivations in HPC proper. There also were strong left middle frontal gyrus and right striatal activations as well as bilateral insular and posterior cingulate deactivations. In addition, we noted bilateral inferior gyrus deactivations anteriorly and positive activations posteriorly. For the patient groups, the left middle frontal gyrus activation appeared similar to the control group, but the HPC activation differed both in intensity and location for the two patient groups, and from each other. Subtraction maps as well as ROI analysis are presented to delineate these differences further. **Conclusions:** These results indicate that a spatial navigation task commonly employed with nonhumans can be adapted for use with humans in an fMRI paradigm designed to assess HPC function. We discuss the manner in which these activations differ between patients with epilepsy versus those with schizophrenia, as well as how these activations may reveal differences that are absent on standard MRI structural analysis. (Supported by NIH NS-40497 and NIH 1 F32 MN64290-01.)

1.243

MEMORY IN PATIENTS WITH TEMPORAL LOBE EPILEPSY: A STUDY USING FUNCTIONAL MAGNETIC RESONANCE IMAGING AND INTRACAROTID AMOBARBITAL PROCEDURE

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Rationale: The memory application of the intracarotid amobarbital procedure (IAP) gives information about medial temporal lobe (MTL) function, but it is invasive and has a high financial cost. There have been some recent attempts to develop a reliable functional magnetic resonance imaging (fMRI) paradigm that may eventually replace the IAP. Using an fMRI paradigm modeled on our IAP memory task, we investigated memory function in healthy volunteers and patients with temporal lobe epilepsy. **Methods:** Eighteen healthy volunteers and nine patients with temporal lobe epilepsy were scanned using a 1.5-T clinical imaging system. The volunteers were of similar age and education to the patients. Structural MRI, EEG, and neuropsychological data were available on the patients. One hundred twenty colored pictures of objects were shown, interleaved with meaningless colored patterns (control condition). These stimuli were chosen for similarity with our IAP, which uses a series of real objects for memory testing. Memorizing objects is expected to engage both the left and the right temporal lobes because objects are both verbal (they have names) and nonverbal (can be pictured). The fMRI task was to memorize the pictures for a later recognition test. Activity of brain regions during picture presentation was compared with that obtained in the control condition. **Results:** Healthy individuals recognized on average 85% of the pictures compared to 72% for the patient group. All healthy subjects showed bilateral activity in the MTL. This finding is consistent with the expected participation of either or both hemispheres during the IAP object memory task. In contrast, among the nine patients studied, only two showed bilateral activity. Six showed unilateral activity in the left MTL, and there was no MTL activity in one. These findings will be discussed in light of the patients' presumed damage according to EEG, anatomic MRI, basic neuropsychological data, and IAP results. **Conclusions:** Our fMRI memory paradigm provides analogous information to that of our IAP and is proving useful as a complementary tool in the preoperative investigation of patients with intractable temporal lobe epilepsy. Furthermore, it opens a window on details of brain structures that underlie IAP performance and memory function. Thus, this fMRI task not only supplements the current IAP with additional clinical information, but it will also allow exploration of brain plasticity in learning and memory. (Supported by grant MT144991 from the Canadian Institutes of Health Research to M. Jones-Gotman. L. Forster is supported by CNPq, Brazil.)

1.244
FUNCTIONAL MAGNETIC RESONANCE IMAGING PANEL OF VERBAL FLUENCY AND AUDITORY AND READING-COMPREHENSION TASKS IDENTIFIES LANGUAGE DOMINANCE COMPARED with THE INTRACAROTID AMYTAL TEST

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Rationale: Functional magnetic resonance imaging (fMRI) language tasks readily identify language areas, but some individual studies disagree with the intracarotid amytal test (IAT). We examined whether a panel of fMRI tasks increases yield in determining hemisphere dominance for language. **Methods:** We studied 26 patients (22 right-handed, three left-handed, one ambidextrous; 13 male, 13 female subjects) aged 12–56 years, with temporal lobe epilepsy using whole-brain 1.5-T fMRI (EPI BOLD) with three tasks: Verbal Fluency (Letters); Reading Comprehension; and Auditory Comprehension. Tasks were covert and unmonitored with silent rest control conditions and performed using a boxcar design with six cycles. Data were analyzed with a region-of-interest analysis from t-maps. The number of activated voxels was determined in inferior frontal gyrus (IFG), midfrontal gyrus (MFG), and Wernicke's area, using a semiautomated program. An asymmetry index (AI) was calculated $[(L - R)/(L + R)]$ for each region at $t = 4$. fMRI language laterality was defined as left, AI >0.20; right, AI <-0.20; bilateral, |AI|<0.20; nondiagnostic, <4 voxels in each ROI. fMRI t maps were also visually rated. All patients had confirmation of language lateralization by IAT or surgery. **Results:** The fMRI task panel provided language lateralization in temporal regions in 24 (92%) patients and frontal regions in 26 (100%) patients. Eight of 78 (10%) individual studies were nondiagnostic. fMRI showed left dominance in 23 patients, right dominance in two, and bilateral in one. IAT showed left dominance in 22, right in two, bilateral in one, and was nondiagnostic in one. Of the 25 diagnostic IATs, there was agreement between IAT and fMRI in 22 of 25 patients; and partial agreement in the other three: IAT was left and fMRI bilateral in two patients; and IAT bilateral and fMRI left dominant in one. Agreement between IAT and fMRI was 0.70 (Cramer V; $p < 0.001$). In the three pateints with incomplete agreement between IAT and fMRI, the fMRI panel showed consistent findings across paradigms. **Conclusions:** An fMRI language paradigm panel identifies frontal and temporal language cortex and is useful for determining language-dominant partial epilepsy patients. A panel of tasks mitigates likelihood of nondiagnostic findings, helps confirm fMRI results, and may provide information not available with IAT. (Supported by NINDS K08 NS 1663 Board of Lady Visitors, Children's National Medical Center Epilepsy Foundation of America.)

1.245
LANGUAGE LATERALIZATION BEYOND WADA TEST: FUNCTIONAL MAGNETIC RESONANCE IMAGING EVALUATION IN PATIENTS WITH LEFT TEMPORAL LOBE EPILEPSY

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Rationale: To assess hemispheric distribution of language function by functional magnetic resonance imaging (fMRI) in patients with intractable left temporal lobe epilepsy (TLE) who underwent the Wada test, and to evaluate whether left hemisphere dysfunction due to epilepsy could be associated with change in language lateralization. **Methods:** Ten right-handed TLE patients (five men, aged 22–48 years) and 10 right-handed healthy controls (four men, aged 24–43 years) were scanned in a 1.5-T GE MR scanner while performing an auditory verb-generation task. Two regions of interest (ROIs) were defined: Broca's area (inferior frontal gyrus, IFG) and Wernicke's area (posterior superior temporal gyrus, STG). The number of activated voxels in each ROI was subject to multiple analyses of variance (ANOVAs). In addition, an individual Lateralization Index $[LI = (L - R)/(L + R)]$ was calculated based on number of activated voxels within each ROI. In addition, all patients underwent a Wada test. **Results:** In all patients, Wada test revealed left language lateralization. In both patients and healthy control groups, fMRI showed an overall left lateralization based on number of activated voxels and LI measure. However, lateralization was overall less pronounced for patients relative to controls (two-way interaction of Hemisphere × Group, $p < 0.05$). Measuring regional lateralization demonstrated that for both groups, Broca's area was more lateralized to the left than Wernicke's area. However, patients showed less difference in activation between Broca's area and the homologous area on the right, and almost no difference between Wernicke's area and its right hemisphere counterpart (three-way interaction of Region × Hemisphere × Group, $F(1, 18) = 5.0$, $p < 0.05$). The reduced lateralization of Broca's area in patients was mainly due to reduced left-hemisphere activation (planned comparison, $p < 0.05$). **Conclusions:** fMRI revealed more language lateralization in Broca's than in Wernicke's area in all subjects. Thus, lateralization by Wada test was more consistent with fMRI measures obtained in IFG than with STG. Left temporal epileptic focus was associated with overall less language representation in the left hemisphere. Surprisingly, this change in laterality was mainly due to reduced activation in the left

Broca's area. This finding suggest greater suceptability of the left frontal language region to intractable, long-standing left TLE.

1.246
FUNCTIONAL MAGNETIC RESONANCE IMAGING PREDICTS POSTSURGICAL MEMORY OUTCOME IN TEMPORAL LOBE EPILEPSY PATIENTS
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Rationale: The goal of this study was to assess the utility of functional magnetic resonance imaging (fMRI) in predicting memory outcome after anteriomesial temporal lobectomy. **Methods:** Twenty-five patients undergoing presurgical evaluation for anteriomesial temporal lobe epilepsy (TLE) and 30 control subjects were studied. fMRI was conducted at 1.5 T during complex visual-scene encoding, using a blocked paradigm with 6 cycles of 40-s blocks of novel scenes or a scrambled control image presented every 4 s. Recognition testing was performed without scanning. Normalization and smoothing parameters were optimized on control data, and nonlinear normalization and a smoothing kernel of $4 \times 4 \times 3$ voxels were used. Summing activation across all positive voxels provided better segregation between patients and controls than suprathreshold voxel counts, and was used to calcuate asymmetry ratios (ARs) from a manually drawn mesial temporal ROI with $AR = (L - R)/(L + R)$. The task was repeated outside the scanner ~3 months after surgery for 19 of the patients (eight left- and 11 right-side TLE by clinical criteria) and the change in the recognition discrimination score (percentage correct – percentage false positives) was correlated with the fMRI AR. fMRI AR was also compared with memory asymmetry on intracarotid amobarbital testing (IAT) for all 25 patients (nine left- and 16 right-side TLE). **Results:** AR in controls was 0.063 ± 0.204 (mean ± SD). Twelve of 25 patients exceeded the mean AR for normals by 1 SD, and only eight exceeded the mean by 2 SDs. The laterality of fMRI AR correlated with IAT asymmetry, but this correlation was not significant ($p = 0.160$, $n = 25$, Fisher's Exact test). Patient ARs (adjusted for seizure laterality) correlated significantly with postsurgical discrimination score change ($p = 0.002$, Spearman Rank Correlation). Absolute ipsilateral activation also correlated negatively with discrimination score change ($p = 0.034$, Spearman), whereas absolute contralateral activation did not, suggesting that memory outcome may be related to the amount of activation ispilateral to the resection. Presurgical discrimination scores for scene recognition correlated significantly with several standardized memory measures (Total Word List Recall, Delayed Story Recall, Delayed Design Recall), suggesting that this task provided a reasonable surrogate of memory performance. **Conclusions:** These data suggest that fMRI may be useful in predicting memory change after anteriomesial temporal lobectomy. Agreement between fMRI and IAT lateralization for memory did not reach significance, and fMRI results were generally noisy, with many patients falling within a large normal range for AR. The reliability of fMRI could be improved through additional signal averaging and/or higher field strength studies. Because fMRI is noninvasive and provides good spatial resolution for functional activation, these results support the concept that fMRI can enhance presurgical evaluation and planning for epilepsy surgery. (Supported by NS37488.)

1.247
MEASUREMENTS OF RETRIEVAL ACTIVATION FOR AUTOBIOGRAPHICAL VERSUS IMPERSONAL EVENTS USING FUNCTIONAL MAGNETIC RESONANCE IMAGING
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Rationale: Our goal was to provide normative data on the systems involved in remote memory retrieval and determine the implications for temporal lobe resection in epilepsy. **Methods:** The retrieval of autobiographic memories versus impersonal, historic events was investigated in an fMRI design that further distinguished between spatial and temporal memory judgments. A word/nonword decision task, designed to control for language processing, served as the baseline measure. Ten subjects were scanned at 1.5-T using gradient-echo echo-planer imaging in a repeated-measures, block design. The images, performed on the coronal–oblique plane perpendicular to the hippocampus, were subsequently subjected to motion correction. **Results:** Region-of-interest analyses indicated that autobiographic events tended to produce the greatest measure of activation in posterior, bilateral regions of the midfrontal gyri, whereas activation for impersonal events was more rostral and significant only in the right hemisphere. Most striking, judgments about the relative location of autobiographic and impersonal events showed significantly greater activation ($p < 0.025$) in bilateral regions of the dorsolateral prefrontal cortex (DLPFC) than did judgments about the sequence of events in time. Most conditions resulted in activation of the left hippocampus ($p < 0.025$); however, location judgements about autobiographic events also produced borderline deactivation ($p = 0.054$) in the right hippocampus relative to baseline. **Conclusions:** Autobiographic memories, especially those related to location, result in greater overall activation in DLPFC than do impersonal events. It is unclear if this is because these types of questions produce greater demands to working memory systems or if autobiographic memory networks are more widely distributed throughout this region of cortex. Regardless, the activation seen in the left hippocampus for most conditions, and deactivation seen in the right hippocampus in response to questions about autobiographic location, suggest that it may work in conjunction with the DLPFC to facilitate memory judgments. (Supported by NIH NS38467 NS40497.)

1.248
COMPARISON OF FUNCTIONAL MAGNETIC RESONANCE IMAGING AND CORTICAL-STIMULATION LANGUAGE MAPPING IN EPILEPSY
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Rationale: To compare language mapping using functional MRI (fMRI) and electrical cortical stimulation (ESM) in patients undergoing surgery for uncontrolled epilepsy. fMRI is a noninvasive technique that has been shown to lateralize language as accurately as the intracarotid amytal procedure (IAP), but there are few data on its value for intrahemispheric localization. Previous O-15 positron emission tomography (PET) activation studies (Bookheimer et al. *Neurology* 1997) had shown a good correlation with ESM. **Methods:** We performed blood oxygenation–level contrast fMRI, and ESM, in two patients with uncontrolled epilepsy. Both had left mesial temporal sclerosis on structural MR, and left speech dominance on IAP. MR was conducted on a conventional 1.5-T scanner using a standard echoplanar sequence. The functional study employed a block design composed of six epoch cycles; each cycle consisted of an experimental task that alternated with a visual control task: Eight functional images were collected during each epoch of 32 s. The stimuli were presented through a MacIntosh computer to a rear projection screen positioned at the end of the scanner bed. For ESM, one patient had intraoperative mapping, and one, extraoperative subdural grids. Stimuli were presented on a laptop computer. Tasks for both fMRI and ESM included object naming and reading prose. **Results:** Patient 1 (intraoperative cortical mapping) had complete speech arrest when inferior frontal (Broca) region was stimulated and impaired naming or reading when superior temporal gyrus was stimulated. No effect was found when middle and inferior temporal gyri, the anterior portion of the superior temporal gyrus, and the inferior portion of pre- and postcentral sulcus were stimulated. FMRI showed left inferior–midfrontal and midsuperior temporal activation on reading and naming tasks. Patient 2 (prolonged subdural grid recording) had complete speech arrest on superior temporal and fusiform gyrus stimulation. No effect occurred in the inferior portion of the lateral frontal region as well as the inferior portion of pre- and postcentral sulcus. fMRI showed left inferior–midfrontal and midsuperior

temporal activation. In each case, resection including anterior temporal cortex, hippocampus, and amygdala was performed without any postoperative language impairment. **Conclusions:** We found incomplete overlap between fMRI and ESM language localization in two patients. ESM identifies regions crucial for specific functions, and fMRI, regions participating in them. Thus, absolute concordance should not be expected. fMRI may prove eventually to be a more conservative technique. (Supported by NINDS Intramural Program.)

1.249

FUNCTIONAL MAGNETIC RESONANCE IMAGING LANGUAGE LATERALIZATION IN 100 PATIENTS WITH EPILEPSY: A COMPARISON WITH THE WADA TEST

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Rationale: To compare language lateralization using BOLD functional magnetic resonance imaging (fMRI) with results of the intracarotid amobarbital procedure (Wada test) in a large number of patients with epilepsy, including a substantial number of patients with atypical language lateralization in the Wada test. **Methods:** We investigated 100 patients with localization-related epilepsy differing widely in age and IQ (52 female subjects; age median, 31 years; range, 12–60 years; IQ median, 89; range, 46–130). During presurgical assessment for epilepsy surgery, all patients had a Wada test (cerebral angiography + hemispheric anesthetization + language testing of the awake hemisphere). Using a standard 1.5-T Siemens Symphony scanner, a standard EPI sequence (16 axial 4-mm-thick slices; FOV, 192 mm; 64 × 64 matrix; TR, 1,600 ms; TE, 50 ms), and the standard on-line statistical postprocessing software of the scanner, we contrasted images sampled during 10 episodes of word generation with images sampled during 10 episodes of a low-level rest condition in all patients individually. The resulting statistical maps were judged visually as typical, atypical, or artefactual. **Results:** By Wada test standards, 70 patients showed a typical, and 30, an atypical language lateralization. The acquisition of fMRI data was easy and quick (15 min/patient). The assessment of fMRI results was reproducible (interrater kappa, 0.86). fMRI results were judged artefactual because of movement in six patients. Bilateral fMRI activation was the most frequent finding (86%). Asymmetric activations, however, were the basis of the classification (92%). fMRI provided typical and atypical results in 85 of the remaining 94 individual cases in concordance with the Wada test. There were discordant results between fMRI and Wada test in nine patients. Atypical language lateralization was associated with left-sided extratemporal lobe epilepsy and with a younger age at an early precipitating injury. **Conclusions:** There was a high concordance of lateralizing language between both tests: 10% discordant findings resulted from bilateral fMRI activations, most likely representing the nondichotomous nature of a brain network for language. In a sequence of diagnostic tests, fMRI of language lateralization can only serve as a filter for the Wada test and thus potentially reduce the number of patients undergoing invasive investigations before epilepsy surgery, when combined with clinical information. (Supported by Society for Epilepsy Research.)

1.250

DIFFUSION TENSOR IMAGING IN TEMPORAL LOBE EPILEPSY

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Rationale: Noninvasive techniques are becoming increasingly important in mapping the seizure focus in patients with intractable epilepsy. Diffusion tensor imaging (DTI) is an innovative noninvasive tool for evaluating structural and physiologic state in biologic tissue by measuring the diffusion process of water molecules. We conducted this study to investigate the potential value of DTI in identifying and localizing the seizure focus in patients with intractable temporal lobe epilepsy (TLE). **Methods:** We evaluated a total of eight patients with intractable TLE being considered for epilepsy surgery with DTI of the brain and compared measurements of diffusivity or trace D and fractional anisotropy (FA) from hippocampal regions bilaterally to those of normal subjects (normal control). DTI imaging was performed on a 1.5-T Vision MR scanner (Siemens Medical Systems, Erlangen, Germany) using a single-shot echo-planar diffusion-weighted imaging sequence. The imaging parameters included TR = 6,000 ms; TE = 100 ms; FOV = 240 ms, and four acquisitions. The maps of trace D and FA were calculated from diffusion-weighted images using software written in IDL (Interactive Data language, U.S.A.). We compared the FA and Trace D indices from multiple and symmetric voxels sampling regions from hippocampal formation in both patients and control groups. We also correlated the measurements with the clinical findings, ictal EEG onset, and other neuroimaging indicators of the seizure focus of all eight TLE patients. **Results:** Five patients demonstrated increased hippocampal diffusivity measurements ipsilateral to the seizure focus when compared to those sampling the contralateral hippocampus and to those of normal subjects. Analysis of the five patients with negative brain MRI revealed increased trace (D) in hippocampal regions of interest in three patients. There was no significant change in anisotropy. **Conclusions:** Trace D calculated from DTI methods is a particularly useful parameter to detect structural abnormalities in vivo and is a useful indicator of the seizure focus. DTI is a promising and noninvasive imaging technique for localizing and mapping the seizure focus in TLE.

1.251

DIFFUSION CHANGES SUGGESTING VASOGENIC EDEMA IN PARTIAL STATUS EPILEPTICUS

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Rationale: During partial status epilepticus (PSE), diffusion-weighted imaging (DWI) has demonstrated focal hyperintensity lesion with decreased apparent diffusion coefficient (ADC). These findings are suggestive of cytotoxic edema due to energy failure of Na^+/K^+-adenosine triphosphatase (ATPase) pump. However, signal intensity on DWI could be influenced by another factors such as vasogenic edema developed during seizure. We hypothesize that the DWI findings other than cytotoxic edema can be observed during PSE. We report DWI abnormalities suggestive of vasogenic edema in a patient with EEG-confirmed PSE. **Methods:** We reviewed the DWI findings in a 76-year-old woman in whom PSE developed after the successful thrombolysis for the presumed left middle cerebral artery (MCA) occlusion. Initial MRI (T_2-weighted, DWI, ADC map, MR angiography) performed on the next day of thrombolysis revealed unremarkable findings despite sensory aphasia with decreasing severity. One month later, she showed prolonged confusion, sensory aphasia, right hemiparesis of mild degree, and sometimes, brief attacks of focal clonic movement in right upper extremity without generalized tonic–clonic seizure. EEG and MRI were performed on the same day during PSE. Follw-up EEG and MRI were performed 3 months later. **Results:** EEG performed during PSE showed ictal discharge localized in left temporoparietooccipital area. DWI and T_2-weighted imaging (T2WI) showed the hyperintense signal in left parietotemporal cortex. The ADC map also showed increased signal in the corresponding area, suggestive of vasogenic edema. MR angiography showed increased signal in the MCA branches of the epileptic hemisphere. Follow-up EEG and MRI were

performed 3 months later on the same day. EEG showed diffuse slowings in left parietotemporooccipital areas. T2WI showed some regional brain atrophy in left parietotemporal cortex with increased signal in the underlying white matter. However, DWI and ADC map did not reveal any significant signal changes. Follow-up MRA no longer showed signal asymmetry of both MCAs. **Conclusions:** During PSE, diffusion changes seen on MRI can be variable dependent upon the severity of cytotoxic edema, vasogenic edema, and blood flow. We report a very rare case of PSE with vasogenic edema on DWI.

1.252

BRAIN ORGANIzATION IN CHRONIC EPILEPSY ASSESSED BY DIFFUSOR TENSOR IMAGING AND FUNCTIONAL MAGNETIC RESONANCE IMAGING

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Rationale: Diffusion tensor imaging (DTI) is a novel MR technique that allows visualization of white matter (WM) tracts by detecting the dominant direction of water diffusion. In epilepsy, DTI has been used to assess distortion of WM tracts associated with seizure foci. Functional MR (fMR) allows demonstration of functionally active neuronal tissue during a specific task. We combined the two techniques to search for disturbances of functional brain organization associated by WM damage. **Methods:** We studied eight patients with chronic epilepsy on a 3-T scanner (GE Medical Systems). DTI was acquired in each patient (b = 3,000, seven directions, 17 slices, 6-mm thick, 1.5 gap) and postprocessed using Functool. fMRI used two different language tasks (noun–verb generation and orthographic lexical retrieval). Lateralization of language was assessed based on the postprocessed, motion-corrected images. Based on 30 controls, language lateralization was considered "typical" if ≥60% of the total activation was on the left. Additional investigations included T_1 anatomic imaging, fluid-attenuated inversion recovery (FLAIR), and whole-brain T_2 relaxometry. **Results:** Four patients had hippocampal sclerosis (HS) in the dominant hemisphere. Two of them had atypical language lateralization (Table 1). Both showed asymmetric WM tracts in the frontotemporal region. T_2 relaxometry was increased in the ipsilateral hippocampus in both patients (≥114 ms, normal ≤107 ms), but normal in the frontal and temporal WM. The other two HS patients had typical language lateralization and normal DTI. Four patients had dysplastic lesions. Two patients had dysplasias in the dominant hemisphere, and both had atypical language lateralization. DTI was abnormal in one patient with left temporal dysplasia, but normal in one patient with a small left frontal pole dysplasia. Both patients with right-sided dysplasia showed typical language lateralization; WM tracts were abnormal in one of these patients. **Conclusions:** Six of the eight patients had a lesion in their dominant hemisphere. Four of these patients showed atypical langage lateralization. In three of these patients, all with temporal lobe lesions, DTI showed a distortion of the WM tracts. Both patients with left-sided lesions, but typical language, had normal DTI. Therefore, this first report of a combination of DTI and fMRI in a series of epilepsy patients suggests that a left-temporal lesion with associated DTI abnormalities may have consequences on language lateralization. (Supported by Brain Imaging Research Foundation, Australia.)

TABLE 1.

Lesion	Hemisphere	Lobe	Language	DTI
HS	Dominant	Temporal	Atypical	Abnormal
HS	Dominant	Temporal	Atypical	Abnormal
HS	Dominant	Temporal	Typical	Normal
HS	Dominant	Temporal	Typical	Normal
Dysplasia	Dominant	Temporal	Atypical	Abnormal
Dysplasia	Dominant	Frontal	Atypical	Normal
Dysplasia	Not dominant	Frontal	Typical	Abnormal
Dysplasia	Not dominant	Parietal	Typical	Normal

1.253

SPATIOTEMPORAL DIPOLE MODELING OF FRONTAL LOBE EPILEPTIFORM ACTIVITY

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Rationale: Dipole modeling of temporal lobe epileptiform (spike and seizure) activity has been reported to add quantitative localizing ability above that provided by visual inspection. Few studies have reported on its use on frontal lobe patients, who are less common and often present a more difficult localization problem than temporal lobe patients. Our objective was to begin to determine if spatiotemporal dipole modeling could increase our localizing ability in frontal lobe patients. **Methods:** Since the installation of our completely digital Grass-Telefactor video-EEG systems, we have identified seven patients at our center with presumed frontal lobe epilepsy. For each of these, we have manually selected representative spikes, sharp waves, and seizures for analysis. All were imported into BESA 2000 (MEGIS, Germany) and bandpass filtered at 1.6–50 Hz. Obviously bad channels were excluded from further analysis. One-second epochs were chosen for modeling; spikes and sharp waves were centered in the epoch. Seizure epochs were chosen as close as possible to EEG onset. Rhythmic seizure activity was sometimes bandpass filtered in a tighter range to remove more noise. We used one to three regional dipoles optimized with a genetic algorithm set to default parameters. This is an objective method that requires no user intervention. After modeling the entire 1-s epoch, we selected spike components (50–200 ms) based on the global field power, and single peaks of rhythmic seizure activity, for further modeling. **Results:** For all seven patients, the dipoles localized to frontal cortex, generally to the side of the presumed epileptigenic zone. In some fits for some patients, they were located very near the midline, making it difficult to lateralize. In some other fits, dipole locations were close to the temporal pole and were thus difficult to ascribe entirely to the frontal lobe. The use of two or three dipoles often was able to account for other brain activity (alpha), eye movements, or electrode noise, thus apparently making the location of the epileptiform activity more robust and precise. The results of modeling only the spike components were almost identical to modeling the entire 1-s epoch. Confirmation of the epileptogenic zone was accomplished in three patients so far by the use of implanted electrodes. For two of these, the correlation and lateralization was complete. For the third, the dipole localization was deep mesial frontal, but difficult to lateralize. Depth electrodes recorded spikes mostly in left orbital frontal and deep midfrontal cortex. **Conclusions:** These initial results demonstrate the potential utility of spatiotemporal dipole modeling for frontal lobe seizure localization. As these patients proceed to intracranial studies and surgery, we will be able to better confirm lateralizing and localizing results. To improve our ability to lateralize midline frontal activity, and separate lateral frontal and anterior temporal activity, we are beginning to record true electrode postions, which should impove localization accuracy over using generic electrode locations. We are also acquiring high-resolution MRI scans to build more realistic head models, which should also improve accuracy. Two-year postsurgical evaluations will provide the final determination of the epileptogenic zone. (Supported by Legacy Health System.)

1.254

LATERALITY OF FUNCTIONAL MAGNETIC RESONANCE IMAGING VISUAL ACTIVATION IN PATIENTS WITH OCCIPITAL LESION

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Rationale: Integrity of visual function is an important consideration in planning resective occipital lobe epilepsy surgery. Resective surgery carries little risk in patients with an established dense hemianopia. The majority of patients being considered for surgery, however, have either normal or minimally affected visual perimetry. The presurgical evalu-

ation of these patients is challenging and often requires intraoperative mapping of the calcarine cortex. The purpose of this investigation was to develop functional MRI (fMRI) techniques to characterize integrity of functional occipital cortex to assist epilepsy surgical planning. Participants will be able to discuss the relation. **Methods:** Six controls and 21 pts were assessed with 1.5-T magnet high-speed gradients for echo-planar imaging acquired coronally, 20 slice locations identical to the co-registered coronal spin-echo volumes. Visual stimulus fMRI EPI scan duration was 3 min 8 s (94 data time points). Stimuli were presented via mirror from a rear-projected 8-Hz reversing checkerboard pattern presented at 20 s alternating 20-s grey screen fixation. Laterality index (LI) was calculated from fMRI maps thresholded at $t > 5$. LI = (Activated L occipital hemisphere voxels – Activated R occipital hemisphere voxels)/(Total activated L occipital hemisphere voxels + Activated R occipital hemisphere voxels). Visual perimetery was obtained in 10 patients and related to fMRI activation. Two LIs were calculated: a narrow region surrounding the striate cortex, and a broader posterior occipitoparietal region. **Results:** First, LI correlated with visual perimetery in all 10 pts. Of the five pts with normal perimetery, fMRI LI ranged from –0.035 to –0.064, indicating a nearly symmetric fMRI response. A patient with left-field deficit had an LI of +0.222, indicating a right hemisphere–dominant response. Four patients with right-field deficits had LIs ranging from –0.302 to –0.474, indicating a left lateralized functional MR response. Second, controls showed a nearly symmetric fMRI response to stimulation (LI, –0.07 + 0.02). Third, the mean direction of the broad but not narrow LI was significantly related to side of lesion. Fifteen had lesions in occipital lobe (striate cortex, nine; nonstriate, six) or in the optic radiation (six). The broader LI (occipitoparietal) was more sensitive compared to the narrow (striate cortex) activation, and the broader LI was examined. Eleven had Rt lesions (LI, –0.32 + 0.09), and 10 had Lt lesions (LI, +0.16 + 0.12); $p < 0.0001$. Finally, examining the ability of the LI to classify individual patients, LI correctly predicted contralateral activation in 14 patients. Four had either a nearly symmetric response (LI range, –0.02 to –0.09). Three of 21 patients had a mislateralization of LI because of diffuseness of the lesion. **Conclusions:** In controls, the fMRI activation task underlying the LI was robust in activating both occipital lobes in a nonlateralized pattern. Furthermore, LI correlates with visual perimetry and was found to be sensitive to the lateralization of the occipital lobe lesion. Although robust at a group level, application to individual patients should be cautiously interpreted, especially in patients with diffuse lesions. Qualitative assessment of fMRI response patterns indicated dispersion of activation away from the lesion in many patients, raising the interesting possibility of reorganization of visual function in occipital cortex.

Neuropsychology/Language/Aphasia/Behavior

1.255
VOCATIONAL PROGRAMS: IDENTIFYING EMPLOYMENT OUTCOMES FOR ADULT INDIVIDUALS WITH EPILEPSY

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Rationale: Adults with epilepsy in New York State vocational rehabilitation programs are falling under a restrictive interpretation of waiver guidelines that will compromise their ability to attain vocational supports. Eligibility requirements include IQ and psychological and behavioral assessments, with results often excluding them from needed services. We seek to examine the employment of adult individuals with active and controlled seizures in vocational rehabilitation programs that will show the need for vocational supports for this population to attain and maintain employment in the community. **Methods:** A 10-item survey was sent throughout New York State to 228 vocational service providers for adult individuals with developmental disabilities. **Results:** Twenty-nine (13%) Vocational Rehabilitation Program Directors responded, identifying 1,082 (14%) adult clients diagnosed with epilepsy of a total client population of 7,582; 93% of agencies offer supported employment, 66% competitive employment, 69% prevocational training, 90% job development/placement, 83% job coaching, 86% follow-along services, 52% workshops and 41% enclaves. Client IQs range from profoundly retarded to normal; 90% of clients with epilepsy have an additional developmental disability including mental retardation (83%), mental health issues (5%), cerebral palsy (2%), Down syndrome (1%), and 14% with additional disabilities. Of those individuals with controlled seizures, 11% are employed in the community, 14% work in a workshop, and 3% work in an enclave. Of those individuals with active seizures, only 6% work in the community, 9% work in a workshop, and 1% work in an enclave. **Conclusions:** Those individuals with epilepsy that are receiving vocational support are less likely than persons with other developmental disabilities to find competitive community employment. Those individuals with active seizures receiving the same supports are considerably less likely to find competitive community employment. Under current New York State waiver guidelines, these individuals receiving vocational supports may no longer be eligible to receive services through their current developmental disabilities providers. Without services, their opportunity to strive for and reach a personal employment goal will be eliminated. (Supported by Epilepsy Foundation of Southern New York.)

1.256
QUALITY OF LIFE IN TREATMENT OF EPILEPSY: LAMOTRIGINE VERSUS CONVENTIONAL ANTIEPILEPTIC DRUG THERAPY

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Rationale: Quality of life (QOL) in studies of epilepsy is typically measured solely as the reduction in seizures and is in need of a more encompassing approach. Quality of life can be independent of seizure frequency. Comparison between treatment groups becomes more meaningful when using a multifaceted approach. **Methods:** Data measuring quality of life were pooled across four clinical trial studies and compared for effects within treatment groups. Basic demographic attributes and 31 questions from the Quality of Life in Epilepsy instrument were used to assess a broad range of health and well-being variables from 651 patients. Data were gathered at two points in time: at screening and at the end of a 32-week treatment. **Results:** We identified 651 patients with epilepsy using the following treatments: 419 lamotrigine (LTG), 158 valproate, 70 carbamazepine, and four phenytoin. Comparisons were made between the LTG ($n = 419$) and the conventional AED group (i.e., all others, $n = 232$) across several QOL indicators including seizure worry, emotional well-being, energy/fatigue, cognitive functioning, medication effects, health state, social functioning, and overall scores on quality of life and health. Across all nine comparisons, the LTG group mean change from baseline (screen) scores was more favorable than or equal to the other conventional AED group on six variables. Of these, statistical differences were found on two important QOL indicators: energy/fatigue ($p = 0.05$) and medication effects ($p = 0.002$). The conventional AED group did not obtain statistical difference on any QOL indicator when compared to the LTG group. On the important indicator, seizure worry, the LTG group had a lower mean change score, but it did not obtain statistical significance. **Conclusions:** There is an increasing awareness of the need for broad-based QOL measures in studies investigating treatment for epilepsy. It has been argued that studies looking only at the frequency of seizures as the sole measure of QOL may be missing other important well-being measures. In these clinical trials data, comparisons were made across several dimensions of QOL between those taking LTG and those taking more conventional AEDs. The results indicate that persons with epilepsy taking LTG either fared equally to those on other treatment medications or had better outcomes on QOL measures; energy/fatigue, and medication effects. (Supported by GlaxoSmithKline.) (Disclosure: Salary: GlaxoSmithKline; Stock: GlaxoSmithKline.)

1.257
QUALITY OF LIFE FOR PATIENTS WITH EPILEPSY IN KOREA
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Rationale: Epilepsy is a chronic condition, which is known to have negative effects on the quality of life. We evaluated major variables associated with the quality of life of epilepsy patients in Korea. **Methods:** We evaluated the quality of life in epilepsy (QOLIE) of 210 epilepsyc adult patients at Keimyung University Epilepsy Center. The QOLIE-31 questionnaires for self-assessment of quality of life were used for this assessment. We have translated and validated the QOL assessment tools (Cramer et al., 1998) to Korean. Seven of the most serious QOLIE concerns were as follows: seizure worry, overall QOL, emotional well-being, energy and fatigue, cognitive function, social function, medication effects, and an overall health questionnaire.The scoring system requires conversion from raw, preceded numeric values to scores of 0–100 points, with higher scores reflecting better QOL. We assessed the correlation between QOLIE concerns and clinical parameters such as age, gender, marital status, education level, age at seizure onset, duration of illness, and number of antiepileptic drugs (AEDs). **Results:** The mean subscores of QOLIE-31 items were 54.9 (medication effects), 52.0 (energy–fatigue), 50.1 (overall QOL), 42.4 (seizure worry), 41.5 (emotional well-being), 36.3 (social function), and 30.9 (cognitive function). The mean of overall health was 59.4. The items of QOLIE did not show any significant correlation with age at seizure onset or duration of illness. However, education level, economic status, number of AEDs, and frequency of seizures could be related with QOLIE. **Conclusions:** We identified several risk factors for poor QOL in patients with epilepsy. We explored different factors including cultural influences that may explain these findings. These results provide information about patients with epilepsy that may be helpful in their emotional support, as well as drug treatment.

1.258
CHILD AND ADOLESCENT PERSPECTIVES ON THEIR QUALITY OF LIFE AFTER EPILEPSY SURGERY
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Rationale: In our clinical experience, children and adolescents often express high expectations for improved physical, psychological, cognitive, and social well-being after epilepsy surgery, yet studies on postoperative quality of life rarely elicit the child's or adolescent's viewpoint. The purpose of this study was to obtain perceptions of youth regarding the impact of epilepsy surgery on their quality of life (QOL). **Methods:** A cohort of 51 children (mean age, 12.5 years; range, 7–18 years) with intractable seizures were recruited from an epilepsy-monitoring program. The present data were obtained using ethnographic interviews with surgical candidates ($n = 30$) before surgery and 1 year later. A comparison group ($n = 21$) was interviewed twice, also with 1 year between the interviews. After transcription of the interviews, content and thematic analyses were undertaken. Frequency (%) and salience of themes were determined, with additional comparison of surgery and control groups. **Results:** Groups were comparable in age, age at seizure onset, proportion of life with seizures, number of medications, and did not differ statistically in IQ. At baseline, both groups indicated high rates of physical, cognitive, and psychosocial distress. Youth who were most troubled at baseline had high expectations that surgery would improve their QOL, particularly if seizures remitted. While some of the surgical youth identified positive changes such as less fatigue, more energy, improved memory, more independence, and improved self-confidence, others reported little or no change, and a few described a decline in their QOL. Both seizure-free and non–seizure-free surgical youth were represented in each of these categories. Youth in the comparison group reported few positive changes, with most indicating no change or a worsening of their QOL. **Conclusions:** Overall, the findings suggest that the expectations children and adolescents have for gains in QOL within the first year after surgery should be discussed before surgery, as these views may be unrealistic and contribute to a sense of dissatisfaction. This study is unique in that it supports our view that children are excellent informants and able to identify salient aspects of their QOL. Furthermore, baseline interviews provided data with which to compare postsurgery outcomes (with a comparison group). At the end of this presentation, participants should be able to discuss the complex processes involved in postsurgical adjustment of children and adolescents. (Supported by the Ontario Mental Health Foundation.)

1.259
QUALITY OF LIFE IN PATIENTS UNDERGOING RIGHT OR LEFT TEMPORAL LOBECTOMY
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Rationale: Overall, a range of quality-of-life (QOL) measures have shown resective surgery for epilepsy to improve QOL in patients with intractable epilepsy, with the most significant change occurring in patients who became seizure free. Relatively little attention, however, has been paid to the effects of lateralisation. This study explored any differences in QOL for right and left temporal lobe epilepsy (TLE) patients, before and after surgery. **Methods:** Seventeen left (L) TLE and 21 right (R) TLE patients were tested before and, where possible, 6 months after surgery, using the Epilepsy Surgery Inventory, ESI-55, QOL measure designed for patients undergoing epilepsy surgery. **Results:** The groups were not significantly different for age, IQ, or preoperative seizure severity/frequency level. They were not significantly different in duration of epilepsy, at $p < 0.05$, although there was a tendency for the left group to have slightly longer duration. Preoperatively, there were no differences in QOL domains between the LTLE and RTLE groups. In addition, there was no evidence of any relation, for either group, between duration of epilepsy and the QOL measures. Postoperatively, data were available for 12 of the LTLE group and 14 of the RTLE group. Again, there were no significant differences, at $p < 0.05$, between the groups in age, IQ, seizure severity/frequency before surgery, or duration. Both groups had favourable seizure outcomes, and there were no significant differences between the groups. Considering data from the combined groups, all but one of the QOL domains showed significant gains postoperatively, at $p < 0.05$ or $p < 0.01$, depending on the domain. However, between-group analysis showed that these gains were based on improvements in the RTLE group, and there were no significant changes in these measures in the LTLE group. As in the preoperative data, there was no significant relation between duration of epilepsy and QOL. **Conclusions:** In this study, where, on average, duration of epilepsy was relatively long at ~24 years, no relation was found between QOL measures, before or after surgery, and duration of epilepsy. Improvements in QOL scores postoperatively were found to be confined to the RTLE group. (Supported by Birmingham Children's Hospital NHS Trust.)

1.260
WORK, LOVE, AND INTRACTABLE EPILEPSY: PREDICTORS OF SOCIAL ROLE ATTAINMENT
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Rationale: Intractable epilepsy often is associated with neurobehavioral deficits, independent of seizures. Psychosocial adjustment is mul-

tiply determined by medical, psychiatric, cognitive, and social factors. At the conclusion, participants will understand (a) how these factors combine with epilepsy to keep patients from filling age-appropriate social roles and (b) the magnitude of these effects among different subgroups. These findings argue for targeting preventive and rehabilitative strategies to specific subgroups at risk for social failure. **Methods:** Analyzed neuroepilepsy, psychiatric, cognitive, and social variables prospectively obtained in 259 consecutive patients referred for presurgical evaluation to a single epilepsy center from 1991 to 1996. Exclusion criteria were FSIQ <70 and age younger than 20 years. Separate logistic regression analyses were used to predict marital history and current employment status. Predictor variables were gender, history of psychiatric treatment, age at onset of epilepsy, IQ, history of special education, memory impairment, and polypharmacy. **Results:** Sample characteristics were similar to others in the literature [mean (SD): age, 36.0 (9.4) years, gender, 54% female, age at onset, 16.4 years (12.2 years); FSIQ, 88.8 (10.7); years of education, 12.7 years (2.2 years). Only 42% were currently employed, and 63% had ever been married. Female gender ($p < 0.02$), late onset of epilepsy ($p < 0.0001$), and absence of special education ($p < 0.0001$) were significant and unique predictors of ever having been married. Only 27% of men with a history of special education had ever married, compared with 60% of women. Higher IQ ($p < 0.0001$) and no history of psychiatric treatment ($p < 0.002$) were significant and unique predictors of being employed. Absence of memory impairment showed a trend association ($p = 0.13$) with employment. **Conclusions:** Persons are more likely to marry if epilepsy starts later in life, after social and vocational skills have developed, unhindered by stigma and activity restrictions associated with epilepsy. Men with a history of special education are particularly unlikely to marry, regardless of when seizures onset. The same pattern is not seen in women. Men with seizures, learning disabilities, and/or behavior problems may be less attractive to women who seek a mate to fill traditional male roles of father and provider. Conversely, epilepsy-induced dependence and lack of vocational skills in women may less often deter men who seek a mate to fill traditional female roles of mother and homemaker. Nevertheless, such dependent relationships may ultimately be unhealthy for women, as indicated by the greater incidence of divorce among women versus men after successful epilepsy surgery. Social and vocational skills training may be particularly useful for both men and womenearly in the course of intractable epilepsy. Employment is most strongly related to IQ and psychiatric history. Intact cognitive skills and a stable emotional history are valued job skills. They are associated with other characteristics that predict vocational success. Nevertheless, 33% of patients with normal-range IQ, no memory impairment, and no psychiatric history were unemployed. Thus, intractable epilepsy is a potent barrier to employment, independent of other neurobehavioral deficits. Intractable epilepsy is a sufficient condition by itself to justify vocational services. (Supported by Strong Epilepsy Center.)

1.261

AN EVALUATION OF THE RELATION BETWEEN QUALITY OF LIFE AND MOOD IN AN OUTPATIENT EXERCISE STUDY

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Rationale: Based on previous literature describing the relation between quality-of-life and mood assessments in patients with epilepsy, we examined the behavioral data from our recently completed study evaluating the effects of a structured outpatient exercise program on outcomes in patients with epilepsy. We hypothesize that there is a relation between patients' quality of life and mood. At the end of this activity, the participants should be able to discuss the relations between these two behavioral measures and its influence by exercise. **Methods:** This prospective, randomized, parallel, controlled study spanned 12 weeks. Twenty-eight patients were randomly assigned to a supervised exercise program (EXERCISE) or instructed to continue with their current level of activity, with no planned interventions (CONTROL). The EXERCISE group exercised for 1 h on three separate occasions per week for the 12-week study. All patients underwent baseline clinical, physiological, and behavioral evaluation. As part of the behavioral measures, patients completed the 65-item Profile of Mood States (POMS) and Quality of Life in Epilepsy Inventory-89 (QOLIE-89) at baseline and week 12. **Results:** Twenty-three patients completed the 12-week study. There were no differences in baseline scores for either measure between the two patient groups. The overall QOLIE-89 score improved from baseline to week 12 in the EXERCISE group ($p = 0.031$), whereas the CONTROL group score did not change ($p = 0.943$). In the EXERCISE group, two of the domain scores were significantly improved at week 12 (physical function and health perceptions). Separate repeated-measures multivariate analyses of variance (MANOVAs) were conducted on the POMS data for each group to determine changes from baseline to the end of the 12-week exercise program. There were no differences over time for the CONTROL group, but there was a significant multivariate effect for time for the EXERCISE group ($p = 0.05$). Repeated measures ANOVAs for each POMS scale and for total mood were conducted for the EXERCISE group. Vigor improved and total mood scores decreased from the beginning to the end of the program. The detailed relations between the domains of each measure will be presented and discussed. **Conclusions:** The results suggest that exercise may modulate both mood and quality of life in patients with epilepsy.

1.262

POSITIVE PSYCHOTROPIC EFFECTS ASSOCIATED WITH THE USE OF LAMOTRIGINE IN A CLINICAL SETTING

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Rationale: Studies of the efficacy of lamotrigine (LTG) in the treatment of epileptic seizures typically are conducted under rather artificial experimental conditions. Although such studies demonstrate the worth of LTG in the treatment of seizures, much less is known about the efficacy and tolerability of LTG in a clinical setting. To address these questions, we conducted a prospective, observational study of outpatients receiving LTG, emphasizing both positive and negative mood and quality-of-life (QOL) changes. Our objective was to assist the clinician in making antiepileptic medication (AED) choices with these data. **Methods:** We recruited subjects treated 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 aged 18 years or older with IQ $\geq$70 were included. Patients completed the Quality of Life in Epilepsy-31 inventory (QOLIE-31), the Profile of Mood States survey (POMS), and a seizure severity scale at baseline, 2 months, 6 months, and 1 year after beginning LTG, with the dosage titrated according to concomitant AEDs. **Results:** Of 24 patients enrolled to date, nine have completed the baseline evaluation and 2-month assessment after LTG initiation. In this 2-month interval, before attaining maximal LTG dosage, four patients improved (three with >50% decrease in seizure frequency), two remained unchanged and seizure free, two remained unchanged with continued seizures, and one had an increase in seizures. There was significant improvement ($p < 0.033$) in the QOLIE-31 Overall Score, with significant improvement ($p < 0.05$) on subtests assessing seizure worry, emotional well-being, and cognitive functioning. The POMS showed significant improvement ($p < 0.05$) in vigor and fatigue, with all patients reporting less fatigue, and eight of nine patients reported increased vigor. **Conclusions:** These preliminary data indicate positive

mood and quality-of-life effects after initiation of LTG. Although the sample size in this initial report is small, the data suggest improved seizure control after only 2 months of treatment and behavioral improvement in several domains. Results of this study will provide information on improvement in both efficacy and quality of life that will assist the clinician in choosing among the abundance of new AEDs. (Supported by GlaxoSmithKline.) (Disclosure: Grant: GlaxoSmithKline.)

1.263
DIFFERENCES IN QOLIE-10 SCORES IN PSEUDOSEIZURE AND EPILEPSY

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Rationale: To determine if the QOLIE-10 is useful in differentiating pseudoseizure from epilepsy. There are few data regarding the efficacy of the QOLIE in discriminating pseudoseizure from epilepsy. We hypothesized that psedudoseizure patients often overstate the impact of their disability on quality of life (QOL) and produce quantitatively different profiles from epilepsy patients. We explored differences in specific questions and total score. **Methods:** Participants were 27 adults (age range, 19–78) who were admitted to the inpatient University of Virginia Epilepsy. Data from QOLIE-10 questionnaires were obtained by retrospective chart review of questionnaires, which are administered routinely to all patients admitted to the Unit. A total score was obtained on 17 participants (Epilepsy, 10; Pseudoseizure, seven), and individual questions were answered more frequently (e.g., all participants answered question 5). **Results:** QOLIE-10 Total Scores were not different between epilepsy (mean, 28.90; SD, 5.78) and pseudoseizure patients (mean, 30.43; SD, 8.06; $p = 0.65$). Compared to the epilepsy group, the mean score was greater in the pseudoseizure group on question 5 (mean, 2.81; SD, 1.52 vs. mean, 4.1; SD, 0.87; $p = 0.02$), and lower in the pseudoseizure group on question 9 (mean, 3.59; SD, 1.22 vs. mean, 2.40; SD, 1.51; $p = 0.04$). A prior diagnosis of an anxiety or depressive disorder was more than twice as likely in the pseudoseizure group, and all pseudoseizure patients had such a diagnosis ($\chi^2 = 14.75$, $p < 0.01$). The prevalence of psychiatric illness in the epilepsy group (23.5%, four of 17) was much lower than in the pseudoseizure group (100%, seven of seven). Age was not predictive of QOLIE-10 Total Score by linear regression ($p = 0.46$). **Conclusions:** Pseudoseizure patients reported more work-related concern (question 5), whereas epilepsy patients reported more fear of having another seizure (question 9). This raises the possibility that the QOLIE-10 is useful in evaluation of pseudoseizures as well as epilepsy, but a larger sample must be examined to determine its validity. Pseudoseizure patients may have more work-related concern because of preoccupation with somatic complaints and less concern of having another seizure because pseudoseizures are less injurious. (Supported by Department of Neurology, University of Virginia Medical Center enter for Organizational Development, University of Virginia Medical Center.)

1.264
PSYCHOSOCIAL CHANGES 1 YEAR AFTER EPILEPSY SURGERY

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Rationale: For patients with pharmacoresistant focal epilepsies, surgical treatment provides the opportunity for a seizure-free life. However, expectations of psychosocial improvements are equally important. This prospective study, launched in 1997, asked for effects of epilepsy surgery on medical, neuropsychological, and psychosocial/socioeconomic changes. Because the newly formed German states show several regional characteristics (such as changes of educational conditions, high unemployment rate), this study was carried out at the Epilepsy Center of the University of Greifswald, Germany. The goal of the study was to identify predictors for a generally good postsurgical outcome at the different levels. Furthermore, it was intended to detect difficulties for the patients and in this case to offer appropriate help. **Methods:** Forty-three adults with focal epilepsy participated in the study. They all received antiepileptic drugs (AEDs). Thirty-five of these patients received surgery (group 1). For the remaining eight, it was not possible to operate (group 2). All patients were tested presurgically (t_1) and at 12-month follow-up (t_2) by standardized assessment instruments such as cognitive performance tests, self-rating scales to determine personality profile, clinical–psychological parameters, health-related quality of life, and a structured interview to assess psychosocial aspects. **Results:** At t_1, those patients treated with surgery and those who were treated conservatively did not differ significantly. One third of patients had cognitive problems that were mostly related to memory dysfunction. Fifty percent of patients showed an increased level of anxiety, whereas 25% of subjects showed an increased level of depression. Approximately half of the patients were unemployed or retired because of their epileptic condition. Vocational rehabilitation was available for only half of those patients. Approximately 40% of all patients were tested to have a poor quality of life. At t_2 cognitive abilities such as attention and visiospatial functions of the patients treated with surgery were improved. The amount of emotional difficulties was significantly reduced. This result was in contrast to the conservatively treated patients. Twenty percent of the surgery patients compared to 40% of the conservatively treated patients were tested to have a poor quality of life. The vocational situation in the surgical group deteriorated at t_2. For these patients, there was a trend from unemployment toward retirement. Employment at t_1, cognitive improvement, and absence of emotional difficulties at t_2, but not the seizure freedom were found to be the best predictors for a good postsurgical quality of life. **Conclusions:** Successful surgical treatment of epilepsy is not necessarily related to improvement of socioeconomic factors. It is possible to improve both psychological difficulties and, to a certain extent, cognitive functioning, which are the basis for a better psychosocial and socioeconomic integration of patients. Additional pre- and postsurgical rehabilitative interventions are necessary, especially with respect to the poor employment situation.

1.265
AMERICAN VALIDATION OF THE QUALITY OF LIFE IN CHILDHOOD EPILEPSY QUESTIONNAIRE

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Rationale: It is clearly recognized that quality of life of children with epilepsy is a critical aspect to management, yet few instruments are available to measure it. The Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) was developed and validated in an Australian population for this purpose (Sabaz M, Cairns DR, Lawson JA, et al. *Epilepsia* 2000;41:765–74). The aim of this study was to adapt and validate the QOLCE for use in the American population and to compare the quality of life of both American and Australian childhood epilepsy patients using this instrument. **Methods:** The subjects were parents of children with epilepsy. Each family received a QOL package by post. This included the QOLCE and the Child Health Questionnaire (CHQ). Higher scores on both instruments reflected higher levels of

functioning. The QOLCE was adapted from Australian English to American English. Clinical data collected about each patient included rating of seizure severity; number of antiepileptic drugs (AEDs) taken, and age at epilepsy onset. To establish reliability of the QOLCE, internal consistency reliability was established for each of the subscales. Construct validity of each QOLCE subscale was established by correlating the QOLCE subscales with similar CHQ subscales. Clinical sensitivity was established by correlating QOLCE subscale and total scores with seizure severity, number of AEDs taken, and age at epilepsy onset. Finally, QOLCE scores from Australian children with epilepsy (data collected from a previous investigation) were compared to QOLCE scores from American children with epilepsy. **Results:** Seventy-one (89% response rate) subjects returned the questionnaire package (45 boys, 26 girls with epilepsy). The age of the children ranged from 4 to 18 years inclusive (mean, 11.17 years; SD, 4.08 years) with a mean age at onset of 5.13 years (SD, 3.72 years). Seizures were classified as severe to very severe (n = 20), moderately severe (21), mild to very mild (16), and 12 children did not experience seizures during the past 6 months. The number of AEDs taken ranged from zero to five (mean, 1.90; SD, 1.01). The internal consistency reliabilities of the subscales ranged from 0.72 to 0.97. Quality of Life in Childhood Epilepsy subscales correlated moderately highly with similar CHQ subscales (0.46–0.70). Twelve of 16 QOLCE subscales and the total QOLCE quality-of-life score had a significant negative relation with a rating of seizure severity ($p < 0.05$). The number of AEDs taken negatively correlated with only one QOLCE subscale. Age at epilepsy onset postively correlated with three QOLCE subscales. When comparing the QOLCE subscale scores for both Australian and American children with epilepsy, no significant differences were found. **Conclusions:** This study demonstrated that the adapted QOLCE is a valid instrument for American children. It was shown to have excellent levels of internal consistency, construct validity, and clinical sensitivity. Showing that the QOLCE can be adapted and validated for another cultural centre extends its value as a useful instrument. There is potential application to other cultural settings, establishing it as a tool able to be used in cross cultural research. [Supported by National Health and Medical Research Council (Australia) (grant number 209512).]

1.266

DIFFERENCES IN HEALTH-RELATED QUALITY OF LIFE (HRQOL): PSYCHOGENIC NONEPILEPTIC SEIZURES VERSUS EPILEPSY PATIENTS AND GENERAL POPULATION

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Rationale: After reviewing the abstract the audience should be able to discuss the differences in health-related quality of life (HRQOL) between the patients with PNES and patients with epilepsy and general population. Psychogenic nonepileptic seizures (PNES) and epilepsy affect HRQOL through limiting the ability to drive and continue employment/education, medication adverse effects, depression, and impaired social/physical functioning. Although several studies evaluated the differences in HRQOL between healthy general population and epilepsy cohorts, studies comparing HRQOL between healthy and PNES subjects are lacking. **Methods:** Patients admitted to an inpatient EMU between 1/20/01 and 3/31/02 were prospectively evaluated. Patients completed epilepsy-specific QOL instrument (QOLIE-89). SF-36 data were extracted from QOLIE-89 for patients with definite PNES (n = 53) and definite epilepsy (n = 53). Population norms were derived from Ware et al., 1993. Data were analyzed using one-sample and independent samples difference-of-means tests (*t* tests). **Results:** See Table 1. HRQOL is 17.3–65.4 points lower in patients with PNES compared to the general population ($p < 0.001$). **Conclusions:** Patients with PNES have lower HRQOL than both the general population and epilepsy patients. Reasons for the low HRQOL in PNES need to be further investigated.

1.267

HEALTH-RELATED QUALITY OF LIFE IS WORSE IN PSYCHOGENIC NONEPILEPTIC SEIZURES THAN IN CLINICAL DEPRESSION

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Rationale: After reviewing this abstract, the audience should be able to understand differences in the health-related quality of life (HRQOL) between patients with psychogenic nonepileptic seizures (PNESs) and patients with clinical depression. Previously we examined the relation between the diagnosis of PNESs and HRQOL, and we found depression contributing to the low HRQOL in this cohort of patients [*Epilepsia* 2001;(suppl 7)]. It is not known whether depression affects patients with PNES in the same way as it affects patients with depression without other comorbidities. **Methods:** Patients admitted to an inpatient EMU between 1/20/01 and 3/31/02 were prospectively evaluated. Patients completed epilepsy-specific QOL instrument (QOLIE-89). SF-36 data were extracted from QOLIE-89 for patients with definite PNESs (n = 53). We used one-sample difference-of-means test (*t* test) to compare the sample data with the population norms for

TABLE 1. *Comparison of average SF–36 scores in the general population, epilepsy patients, and patients with PNES*

SF–36 Subscale	Mean			Difference of means (*t* test); p value		
	General population	Epilepsy (ES)	PNES	ES vs. general population[a]	PNES vs. general population[a]	PNES vs. ES[b]
Physical functioning	84.2	74.6	58.1	0.029	<0.001	<0.001
Role limitations: Physical	81.0	47.2	15.6	<0.001	<0.001	<0.001
Role limitations: Emotional	81.3	62.6	46.5	0.002	<0.001	0.057
Vitality	60.9	43.6	28.4	<0.001	<0.001	<0.001
Mental health	74.7	60.6	50.6	<0.001	<0.001	<0.036
Social functioning	83.3	62.4	37.6	<0.001	<0.001	<0.001
Bodily pain	75.2	67.9	51.3	0.031	<0.001	0.002
General health	72.0	56.0	42.6	<0.001	<0.001	0.002

[a] One-sample *t* test, n = 106.
[b] Independent samples *t* test, n = 106.

clinical depression (Ware et al., 1993). **Results:** See Table 1. Patients with PNES scored below the depression norms on 5 of 8 SF-36 subscales. **Conclusions:** Although depression affects both cohorts of patients, HRQOL in patients with PNES is worse than in patients with clinical depression. Therefore, factors other than depression probably add to the explanation of low HRQOL in patients with PNES. These factors need to be explored further before effective therapies are designed.

TABLE 1. *Comparing average SF-36 scores in patients with PNES to the population norms for clinical depression*

SF-36 subscale (0–100)	Mean (SD)		*t* test; p value
	Clinical depression	PNES	
Physical functioning	71.6 (27.2)	58.1 (25.2)	<0.001
Role limitations: physical•44.4 (40.3)	15.6 (27.0)	0.223	
Role limitations: emotional	38.9 (39.8)	46.5 (45.0)	<0.001
Vitality (energy/fatigue)	40.1 (21.1)	28.4 (19.0)	<0.001
Mental health (emotional well-being)	46.3 (20.8)	50.6 (24.4)	0.202
Social functioning	57.2 (27.7)	37.6 (29.0)	<0.001
Bodily pain	58.8 (26.7)	51.3 (28.2)	0.057
General health	52.9 (23.0)	42.6 (19.3)	<0.001

1.268

PATIENT-FUNDING SOURCES PROVIDE AN INDEX OF INTELLIGENCE AND PSYCHOSOCIAL ADJUSTMENT IN PATIENTS WITH EPILEPSY

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Rationale: The funding sources for treatment for epilepsy is considered important for physicians and hospitals to be paid, but knowledge of funding source may also provide an index of other factors relevant to patient care. The objective of this study is to determine if funding source provides a basic index of mental abilities and psychosocial functioning in patients with epilepsy. **Methods:** A total of 85 adults admitted for long-term EEG monitoring composed the subjects of the study. Each was evaluated by type of funding source. It was found that 52 patients were funded by Medicaid, Medicare based on disability, or a combination of each, and that 33 patients were funded by non–welfare-related commercial insurance plans. Intelligence was evaluated by means of the Wechsler Adult Intelligence Scale–III (WAIS-III), and psychosocial adjustment by the Washington Psychosocial Seizure Inventory (WPSI). **Results:** The WAIS-III VIQ was significantly ($p = 0.002$) lower for the welfare (M, 85.71; SD, 12.08) than the insurance-covered group (M, 95.30; SD, 13.81). The same pattern was found for the PIQ ($p = 0.042$; welfare group: M, 87.94; SD, 12.35; insurance group: M, 94.06; SD, 13.75) and for the FSIQ ($p = 0.004$; welfare group: M, 85.54; SD, 12.10; insurance group: M, 94.36; SD, 13.86). With regard to psychosocial adjustment, no differences were found on the validity (Lie, Rare Items) scales of the WPSI. However, statistically significant differences were found on seven of eight WPSI clinical scales, with the results always showing fewer problems with the insurance-covered group than the welfare group: Emotional Adjustment ($p = 0.019$); Interpersonal Adjustment ($p = 0.003$); Vocational Adjustment ($p = 0.001$); Financial Status ($p = 0.004$); Adjustment to Seizures ($p = 0.008$); Medicine and Medical Management ($p = 0.045$); Overall Psychosocial Functioning ($p = 0.001$). While the substantial differences found in the vocational and financial areas were expected, of considerable interest is the fact that emotional and interpersonal adjustment were significantly worse with welfare-funded patients than with insured patients. In addition, patients on welfare perceived their seizures to be more disabling than insured patients, and they also tended to take a dimmer view of the advice offered by physicians than insured individuals. Another strong finding was that only the Family Background scale failed to show a difference between the welfare and insured patients, which argues against families of origin being blamed for the other differences between the welfare and insured groups. **Conclusions:** Patients who are funded by Medicaid, or disability-related Medicare, have diminished intelligence in comparison with patients covered by health insurance, and especially so in verbal skills, which includes their ability to present themselves orally. In addition, these same patients show significantly greater psychosocial concerns than patients covered by health insurance that is not welfare based, and these concerns are broader than merely being out of work or momentarily short of funds. This study shows that the type of funding a patient has can be an index to help the provider assess a patient's adjustive resources and perhaps also the amount (and cost) of care that will be required.

1.269

VALIDITY OF THE HEALTH UTILITIES INDEX (HUI-III) IN EPILEPSY

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Rationale: Instruments that measure health state preferences (utilities) are essential to obtain quality-adjusted life years, or QALYs. The latter are the standard metric cost-effectiveness analyses. There are very few data on the use of utility instruments in epilepsy. We assess the validity and clinical relevance of the Health Utilities Index (HUI-III) in epilepsy. The HUI-III is one of the most commonly used instruments worldwide to obtain health state preferences and QALYs, but there are no data on its performance and relevance in epilepsy. At the end of this activity, the participants will have an understanding of the validity and clinical relevance of the HUI-III in patients with epilepsy. **Methods:** We evaluated 80 surgically or medically treated adults with temporal lobe epilepsy. All patients answered a battery of instruments including the self-administered Quality of Life Inventory in Epilepsy-89 (QOLIE-89) and HUI-III. Instruments were completed in the same order and on the same day, and they were reviewed for completeness and validity of responses. We assessed the internal consistency (Cronbach's α), floor and ceiling effects of the constituent subscales, and the global score of the HUI-III. Construct validity of HUI-III was assessed using the QOLIE-89 constituent subscales as criterion constructs. Test–retest reliability and responsiveness of HUI-III were also assessed. **Results:** The response rate was 100%. The internal consistency of HUI-III was satisfactory for all multiitem subscales and for the global score (Cronbach's $\alpha = 0.72$–0.9). Floor effects occurred in 0–2.5%, and ceiling effects occurred in 31–93% of individuals across subscales. The global, multiattribute HUI-III utility score demonstrated adequate validity. Construct validity varied among subscales, but it was generally adequate. The HUI-III subscales demonstrating stronger associations with corresponding QOLIE-89 constructs were pain, cognition, emotion, ambulation, and hearing. **Conclusions:** The HUI-III demonstrated adequate reliability and validity in a population of medically and surgically treated patients with temporal lobe epilepsy. We conclude that HUI-III yields reliable and valid information about health state preferences in patients with epilepsy. Its use in this population for the purpose of obtaining QALYs and performing cost-effectiveness analyses seems justified. [Supported by The Physicians' Services Incorporated Foundation (Canada).]

1.270

A PROSPECTIVE OUTPATIENT STUDY OF QUALITY OF LIFE IN TEMPORAL LOBE EPILEPSY AND JUVENILE MYOCLONIC EPILEPSY

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Rationale: Most quality-of-life (QOL) studies deal with an undifferentiated outpatient epilepsy group or with pre- and postsurgical outcomes. We initiated this study to determine if differences in QOL exist between types of epilepsy in an outpatient setting. **Methods:** The QOLIE-10 (QOL in epilepsy, 10 item) was given to all outpatients to complete at the initial and subsequent visits, typically every 3 months (Cramer et al. *Epilepsia* 2000;41:29–38). Patients with juvenile myoclonic epilepsy (JME) or temporal lobe epilepsy (TLE) were then analyzed at the first and subsequent visits. We made scatterplots for each of the 10 domains as well as the total score, over time, and plotted the mean score by group for each domain. We hypothesized that the QOLIE scores would improve with time and that the JME would have lower scores (better QOL) than the TLE. The clinical diagnosis was made based on the history, EEG, seizure semiology, and magnetic resonance imaging (MRI). **Results:** The duration of follow-up from the initial visit ranged from 200 to 800 days, for three to eight visits in both groups. There were 33 subjects in the JME group and 98 in the TLE group. The scatterplots showed no significant correlation with time for the individual domains in either group, although there was a trend for mental effects of medication to decrease in JME patients and physical effects of medications to decrease in TLE patients. The highest score in the JME group was for overall QOL (2.4 ± 0.86). For the TLE subjects, the highest score was in Fear (of Seizures 2.89 ± 1.21) with Memory close behind (2.62 ± 1.0). Across the total period of evaluation, the domains differing significantly ($p \leq 0.05$) between the groups included: Driving (1.17, JME; 1.89, TLE), Memory (1.82, TLE; 2.62, TLE), Work (1.50, JME; 2.25,TLE), and Social (1.72, JME; 2.27, TLE). The total QOLIE-10 score trended to a significant difference (JME, 19.3; TLE, 22.7; $p = 0.06$). **Conclusions:** Quality of life did not significantly change over the period of this study (1–3 years) in either TLE or JME subjects. In general, the TLE subjects endorse a lower quality of life than the JME subjects, with driving, memory, work, and social issues being the worst areas of function. Further evaluation of the relationship of trends in QOL to antiepileptic medication changes and seizure frequency will be made.

AEDs

1.271
LEVETIRACETAM REDUCES CAFFEINE-INDUCED INTRACELLULAR CALCIUM TRANSIENTS IN CULTURED RAT HIPPOCAMPAL NEURONS

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Rationale: Levetiracetam (LEV; Keppra) is a novel antiepileptic drug (AED) with proven efficacy in controlling refractory partial seizures in adults. LEV has been reported to exert several nonconventional effects on neurons. Specifically, LEV was previously shown to antagonize a non-γ-aminobutyric acid $(GABA)_A$ receptor–associated epileptiform effect of bicuculline in rat hippocampus (Margineanu and Wülfert. *Br J Pharmacol* 1997;122:1146), and thapsigargin, a depletor of intracellular Ca^{2+} stores, mimicked that antibicuculline effect (Wülfert and Margineanu. *Neurosci Lett* 1998;243:141). Therefore, we investigated whether LEV opposes the release of Ca^{2+} from intraneuronal stores. **Methods:** The effect of LEV on the caffeine, 10 m*M* (CAF)-induced intracellular calcium ($[Ca^{2+}]_i$) response was investigated in cultures of rat hippocampal cells, treated with cytosine-1-β-D-arabinofuranoside to suppress the growth of glial cells and to promote neuronal survival. Ca^{2+} imaging was performed with a Photon Technology System using the calcium-sensitive probe fura-2. **Results:** In 9- to 10-day old neuronal cultures, LEV reduced significantly the CAF-induced $[Ca^{2+}]_i$ response. Compared to control values (means ± SEM), this was apparent after incubation with both 10 μ*M* LEV (7.5 ± 1.8 vs. 4.6 ± 1.1; n = 25), 32 μ*M* (4.0 ± 0.5 vs. 1.9 ± 0.4; n = 22), and 100 μ*M* (6.3 ± 0.8 vs. 4.7 ± 0.5; n = 23), whereas a concentration of 1 μ*M* was inactive (5.7 ± 0.4 vs. 5.6 ± 0.5; n = 30). In contrast, incubation of cultured neurons with 32 μ*M* inactive R-enantiomer of LEV had no effect on CAF-induced $[Ca^{2+}]_i$ response (4.8 ± 0.7 vs. 4.6 ± 0.5; n = 18). Similarly, the reference AEDs carbamazepine (50 μ*M*) and clonazepam (1 μ*M*) were also devoid of significant effects on CAF-induced $[Ca^{2+}]_i$ response. **Conclusions:** These data suggest that LEV inhibits caffeine-induced release of Ca^{2+} from intraneuronal stores. This excitability-reducing effect might contribute to the antiepileptic activity of the drug. Further investigations are warranted to characterize the subcellular mechanisms by which LEV may modulate intraneuronal Ca^{2+} release. (Supported by UCB S.A. Pharma Sector.) (Disclosure: Grant: UCB S.A.)

1.272
THE ROLE OF GLUTAMATE RECEPTORS IN THE 6-HZ PSYCHOMOTOR SEIZURE MODEL

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Rationale: Glutamate is the major excitatory neurotransmitter within the CNS that acts on ionotropic and metabotropic receptors: *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainate (KA), and mGluRs 1-8, respectively. Antagonists at the NMDA and AMPA/KA receptors as well as mGluR agonists/antagonists have been shown to possess anticonvulsant activity in a number of traditional animal seizure models (e.g., MES and DBA/2 sensory-induced seizures). The 6-Hz model of partial seizures, recently described by Barton et al., 2001, is an alternative low-frequency, long-duration stimulation paradigm resulting in a seizure characterized by jaw and forelimb clonus, stun, and Straub tail. The unique aspect of this model is that it is the only acute seizure model in which levetiracetam has displayed anticonvulsant activity, suggesting that the 6-Hz seizure model may be useful in identifying compounds with unique anticonvulsant profiles. The purpose of the present study was to examine the role glutamate receptors play in the 6-Hz seizure using a number of NMDA, AMPA/KA, and mGluR modulators. **Methods:** Tonic-extension seizures were induced in CF-1 mice via corneal stimulation at 60-Hz, 0.2-s duration, and 50 mA. Partial seizures were induced via corneal stimulation at 6-Hz, 3-s duration, and 32 mA. Various doses (0.1–100 mg/kg) of NMDA, AMPA/KA, or mGluR modulators were administered to animals before 60-Hz or 6-Hz stimulation. Behavioral toxicity was evaluated before electrical stimulation by a trained observer. **Results:** Complete tonic-extension protection was obtained with the NMDA-receptor antagonists LY235959 and MK-801, and AMPA/KA antagonists LY293558 and LY300168. The seizure protection afforded by NMDA and AMPA/KA antagonists, however, was only at doses producing behavioral impairment marked by ataxia and sedation. In contrast, LY235959, MK-801, LY293558, and LY300168 were only partially effective in blocking the 6-Hz seizure (0, 60%, 0, and 30% protection, respectively) at doses devoid of behavioral impairment. The mGluR2/3 agonists LY379268 and LY389795 were effective in blocking both the tonic extension and 6-Hz seizures at doses devoid of behavioral impairment. In addition, the mGluR5 antagonist, MPEP, was effective in blocking both the tonic extension and 6-Hz seizures at doses devoid of behavioral toxicity. **Conclusions:** Previous studies have demonstrated the anticonvulsant potential of glutamate-receptor modulators against the electroshock-induced tonic extension. In the present study, however, NMDA and AMPA/KA antagonists were not effective in blocking the electrically induced 6-Hz seizure at doses devoid of behavioral impairment. These results suggest that NMDA and AMPA/KA receptor antagonists may not be a useful therapeutic strategy for the treatment of partial seizures. In contrast, the block of partial seizures by modulation of mGluRs may prove to be useful in treating partial seizures and supports their further development. (Supported by Eli Lilly and Company.) (Disclosure: Salary: Employed by Eli Lilly and Company.)

1.273

LOCALIZATION AND PHOTOAFFINITY LABELING OF THE LEVETIRACETAM BINDING SITE IN RAT BRAIN AND CELL LINES

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Rationale: To identify the protein constituent of the levetiracetam (LEV; Keppra) binding site (LBS) in situ, we synthesized the photoaffinity label [^{3}H]ucb 30889, an LEV analogue bearing a substituted aryl group on the 4-position of the pyrrolidone and that binds to the same site. This radioligand was used to study the mapping of the novel binding site within the brain and both its cellular and subcellular distribution. **Methods:** For rat brain autoradiography, 25-μm slices were incubated with 1.3 n*M* [^{3}H]ucb 30889 for 120 min at 4°C in 50 m*M* Tris-HCl buffer. Binding assays with rat brain membranes and various neuronal cultures were performed under similar conditions. Nonspecific binding was determined by the inclusion of 1 m*M* LEV in the assay. For photolabeling, membranes were incubated with 40 n*M* [^{3}H]ucb 30889 for 120 min at 4°C in 50 m*M* Tris-HCl buffer, followed by irradiation with UV light for 30 min. **Results:** [^{3}H]ucb 30889 binding sites were heterogeneously distributed in the rat brain. While there was no apparent binding in the white matter, there was a high level of binding in the dentate gyrus, the superior colliculus, several thalamic nuclei, and in the molecular layer of the cerebellum. Binding was less pronounced in the cerebral cortex, the hypothalamus, and the striatum. [^{3}H]ucb 30889 binding in whole-cell binding assays (rat and mice brain neuronal primary cultures and PC12 cells) showed high levels of specific binding. After fractionation of rat brain synaptosomes by sucrose gradient and differential centrifugation, the LBS was localized predominantly in synaptic membrane and microsomal fractions, whereas there was no specific binding in the mitochondrial fraction. On UV-irradiation, a protein of 97 ± 10 kDa was specifically photolabeled by [^{3}H]ucb 30889 in rat brain synaptosomes and microsomes. The inclusion of 1 m*M* LEV in the binding assay prevented this labeling. Biochemical experiments indicated that the photolabeled protein is not N-glycosylated and may likely be a membrane protein. **Conclusions:** The localization of [^{3}H]ucb 30889 binding sites in rat brain does not match the distribution of classic receptors and ion channels such as the glutamate receptors, the $GABA_A$ receptor as well as the Na^+ and Ca^{2+} channels. This novel binding site is present in various neuronal cell types and brain areas. (Supported by UCB S.A., Pharma Sector.) (Disclosure: Salary: UCB S.A.; Grant: UCB S.A.)

1.274

BINDING CHARACTERISTICS OF [^{3}H]UCB 30889 IN RAT BRAIN: A NEW RADIOLIGAND WITH HIGH AFFINITY FOR LEVETIRACETAM BINDING SITES

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Rationale: Levetiracetam (Keppra; LEV), a novel antiepileptic drug (AED) with a high safety margin, has been shown to bind to a specific binding site located preferentially in rat brain (LEV binding site or LBS. Noyer et al. *Eur J Pharmacol* 1995;286:137–46). However, [^{3}H]levetiracetam displayed only micromolar affinity for these sites, making it unsuitable for further characterization. The present study describes the binding properties of [^{3}H]ucb 30889, (2S)-2-[4-(3-azidophenyl)-2-oxopyrrolidin-1-yl]butanamide, a new, more potent, analogue of LEV. **Methods:** [^{3}H]ucb 30889 binding experiments were conducted on crude rat brain membranes at 4°C. Incubation time for equilibrium studies was 120 min. For kinetic and competition studies, [^{3}H]ucb 30889 was used at a concentration of 1.3 n*M* in 0.5 ml of a Tris-HCl (pH 7.4) buffer containing 2 m*M* Mg^{2+}. Localization of the LBS in brain substructures was assessed by autoradiography on 25-μm-thick slices incubated under similar conditions. Nonspecific binding was determined by the inclusion of 1 m*M* LEV in the assay. **Results:** [^{3}H]ucb 30889 binds reversibly and with high affinity to binding sites in rat cerebral cortex. Binding kinetics were biphasic: half-times for association and dissociation were respectively, 3 ± 2 min and 4 ± 1 min for the fast component (25–50% of the sites), and 47 ± 13 min and 61 ± 15 min for the slow component. Saturation binding curves were compatible with a homogeneous population of binding sites with a B_{max} of 3,713 ± 407 fmol/mg prot and a K_d of 30 ± 8 n*M*. pIC_{50} values for a variety of analogues and other compounds known to interact with the LBS, such as pentylenetetrazol or bemegride, were identical whether obtained with [^{3}H]ucb 30889 or [^{3}H]levetiracetam. Sites labeled by [^{3}H]levetiracetam and [^{3}H]ucb 30889 also have the same tissue distribution (CNS only). Preliminary autoradiography binding studies in rat brain revealed that [^{3}H]ucb 30889 labels specific sites diffusely localized throughout the brain, which can be dose-dependently inhibited by LEV. **Conclusions:** Competition binding curves and tissue distribution of specific binding indicates that [^{3}H]ucb 30889 and [^{3}H]levetiracetam bind to the same site (LBS) present in variable densities throughout the brain. Furthermore, [^{3}H]ucb 30889 displays a 30-fold higher affinity for LBS than [^{3}H]levetiracetam. Its biphasic kinetics could be related to site heterogeneity, negative cooperativity, or isomerization, although the first hypothesis is not supported by equilibrium data. (Supported by UCB S.A. Pharma Sector.) (Disclosure: Salary: UCB S.A.)

1.275

EFFECT OF TOPIRAMATE ON MITOCHONDRIAL FUNCTION AND DYSFUNCTION IN A CHRONIC MODEL OF EPILEPSY

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Rationale: Topiramate (TPM) showed in several studies a neuroprotective effect on the survival of pyramidal neurons by a yet unknown mechanism. Because mitochondria are intimately involved in pathways leading to pyramidal cell death in epilepsy, we evaluated putative effects of TPM on mitochondrial function in the rat hippocampus in vitro and in vivo using the pilocarpine model of chronic epilepsy. **Methods:** We investigated the in vitro action of TPM on the oxygen consumption of digitonin-treated rat homogenates and 400-μm-thick rat hippocampal slices with different mitochondrial substrates. To evaluate the in vivo action of TPM, 30-day-old Wistar-rats were injected with pilocarpine and received, 40 min after onset of status epilepticus, different doses of the drug (20, 40, and 100 mg/kg). The status epilepticus was terminated by diazepam (DZP; 4 mg/kg; injected 3 h and 40 min after onset of status epilepticus). Neuronal cell counts and mitochondrial enzyme activities in hippocampal subfields were determined in the chronic epileptic state 30 days after pilocarpine injection. **Results:** TPM (2.5 m*M*) inhibited, in digitonin-treated rat hippocampal homogenates, 20% of pyruvate-dependent respiration while the succinate-dependent respiration was unaffected, indicating mild inhibition of respiratory chain complex I. In hippocampal slices, a comparable inhibitory effect on respiration with NAD-dependent substrates was observed at 1 m*M* TPM. In our in vivo experiments, TPM protected rat hippocampal CA1 and CA3 neurons against seizure activity–related cell damage and rescued mitochondrial function after status epilepticus, showing effects >40 mg/kg. **Conclusions:** Our findings confirm the neuroprotective action of TPM on the survival of hippocampal pyramidal cells in pilocarpine-treated epileptic rats. Assuming a possible in vivo accumulation of the drug, we suggest that the observed mild inhibitory action of mitochondrial respiratory chain complex I by TPM might precondition the rat hippocampal pyramidal cells against seizure activity–related cell damage. (Supported by a grant

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1.276
TOPIRAMATE DISPLAYS ANTIEPILEPTIC PROPERTIES IN GENETIC MODELS OF ABSENCE AND AUDIOGENIC EPILEPSY

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Rationale: The anticonvulsant drug (AED) topiramate (TPM) has a broad spectrum of antiepileptic activity (3) and is clinically effective against simple or complex partial seizures and generalized tonic–clonic seizures in adults and children. The antiepileptic efficacy of TPM has been demonstrated in a variety of seizure models. Here, the antiepileptic effects of TPM were assessed in two models of genetically determined generalized epilepsy. The model of nonconvulsive epilepsy used was a genetic model of absence seizures, the GAERS (genetic absence epilepsy rat from Strasbourg) and the model of convulsive seizures was a genetic audiogenic rat model, the Wistar AS. **Methods:** GAERS were equipped with four cortical electrodes over the frontoparietal cortex and the duration of spike-and-wave discharges (SWDs) on the EEG was recorded for periods of 20 min up to 120 or 300 min after the injection of TPM. In Wistar AS, the occurrence of, latency to, and duration of one or two wild running episodes and tonic seizures were recorded at 60 min after the injection of TPM. **Results:** In the 16 GAERS studied, TPM (10, 30, and 60 mg/kg) dose-dependently reduced the expression of SWDs that almost totally disappeared at the two highest doses between 40 and 120 min, whereas 10 mg/kg TPM reduced the duration of SWDs by 42–72%. SWD duration returned to control levels by 180 and 280 min after the injection of 30 and 60 mg/kg TPM, respectively. In Wistar AS, 10 mg/kg TPM induced the occurrence of a second running episode not present in control rats, indicative of a decrease in sensitivity of the rats to the auditory stimulus and increased by 330% the latency to the tonic seizure that was still induced in the eight rats studied. At 30 and 60 mg/kg TPM, the latency to wild running increased by 140%, the second running episode was suppressed in six and seven rats, respectively; whereas the tonic seizure occurred only in one of the eight rats studied at these two doses. **Conclusions:** The present results support the broad spectrum of antiepileptic activity of TPM, confirming its efficacy in primary generalized seizures both of tonic–clonic nature and of the absence type. (Supported by a grant from Johnson and Johnson Pharmaceutical Research and Development, LLC.) (Disclosure: Grant: Johnson and Johnson Pharmaceutical Research and Development, LLC.)

1.277
THE INFLUENCE OF GENDER ON THE AGGRAVATION BY CARBAMAZEPINE OF LOW-DOSE PENTYLENETETRAZOL-INDUCED ABSENCE SEIZURES IN POSTPUBESCENT RATS

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Rationale: Although the aggravation of absence seizures by carbamazepine (CBZ) is well recognized, the underlying pharmacodynamic mechanisms are uncertain. It has been observed clinically in postpubescent patients that this aggravation is more common in female subjects, suggesting an influence of sex hormones. The purpose of this study was to determine whether CBZ aggravates absence seizures in the low-dose pentylenetetrazol (PTZ) rat model in postpubescent male and female animals, and whether this was influenced by the gender of the animal. **Methods:** Male and female inbred Sprague–Dawley rats were implanted with EEG electrodes under general anesthesia. After a 7-day recovery peroid, rats were administered PTZ (20 mg/kg, i.p.) after pretreatment with vehicle or CBZ (20 mg/kg, i.p.). The duration of spike-and-wave discharges (SWDs) was quantified for six sequential 15-min intervals post-PTZ administration. **Results:** The total cumulative SWD for 90 min after PTZ was significantly higher in the CBZ versus vehicle pretreatment arm for both female (mean, 110 vs. 62; $p = 0.03$) and male (mean, 89 vs. 60 s; $p = 0.03$) rats. The increase in SWD duration in the CBZ (vs. vehicle) arm was greater in female (vs. male) rats for the first five of the six 15-min intervals after PTZ administration. CBZ pretreatment resulted in significant reductions in both SWD frequency (male, $p = 0.003$; female, $p < 0.0001$) and latency to onset of SWD (male, $p = 0.002$). Additionally, the frequency of SWD in CBZ-pretreated rats was significantly lower in females compared to males (5.8 vs. 6.1 Hz; $p = 0.02$). **Conclusions:** CBZ consistently aggravates absence seizures in the low-dose PTZ model in both female and male postpubescent rats. Additionally, the results provide evidence of a possible sex difference in the aggravation of SWD by CBZ. [Supported by (T.J.O'B.) a Viertel Clinical Investigator Grant from the Sylvia and Charles Viertel Charitable Foundation.]

1.278
EFFECT OF ANTIEPILEPTIC DRUGS ON ESTROGEN-RECEPTOR FUNCTION STUDIED IN THE HUMAN BREAST CANCER CELL LINE MCF-7

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Rationale: Several antiepileptic drugs (AEDs) affect sex steroid hormone levels. In women, hyperandrogenism has recently been described after long-term use of valproate (VPA), whereas phenytoin (PHT) reduces free estrogen levels. The underlying mechanisms behind these effects are still unclear. Displacement of estrogen from its receptor by AEDs would contribute to a relative androgen dominance. The aim of this study was (a) to evaluate the affinity of VPA, phenobarbital (PB), PHT, or lamotrigine (LTG) to the estrogen receptor, and (b) to evaluate if any of the AEDs stimulated growth in the estrogen-dependent human breast cancer cell-line MCF-7. **Methods:** Binding affinity of AEDs to αestrogen receptors (ERs) was studied by incubating ERs isolated from MCF-7 cells with radiolabelled 17β-estradiol in combination with unlabelled 17β-estradiol or the different AEDs for 2 h. Cell growth of MCF-7 cells was measured after 6 days in an estrogen-depleted medium with or without AEDs. **Results:** None of the AEDs studied showed affinity to the ER when tested in cytosolic cell extracts. VPA, but none of the other AEDs, induced a slight increase in cell growth ($19 \pm 11\%$, 100 μM). This was abolished by the addition of the estrogen-receptor antagonists ICI 182,780 (1 nM) or 4-hydroxy tamoxifen (100 nM). **Conclusions:** None of the AEDs studied (VPA, PB, PHT, LTG) showed affinity to the estrogen receptor. VPA was able to induce cell growth at low therapeutic concentrations. The estrogen receptor seems to be involved because the effect was abolished by estrogen-receptor antagonists. Because no binding to the estrogen receptor was observed, the induced cell growth could be a result of another signaling pathway cross-talking with the ER pathway.

1.279
THE EFFECT OF TOPIRAMATE ON EXCITATORY SYNAPTIC TRANSMISSION IN MOUSE HIPPOCAMPUS

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Rationale: The present study examines the effect of the antiepileptic drug (AED) topiramate (TPM) on synaptic transmission at a fast excitatory synapse of immature mouse brain. **Methods:** We employed fluorescence imaging techniques to investigate whether TPM modu-

lates presynaptic Ca2+ channel function and neurotransmitter release at the CA3–CA1 synapse in hippocampal slices prepared from 3- to 4-week-old mouse brain. Shaffer axon collateral terminals from CA3 pyramidal cells were loaded with Ca2+-sensitive fluorescence indicators. The presynaptic Ca^{2+} influx ($[Ca_{pre}]$) at those terminals was measured optically, and the amount of evoked neurotransmitter release was assessed by measuring the excitatory field synaptic potential (fEPSP) with extracellular recording electrodes. **Results:** Application of 100 μM TPM resulted in a 13% reduction of the evoked fEPSP. Since the Ca2+ signal was generated by a population of terminals, the effect of TPM on presynaptic Ca2+ channels was quantified by measuring the fluorescent Ca2+ signal as well as the presynaptic fiber volley size. On average, 100 μM TPM reduced the fluorescent Ca2+ signal by 5%. The size of the fiber volley also exhibited a 6% reduction, which would entirely account for the similar amplitude decrease in optical Ca2+ signal. Of the 13% inhibition of synaptic transmission by 100 μM TPM, ~5–6% was thus due to a reduction of the excitability of axon terminals. The remainder was due to an inhibition by TPM of mechanisms downstream of the presynaptic Ca2+ entry, such as a modulation of postsynaptic glutamate receptors. Therefore, our results indicate that TPM has no significant effect on presynaptic Ca2+ channel function evoked by single stimuli at this central synapse. **Conclusions:** Our results indicate that TPM has no significant effect on presynaptic Ca2+ channel function evoked by single stimuli at this central synapse. (Supported by NINDS 29709 and Johnson and Johnson Pharmaceutical Research and Development, LLC.) (Disclosure: Grant: This project is supported by a research grant from Johnson and Johnson Pharmaceutical Research and Development LLC.)

1.280

TOPIRAMATE PROTECTS HIPPOCAMPAL LAYER CA1 IN THE LITHIUM–PILOCARPINE MODEL OF EPILEPSY BUT DOES NOT PREVENT EPILEPTOGENESIS

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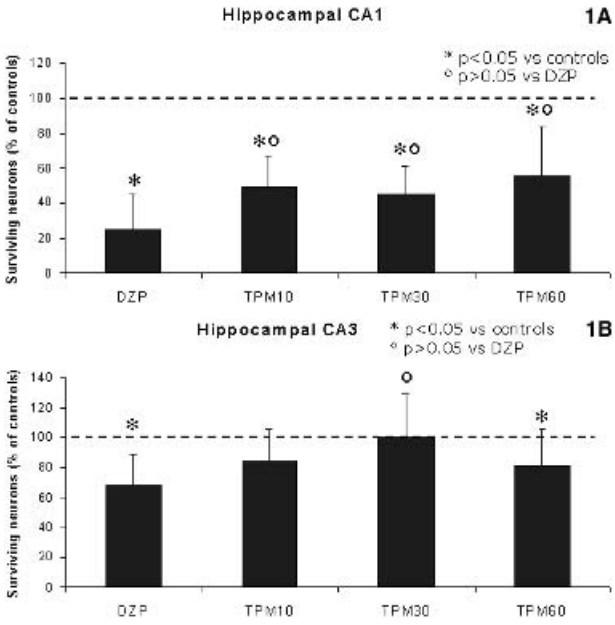
Rationale: The lithium–pilocarpine (Li-Pilo) model reproduces the main characteristics of human temporal lobe epilepsy. After status epilepticus (SE), rats exhibit a "silent" seizure-free phase followed by a chronic phase during which spontaneous recurrent seizures (SRSs) occur. Extensive damage is present in hippocampus, thalamus, amygdala, and ventral cortices. The neuroprotective and antiepileptogenic effects of the anticonvulsant drug, topiramate (TPM), were investigated in this model. **Methods:** Adult Sprague–Dawley male rats were subjected to SE by injection of LiCl (3 mEq/kg) followed 20 h later by Pilo (25 mg/kg). TPM at three doses (10, 30, or 60 mg/kg) was injected at 1 and 10 h of SE. Thereafter injections were repeated twice a day for 6 days. Another group of animals received two injections of diazepam (DZP, 2.5 then 1.25 mg/kg) at 1 and 10 h of SE and injections of vehicle for 6 days. Neuronal damage was assessed 14 days after SE by performing cell counting on thionine-stained sections. Occurrence of SRSs was video-recorded for 10 h per day in a separate group of rats. **Results:** In DZP-treated rats, the number of neurons was dramatically reduced (54–100%) after SE in all subregions of hippocampus and layers II to IV of ventral cortices. At all doses, TPM induced a 24–30% neuroprotection in layer CA1 of hippocampus ($p < 0.05$). In CA3b, the 30-mg/kg dose reduced neuronal death by 100%. In DZP-exposed rats, Li-Pilo SE induced a 44–100% loss in piriform and ventral entorhinal cortex. No protection was afforded by TPM in these cortices. All rats subjected to SE became epileptic. TPM did not change the latency to SRS (16.4 days in DZP-treated vs. 14–16.9 days in TPM-treated rats). The frequency of the SRS recorded over 4 weeks was increased by twofold in TPM30 compared to DZP rats, but the difference was not significant, probably because of the large interindividual variability (Figs. 1A and B). **Conclusions:** TPM displayed neuroprotective properties that were effective only in CA1 and CA3b possibly linked to specific sensitivity of pyramidal cell populations to the drug. The neuroprotection of CA1 by TPM was not efficient in preventing the occurrence of SRS, which confirms that this area is not critical in the process of epileptogenesis. (Supported by a grant from Johnson and Johnson Pharmaceutical Research and Development, LLC.) (Disclosure: Grant: Supported by a grant from Johnson and Johnson Pharmaceutical Research and Development, LLC.)



1.281

LEVETIRACETAM DOES NOT MODULATE SK CHANNEL ACTIVITY IN CA1 HIPPOCAMPUS PYRAMIDAL CELLS IN VITRO

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Rationale: Small-conductance Ca^{2+}-activated K^+ channels (SK channels) underlie the prolonged postspike afterhyperpolarization (AHP) observed in many central neurons and modulate firing frequency and pattern. Neuronal hyperactivity such as occurs during seizures is associated with a increase in intracellular Ca^{2+}. Levetiracetam (LEV; Keppra) has been reported to suppress a non–γ-aminobutyric acid $(GABA)_A$-mediated epileptogenic effect of bicuculline (Margineanu et al. *Br J Pharmacol* 1997;122:1146), and we reported that bicuculline blocks SK channels (Seutin and Johnson. *TIPS* 1999;20: 268). This suggests a putative interaction with the SK channel-blocking properties of this compound. Thus, the possibility that LEV could interfere with Ca^{2+} signaling and facilitate SK channel activation, thereby reducing neuronal excitability, has been explored in this work. **Methods:** Intracellular recordings of CA1 hippocampus pyramidal cells were performed in rat brain slices. These cells possess both I_{AHP} and sI_{AHP} currents underlying a medium and a slow AHP, respectively, and involved in setting frequency of discharge and spike-frequency adaptation. Cell excitability was measured by giving depolarizing pulses of increasing amplitude and counting the number of evoked action potentials (APs). Reference compounds used for validation purposes were apamin (I_{AHP} blocker), isoproterenol (indirect sI_{AHP} blocker), and EBIO (1-ethyl-2-benzimidazolinone), a stabilizer of the Ca^{2+}-calmodulin-SK channel interaction. **Results:** Validation experiments showed that (a) apamin increased the number of APs evoked in CA1 neurons without modifying spike-frequency adaptation; (b) isoproterenol increased the number of APs and suppressed spike frequency adaptation; (c) EBIO induced a marked and reversible decrease

of the excitability of CA1 neurons, an effect which persisted in the presence of either apamin or isoproterenol. These results are in agreement with published data (Pedarzani et al. *J Biol Chem* 2001;276: 9762). LEV (10–100 μ*M*) failed to modify the excitability of CA1 neurons when applied alone or in the presence of apamin or isoproterenol. Furthermore no effect of LEV was observed on AP parameters, input resistance, or resting membrane potential. **Conclusions:** The present results do not support the hypothesis that a modulation of SK channels is involved in the antiseizure activity of LEV. The lack of effect on AP parameters is in agreement with previous data showing that LEV does not block voltage-dependent Na^+ channels, and the lack of action on basal input resistance and membrane potential demonstrate that LEV does not modulate the activity of the leak channels expressed by these neurons. (Supported by UCB S.A. Pharma Sector.) (Disclosure: Grant: UCB S.A.)

1.282

ERYTHROPOIETIN IS ANTICONVULSANT AGAINST KAINIC ACID–INDUCED SEIZURES, BUT NOT PILOCARPINE, PENTYLENETETRAZOL, OR ELECTROSHOCK SEIZURES

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Rationale: Brines et al. (1) demonstrated that pretreatment with erythropoietin (EPO) 24 h (but not 30 min) before kainic acid administration in mice increased the latency to status epilepticus and decreased their mortality rate. In the present study, we investigated this phenomenon in greater detail and compared the results with another model of status-like seizures (induced by pilocarpine) and two models of seizure threshold. **Methods:** Erythropoietin (Eprex) 1,250, 2,500, or 5,000 IU/kg, or saline vehicle was administered s.c. to groups of 10–12 male NMRI (25-g) mice either 1 or 24 h before testing. Kainic acid seizures: Mice were then injected i.p. with 30 mg/kg kainic acid, and the seizure occurrence observed and rated on a modified rating scale (1, mild forelimb activity; 5, continuous status epilepticus). Pilocarpine seizures were induced by 250 mg/kg i.p. injection and mice observed for clonic convulsions for 30 min. Maximal electroshock threshold and i.v. pentylenetetrazole (PTZ) threshold were determined by standard procedures (2). **Results:** After 1-h pretreatment, EPO did not affect the measures in any of the convulsant models used. However, at 24-h pretreatment, EPO significantly reduced the incidence of stage 3 and stage 4 seizures in the kainic acid model (e.g., stage 4, incidence of eight of 12 in Vehicle group c.f. 1/12 EPO 2,500 IU/kg; $p < 0.05$). No other seizure models were significantly affected at this time. **Conclusions:** We conclude that the effect of EPO is selective to kainic acid–mediated seizures and not status models in general, as another model of status-like convulsions (the pilocarpine model) was not affected by EPO. This action is only seen when a long pretreatment time is used, implying that the mechanism of action is likely to involve downstream signaling pathways after receptor activation. These results indicate that EPO is unlikely to be of use as an anticonvulsant therapy. (Supported by H. Lundbeck A/S.) (Disclosure: Salary: H. Lundbeck A/S.)

1.283

EFFECTS OF ZONISAMIDE ON MOLECULAR REGULATION OF GLUTAMATE AND γ-AMINOBUTYRIC ACID TRANSPORTER PROTEINS IN RATS WITH CHRONIC HIPPOCAMPAL SEIZURES

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Rationale: Epileptiform discharges and behavioral seizures may be the consequences of excess excitation associated with the excitatory neurotransmitter glutamate, or from inadequate inhibitory effects of γ-aminobutyric acid (GABA). Synaptic effects of these neurotransmitters are regulated by the action of transporter proteins that remove amino acids from the synaptic cleft. Excitation initiated by the synaptic release of glutamate is attenuated by the action of glial transporters GLAST and GLT-1, and the neuronal transporter EAAC-1. GABA is removed from synaptic regions by the action of the transporter proteins GAT-1 and GAT-3. At the end of this activity, participitants will have better understanding of the molecular effects of zonisamide (ZNS). **Methods:** Albino rats with chronic, spontaneous recurrent seizures induced by the amygdalar injection of FeCl3 were treated for 14 days with ZNS; 40 mg/kg, i.p.). Control animals had saline injection into amygdalar regions. Treatment control for both groups of intracerebrally injected animals was i.p. saline. Western blotting was used to measure glutamate and GABA transporters in hippocampus and frontal cortex. **Results:** Epileptogenesis correlates with collapse of glutamate regulation, with downregulation of glial glutamate transporters associated with upregulation of neuronal EAAC-1. ZNS had unique effects with increase in the quantity of EAAC-1 protein in hippocampus and cortex and downregulation of the GABA transporters GAT-1 and GAT-3. These changes occurred in both experimental and ZNS-treated control animals. **Conclusions:** These data demonstrate that ZNS has molecular effects in that upregulation of EAAC-1 and decreased production of GABA transporters will increase tissue and synaptic concentrations of GABA. In vitro assessment of the mechanisms of action of various AEDs have shown an effect on ionic channels. However, our study suggests that the impact of drugs on molecular function of neural tissue is of critical importance both in understanding all of the mechanisms of action of drugs and in the future design and development of drugs that may have pharmacogenetic effects. [Supported by a Grant-in-Aid for Encouragement of Young Scientists (12770537) from the Ministry of Education, Science, Sport and Culture of Japan (to Y.U.).] (Disclosure: Honoraria: Elan Pharmaceuticals.)

1.284

VARIABILITY OF TOTAL PHENYTOIN SERUM CONCENTRATIONS IN ELDERLY NURSING HOME RESIDENTS

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Rationale: Approximately 6% of all elderly nursing home residents receive phenytoin (PHT). Measurements of PHT concentrations are often performed to guide therapy; however, no large systematic evaluations of the variability of total PHT concentrations have been done. The goal of this project was to evaluate the intraresident variability among multiple measurements of total PHT serum concentrations in nursing home residents. **Methods:** This study consisted of 54 residents who had at least three PHT concentrations measured while on the same dose of PHT for ≥4 weeks and who were not taking any interfering concomitant medications. These were a subset of 387 elderly nursing home residents from 112 nursing homes across the United States who had total PHT concentration measurements between June 1998 and December 2000. All changes in comedications between serum concentration measurements were also examined, and all highly protein bound (≥90% protein bound) were identified. **Results:** Subjects resided in 30 nursing homes in all regions of the United States: North Central States (27.8%), Pacific and Mountain States (53.7%), Southern States (14.8%), and Northeastern States (3.7%). The mean age was 80.1 years (range, 65–100 years), and 59.3% were women. The mean daily dose of total PHT concentrations per resident was 4.9 ± 1.5 mg/kg/day. The person with the smallest variability had a minimal concentration of 10.0 μg/ml and a maximum of 10.4 μg/ml. The person with the largest variability had a minimum concentration of 9.7 μg/ml and a maximum of 28.8 μg/ml. There were no unbound PHT concentration measurements in these residents. There was no trend towards higher or lower PHT concentrations over time. Sixteen subjects had data regarding serum albumin concentrations (mean, 3.5 ± 0.5) with six of the 16

having at least one serum albumin <3.2 g/dl. Serum creatinine concentrations (mean, 0.89 ± 0.26 mg/dl) and blood urea nitrogen (mean, 23.4 ± 7.7 mg/dl) values were available on 40.7% of the residents. **Conclusions:** Total PHT concentrations in an elderly nursing home resident varied twofold to threefold, even though there was no change in dose. The variability observed in this study could not be explained by any one factor. These results have important clinical and public health implications considering the side-effect profile of PHT, and the vulnerability of elderly nursing home residents. The findings of this study suggest that there may be considerable variability in the total PHT concentrations in the elderly nursing home resident and that measurement of a single total PHT concentration should not be used for determining dose changes. (Supported by NIH-NINDS P50-NS16308.)

1.285

PRELIMINARY REPORT ON CARBAMAZEPINE PHARMACOKINETICS IN PATIENTS WITH EPILEPSY GIVEN A PARENTERAL FORMULATION

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Rationale: Carbamazepine (CBZ) is a widely prescribed antiepileptic drug exhibiting complex pharmacokinetics (PK) which complicate its use. Although extensively studied, there are no reports describing absolute bioavailability and elimination half-life in patients under steady-state conditions. One obstacle to conducting such studies is the lack of a parenteral CBZ formulation. We have developed an investigational, intravenous, stable-labeled CBZ formulation to rigorously characterize steady-state CBZ PK in adult and elderly patients. The purpose of the present study was to obtain preliminary CBZ PK information in adults. **Methods:** Adults 18 years or older with epilepsy on maintenance CBZ therapy were eligible to participate in the study. Exclusion criteria included presence of significant cardiac problems or use of potentially interacting comedications. On the day of the study, patients were given a single 100-mg intravenous infusion of a ^{5}H-dibenz[b,f]azepine-5-,^{13}C, ^{15}N-carboxamide (SL-CBZ) formulation as part of their morning dose. The remainder of the dose was given orally. Blood samples were collected just before and ≤96 h after SL-CBZ administration. Both CBZ and SL-CBZ were measured in plasma using LC-MS. Unbound drug was separated from total CBZ by ultrafiltration. Noncompartmental PK analysis was done with WinNonlin 3.0. **Results:** Seven patients (three women and four men) ranging in age from 34 to 53 years have completed the study. CBZ daily doses ranged from 400 to 2,400 mg. Daily dose and PK information are included in Table 1. **Conclusions:** CBZ induces its own metabolism; as a result, CBZ PK determined following a single dose cannot be extraprolated to steady-state conditions. This is the first study using a parenteral formulation to rigorously characterize CBZ PK in patients on maintenance therapy. Our preliminary results indicate that there is wide interpatient variability in CBZ bioavailability and elimination half-life, whereas distribution volume is relatively constant. Use of a parenteral SL-CBZ formulation permits comprehensive characterization of the effects of age, gender, comedications, and genotype on CBZ PK in patients without interrupting therapy. (Supported by NIH-NINDS P50-NS16308 and M01-RR00400.) (Disclosure: Consulting: Novartis; Honoraria: Novartis.)

1.286

AN EVALUATION OF DIAZEPAM ADMINISTERED INTRAMUSCULARLY USING AUTOINJECTOR TECHNOLOGY AS COMPARED TO DIAZEPAM GIVEN RECTALLY UNDER "IDEAL" AND "REAL-LIFE" CONDITIONS

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Rationale: Diazepam (DZP) is available in a rectal formulation (Diastat) for use by caregivers to stop emergency seizure conditions. However, many patients and caregivers are opposed to rectal administration. Intramuscular (i.m.) administration offers an acceptable alternative. However, older data suggest that the absorption of DZP is better rectally. The autoinjector system (Diaject) can inject DZP deep into muscle tissue with greater dispersion than conventional i.m. devices. The objectives of this study were to compare the pharmacokinetics, safety, and preference of DZP administered i.m. by the autoinjector system to DZP administered rectally under two different conditions. **Methods:** Twenty-four subjects entered into an open-label, three-way, randomized, crossover study in which they received 10 mg of DZP rectally under "ideal" conditions in which the bowel had been cleansed (I), rectally under "real-life" conditions (RL), and i.m. using the autoinjector (IM) The concentrations of 16 blood samples collected over 24 h and assayed for DZP using a LCMS-MS procedure were used to determine area under the curve (AUC), T_{max}, and C_{max} of DZP for each method. The data were analyzed by analysis of variance and Duncan's test. **Results:** The absorption from the IM administration was very consistent, while there was significant variability in I and RL. The coefficient of variation at each time point, especially in the early sampling times, is much higher for I and RL than IM. Duncan's test showed that IM administration results in greater ($p < 0.05$) absorption (AUC_{30min} = 4,695; CV, 31.1%, $AUC_{24\ h}$ = 165,085; CV, 22.4%) than I ($AUC_{30\ min}$ = 3,806.7; CV, 51.1%; AUC_{24h} = 142,077; CV, 36.16%) or RL (AUC_{30min} = 3,944.3; CV, 43.9%; AUC_{24h} = 122,692; CV, 41.9%). C_{max} was 233.9 (I), 209.1 (RL), and 303.9 (IM). There was no significant sequence–treatment interaction. Eight subjects had 10 episodes of oozing after rectal administration. The volume was small and did not correlate with lower AUC or C_{max}. The subjects tolerated all three doses well. Sixteen of 24 in I, 21 of 24 in RL, and 23 of 24 in IM had mild CNS side effects. Subjects reported discomfort with all routes of administration; however, 17 of 24 (71%) of the subjects preferred the IM route. The nurse administering the DZP rated the difficulty of administration as 0.58, 0.50, and 0.04 for I, RL, and IM. She preferred the IM route of administration. **Conclusions:** DZP is rapidly and reliably absorbed when administered IM by the autoinjector system (Diaject). There are higher peaks and greater absorption with less variability with IM than with either I or RL. Both rectal routes had highly variable absorption. Cleansing the bowel did not result in better or less variable absorption. The higher number of CNS side effects seen with IM may be reflective of faster and greater absorption. The autoinjector system has the potential to be a very clinically useful method for administering DZP for the treatment of emergency seizure conditions. (Supported by Meridian Medical Technologies, Inc., Columbia, MD.) (Disclosure: Salary: Warnarka & Mesa; Grant: Garnett; Stock: Warnarka & Mesa; Other: Warnarka & Mesa, bonus.)

TABLE 1. *Carbamazepine pharmacokinetics after i.v. administration*

	Daily dose (mg/day)	C_{pss} (mg/L)	% free	CL (L/h/kg)	Half-life (h)	V_d (L/kg)	% absorbed
Oral CBZ	1,000 ± 650	7.0 ± 2.5	30 ± 3				76 ± 24
SL-CBZ	100			0.06 ± 0.02	20.6 ± 11.4	1.1 ± 0.2	

1.287

INDIVIDUAL BIOEQUIVALENCE ANALYSES OF BERTEK'S PHENYTEK (1 × 300 MG EXTENDED PHENYTOIN SODIUM) VERSUS PARKE-DAVIS' DILANTIN KAPSEALS (3 × 100 MG)

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Rationale: The objective of the fasting study was to investigate the individual bioequivalence of Bertek's 300-mg extended phenytoin sodium (PHT) capsule (Phenytek) to three Parke-Davis' 100-mg Dilantin Kapseals after administration of a single, 300-mg oral dose in healthy volunteers. Extended PHT 300 mg is the most commonly prescribed daily dose for seizure patients. Although PHT has been available since 1938, no single, extended PHT 300-mg dosage unit is available. The current study demonstrated individual bioequivalence between a new 300-mg extended PHT capsule, Phenytek (Bertek) to 3 × 100 mg Dilantin Kapseals. **Methods:** The study utilized single-dose, four-period, two-treatment, replicate, and crossover design. After a supervised overnight fast of ≥10 h, each subject received either a single, oral 300-mg (1 × 300 mg) dose of Bertek's extended PHT capsules (Phenytek) or 3 × 100 mg Parke-Davis' Dilantin Kapseals with 240 ml of water in this study. A 3-week washout separated each period. Serial blood samples, 10 ml (1 × 10 ml), were collected at predose and at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12, 16, 24, 36, 48, 72, and 96 h postdose. Plasma samples were stored in suitably labeled tubes at –70°C ± 15°C until analysis. The assay was linear from 0.050 to 10.00 μg/ml. The method developed for the analysis of PHT in human plasma (heparin) was performed using high-performance liquid chromatography with ultraviolet detection, which had a limit of quantification of 0.050 μg/ml. The between-day precision of the assay was ≤5.8%. The between-day accuracy varied within –1.4% and 1.4% of the nominal concentration. Single-dose pharmacokinetic parameters for PHT were calculated using noncompartmental techniques. The individual bioequivalence criterion described in the FDA Guidance, entitled "Statistical approaches to establish bioequivalence," was used to calculate a 95% upper confidence bound for a linearized form of individual bioequivalence. Both reference-scaled method and constant-scaled method were used. **Results:** Twenty-four subjects completed the study . The corresponding ratio of means (Phenytek/Dilantin Kapseals) for AUCL, AUCI, and CPEAK were 105.27, 104.64, and 106.90%. For all pharmacokinetic metrics in this study, the within-subject variability was low (CV <12%). For all three metrics (AUCl, AUCI ans CPEAK), the within-subject variabilities of the test and reference products were very similar. The Phenytek variability was smaller than that for Dilantin Kapseals. The Subject × Formulation interaction was very small for all metrics, except possibly for CPEAK. **Conclusions:** Since the within-subject standard deviations are <0.2, the applicable criterion is the constant scaled. All metrics pass individual bioequivalence criterion. Phenytek (300 mg) is individually bioequivalent to Dilantin Kapseals (3 × 100 mg). (Supported by Mylan Pharmaceuticals Inc. and Bertek Pharmaceuticals Inc.) (Disclosure: Salary: Mylan; Stock: Mylan.)

1.288

LEVETIRACETAM ACCUMULATION IN HUMAN BREAST MILK

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Rationale: Levetiracetam (LEV) is a new antiepileptic drug (AED) with favorable pharmacokinetics. However, it was unknown whether LEV is excreted in human milk. We ware able to determine breast milk concentrations together with serum concentrations in a mother with epilepsy treated with LEV as well as in her neonate. **Methods:** Single-case observation LEV breast milk and serum concentrations were measured by high-pressure liquid chromatography. **Results:** A pregnant woman with epilepsy had been treated with phenytoin (PHT, 3 × 100 mg) as well as valproic acid (VPA, 4 × 500 mg). After preterm labor, her baby was delivered at 34 weeks by cesarian section with normal adaptation. The boy went through a transient respiratory distress syndrome in the first 3 days but was otherwise normal. Alimentation with mother's milk was started. Seven days after the delivery, the mother had a generalized tonic–clonic seizure, and LEV was added to her other AEDs. Afterwards the boy became increasingly hypotonic and drank worse. The breast-milk concentrations of LEV determined in parallel to the serum concentration 3 h after drug intake were 99 μ*M* and 3 times higher than in maternal serum (32 μ*M*; milk/plasma ratio, 3.09). Ninety-six hours after the mother had stopped breastfeeding, LEV serum level in her baby was 6 μ*M* and the boy was discharged healthy 10 days later. **Conclusions:** This clinical observation, which is in line with experimental data in lactating rats (with a milk/plasma ratio of 2.6, 24 h postdose), strongly encourages either close monitoring of babies breastfed by LEV-treated mothers or avoidance of LEV during breastfeeding. (Disclosure: Salary: UCB Advisory board membership; Honoraria: UCB Honoraria for speaking.)

1.289

THE CONTRIBUTION OF CYP2C9 AND CYP2C19 POLYMORPHISMS TO PHENYTOIN DISPOSITION IN PERSONS WITH EPILEPSY

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Rationale: Interpatient differences in absorption, protein binding, and the activity of metabolizing CYP450 enzymes contribute to the large variability seen in phenytoin (PHT) concentration–dose relations, but their respective effects are not well characterized. Our goal was to determine the association between the presence of CYP2C9 and 2C19 variants and PHT pharmacokinetics (PK) using a parenteral, stable labeled PHT formulation. **Methods:** Patients on maintenance PHT therapy, but no interacting drugs, were given an intravenous injection of 100 mg [2-13C,1,3,-15N2] 5,5- diphenylhydantoin (SL-PHT) with the remainder of their daily dose given orally. Blood samples were collected just before and ≤192 h after the SL-PHT dose. Both unlabeled and SL-PHT were measured by gas chromatography–mass spectroscopy (GC-MS). Unbound drug was separated from total PHT by ultrafiltration. Noncompartmental PK analysis was performed with WinNonlin 3.0. Genotyping of the 2C9*2/*3 and 2C19*2/*3 variants was done using published PCR-RFLP assays, with some modifications. Statistical comparisons among groups were done by analysis of variance. **Results:** Dose and genotype data are available for 28 adult white patients, and PK data are available for 16 of these patients. The allelic frequencies are 0.125 for 2C9*2, 0.054 for 2C9*3, 0.125 for 2C19*2, and 0 for 2C19*3. Patients were assigned to one of three groups based on genotype (Table 1). Preliminary comparisons of mg/kg doses and unbound PHT clearance (CLu) normalized to weight, showed a significant difference between group 1 and group 2 ($p = 0.0112$ and 0.03, respectively) and no difference between group 1 and group 3 ($p = 0.3$ and 0.4, respectively). Group 1: none of the screened polymorphisms present. Group 2: heterozygous for either 2C9*2 or 2C9*3 polymorphisms, no 2C19 polymorphisms. Group 3: heterozygous for 2C19*2, no 2C9 polymorphisms. **Conclusions:** The allelic frequencies of the variants observed in our patients agree with reported values for whites. Patients with the 2C9 polymorphisms, but not those with the 2C19 polymorphism, appear to require lower mg/kg doses than patients without any of the screened polymorphisms. When unbound PHT plasma concentrations are comparable, patients with the 2C9 polymorphisms have lower CLu/wt, while patients with the 2C19*2 polymorphism do not have a lower CLu/wt, than group 1. These preliminary results offer evidence that genotyping patients who are being considered for PHT therapy may reduce the risk of toxicity. (Supported by NIH-NINDS P50-NS16308 and M01-RR00400.)

TABLE 1. *Patient groups*

Patient group	Dose/weight mg/kg/day, average ± SD (range)	Unbound PHT plasma concentration (μg/ml), average ± SD (range)	CLu (L/kg/h), average ± SD (range)
Group 1	5.7 ± 1.3 (3.4–8.6, n = 13)	1.69 ± 0.817 (0.446–2.87, n = 7)	0.101 ± 0.03 (0.042–0.135, n = 7)
Group 2	3.7 ± 0.85 (3.1–5.2, n = 8)	2.377 ± 0.237 (2.19–2.643, n = 3)	0.037 ± 0.01 (0.029–0.047, n = 3)
Group 3	4.88 ± 0.6 (3.7–5.5, n = 6)	2.268 ± 1.452 (0.579–2.652, n = 6)	0.082 ± 0.047 (0.039–0.17, n = 6)

1.290

PHARMACOKINETIC COMPARISON OF OXCARBAZEPINE ORAL SUSPENSION FORMULATION VERSUS FILM-COATED TABLETS

Paul M. Levisohn, Gerard Flesch, and Joseph D'Souza (Children's Epilepsy Program, The Children's Hospital, Denver, CO; Novartis Pharmaceuticals, Basel, Switzerland; Novartis Pharmaceuticals, East Hanover, NJ)

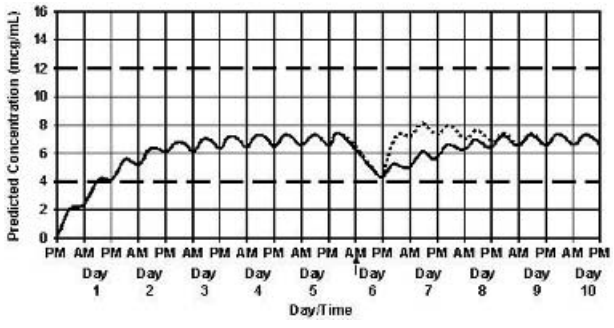
Rationale: Oxcarbazepine (OCBZ) is an antiepileptic drug (AED) used in many countries worldwide. Three different film-coated tablet strengths are available (150, 300, and 600 mg). However, the administration of tablets to children and the elderly is sometimes troublesome. Therefore, a new oral OCBZ oral suspension has been developed that does not show discoloration or increased viscosity over time. A single-center, open-label trial was performed to support switching patients from the film-coated tablet to the oral suspension and vice versa. **Methods:** Healthy male volunteers, aged 18–50 years, were randomized to one of two OCBZ treatment groups (oral suspension 6% or 600-mg film-coated tablets) in a crossover design. During each treatment period, a single OCBZ 600-mg dose was administered in the morning on Day 1 to determine single-dose pharmacokinetics (PK) over the next 72 h. On Day 4, a second dose was administered in the morning, and thereafter every 12 h until the final dose on the morning of Day 8 to determine steady-state PK over the next 12 h. Both single-dose and steady-state PK were done under fasted conditions. MHD concentrations were determined by HPLC. Pharmacokinetic variables determined by model-independent analysis included AUC [h(μM)], C_{max} (μM, and t_{max} (h). Log-transformed AUC values and C_{max} of the different formulations were compared by means of the 90% confidence interval (CI). **Results:** Twenty subjects were enrolled: 17 subjects received film-coated tablets, and 15 received the oral suspension. At steady state, the oral suspension was equivalent to the film-coated tablet with regard to AUC and C_{max}. The AUC and C_{max} ratio of means were 1.02 (CI, 0.99–1.06) and 1.01 (CI, 0.95–1.06), respectively. At single dose, the oral suspension was equivalent to the film-coated tablets with respect to AUC (ratio, 0.93; CI, 0.90–0.97). In terms of C_{max} at single dose, the ratio of means for the oral suspension and the film-coated tablets was 0.77 (CI, 0.72–0.82). Single-dose pharmacokinetic data, however, are not clinically relevant in epilepsy patients who receive long-term treatment with AEDs. Therefore, multiple-dose pharmacokinetics were performed. The most common adverse events were dizziness, headache, and nausea. There were no clinically relevant changes in vital signs or ECG parameters. **Conclusions:** This study shows that the new oral suspension and the film-coated tablets of OCBZ are bioequivalent at steady state. Furthermore, this study confirms that patients can be switched from the film-coated tablets to the new oral suspension formulation of OCBZ. (Supported by Novartis Pharmaceuticals.) (Disclosure: Salary: Drs D'Souza and Flesch, Novartis; Consulting: Dr. Levisohn, Novartis; Honoraria: Levisohn, Novartis Pharmaceuticals.)

1.291

SIMULATION OF THE EFFECT OF PATIENT NONADHERENCE ON PLASMA CONCENTRATIONS OF CARBAMAZEPINE FROM CARBATROL Q12 HOURS

Angus M. McLean and William R. Garnett (BioPharm Global Inc, Gaithersburg, MD; Department of Pharmacy and Pharmaceutics, Virginia Commonwealth University, Medical College of Virginia, Richmond, VA)

Rationale: Carbamazepine extended-release capsules (CBZ-ERC) twice daily have been demonstrated to be effective in the treatment of seizure disorders. Although twice-daily dosing regimens are consistently associated with improved levels of patient adherence, doses will still be missed, and patients will ask clinicians if or when to take the missed dose. The objective of the current computer simulations was to assist in the development of recommendations by investigating both the effect of missing doses on plasma CBZ levels and the optimal dosing strategy to return plasma concentrations to normal steady-state levels. **Methods:** Mean plasma concentrations measured in a previous study after treatment with one dose of 400 mg Carbatrol (CBZ-ERC) were fitted to a one-compartment mathematical model. This model was then used in the simulation of plasma concentrations after 400 mg every 12 h, allowing for the enzyme induction that occurs after multiple doses of CBZ. Simulations of several possible situations were carried out that included missing either one or two doses and then alternatively: skipping the dose(s) completely, taking the missed dose 3 h later, taking the missed dose 9 h later, or taking two doses at the time of the next scheduled dose. **Results:** All of the simulations indicate that taking the missed dose of CBZ-ERC as soon as it is remembered, up to two missed doses 3 h before the next scheduled dose, will not lead to potentially harmful spikes in plasma levels of CBZ. The simulations also indicated that the trough after missing one dose of CBZ-ERC would remain ~4 μg/ml. A simulation of the plasma concentration after missing one dose and contrasted to taking two at the time of the next scheduled dose is shown. Solid line indicates simulated steady-state plasma concentrations of CBZ. Dotted line indicates simulated plasma concentrations of CBZ on taking the missed dose combined with the next scheduled dose and continuing with dosing regimen. Arrow indicates time of missed dose. Dashed lines indicate the typical target range for CBZ concentration. **Conclusions:** With conventional, immediate-release tablets of CBZ, it is recommended that a missed dose not be taken too close in time to the next scheduled dose because of concerns about spikes in plasma drug levels and resultant side effects. It is essential to stress the importance of medication adherence when counseling patients with epilepsy, regardless of which medication or formulation they have been prescribed. The current computer simulations of missing a dose or doses of CBZ-ERC suggest that when a dose is occasionally missed, taking it as soon as it is remembered, even when this implies taking two doses at one time, would not only be safe but would be the best strategy to return plasma concentrations of CBZ to steady-state levels. This may be due to the unique extension of release provided by the Microtol release system (Fig. 1.) (Supported by Shire US Inc.) (Disclosure: Salary: A. McLean, Shire; Grant: W. Garnett, Shire; Equity: A. McLean, Shire; Consulting: A. McLean, Shire; Stock: A. McLean, Shire; Honoraria: W. Garnett, Shire.)



1.292

LEVETIRACETAM BLOOD LEVELS HAVE UTILITY IN CLINICAL MANAGEMENT OF EPILEPSY

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Rationale: Current clinical concepts of treatment with new-generation antiepileptic drugs (AEDs) forego monitoring for serum concentrations. This is based on the wide therapeutic windows suggested for these drugs. It is also implied that these AEDs have more important pharmacodynamic rather than pharmacokinetic modes in deriving their effect. Clinicians are encouraged to dose drug to effect. AED levels of new-generation AEDs have utility in solving clinical problems of noncompliance and drug toxicity (especially in polypharmacy). Clinical experience with levetiracetam (LEV) suggested that there was clinical usefulness in monitoring antiepiletic drug levels (AEDLs) as a guide for dosing, and that serum drug levels may correlate with efficacy as measured by seizure reduction. At the end of this session the participant should be able to discuss the potential usefulness of serum LEV concentrations and control of seizures. **Methods:** The clinical records of all patients who were introduced to LEV treatment were reviewed retrospectively. In a referral private practice, 87 patients had been treated with LEV at date of abstraction. Data were recorded for standard demographics, seizure types, medication use, adverse drug events, seizure frequency per month, and all LEV serum concentrations. There were 46 patients who had one or more determinations for LEV concentrations. All AEDLs were randomly drawn samples. This patient sample was reduced to include only those patients who had been followed for >6 months of LEV treatment and who had an AEDL in the second 3-month interval. It was assumed that this interval represented a stable period of treatment after the addition of LEV and that other treatments were not being modified. Noncompliant and pseudoseizure patients were excluded. The data were analyzed by the Pearson correlation method to correlate percentage seizure reduction and LEV serum concentration, dose and seizure reduction, and dose and AEDL. **Results:** Twenty-nine patients fulfilled our criteria; 79% patients had partial seizures and 21% had generalized seizures. Children represented <10% of patients; 27 patients were on multiple medications with an average of ~1.5 drugs per patient. Seizure frequencies ranged from one to 60 per month in the 3-month pretreatment baseline. LEV doses ranged from 1,000 mg/day to 4,000 mg/day. Random LEV serum concentrations ranged from 6 μg/ml to 65 μg/ml. The analysis revealed a statistically significant correlation of LEV serum concentration with percentage reduction of seizures ($p = 0.0012$). The r value was 0.56, which reflects variability in LEV concentrations. The results indicated the there was no correlation for dose and percentage seizure reduction ($p = 0.8066$). Additionally, there was no statistical significance in correlation for dose and LEV AEDL ($p = 0.0925$). **Conclusions:** There appears to a greater reduction in seizures for those patients with higher LEV concentrations. In this study we found a ≥75% reduction in seizures if the AEDL was ≥35 μg/ml. Dosing LEV with guidance by AEDLs may be more efficient and effective than simply "dosing to effect." These results warrant prospective investigations to include trough and peak AEDLs, monotherapy, inducing and noninducing comedications, and age-controlled populations. (Supported by Epilepsy Services and Research, Inc. and UCB Pharma, Inc.) (Disclosure: Grant: UCB Pharma, Inc. Epilepsy Services and Research, Inc.; Consulting: UCB Pharma, Inc.; Materials: Epilepsy Services and Research, Inc.; Royalties: Epilepsy Services and Research, Inc.; Honoraria: UCB Pharma, Inc.)

1.293

OPTIMIZING LAMOTRIGINE BLOOD LEVELS DURING CONVERSION FROM VALPROATE/LAMOTRIGINE COMBINATION TO LAMOTRIGINE MONOTHERAPY

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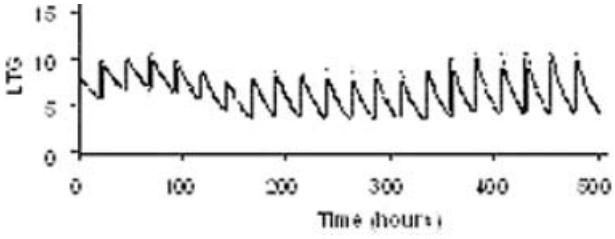
Rationale: To determine a safe method of withdrawing valproic acid (VPA) from a VPA/lamotrigine (LYG) combination as evaluated by fluctuation in trough levels of LTG. VPA inhibits the clearance of LTG. The maximal inhibition of LTG clearance that can be achieved is 66%, and is achieved with VPA doses of 500 mg/day. The VPA concentration resulting in half of this maximum clearance is 2.05 μg/ml (Gidal et al., *Epilepsia* 2001;42:89). Withdrawal of VPA from a LTG/VPA regimen is complicated by this interaction. **Methods:** NONMEM was used to construct a mechanistic pharmacokinetic model of the interaction of VPA and LTG (Lamictal). Simulations with this model were used to examine the risk of subtherapeutic or toxic concentrations for four candidate VPA withdrawal regimens. All regimens started with VPA, 500 mg/day, and LTG, 200 mg/day, each divided twice daily. Metrics used for comparison are the median trough value for LTG and the 90% confidence interval for the ratio of the pretransition trough to the lowest and highest trough values achieved during the transition (ratio range). Criteria for optimal regimen selection were high minimal trough value, small range, and ease of utilization. **Results:** The trough ranges achieved with four candidate regimens are shown, and median hourly levels are graphed for the "optimal" regimen (Fig. 1). Median LTG levels during withdrawal according to the regimen in line one of Table 1. **Conclusions:** Transition from a combined regimen of VPA and LTG to LTG alone can be achieved with low risk of subtherapeutic or toxic concentrations. The conversion regimen which combines smoothest control of LTG blood levels and ease of use is, Step 1, adjust LTG to 200 mg/d and gradually decrease VPA to 500 mg/d, maintain for 1 week. Step 2, Decrease VPA to 250 mg/d and increase LTG to 300 mg/d, for 1 week. Step 3, Discontinue VPA, and make weekly increases in LTG until achieving the target dose of 500 mg/d or as clinically indicated. (Supported by GlaxoSmithKline Research and Development.) (Disclosure: Salary: Mark Sale and David Blum are employees of GlaxoSmithKline; Grant: Barry Gidal received grant support from GlaxoSmithKline to assist in the conduct of this study.)

TABLE 1.

VPA (500 mg/day)	LTG (200 mg/day)	Ratio range (905 CI)
1. Reduce to 250 mg/day for 1 wk	Weekly increases of 100 mg/day to maintenance at 500 mg/day	0.56–1.51 (see Fig. 1)
2. Abrupt withdrawal	Weekly increases of 100 mg/day to maintenance at 500 mg/day	0.44–1.22
3. Reduce to 250 mg/day for 1 wk	Increase to 300 mg/day at day 4, then weekly increases of 100 mg/day to maintenance at 500 mg/day	0.56–1.49
4. Abrupt withdrawal	No change (remain at 200 mg/day)	0.24–1.00



1.294

CONVERSION FROM VALPROATE MONOTHERAPY TO LAMOTRIGINE MONOTHERAPY: A CLINICAL AND PHARMACOKINETIC STUDY

Adriana Serje, Harold H. Morris, Collin Covinga, and Kim Merner (Neurology, The Cleveland Clinic Foundation, Cleveland, OH)

Rationale: Valproate (VPA) has a significant inhibitory effect on lamotrigine (LTG) clearance. Clinically, this becomes problematic

when patients are being converted from VPA to LTG as the concentration of LTG decreases with the discontinuation of VPA. During this time, patients are at risk for increased seizures and side effects.This report reflects our experience using a standard protocol. At the end of this presentation, the participants should be able to discuss a method for switching patients from VPA to LTG. **Methods:** A retrospective chart review approved by our Institutional Review Board was conducted of patients who were switched between 1997 and 2001 from VPA monotherapy to LTG monotherapy using a predefined method. LTG was started at 25 mg every other day, with gradual increases to a dose of 200 mg/day (or LTG >5 mg/L), and then VPA was gradually tapered to 250 mg/day and removed 1 week later. The day after the last VPA dose, the dose of LTG was doubled. Medical records were evaluated for changes in seizure frequency and the presence of side effects. LTG plasma concentrations were collected before VPA removal and at steady state on LTG monotherapy. **Results:** Eleven adult patients with generalized epilepsy were included in this study. All were receiving VPA monotherapy before conversion. The median dose of VPA before conversion was 1,000 mg/day (750–4,500 mg/day). Immediately before conversion, the median LTG dose was 200 mg/day (150–600 mg/day). The median LTG dose after transition was 400 mg/day (200–600 mg/day). Median LTG concentration before and after switch to LTG monotherapy were 7.9 mg/L (3–12.4 mg/L) and 8.4 mg/L (3.9–25 mg/L), respectively. No patient had seizures during or immediately after the transition period. Two patients experienced nausea, vomiting, and dizziness during the conversion. **Conclusions:** Overall, the conversion to LTG monotherapy was well tolerated. LTG plasma concentrations were comparable before and after transition to monotherapy, and none of the patients experienced seizures during the conversion period. This pilot study suggests our titration method may be used safely in clinical practice.

1.295
PRELIMINARY POPULATION PHARMACOKINETICS OF LAMOTRIGINE IN INFANTS AGED 1–24 MONTHS

Jagdev Sidhu, Jonathan Bullman, David Onks, Paul Caldwell, and John Messenheimer (Clinical Pharmacokinetics, GlaxoSmithKline, Harlow, Essex, United Kingdom; Epilepsy Clinical Development, Research Triangle Park, NC)

Rationale: To evaluate the population pharmacokinetics model (PK) for lamotrigine (LTG) in an ongoing study of infants with partial seizures, aged 1–24 months. A population pharmacokinetic model developed with adult data has previously been validated in children (median age, 7.6 years). This model has presently been used to evaluate preliminary data from a clinical study in infants (1–24 months). **Methods:** The population consisted of 65 infants (weight range, 3.4–16 kg; 30 boys) with partial seizures uncontrolled by one or more antiepileptic drugs (AEDs). Serum LTG (Lamictal) concentrations (N = 187) were determined at week 2 (1 sample) and approximately at the end of week 5 (typically three to seven samples; n = 25 infants). Serum LTG PK data were analysed using NONMEM. In addition to demographic factors, the influence of concomitant AEDs on LTG PK was evaluated. A one-compartment model with first-order absorption and elimination [parameterised in terms of apparent clearance (CL/F), distribution volume (V/F), and absorption rate constant (Ka)] was used to describe LTG PK. **Results:** Parameter values for the final population PK model are given in Table 1. For an infant with the population median weight of 10.9 kg not receiving an enzyme-inducing AED (EIAED), this model estimates a LTG CL/F and V/F of 0.762 L/h and 84 L, respectively. Coadministration of an EIAED is predicted to cause a 1.77-fold increase in LTG CL/F. The median predicted LTG half-life (T1/2) across all infants was 80 and 48 h for those without and with concomitant EIAED intake, respectively. Importantly, there was still a large degree of unexplained variability in CL/F (53%). **Conclusions:** Compared with older children and adults, substantially longer LTG T1/2s were encountered in this group of infants, which could primarily be attributed to very large volumes of distribution. The large unexplained variability in LTG CL/F indicated that factors other than weight or EIAED intake contribute to metabolic variations in this group. (Supported by GlaxoSmithKline.) (Disclosure: Salary: Glaxo SmithKline, employee.)

1.296
LAMOTRIGINE SERUM CONCENTRATION DURING TAPER OF PHENYTOIN: TIME COURSE OF DEINDUCTION

Mary Ann Werz and Barbara E. Swartz (Neurology, University Hospitals of Cleveland; Case Western Reserve University, Cleveland, OH)

Rationale: Phenytoin (PHT) is a powerful inducer of lamotrigine (LTG) metabolism. Therefore, in refractory epilepsy patients, it may be difficult to achieve adequate LTG serum concentrations during adjunctive treatment with PHT. Furthermore, a transient exacerbation of seizures may occur during conversion to monotherapy dependent on the time course of deinduction of LTG glucuronidation enzymes. Analysis of data from the published active control, conversion to monotherapy trial suggested that LTG serum concentrations doubled after discontinuation of PHT. Furthermore, LTG serum concentrations did not increase until PHT was completely stopped. Interpretation of this study is potentially limited by the rapid withdrawal of PHT in weekly decrements of 20%, as a week may be insufficient for deinduction of hepatic enzymes to reach "steady state." Our objective is to reinvestigate the pharmacokinetics of LTG deinduction using 3-week intervals between PHT decrements. **Methods:** Patients treated with PHT with either incomplete control or unacceptable side effects were recruited for conversion to LTG monotherapy. Four patients have thus far completed, with three patients currently enrolled and a total of 10 patients anticipated. LTG was titrated to 400- to 500-mg total daily dose over 3 months. PHT was then withdrawn every 3 weeks in decrements of one-third the initial dose. Serum concentrations were measured weekly for 10 weeks. Blood draws occurred on the same day of the week and at the same time of day. PHT dose reductions were scheduled to occur immediately after a blood draw. Patients did not alter other medications during the protocol: two patients were taking no other medications, one patient was taking nifedipine, and one, conjugated estrogen, aspirin, paroxetine, 1 mg lorazepam per day, vitamin D, and calcitonin nasal spray. PHT was measured at our institution using the CEDIA Phenytoin II (ROCHE) immunoassay. LTG was measured at ARUP Laboratories by HPLC. **Results:** Four of four patients have thus far been successfully converted to monotherapy. Baseline serum concentrations of LTG

TABLE 1.

Parameter	Population estimate	CV (%)[a]
Apparent clearance (CL/F; L/h) = (01+(WT−10.9) *02)*(1+03*EIAED) (EIAED: 0-no, 1 = yes)	0.1 = 0.762 02 = 0].0875 03 = 0.77	01 = 14 02 = 15 03 = 37
Apparent distr. vol. (V/F; L) = 04*WT	04 = 7.73	04 = 21
Absorption rate constant (h^{-1})	1.12	17
IIV – CL/F (%)	53	—
IIV – V/F (%)	Not estimated	—
IIV – Ka (%)	62	—
RRV (%) – proportional	23	—
RRV (μg/mL) – additive	0.039	—

[a] Coefficient of variation (or precision) of parameter estimate; IIV, interindividual variability; RRV, random residual variability.

ranged from 3.6 to 4.3 μg/ml, attained on 400-mg total daily dose, with PHT serum concentrations ranging from 8.7 to 27.0 μg/ml. Decrease in PHT doses ≤67% did not affect LTG serum concentrations. At that time, PHT serum concentrations averaged 2.4 μg/ml (range, 2.2–2.7 μg/ml). One, two, and three weeks after PHT cessation, LTG serum concentration had increased 57, 68, and 80%, respectively. **Conclusions:** LTG serum concentrations increase 70–80% after withdrawal of PHT. The increase does not occur until PHT dosing is completely stopped. The increase then occurs quite quickly, with the majority occurring within the first week of complete PHT withdrawal. Complete deinduction of glucuronidation appears to require 2–3 weeks although our current small sample size limits complete accuracy of the time course. Highly refractory epilepsy patients may require special efforts at seizure prophylaxis during taper from PHT and for several weeks thereafter. (Supported by Investigator Initiated award from Glaxo-SmithKline.) (Disclosure: Grant: Glaxo-Smith-Kline; Consulting: Glaxo-Smith-Kline; Honoraria: Glaxo-Smith-Kline.)

1.297
THE TIME COURSE OF DEINDUCTION OF LAMOTRIGINE WITH CARBAMAZEPINE AND PHENYTOIN

R. Eugene Ramsay, Barry E. Gidal, and Flavia M. Pryor (International Center for Epilepsy, Neurology Dept, University of Miami, Miami, FL; Neurology, Miami VA Medical Center, Miami, FL; Departments of Pharmacy and Neurology, University of Wisconson, Madison, WI)

Rationale: Enzyme induction is a process by which either the quantity or activity of a cytochrome (CYP) enzyme is increased above its baseline. CYP induction results from an increase in gene transcription triggered by selected substances and drugs. This results in increased drug clearance and a lower drug plasma level. Once an enzyme inducer is started, it generally takes 2–4 weeks to reach the higher drug clearance, although the time course of induction has not been well characterized. When an inducing drug is stopped, the effect is lost, and drug clearance returns to baseline. This process is known as deinduction, and the time course has been assumed to be the same as induction. However, no studies have looked at the time course and the effect of dose of the inducer on deinduction. The pupose of this project was to determine the time course and the dose at which induction effect is lost. **Methods:** The antiepileptic drugs (AEDs) that are potent CYP 3A4/5 and uridine-diphosphate glucuronyl transferase (UGT) inducers include carbamazepine (CBZ) and phenytoin (PHT). Lamotrigine (LTG) is a substrate for primarily for UGT. Patients selected for the study were on stable doses of one of the enzyme-inducing AEDs (CBZ or PHT) and were also taking LTG. Patients were included who were to have the inducer discontinued and maintained on LTG monotherapy. Two trough plasma levels for the inducer and LTG were drawn before any changes in dose were made. Unit dose reduction was done weekly (PHT, 100 mg; CBZ, 200 mg) and plasma samples were obtained weekly during the taper. Plasma samples were 3 times a week for 2 weeks after the inducer was stopped and then weekly for 3 more weeks. Plasma concentrations were assayed using HPLC. **Results:** Ten patients taking LTG were studied. Plasma levels of LTG did not decline as CBZ or PHT doses were initially reduced. The plasma concentrations increased by 20–30% when CBZ or PHT was reduced to the last tablet/capsule. Further deinduction did not occur while low levels of inducer were present. LTG levels did not increase with plasma levels of PHT as low as 0.4 μg/ml and CBZ as low as 0.3 μg/ml. LTG levels increased progressively over a 2-week period after the plasma concentration of the inducing agent reached zero (0). Plasma levels of LTG increased 70–80% after the inducer was discontinued. For both PHT and CBZ, it takes 4–5 days to completely clear the system once the agent has been discontinued (i.e., plasma levels of 0). It takes an additional 2–3 weeks for the phenomenon of deinduction to be completed. Overall the LTG plasma level increase was ~100%. **Conclusions:** Loss of induction (deinduction) was not observed as the dose of an AED inducer was initially reduced. A small loss of induction occurred as the plasma level of the inducer approached zero and the majority of deinduction occurred in the 2 weeks after the inducer cleared the system. The time course of deinduction was similar for both CBZ and PHT.

Treatment—Surgical (Adult and Pediatric)

1.298
ROLE OF TEMPORAL LOBE STRUCTURES AND INSULAR CORTEX IN THE ICTAL SEMIOLOGY AND SEIZURES SPREAD PATTERN OF THE SO-CALLED MESIOTEMPORAL LOBE SEIZURES: A SISCOM IMAGING STUDY OF 21 PATIENTS

Serge Chassagnon, Laurent J. Vercueil, Izzie J. Namer, Pierre Kehrli, Maria P. Valenti, Philippe Kahane, Antoine Depaulis, Philippe Esposito, and Edouard Hirsch (Neurology, Hospital, Strasbourg, France; Neurology, Hospital, Grenoble, France; Nuclear Medicine, Hospital, Strasbourg, France; Neurosurgery, Hospital, Strasbourg, France; INSERM 398, Research Laboratory, Strasbourg, France)

Rationale: To study the spatial extent of ictal perfusion changes during mesiotemporal lobe seizures (MTLS) with respect to ictal semiology, using SISCOM single-photon emission computed tomography (SPECT) imaging. **Methods:** Twenty-one adult patients with refractory MTLS associated with hippocampal sclerosis (n = 20) or amygdala gliosis (n = 1) were studied using substraction ECD-SPECT coregistered to magnetic resonance imaging (MRI; SISCOM). SPECT examinations were conducted under video-EEG monitoring, and all ictal SPECTs were confirmed as true ictal [ratio captation latency/seizure duration (CL/SD) <1]. Semiquantitative measurements of ictal blood flow (BF) changes were made in 20 regions of interest including limbic, paralimbic, neocortical, and subcortical areas. Patients were divided in two groups, according to the absence (group 1, n = 6) or the presence (group 2, n = 15) of consciousness impairment during ictal SPECT. Seventeen of the 19 operated-on patients were seizure free (mean follow up, 22 months) after anterior temporal lobe resection (n = 15) or disconnection (n = 4). Two patients are waiting for surgery. **Results:** In group 1 (CL/SD ratio, 0.65 ± 0.41), the most reliable focus of hyperperfusion was restricted to the temporal pole. Seizures consisted in epigastric aura in all six cases. In group 2 (CL/SD, 0.50 ± 0.33), ipsilateral ictal hyperperfusion affected in addition the insula, and to a lower extent, MTL structures, the lateral temporal cortex, and the thalamus. Seizures consisted in automotor seizures, and consciousness was impaired from seizure onset (n = 4) or after the occurrence of an aura (n = 17). Other paralimbic areas and basal ganglia were not consistently affected by BF changes. **Conclusions:** In MTL seizures manifesting only with epigastric auras, the temporal pole appears as a key structure in the occurrence of symptoms. The occurrence of consciousness impairment seems to be related to the involvement of a large temporoinsulothalamic network, the insular part of which could constitute the main efferent output from temporal lobe structures toward subcortical areas.

1.299
REALISTIC CHARACTERIZATION OF CEREBRAL SPIKE AND SEIZURE SOURCES WITH AN EEG DIPOLE PATCH MODEL

Susan M. Hawes-Ebersole, Michael Wagner, Manfred Fuchs, and John S. Ebersole (Neurology, The University of Chicago, Chicago, IL; Neuroscan, Inc., Hamburg, Germany)

Rationale: Traditional equivalent dipole models of EEG spikes or seizures are unrealistic because they have no spatial extent, unlike true cerebral sources. Point-like dipoles attempting to model extended sources are also usually located deep to the generator cortex in underlying white matter. Both tend to make traditional dipole models unappealing and more difficult to interpret. **Methods:** We have developed and tested a new dipole model that has an adjustable spatial extent in eight surgical candidates with complex partial seizures. This "dipole patch" is composed of many individual dipoles that are constrained to follow the surface of the patient's own cortex (derived from 3-D MRI reconstructions) in both position and orientation (surface normals). Dipole patch solutions for EEG spikes or seizures were compared to single-dipole models and to the location and extent of cerebral sources

recorded with intracranial electrodes. **Results:** Dipole patch solutions with a physiologic goodness of fit were obtained for spikes or initial seizure rhythms in all patients. The location of dipole patches as compared to underlying cerebral sources was accurate at a sublobar level, as validated by intracranial EEG. Dipole patches of 1.5- to 3-cm radius most accurately simulated the spatial extent of real cortical sources. Single-dipole solutions usually fell within the boundary of the dipole patch or its underlying white matter, but often they did not lie at the geometric center of the patch. **Conclusions:** The dipole-patch model of EEG spikes and seizure rhythms is probably the most realistic representation of actual cortical sources currently available. In this technique, the location accuracy achieved with a dipole model using a realistic boundary element head model is enhanced by the spatial extent and realism of an extended generator area that is constrained to cortical anatomy. Other extended source models are not limited to realistic source areas nor are they constrained to anatomically contiguous cortex. The dipole-patch model offers not only the most realistic characterization of spike or seizure foci, but it also provides the best EEG source model for comparisons with other functional imaging technologies. A realistic functional representation of spike and seizure sources is a significant improvement in noninvasive localization of epileptogenic foci. (Disclosure: Salary: Neuroscan, Inc.)

1.300
ASSOCIATION OF TEMPORAL LOBE INTERICTAL DELTA SLOWING AND POSITRON EMISSION TOMOGRAPHY HYPOMETABOLISM WITH INTRACRANIAL EEG-DEFINED SEIZURE ONSET

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Rationale: We have previously shown that in patients with temporal lobe epilepsy, interictal, temporal polymorphic delta slowing on scalp EEG may correlate with regional fluorodeoxyglucose–positron emission tomography (FDG-PET) hypometabolism in both presence and severity (*Epilepsia* 2001;S7:24.). The relative contribution of these measures of cerebral dysfunction to the localization of the underlying epileptogenic zone remains unclear. At the end of this activity, the participants should be able to discuss the relation between PET hypometabolism and focal delta slowing with seizure onset as determined by intracranial monitoring. **Methods:** We retrospectively evaluated 32 temporal lobes of 16 consecutive patients between 2000 and 2002, who had an indeterminate noninvasive evaluation for lateralization of temporal lobe onset and had subsequent intracranial recording with bilateral temporal subdural strips. Scalp EEG interictal delta activity and imaging studies including FDG-PET were reviewed. Statistical analysis was performed using the Spearman rho statistic for categoric correlation. **Results:** Fourteen patients had unitemporal seizure onset during intracranial monitoring. Six patients (42.9%) had bilateral PET hypometabolism, whereas eight (50%) had unilateral PET hypometabolism with correct lateralization in five patients (62.5%). Two patients had bilateral delta slowing, whereas unilateral polymorphic delta slowing was seen in 10 patients with correct lateralization in nine (90%). The presence of interictal delta slowing was significantly correlated with the side of seizure onset obtained from intracranial monitoring ($r = 0.50$; $p < 0.01$), whereas PET hypometabolism was not. No definite correlation was seen between these two parameters. **Conclusions:** Although a correlation has been previously shown between FDG-PET and focal delta slowing, in patients with difficult to lateralize seizure onset, focal delta slowing may be more specific for the underlying epileptogenic zone.

1.301
DETECTION AND LOCALIZATION OF SUBCLINICAL SEIZURES: DIFFERENCES BETWEEN MAGNETOENCEPHALOGRAPHY AND EEG

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Rationale: In epilepsy, magnetoencephalography (MEG) is a diagnostic procedure ordinarily employed to localize interictal discharges. Ictal events are generally not recordable using MEG because (a) the requirement that the patient remain completely immobile precludes recording durations long enough to capture seizures, and (b) movement artifact obscures MEG waveforms. Development of MEG localization tools for epilepsy has been directed towards use on interictal discharges. In the course of MEG recording, however, subclinical seizures are sometimes obtained. We have examined the detection and localization characteristics of MEG and EEG for subclinical seizures. The aim of this study was to evaluate the differences between subclinical ictal patterns seen on MEG and EEG in terms of identification and localization. **Methods:** We studied 43 consecutive epilepsy patients who underwent continuous video-EEG monitoring, had simultaneous EEG and MEG recording for an average of 22.0 min, proceeded to epilepsy surgery, and were followed up for ≥1 year. Ictal and interictal discharges were identified and localized from the raw EEG and MEG waveforms independently by separate investigators who were blinded to the clinical information. Detection and localization of subclinical seizures were compared between EEG and MEG. **Results:** Subclinical seizures were seen in four patients (see Table 1). The seizure interpretation was concordant between EEG and MEG in one case (case 8). In the cases where the seizure interpretation was not concordant (cases 2, 14, 44), the other modality showed simultaneous interictal activity in the same region. In cases 2 and 14, rare spiking was seen during the corresponding ictal pattern. In case 44, the EEG showed runs of spikes lasting for the duration of the MEG seizure pattern. The localization of the seizures was supported by clinical diagnosis in all cases. **Conclusions:** From visual review of the amplitude versus time waveforms, there were differences in seizure identification between EEG and MEG. Some differences may be due to interinvestigator difference in interpretation. There are also theoretical differences in the sensitivity to epileptiform discharges that can contribute to a morphologic difference. MEG recording during the presurgical evaluation of epilepsy patients may provide useful ictal as well as interictal information. (Supported by Uehara Memorial Foundation.)

TABLE 1. *Concordance in frequency and localization of the ictal and interictal activity between the EEG and MEG*

Case	EEG	MEG	Clinical diagnosis
2	1 spike, Rt temporal	Seizure (9 s), Rt temporal	Rt mTLE
8	Seizure (35 s), Lt temporal	Seizure (15 s), Lt temporal	Lt FTLE
14	Seizure (6 s), Lt mesial temporal	Two spikes, Lt temporal	Lt TLE
44	44 spikes, Rt anterior temporal	Seizure (26 s), Rt temporal	Rt mTLE

1.302
PRESURGICAL LOCALIZATION OF FRONTAL LOBE EPILEPSY USING INTERICTAL EEG AND MAGNETOENCEPHALOGRAPHY WITH ELECTROCORTICAL VALIDATION

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Rationale: The localization of frontal lobe epilepsy (FLE) is complex, and surgical management, therefore, remains less successful in comparison with temporal lobe epilepsy. This study aims at demonstrating that advanced source analysis of simultaneously recorded interictal EEG and MEG is a useful additional tool for the presurgical localization of FLE. **Methods:** Sixteen patients with FLE participated in this study. Six of these patients were candidates for epilepsy surgery

and underwent preoperative subdural recordings (electrocorticography; ECoG). Before these recordings, the onset and dynamics of the interictal EEG and MEG discharges of each of these patients were studied, using equivalent and dipole source distribution models. On a cortical rendering, the analysis results of the interictal transients were plotted relative to the anatomy obtained from 3D-MRI, thus enabling the systematic assessment of the onset and propagation path underlying the interictal EEG and MEG compared to the interictal ECoG. **Results:** Advanced source analysis of the interictal EEG and MEG transients enabled us to delineate the irritative zone and to differentiate this area from the secondary propagation areas. The localization of the irritative zone was in good agreement with the interictal onset area determined on the basis of the subdural recordings for each of the six patients, whereas four of these patients who underwent resective surgery were seizure free after their operation. However, independent source analysis of the interictal EEG and MEG discharges revealed distinct propagation patterns underlying these discharges. This probably explains the differences in shape and spatial distribution that occurred in the simultaneously recorded interictal EEG and MEG discharges of most of the patients studied. **Conclusions:** The results of this study indicate that advanced source analysis of both interictal EEG and MEG is successful in guiding the intracranial recordings. [Supported by The Epilepsy Foundation of the Netherlands (grant 20-10).]

1.303

SUBTRACTION ICTAL SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY COREGISTERED TO MRI (SISCOM) IN PRESURGICAL EVALUATION OF CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: Ictal EEG has been used as the "gold standard" for localizing the epileptogenic zone in patients being evaluated for epilepsy surgery. Children with extratemporal lobe epilepsy and with nonlesional epilepsy are especially challenging. SISCOM has been shown to be valuable in many adult patients with difficult-to-localize seizures. We determined the relation of SISCOM to intracranial ictal EEG (ICiEEG) in children with intractable epilepsy and the usefulness of SISCOM in pediatric presurgical evaluation. **Methods:** SISCOM images were reviewed by two blinded reviewers. Each SISCOM was classified as focal, regional, multifocal, or nonlocalizing. Each focus was classified as primary, secondary, or tertiary. The results were correlated with the ICiEEG of habitual clinical seizures and classified as concordant or nonconcordant. **Results:** Thirty-two of 45 children (aged 18 years oor younger) who had SISCOM during presurgical evaluation underwent resective surgery. A lesion was present in 19 children, and the MRI findings were normal in 13 (41%) children. An ICiEEG was obtained in 24 of the 32 children. In 20 (83%), the SISCOM was concordant with ICiEEG. Of the eight children who did not have ICiEEG, the SISCOM was concordant with the site of surgery in five. Twenty-five (78%) of the 32 patients were class I. **Conclusions:** These data suggest that SISCOM images correlate strongly with ICiEEG in children with medically intractable epilepsy. They also suggest that SISCOM is useful in determining the site for placement of intracranial electrodes.

1.304

MAGNETOENCEPHALOGRAPHY IN FOCAL EPILEPSIES ASSOCIATED WITH CAVERNOMAS

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Rationale: The aim of the study was to assess magnetoencephalography (MEG) contribution to presurgical evaluation in patients with focal epilepsies associated with cavernomas. **Methods:** Among 82 operated-on epilepsy patients with MEG findings during presurgical evaluation, histologic assessment of the removed tissue had revealed cavernomas in eight cases. Three cases are selected to demonstrate the potential complexity of localizing epileptic activity in relation to such lesions. MEG was recorded with a 74-channel dual unit biomagnetometer (Magnes II, 4D-Neuroimaging). Co-registered magnetic tomography resonance (MRT) data were available for all patients. Standard procedures of epileptic spike localizations were based upon the model of an equivalent current dipole in a homogeneously conducting sphere. In two cases, additional current density reconstructions were carried out, and realistically shaped head models were computed, according to the boundary element method (BEM). **Results:** In the first patient, MEG spike localization revealed a circumscribed center of epileptic activity at the very border of the lesion. The subsequent resection resulted in abolition of seizures. Two lesions were found in the second case, one in the frontal lobe, the other one in the temporal lobe. MEG spike localizations clearly indicated epileptogenicity of the temporal lobe. The patient markedly benefited from removal of the temporal lesion. The third patient had a poor outcome after resection of a cavernoma in the basal region of the left temporal lobe. Postoperative MEG spike analysis yielded localizations in the dorsal part of the temporal lobe, distant from the resection cavity. Fractionated stereotactic radiotherapy of this site significantly reduced seizure frequency. **Conclusions:** The results illustrate the worthwhile contribution of MEG in presurgical epilepsy evaluation in symptomatic epilepsy with lesional etiology. [Supported by Deutsche Forschungsgemeinschaft (DFG), STE 380/9 – 1.]

1.305

POSTOPERATIVE SEIZURE OUTCOME IN PATIENTS WITH REFRACTORY TEMPORAL LOBE EPILEPSY ACCORDING TO THEIR MAGNETIC RESONANCE IMAGING FINDINGS

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Rationale: Neurophysiological findings (NF), specially video-EEG recordings, were the main primary tests before the introduction of MRI. We report on the results obtained while using MRI instead of NF as a primary screening test in patients with temporal lobe epilepsy. **Methods:** Three hundred seventeen epilepsy patients were studied. Age ranged from 5 to 54 years (mean, 26 years). All patients had a clinical history suggestive of temporal lobe epilepsy and underwent high-resolution 1.5-T MRI with thin slices perpendicular to the hippocampal axis. They were divided in four groups according to their MRI findings: Group I, normal MRI (n = 23); Group II (n = 239), unilateral mesial temporal sclerosis (MTS); Group III (n = 6), bilateral MTS and Group IV (n = 49), non-MTS temporal lobe lesions. All Group I patients underwent video-EEG recording. Those with unilateral interictal or ictal findings were submitted to corticoamygdalohippocampectomy (CAH) at the side of the NF; those with bilateral findings were submitted to bilateral subdural grids implantation and CAH according to the invasive NF. Group II patients were submitted to CAH at the side of the MRI-defined MTS, without video-EEG monitoring or electrocorticography. Group III patients were submitted to bilateral subdural grids implantation and CAH according to the invasive NF. Group IV patients underwent lesionectomy with electrocorticographic guidance for additional margin resection without preoperative video-EEG recording. **Results:** Overall, 86% of the patients were rendered seizure free postoperatively; 73% were seizure free in Group I, 87% in Group II, 83% in Group III, and 91% in Group IV. **Conclusions:** MRI seems to be a very good primary screening test in patients with refractory temporal lobe epilepsy. It is easy to perform and analyze, can be performed on an outpatient basis, is much less expensive than intensive video-EEG monitoring, and obviates the need for seizure recording in

≤80% of the patients with temporal lobe epilepsy. (Supported by Sao Paulo Secretary of Health.)

1.306
STEREO-EEG EXPLORATION OF PERIVENTRICULAR NODULAR HETEROTOPIA AND OVERLYING CORTEX IN PATIENTS WITH INTRACTABLE FOCAL EPILEPSY
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Rationale: We studied patients with periventricular nodular heterotopia (PNH) and medically intractable focal epilepsy to define the role of the heterotopic grey matter nodules and the cortex on epileptogenesis. **Methods:** All patients (n = 8) with PNH and intractable focal epilepsy who underwent stereo-EEG evaluation at the Montreal Neurological Hospital and Institute between February 1994 and April 2002 were reviewed. Patients were implanted stereotactically using an image guidance system (SSN Inc., Montreal, Canada). We included only those in whom at least one nodule was explored. The epileptic focus was defined according to the result of the intracranial ictal recordings. **Results:** Six patients (three men; mean age at seizure onset, 11.6 years) were studied. PNH was bilateral, diffuse, and contiguous in two, bilateral focal in two, and unilateral focal in two. All but one had bilateral electrode implantation, and the number of nodules explored varied from one to five per patient. Two hundred ten EEG and electroclinical seizures were reviewed. In two patients (one with bilateral contiguous PNH, one with a single nodule in the right atrium), seizure onset was in an atrophic hippocampus, and no interictal or ictal epileptic activity (EA) was seen in the heterotopia studied. In another patient (with two adjacent nodules in the left occipital horn), seizure onset was in the adjacent occipital neocortex within 2 cm of the nodules. In the three remaining patients (one with bilateral contiguous PNH, and two with bilateral focal PNH), seizure onset was regional, multifocal, or bilateral in the overlying temporooccipital cortices (two patients) or frontotemporal (in a patient who had an additional frontal lesion). Occasional additional interictal and ictal EA was also seen in one or several grey matter nodules. **Conclusions:** Patients with PNH often have intractable epilepsy. Seizures may result from complex interaction between the heterotopia and cortex, may be due to dual pathology, and occasionnaly the nodule may be contralateral to the focus. Invasive recordings are essential to understand the role of PNH in epileptogenesis.

1.307
REPOSITIONING OF INTRACRANIAL ELECTRODES WITH 1-WEEK INTERVAL: ELECTROGRAPHIC SEIZURE PATTERN AND SURGICAL OUTCOME
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Rationale: The purpose of this study was to investigate the change of electrographic patterns with the repositioning of implanted electrodes after it failed to catch the true local-onset zone. We focused on the following aspects: (a) the reasoning background of the repositioning electrodes, (b) topographic and frequency characteristics of ictal EEG onset before and after the repositioning, (c) the effectiveness of repositioning or additional implantation of intracranial electrodes on surgical outcome, and (d) the relationship between change of intracranial EEG onset pattern and surgical outcome. **Methods:** Of 183 cases with intracranial recordings between 1994 and 2000, 18 cases underwent a second invasive study consisting of repositioning or additional implantation of intracranial electrodes performed 7 days after the initial invasive study. All patients underwent resective surgery and were followed up for >1 year. **Results:** The repositioning of intracranial electrodes identified a new ictal-onset zone in 13 patients. In another four cases, the second evaluation made the change of decision on the resection margin. No change on the decision of resection was made in one case. The assumptions of failure in the localization of ictal-onset zone during the initial evaluation were based on the following reasons: (a) ictal onset in the partially sampled area (five cases), (b) ictal onset in the distal end of strip or grid (four cases), (c) simultaneous or independent ictal onset in two separate areas (five cases), (d) widespread ictal onset zone (two cases), (e) preceding clinical onset before electrographic change (two cases). Of eight patients with regional ictal onset in the initial evaluation, six had focal ictal onset in the second invasive study. Four of them were seizure free after the operation. Four of five patients with two separate ictal-onset zones in the first study, the second invasive study found regional ictal-onset zones, and only one of them was seizure free after the resection. There was no relation between the frequency of ictal rhythm and the surgical outcome. There was no additional morbidity or mortality with the second invasive studies. **Conclusions:** The repositioning or addition of intracranial electrodes with 1-week intervals in the patients who had unsuccessful initial intracranial evaluation allowed good surgical outcome in half of them. Two thirds of those patients in whom were ultimately found focal ictal-onset zone by the second evaluation became seizure free after the operation. The spatial restriction of ictal rhythm is the important predictor for good surgical outcome. These results support consideration of 1-week interval repositioning of intracranial electrodes in selected patients. (Supported by Seoul National University Hospital.)

1.308
MAGNETIC SOURCE IMAGING FOR NEOCORTICAL EPILEPSY: PREDICTING ELECTROCORTICOGRAPHIC LOCALIZATION BY MAGNETIC SOURCE IMAGING
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Rationale: Magnetic source imaging (MSI) is utilized for presurgical localization of epileptic foci, but it is often difficult to determine a priori when the MSI data will accurately predict the ECoG-determined zone of sezire origin. To better illucidate this relation, we correlated MSI and ECoG results for patients with neocortical epilepsy. Our primary objective was to understand how MSI data can be incorporated into surgical planning for neocortical epilepsy. **Methods:** Twenty-three patients with suspected focal epilepsy underwent MEG/MSI studies at our institution and subsequently had invasive intracranial electrode monitoring (ECoG) to localize the zone of seizure origin for surgical resection. MSI results were retrospectively stratified by the number of IIS recorded during a 4-h recording session into three groups: Class I (no spikes), Class II (fewer than five spikes), and Class III (more than six spikes). Class III was further subdivided based on the clustering density of IIS: Class IIIA, >4-mm mean distance between IIS; Class IIIB, <4-mm mean distance between IIS. We analyzed these groups to determine when MSI results correlated with the ECoG-determined zone of seizure origin. In addition, we assessed if the MSI provided critical localization data and correlated with surgical outcome. **Results:** Twenty-three patients with MSI studies underwent invasive monitoring, including 19 with suspected neocortical epilepsy and four with mesial temporal lobe epilepsy. Depth electrodes were utilized in nine cases, subdural grids in nine cases, depth electrodes followed by subdural grids and strips in four cases, and intraoperative ECoG only in one case. ECoG was able to localize the zone of seizure origin in 16 of 23 (70%) of these cases. In 11 of the 16 (69%) cases in which the ECoG was able to localize the zone of seizure origin, the MSI IISs were classified as Class IIIB (many, diffuse) and regionally correlated to the MSI localization in all cases (i.e., same lobe). In contrast, no Class IIIB cases were identified when ECoG was unable to localize the zone of seizure origin. This difference trended toward but did not achieve statistical significance ($p < 0.0.23$), presumably due to the relatively small number of cases available for analysis. In three cases (all Class IIIB) MSI was used to focus invasive electrodes in locations that would not have otherwise been targeted and provided unique localization data not evident from other imaging modalities that strongly influenced the

surgical management of the patient. The classification of MSI findings into subgroups and subsequent statistical analysis generated a model predicting that Class IIIB MSI data are likely to provide reliable information to guide surgical placement of electrodes, but all other groups do not provide reliable enough localization information to guide surgical decision making. **Conclusions:** When an MSI study revealed six or more IIS densely clustered in a single anatomic location, then the MSI is likely to correspond to the zone of seizure origin identified by ECoG and may be useful to focus the placement of intracranial electrodes. In all other situations, MSI does not appear to easily predict the zone of seziure origin, and has minimal influence on surgical planning. (Supported by NIH NS20806 from the Epilepsy Branch and NCRR RR13176.)

1.309

AFTERDISCHARGES PROVOKED BY ELECTRICAL STIMULATION OF HUMAN CORTEX: PROPERTIES AND SIGNIFICANCE

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Rationale: Although localising significance of electrically evoked clinical and subclinical seizures for epileptogenesis remains undetermined, whether scrutiny of afterdischarge morphologies and other properties would clarify this issue remains undetermined. This report describes afterdischarge (AD) properties from electrical cortical stimulation via subdural electrodes in 29 patients. **Methods:** We used biphasic usually monopolar stimuli at 0.3 ms, 50 Hz, and 1–18 mA strengths in patients undergoing strip or grid subdural EEG for surgical candidature. **Results:** AD thresholds varied moderately among patients and only slightly among regions with mesial occipital and mesial frontal areas lower than convexity nontemporal regions. The 33,058 stimuli evoked 402 (12%) ADs whose morphologies were 1- to 4-Hz spike or polyspike bursts (163), sequential spikes (146), spike–waves (55), rhythmic waves (32), and rhythmic waves plus spikes (six). ADs lasted 1–20 s, with those of 20 of 29 patients from 6 to 15 s. Morphologic evolution as subclinical seizures (Blume et al. EEG morphology of partial epileptic seizures. *Electroencephalogr Clin Neurophysiol* 1984; 57:295–302) occurred in 39 (10%). Fourteen (44%) of 32 rhythmic wave ADs so evolved, more than from other AD morphologies [25 of 370 (7%); $p < 0.0001$]. However, origin of such evolving ADs correlated with spontaneous seizure onset in only six (40%) while origins of electrically evoked clinical seizures correlated with spontaneous seizure origin in only six (46%) of 13 instances. **Conclusions:** Subclinical or clinical seizures evoked by electrical stimulation of human cortex do not reliably localize epileptogenesis.

1.310

NONLESIONAL PARIETAL "PLUS" EPILEPSY: CLINICAL AND SURGICAL ASPECTS

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Rationale: To elucidate clinical, electrographic, and surgical characteristics of nonlesional localization-related epilepsy with parietal foci encountered in a large surgical center. Discrete syndromes associated with nonlesional parietal lobe epilepsy remain enigmatic due to infrequent presentation, clinical underrecognition, and erroneous localization. We reviewed cases of nonlesional parietal onset within our surgical database to determine the range of presentation as determined by semiologic, electrographic, and surgical-outcome analysis. **Methods:** The NYU epilepsy surgery database was queried for the years 1994–2001. Seven patients were identified possessing invasive intracranial EEG evidence of parietal onset as well as absence of a neuroanatomic correlate on magnetic resonance imaging (MRI). Noninvasive and invasive EEG, ictal semiology, resective strategy, pathology, and outcome were reviewed. **Results:** Of the total, five of seven were erroneously presumed extraparietal based on noninvasive ictal EEG and interpretation of clinical semiology. Two of seven had failed prior epilepsy surgery on nonparietal cortices performed years earlier. Elementary somatosensory sensations were a component of the early ictal period in four of seven. One unique patient had somatosensory "reflex" triggering of motor partial seizure by touching the affected limb. However, all seven displayed extraparietal clinical features at onset; seven of seven frontal (unilateral or bilateral motor), two of seven temporal (acoustic aura, language disruption), one of seven occipital (transient amaurosis, cephalgia). Three of seven patients exhibited two discrete clinical seizure types, verified electrographically in one. Of great importance was the elaboration in five of seven of a highly stereotyped parietofrontal electroclinical syndrome involving simultaneous onset in parietal cortices as well as primary motor and/or supplementary motor area (SMA), manifest by typical motor partial or SMA-type clinical seizures. This finding resulted in a combined resection of both parietal and frontal tissues in four of seven. In six of seven, invasive electrodes were replaced after initial excision to obtain greater parietal coverage and potentially define the need for extension of the resection. Microscopic pathology and outcome will be discussed. **Conclusions:** Our data indicate that nonlesional parietal lobe epilepsy is an infrequently encountered and cryptic entity, often masquerading as a frontal, temporal, or occipital neocortical syndrome. Invasive EEG analysis has the potential for false localization of the ictal-onset zone or underestimation of its extent. Due to the relative clinical silence of the parietal cortex, most seizures of parietal onset exhibit extraparietal clinical features that are a consequence of early spread. The majority of our patients elaborated a distinct syndrome characterized by a complex parietofrontal epileptogenic zone and primary motor or SMA type seizures, thereby defining a parietal "plus" syndrome. The concept of a pure nonlesional parietal syndrome appears artificial, as our data indicate that epileptic networks are determined by neural connectivity that does not respect lobar boundaries. Anticipation of this paradigm is essential early in presurgical planning to allow appropriate parietal area coverage.

1.311

METHOHEXITAL SUPPRESSION AUGMENTS SCALP DIPOLE-SOURCE LOCALIZATION MODELING OF COMPLEX INTERICTAL EPILEPTIFORM DISCHARGES

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Rationale: The accuracy of interictal scalp dipole source localization may be influenced by multiple generators located outside of the epileptogenic zone (EZ). Methohexital (MHX) may augment dipole-source modeling by improving the signal-to-noise ratio (SNR) eliminating fast propagation outside of the EZ. At low doses, MHX is known to activate epileptiform activity. At high doses, MHX suppresses epileptiform discharges and the propagation to distant sources. Autonomous epileptogenic lesions remain more resistant to MHX and are the last to be suppressed. These discharges are the first to return during drug elimination. The reader will understand the potential utility of augmenting dipole-source modeling with the MHX suppression test (MHXST) enhancing accuracy of depth, location, and complexity of the sources of scalp interictal activity. **Methods:** Retrospective data were analyzed from three subjects with Landau–Kleffner syndrome. An initial MHXST was performed during phase I scalp recordings. Scalp EEG was digitally recorded using 26 channels with single-density electrode placement. EEG data were imported into BESA2000 (MEGIS, Munich, Germany). Spatiotemporal dipole modeling (STDM) was performed on a 50-ms segment before and after each interictal discharge maximum. The source models were defined by number of dipoles, temporal delay of dipoles, dipole locations defined by the x, y, z coordinates for the fitted center, dipole orientations, and global field power (GFP) defined by the goodness of fit (GoF), and residual variance (RV). The GFP is a measure of signal strength against the background noise, and therefore, represents the SNR. **Results:** The scalp MHXST revealed multiple dipole components of discharge morphology not seen during baseline scalp recordings in subjects 1 and 2. Subject 1: Two baseline surface dipoles modeled the waveform mor-

phology. Dipole 1 was radially oriented, localized in the superficial left sylvian fissure (LSF). Dipole 2 represented rapid propagation to the contralateral hemisphere. During MHX suppression, the dipole model placed the initial radial dipole deeper within the LSF. The first interictal discharge to reappear during drug elimination was modeled by three ipsilateral dipoles. The initial radial dipole was localized deepest in the LSF when compared to MHX suppression and baseline interictal data. Subject 2: a single tangential dipole was seen deep within the LSF during baseline scalp recording (GoF, 90.630%). Both MHX suppression and initial return of interictal activity were best fit to three dipole components. Dipole 1 for each condition was located deeper in the LSF than the modeled baseline scalp dipole. Subject 3: a single tangential dipole was modeled within the LSF during baseline scalp recording (GoF, 90.862%). Both MHX suppression and initial return of interictal activity concurred (GoF, 93.09 and 87.88%) but with a deeper dipole localization. **Conclusions:** MHX may reveal complex dipoles improving the depth and location of the epileptic focus. Furthermore, MHX at high doses does not activate regions outside of the EZ, as suggested by subject 3. The MHXST can be used as a tool to refine scalp dipole modeling by improving the overall SNR of the EZ.

1.312
FRAMELESS STEREOTACTIC PLACEMENT OF DEPTH ELECTRODES USING THE STEALTHSTATION SURGICAL NAVIGATION SYSTEM

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Rationale: Depth electrodes are useful in the identification of deep epileptogenic foci. Computed tomography (CT), magnetic resonance (MR), and angiography-guided frame-based techniques are safe and accurate, but require 4-point rigid skull fixation that can limit cranial access for placement of additional grids and strips. We designed and implemented a custom-built adaptor for use with the StealthStation Frameless Neuronavigation System. **Methods:** A slotted, custom-designed adaptor was built (Ad-Tech, Racine WI) to interface with the StealthStation Guide Frame-DT and 960-525 Stealth Fighter (Medtronic, Louisville, CO). The Mach 4.0 Cranial Navigation Software was used to plan the trajectory and entry site based on a preoperative SPGR MRI. Anatomic accuracy was assessed based on whether the electrode was (a) within, (b) touching, or (c) outside of the target tissue. Physiologic accuracy was assessed based on whether adequate recordings were obtained. **Results:** Sixteen depth electrodes were placed into 20 targets in seven patients. Eight electrodes were placed laterally though a craniotomy into the hippocampus and amygdala. Four electrodes were placed through occipital burr holes along the length of the hippocampus into the amygdala. Four electrodes were placed into targets deep in the frontal lobe. Of 20 targets, 19 (95%) had electrode contacts either within or touching the target, 18 of which (90%) provided adequate recordings. There were no complications. **Conclusions:** Depth electrodes can be placed safely and accurately using a commercially available frameless stereotactic navigation system and a custom-made adaptor.

1.313
ELECTROCORTICAL MAPPING OF THE OCCIPITAL LOBE WITH SUBDURAL ELECTRODES: RESULTS IN FOUR PATIENTS

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Rationale: To report electrocortical mapping results using subdural electrodes in four patients with focal epilepsy being evaluated for epilepsy surgery. **Methods:** All four patients were candidates for occipital lobectomy or basal temporal topectomies. Subdural electrodes were implanted, consisting of grid and/or strip electrodes. An Ojemann Cortical Stimulator (Radionics Inc., Burlington, MA) was used to activate adjacent pairs of electrodes at currents of 0.5–8 mA for 3 s in duration. Fifty-one pairs of electrodes were stimulated with positive responses in 25 pairs. Stimulations producing afterdischarges were not included in the analysis. A 40×70-cm^2 cardboard, divided into equal quadrants by perpendicular lines, was held 30 cm from the patient. The patients' eyes were fixed at the center of the board during stimulation, allowing the patients to indicate the location of the visual response. **Results:** Colorful "target" phosphenes (two patients), which tended to be centrally located, were activated by stimulation near to the calcarine sulcus. White or unicolor phosphenes (four patients) tended to be located more peripherally or would move from the center to the periphery, but remained in quadrants opposite to the association cortex stimulated. Formed hallucinations and illusions of spatial rotation were reported by individual patients with stimulation of the lateral temporooccipital and laterobasal occipital areas, respectively. **Conclusions:** The characterization of phosphenes produced by occipital lobe stimulation may differentiate the primary visual area and peristriate visual association cortices. Formed hallucinations and the illusion of movement were activated in occipitotemporal association areas.

1.314
ANALYSIS OF ELECTROCORTICOGRAPHY COHERENCE PATTERNS RECORDED FROM EPILEPTIC PATIENTS IS HELPFUL FOR DELINEATING THE BORDERS OF EPILEPTOGENIC TISSUE

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Rationale: Determining the borders of the epileptogenic region of cortex that must be resected to permanently eliminate epileptic seizures has been a matter of considerable debate, but we have found that the analysis of ECoG coherence patterns may be helpful in this regard, and we have investigated whether interictal EcoG coherence patterns may be used to predict the location of epileptic foci. **Methods:** Subdural ECoGs were recorded from 12 medically refractive pediatric epilepsy patients as part of their routine surgical workup. Recording arrays were implanted over the frontal, parietal, occipital, or temporal lobes for 4–10 days, depending on the patient's seizure semiology and imaging studies. Two-minute segments of the ECoG were analyzed for changes in power and lateral coherence during the interictal, preictal, ictal, and postictal periods. Differences in coherence magnitude and phase were registered to intraoperative photographs or 3-D–rendered MRIs. **Results:** Coherence patterns revealed a rich topography, with reduced coherence across sulci and major fissures. As has been reported by others, coherence increased during the ictal and postictal periods, especially within the epileptic regions. However, this was not the case when multiple independent epileptic discharges were present. The clearest differences were between areas that participated in the subsequent seizures and areas that remained seizure free, according to conventional measures. Post hoc analyses of interictal records revealed higher coherence in areas that were resected compared to areas of normal function. **Conclusions:** Our findings suggest that analysis of coherence patterns can supplement visual inspection of conventional records to help identify the borders of properly functioning and pathologic regions of cortex. With further study, analysis of coherence may allow us to identify epileptic foci from interictal recordings, possibly obviating the need for extended monitoring. (Supported by NIH NS40514-02.)

1.315
IMAGE GUIDANCE IN EPILEPSY SURGERY: FROM DEPTH ELECTRODE PLACEMENT TO HEMISPHERIC DISCONNECTION

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Rationale: Frameless image-guidance systems have become widely available to neurosurgeons over the past few years. Epilepsy surgeons have on the whole embraced this technology, but there remains some reticence with regard to accuracy for electrode placement when compared to frame stereotaxis. The level of intraoperative usefulness of image guidance with regard to well-recognized anatomic structures has also been debated. **Methods:** In a series of 50 consecutive image-guided epilepsy surgery cases, we have analyzed both accuracy and surgical utility. Cases included seven frameless depth-electrode placements. In these, true surgical accuracy was assessed by fusing postimplantation MRIs with preimplantation studies with planned trajectories. The difference between planned trajectory and final electrode position was measured. Accuracy was also assessed in 32 nonlesional and nine lesional epilepsy cases and in two functional hemispherectomies. **Results:** In 42 depth-electrode placements, targeting accuracy was 2.2 ± 1.1 mm. Temporal lobe cases included anterior temporal resections, selective mesial resections, subpial transsections, and combined/hybrid procedures. Usefulness in the temporal lobe was mainly in finding the temporal horn, defining the superomesial extent of amygdalar resection, and confirming the posterior extent of hippocampal resection. To optimize accuracy in the amygdala, we recommend that this area be addressed before opening the temporal horn of the ventricle, especially in patients with significant atrophy. In functional hemispherectomies, guidance for disconnective incisions was extremely useful. The most obvious application was for lesion resection. Usually lesions presenting with epilepsy are nonenhancing. In this context, image-fusion of FLAIR MRI sequences was paramount. Fusion of functional images was occasionally performed. **Conclusions:** The spectrum of applications of image guidance in epilepsy surgery has been reviewed, and future perspectives will be discussed.

1.316
ELECTROCORTICOGRAPHY IMPROVES EPILEPSY SURGERY OUTCOMES: REULTS OF 183 PATIENTS FROM MILWAUKEE

George L. Morris, Francesca Galli, Ilana Ruff, Wade M. Mueller, and Lalitha Gunamraj (Regional Epilepsy Center, St. Luke's Medical Center, Milwaukee, WI; Department of Neurology, University of Florence, Florence, Italy; Department of Neurosurgery, MCW, Milwaukee, WI)

Rationale: Determine the influence of electrocorticography (ECoG) on the postoperative seizure status of surgically treated medically resistant epilepsy patients. Recording the electroencephalogram from the cortical surface or electrocorticography may assist in a more efficacious outcome to epilepsy surgery. Abnormal results and the type of abnormalities may have a role in modifying the surgery. We reviewed the seizure-outcome results of patients without and with ECoG and the nature of the abnormalities to determine if ECoG influences surgical outcome. **Methods:** A retrospective review of all patients with a surgical treatment of epilepsy by the Comprehensive Epilepsy Program in Milwaukee, WI, was made for the presence of ECoG at the time of surgery and the nature of the results. This information was added to a prospective database of surgical patient evaluation and outcome. Analysis was performed on the presence of ECoG and its findings and the subsequent seizure-status outcome. Pearson $\chi 2$ values were generated for the comparisons. **Results:** The database produced 183 epilepsy surgery patients with 6-month seizure-outcome information. ECoG was performed on 90. The performance of ECoG or the presence of an abnormality had no influence on seizure outcome (60% with ECoG and 75% without seizure free; $p = 0.0114$ and 78 of 90 abnormal ECoGs, $p = 0.452$) Epilepsy surgery was performed in the temporal lobe in 164. Complete information was present in 133 patients. ECoG was not performed in 59 and was done in 74. A significantly better outcome was seen with ECoG (85% with vs. 61% without ECoG seizure free; $p = 0.006$). ECoG was abnormal in 89% without significant differences in seizure outcome. Epileptiform abnormalities were present in 65 of 66 abnormal ECoG studies. The location of these abnormalities also had no significant influence on seizure outcome. **Conclusions:** ECoG influences the outcome of epilepsy surgery at our center but only in temporal lobectomy and not dependent on the presence of an abnormality. Patient numbers are seemingly large enough to find effects but because of a few non–seizure-free outcomes, some groups were small. Further analysis of patient evaluation features may help indicate the group best assisted by ECoG.

December 9, 2002
Platform Session A: Basic Science 1
3:30 p.m.–5:30 p.m.

A.01
GLIA ACTIVATION AND CYTOKINE SYNTHESIS IN THE RAT HIPPOCAMPUS AFTER LIMBIC SEIZURES DURING POSTNATAL DEVELOPMENT

Annamaria Vezzani, Marisa Aliprandi, Carlo Perego, Massimo Rizzi, Cristina Richichi, and Maria Grazia De Simoni (Neuroscience, Mario Negri Institute for Pharmacologic Research, Milano, Italy)

Rationale: Our previous evidence has shown that limbic seizures in adult rats induce a rapid and reversible cytokines synthesis in the hippocampus both in microglia and astrocytes. This occurred to a larger extent when seizures were associated with neuronal loss. Intracerebral application of interleukin (IL)-1β exacerbates seizures while tumor necrosis factor (TNF)-α has anticonvulsant activity. The aim of this study was to assess whether cytokine synthesis and glia activation are triggered by seizures in immature brain. We also compared the pattern of cytokine induction with the occurrence of age-dependent seizure-induced neuronal cell injury using 10- and 15-day-old and preadolescent 21-day-old rats. **Methods:** Limbic seizures were induced in 10- and 15-day-old rats by systemic injection of 1.3 and 5 mg/kg kainic acid, respectively, whereas 10 mg/kg kainate was used in 21-day-old rats. Behavioral seizures resembling generalized clonic convulsions lasted for 90 min on average in the different age groups and had an onset time of ~15 min in the 10-day-old group and of 20-30 min in the other groups. For reverse transcription–polymerase chain reaction (RT-PCR) measurements of cytokines mRNA (IL-1β, IL-6, TNF-α, IL-1Ra), rats were killed by decapitation 2–24 h after the end of seizures, and their hippocampi were frozen at –70°C until assay. Different groups of rats were killed by transcardial perfusion using buffered saline followed by 4% paraformaldehyde and adjacent 40-μm coronal forebrain sections were cut at a cryostat for histochemical detection of neuronal injury by Fluoro-Jade and specific astrocyte (glial fibrillary acidic protein) and microglia (OX-42) markers. **Results:** In 10-day-old pups, seizures induced a decrease in IL-1β, IL-1 receptor antagonist (Ra), and TNF-α mRNAs within 24 h from seizure onset, whereas IL-6 mRNA did not change. In 15-day-old rats, IL-1β did not change at 2 h while a 2.5-fold increase was found 4 h after seizures and then returned to basal level by 24 h. None of the other cytokines was modified in these rats. In 21-day-old rats, the pattern of cytokine changes was similar to the adult (3-month-old) rats. Thus, IL-1β and IL-1Ra were increased by four- and twofold, respectively, TNF-α by 1.5-fold, and IL-6 by fivefold. Microglia and astrocyte activation occurred after seizures at all age groups, 2–24 h after seizures, particularly in the hippocampus and entorhinal cortex. Astrocytes were mostly activated in CA3 and dentate gyrus at 2 h and then in all hippocampal subfields at later times. Fluoro-Jade staining revealed a few positive neurons in the hilus of 15-day-old rats, 24 h after seizures. In 21-day-old rats, various positive neurons were localized in the CA3 pyramidal layer, hilus, and superficial layers of the temporal cortex. **Conclusions:** Our evidence indicates that limbic seizures do not induce cytokines in brain until the onset of seizure-dependent neuronal cell injury (i.e., 15- and 21-day-old rats). The lack of cytokine production is not due to functional impairment of glia because both microglia and astrocytes are activated at all ages similar to adult rat brain. We suggest that the lack of proinflammatory cytokine induction in the immature brain during seizures may play a role in its refractoriness to nerve cell damage. (Supported by CURE, Telethon Onlus GPO285/01.)

A.02

CALCIUM WAVES MEDIATED BY ADENOSINE TRIPHOSPHATE PROPAGATE THROUGH RADIAL GLIAL CELLS OF THE PROLIFERATIVE VENTRICULAR ZONE

Tamily A. Weissman, Lidija Ivic, Stephen C. Noctor, Alexander C. Flint, and Arnold R. Kriegstein (Department of Neurology, Columbia University, New York, NY; Center for Neurobiology & Behavior, Columbia University, New York, NY)

Rationale: Attendees will learn that calcium waves propagate through neuronal stem cells of the developing cerebral cortex, and are triggered embryonically by mild trauma as well by endogenous levels of adenosine triphosphate (ATP). In the developing embryonic neocortex, newborn neurons migrate along radial glial fibers from the proliferative ventricular zone (VZ) into the postmitotic cortical plate where specific cortical layers are established. Radial glial cells span the width of the cortex during early development and provide a scaffold for migration. In addition to their role as migratory guides, radial glial cells have recently been shown to function as neuronal stem cells. Immature neurons climb along their own parental radial glial fibers into the developing cortex. Radial glial cells then transform into astrocytes during the first postnatal week and may therefore be considered a part of the astrocytic lineage. Although a key role for radial glia in neuronal production and migration has been demonstrated, radial glial signaling has not been explored in detail. Because the radial glial cell is crucial to neurogenesis and migration, potential signaling pathways could be important in the establishment of the laminated cortex. **Methods:** To begin to investigate radial glial signaling, we have used calcium imaging to monitor activity throughout the ventricular zone. Acute coronal slices from E16 rat brain were loaded with the calcium indicator Fluo-3 for 1–2 h. Calcium activity within cortical slices was then monitored using an epifluorescence microscope and digital camera. Slices were stimulated using an extracellular electrode. Drugs were applied either focally or via bath perfusion. In some experiments, whole-cell recording, immunohistochemistry, and Western blotting techniques were used. **Results:** We find that electrical or mechanical stimulation triggers a robust, slowly propagating calcium wave that travels throughout the VZ at a rate of 5.8 ± 2.0 mm/s. Dye-filling experiments show that radial glial cells participate in the waves. The calcium wave is mediated, at least in part, by a diffusible signal, because a wave can be elicited in a separate cortical slice located ≤150 mm away. The wave is not dependent upon extracellular calcium but does require the ATP-receptor subtype P2Y1 and calcium release from IP3-sensitive intracellular calcium stores. **Conclusions:** These findings show that robust calcium waves propagate through radial glial cells of the embryonic cortical ventricular zone. Similar to calcium waves in astrocytes, these waves rely on ATP signaling and calcium release from IP3-mediated intracellular stores. We propose that release and signaling via metabotropic ATP receptors triggers and sustains this propagating wave throughout radial glial cells of the VZ. Currently we are examining whether VZ calcium increases triggered by ATP can cause changes in gene expression or rates of proliferation, migration, or secretion. Because radial glial cells are involved in neurogenesis and neuronal migration, these calcium waves may be involved in the establishment of the laminated cortex. (Supported by grants from the NINDS and the March of Dimes Birth Defects Foundation.)

A.03

IMMATURE-LIKE ASTROCYTES ARE ASSOCIATED WITH DENTATE GRANULE CELL MIGRATION IN HUMAN TEMPORAL LOBE EPILEPSY

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Rationale: In human temporal lobe epilepsy, a dispersion of dentate granule cells is frequently described in adults who had an early risk factor. To elucidate the role of glia in this phenomenon, we investigated neuronal dispersion, astrocyte organization, and expression of intermediate filaments of mature and immature astrocyte in surgical specimens of patients with medial temporal lobe epilepsy. **Methods:** Surgically removed hippocampi were obtained from seven patients with a history of febrile seizure (FS+) and hippocampal sclerosis, and from five patients with MTLE without hippocampal sclerosis or febrile seizures (FS–). We evaluated granule cell dispersion by measuring granular layer width. Astrocyte organization was studied using double immunofluorescence to detect GFAP (glial fibrillary acidic protein) and vimentin (an intermediate filament characteristic of the immature astrocytic skeleton). Concerning specifically the dentate granular layer, we focused on three qualitative parameters: (a) radial position of GFAP- and/or vimentin-positive processes, (b) presence of vimentin-positive cell bodies within the granular layer, and (c) presence and orientation of vimentin-immunoreactive microvessels inside the granular layer. **Results:** Histologic and immunohistochemical observations revealed striking differences in dentate gyrus. Patients (FS–) had no dispersion (three) or very partial dispersion in part of granular layer (two). These patients showed no or few radial GFAP-positive astrocytic processes. For patients (FS+) an homogeneous dispersion was observed all along the dentate gyrus (>120 μm). In this layer we detected numerous astrocytic processes that were radially oriented and vimentin positive. However, in two patients with the maximal dispersion (500–1,200 μm), radial glia expressed only GFAP. In all (FS+) patients numerous microvessels that were strongly vimentin-positive and radially orientated through the granular layer were observed. Quantitative analysis revealed a significant increase of both GFAP and vimentin immunostaining in the granular layer of patients (FS+) compared to the other patients (FS–). **Conclusions:** This study shows for the first time that an immature phenotype of astrocytes is associated with granular layer dispersion in adult epilepsy patients with hippocampal sclerosis and a history of febrile seizure. We suggest that granule cell migration that occurs in adult epileptic focus results from the transient occurrence of immature-like glia. Even if the primum movens in migration processes remains unknown, future studies should focus on the characterization of the neuronal and vascular factors involved in the regulation of the radial glia phenotype and on their modifications under pathological conditions. At the end of this study participants should be able to discern multiple roles of gliosis in secondary epileptogenesis

A.04

EXPERIMENTALLY INDUCED CORTICAL MALFORMATIONS: FAST OPTICAL IMAGING OF INITIATION AND PROPAGATION OF EPILEPTIFORM ACTIVITY

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Rationale: Malformations of cortical development are a heterogeneous group of disorders often found in patients with drug-resistant epilepsy. Electrophysiological studies of human dysplastic cortex and rodent models revealed intrinsic epileptogenicity in the malformation itself as well as in its vicinity and widespread alterations in distribution and function of inhibitory and excitatory neurotransmitters. Little is known about the exact site of initiation of epileptic activity and about its temporal and spatial propagation. We addressed this questions in an animal model of cortical dysplasias in rats. **Methods:** *Lesion induction:* At day of birth (P0) a copper probe cooled with liquid nitrogen was placed on the exposed skull resulting in a longitudinal deep microsulcus in adult rats. Sham-operated animals were treated similarly with an uncooled copper probe. *Optical imaging:* 500-μm-thick coronal brain slices were incubated with the voltage-sensitive dye RH 795 for ≥1 h before recordings. Field potentials were recorded with standard glass electrodes filled with KCl. Voltage-related fluorescence changes were recorded with a 464-element photodiode array (fields of view, 3.50 or 1.75 mm diameter, 800 frames/s) and calculated as fluorescence change relative to resting light intensity (dI/I) using NeuroPlex software. *Induction of epileptiform activity:* Epileptiform activity was induced by immersion in Mg-free bath solution. To trigger epileptiform events, short electrical stimuli were applied to the junction of deep layer VI and white matter in remote brain regions. *Histology:* After recording, the slices were postfixed, cut, and processed for either cresyl-violet stain-

ing or immunohistochemistry using NeuN as a neuronal marker. **Results:** All freeze-lesioned animals (n = 12) showed the formation of a typical deep microgyrus, which consisted of cells originally committed to superficial cortical layers and a loss of deep cortical layers. Mostly the dysplasia was located in the hindlimb representation cortex HL or in the frontal motor cortex Fr. After 20–40 min of immersion in Mg-free bath solution, epileptiform activity emerged in slices from freeze-lesioned as well as sham-operated animals. In *sham-operated controls,* epileptiform activity was initiated in different cortical areas, which remained stable initiation sites even with electrical stimulation in remote brain regions. Spontaneous and evoked epileptiform activity arouse predominantly from superficial cortical layers in the medial somatosensory cortex Par1 and in HL. Spread of epileptic activity to adjacent areas was concentrated on superficial cortical layers. In slices with *freeze-lesions,* spontaneous epileptic activity always initiated in the dysplastic cortex. This was also the case for evoked activity, which only rarely originated in Par1 (as in controls). Similar to controls, the epileptic activity predominantly spread through superficial cortical layers to adjacent areas. **Conclusions:** This study demonstrates that the initiation site of epileptic activity in an animal model of cortical dysplasia lies within the dysplastic cortex itself and shows spread of this activity into the surrounding cortical areas predominantly through superficial cortical laminae. [Supported by grants from HHU and DFG (SFB 194, SP108/16-2).]

A.05

FUROSEMIDE AND BLOCKADE OF SEIZURE ACTIVITY IN VITRO

Nicholas M. Barbaro, D. Koji Takahashi, and Scott C. Baraban (Neurological Surgery, University of California, San Francisco, San Francisco, CA)

Rationale: Furosemide, a blocker of chloride cotransporters, exerts a powerful inhibitory effect on epileptiform activity. Furosemide has been shown to abolish bursting in the 4-aminopyridine (4-AP) and zero-magnesium hippocampal slice models in rats, mice, and human tissue; kainic acid–induced, and audiogenic seizure models in vivo. There is preliminary evidence from population studies that the use of furosemide reduces the incidence of epilepsy in patients. The exact mechanism of action of furosemide has not been elucidated, but is presumed to be through nonsynaptic mechanisms, which could include effects on pH, control of extracellular space volume, or regulation of extracellular potassium. Here we studied the ability of furosemide to eliminate epileptiform bursting in the presence of agents that block the inwardly rectifying potassium channels (K_{IR}) responsible for extracellular potassium buffering. **Methods:** Horizontal 400-μm-thick brain sections were made from adult mice and stored in artificial CSF, then transferred to a gas-interface–type recording chamber and continuously perfused with aCSF at 33–35°C. Input–output curves and paired-pulse stimulation plots were obtained by stimulating Schaffer collaterals and recording in CA1. Comparisons were made before and after the addition of furosemide (2.5 m*M*). In separate experiments, slices were perfused with aCSF containing 4-AP (100 μ*M*) until epileptiform bursts occurred at regular intervals. In some experiments, the K_{IR} channel blockers barium chloride ($BaCl_2$, 100 μ*M*) or cesium chloride ($CsCl_2$; 1m*M*) were added to aCSF containing 4-AP, and then furosemide was added. In other experiments, bursting was initiated with 4-AP, and then furosemide was added until bursting ceased (typically 30–45 min), and either barium or cesium was subsequently added. Recordings were continued for ≥60 min after addition of the final solution. **Results:** The addition of furosemide to the bathing medium had no effect on input–output function or on paired-pulse facilitation (five slices). Analysis of a single-stimulus evoked CA1 population spike during baseline (10 min) and prolonged perfusion with furosemide (40 min) was also performed (three slices). Furosemide exposure resulted in the development of a second population spike response [consistent with its blockade of γ-aminobutyric acid (GABA)-A channels], but no significant change in spike amplitude. In seizure studies, 2.5 m*M* furosemide reliably abolished 4-AP–induced bursting within 45 min, as expected. When perfused for 1 h after slice before exposure to aCSF containing barium or cesium (30–40 min), furosemide consistently failed to block epileptiform bursting (eight slices). Likewise, the addition of barium/cesium to a combination of furosemide + 4-AP aCSF resulted in a return of epileptiform bursts within 30 min (four slices). **Conclusions:** Our results demonstrate that furosemide does not produce an antiepileptic action when K_{IR} channels are blocked. Furosemide does not inhibit input/output function or paired-pulse facilitation, suggesting that it does not produce a significant reduction of synaptic activity. Therefore, we propose that further investigation into the role of K_{IR} channel modulation as an antiepileptic mechanism for furosemide is warranted and may ultimately lead to the development of novel therapeutic treatments. (Supported by University of California at San Francisco Academic Senate Funds.)

A.06

INCREASED EXPRESSION AND FUNCTION OF MITOCHONDRIAL UNCOUPLING PROTEIN IN THE NEONATAL BRAIN CONTRIBUTE CRITICALLY TO DIMINISHED SEIZURE-INDUCED NEURONAL DEATH

Céline M. Dubé, Kristina A. Dorenbos, Patrick G. Sullivan, Oswald Steward, and Tallie Z. Baram (Anatomy and Neurobiology, University of California, Irvine, Irvine, CA; Reeve-Irvine Research Center, University of California, Irvine, Irvine, CA; Center for the Neurobiology of Learning and Memory, University of California, Irvine, Irvine, CA)

Rationale: Prolonged seizures kill neurons in hippocampus and other regions contributing to the limbic circuit. In contrast, the neonatal brain is generally resistant to status epilepticus–induced excitotoxicity. The mechanisms for this phenomenon have not been elucidated. Here we tested the hypothesis that early in life, altered mitochondrial function protects limbic neurons from excitotoxicity. **Methods:** Mitochondrial uncoupling and the expression of the uncoupling protein 2 (UCP2) were determined in limbic structures of neonatal and adult rats. Induction of reactive oxygen species formation, mitochondrial function, and neuronal injury were compared after prolonged seizures (induced by kainic acid) using standard methods. **Results:** Basal expression of UCP2 was higher and mitochondria were more uncoupled in immature limbic neurons. Unlike those in the adult, prolonged seizures did not increase reactive oxygen species formation or result in mitochondrial dysfunction in neonatal brain. The enhanced UCP2 expression and function in neonatal brain were due to the high fat content of maternal milk, so that substituting a low-fat diet reduced UCP2, restored mitochondrial coupling to adult levels, and permitted seizure-induced neuronal injury. **Conclusions:** Modulation of UCP2 expression and function by dietary fat protects neonatal neurons from seizure-induced death by preventing mitochondrial dysfunction. This mechanism may be applicable to neuroprotective strategies in the prevention and therapy of epilepsy. (Supported by NIH NS28912, NS35439, NS074444, NS32280, Neotherapeutics fellowship.)

A.07

SELECTIVE LACK OF BENZODIAZEPINE MODULATION IN NEURONS ACUTELY DISSOCIATED FROM THE NUCLEUS RETICULARIS THALAMUS OF AN ACQUIRED ABSENCE EPILEPSY MODEL IN RATS

Jie Wu, Kevin Ellsworth, Kris Smith, and Robert S. Fisher (Neurology, Barrow Neurological Institute, Phoenix, AZ; Neurosurgery, Barrow Neurological Institute, Phoenix, AZ; Neurology, Stanford University School of Medicine, Stanford, CA)

Rationale: The objective of this study is to elucidate γ-aminobutyric acid (GABA)-A receptor modulation in an unique acquired absence epilepsy model using patch-clamp techniques. Block of cholesterol synthesis in neonatal rats leads to life-long seizures with an associated EEG pattern of spike–waves (SW). This model for inhibition of synthesis of cholesterol provides a model of "acquired spike–wave epilepsy" (ASWE). Accumulating lines of evidence indicate that abnormality of GABA-A receptors on thalamic reticular (nRt) plays an important role in thalamocortical mechanisms underlying genesis of absence epilepsy. **Methods:** Experiments were performed using Long–Evans Hooded and Sprague–Dawley rats, ages 14–20 days, previously

treated with a cholesterol-synthesis inhibitor, U18666A (10 mg/kg, i.p.) at postnatal days 1, 5, 9, and 13. The neurons were enzyme-mechanically dissociated from the nRt. The patch-clamp whole-cell recording techniques were applied to record GABA-induced currents in single dissociated nRt neurons. GABA-A receptor agonists and modulators were applied through a multibarrel application system. **Results:** 1. nRt neurons in Long–Evans ASWE model rats showed selective lack of benzodiazepine (BZD) modulation. Bath-applied GABA induced an inward current at a holding potential of –45 mV. Coapplication of GABA with diazepam enhanced GABA-induced current in control, but not in ASWE model, nRt neurons. However, pentobarbital (PTB) potentiated GABA responses of nRt neurons in both control and ASWE model rats. 2. Zn^{2+} exhibits different modulations on GABA-induced currents in ASWE model and control Long–Evans rats. Under whole-cell recording conditions, 100 μM ZnCl was coapplied with 100 μM GABA to recorded neuron. In nRt neurons of the ASWE model, ZnCl suppressed GABA peak current by 59%, whereas in control nRt neurons, ZnCl only suppressed GABA peak current by 6%. 3. The Long–Evans Hooded rat is more sensitive to cholesterol-synthesis blockers (AY-9944 or U18666A) than is the Sprague–Dawley rat. We compared BZD modulation between these two species. Long–Evans Hooded ASWE model rats exhibited total loss of benzodiazepine modulating ability. In contrast, Sprague–Dawley ASWE model rats showed a diazepam (DZP) potentiation in a concentration-dependent manner. However, the DZP potentiation in Sprague–Dawley rats was significantly lower in ASWE model animals compared to controls. **Conclusions:** GABA modulation in nRT neurons is abnormal in the ASWE model. Neurons in the model demonstrate selective loss of BZD regulation and high sensitivity to Zn^{2+}. These findings are more prominent in Long–Evans than in Sprague–Dawley rats, corresponding to propensity for showing EEG spike–waves. Regulation of GABA-A receptor function by BZD and Zn^{2+} is mainly related to the γ-2 subunit, so our results raise the possibility of abnormal γ-2 subunit expression of GABA-A receptors in the ASWE model. (Supported by The Sandra Solheim Aiken and Maslah Saul MD and James and Carrie Anderson Fund, the Barrow Neurological Institute Womens' Board, and the Bioengineer Seed Foundation of Arizona State University.)

A.08

EXCITATORY AND INHIBITORY METABOTROPIC POSTSYNAPTIC RESPONSES IN THALAMIC RETICULAR NEURONS: GLUTAMATERGIC AND NEUROPEPTIDE Y–ERGIC MECHANISMS THAT REGULATE EPILEPTIFORM THALAMIC NETWORK RESPONSES

Qian-Quan Sun, Anita E. Bandrowski, David A. Prince, AND John R. Huguenard (Neurology & Neurologic Science, Stanford University, Stanford, CA)

Rationale: Thalamic oscillatory responses play an important, if not essential, role in the genesis of spike–wave discharges underlying absence epilepsy. The specific neuronal circuitry and roles of ionotropic receptors [AMPA, *N*-methyl-D-aspartate (NMDA) and γ-aminobutyric acid $(GABA)_A$] have been described in a series of experiments over the last decade. In contrast, with the exception of $GABA_B$ inhibitory postsynaptic potentials (IPSPs), little is known regarding the metabotropic receptor-mediated synaptic responses produced by endogenously released neurotransmitters. We tested for functional synaptic currents mediated by neuropeptide Y (NPY), a peptidergic neurotransmitter endogenous to the thalamus, and glutamate, which activates both ionotropic and metabotropic responses. **Methods:** Whole-cell recordings were obtained from thalamic reticular neurons (RTN) in horizontal slices obtained from P13–18 rats. Stimulus trains were applied to the internal capsule to activate corticothalamic fibers and mimic the periodic activity of absence seizures. In some cases, excitability was increased by the addition of 10 μM bicuculline. In other experiments, network oscillatory responses were recorded via extracellular multiunit electrodes in slices maintained in an interface chamber. **Results:** 1. Brief trains of four extracellular stimuli applied to the corticothalamic tract resulted in a slow excitatory postsynaptic potential (~4 mV and 200 ms), which was abolished by the specific group I mGluR antagonist AIDA (1 mM). 2. Application of the group I mGluR agonist DHPG (100 μM) mimicked this response and resulted in a decreased membrane conductance with an estimated reversal potential of less than –80 mV, suggesting that mGluR-I receptors are negatively coupled to K^+ channels. 3. With 3-Hz repetitions of the brief stimulus train (to mimic spike–wave activity), there was the progressive appearance of a long-lasting (≤10 s) inhibitory synaptic potential, which was blocked by the Y1 receptor antagonist BIBP3126 (100 nM). 4. NPY-knockout mice lacked a BIBP3226–sensitive IPSP. 5. Network oscillatory responses were prolonged by application of BIBP3226, whereas AIDA application had the opposite effect. **Conclusions:** NPY release, presumably from RTN cells, is triggered by epileptiform thalamic activity, and it serves to autoregulate such activity through its inhibitory actions in RTN. The long-lasting effects of Y1 receptor activation provide an enduring (seconds-long) suppression of RTN excitability, as would be desired for an endogenous antiepileptic compound. By contrast, glutamate release, likely from corticothalamic terminals in RTN, activates group I mGluRs to cause an intermediate term (<1 s) enhancement RTN excitability. We speculate that mGluR activation may play a facilitatory role in the genesis of absence seizures, whereas Y1 receptors may mediate their termination. Such effects would indicate the potential for new approaches in the pharmacotherapy of absences. Further, these results suggest that the release of endogenous neuroactive substances may be a common feature of epileptiform activity. (Supported by NIH Grant NS06477 from the NINDS and the Pimley Research and Training Funds.)

December 9, 2002
Platform Session B: Neuropsychology/Nursing/Psychosocial
3:30 p.m.–5:30 p.m.

B.01

REPEATED INTRACAROTID AMOBARBITAL TESTS

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Rationale: The intracarotid amobarbital test (IAT) is the gold standard to determine language and memory lateralization in candidates for epilepsy surgery. A literature review revealed five series with a total of 87 cases of repeated IATs. Our goal was to determine the frequency of repeated IATs at our center, and to estimate the retest reliability of the IAT for both language and memory lateralization. **Methods:** The 1,249 consecutive IATs on 1,190 patients between 1989 and 2001 were reviewed. Test–retest interval, side of injection, time until first verbal response, and memory scores were documented. All patients were separately catheterized for the retest procedure, and all tests were performed on separate days. Amobarbital dose was decreased in most of the repeated procedures. A memory test change outside the 95% confidence interval was considered significant. Correlations were calculated with Pearson's correlation coefficient. **Results:** The 53 patients (4.4%) underwent a second IAT, and three patients (0.24%) had a third IAT. The charts of three patients were missing. Therefore, 50 patients with 31 uni- and 19 bilateral repeated IATs were included (69 hemispheres , 45 left). Retest interval ranged from 1 to 1,119 days (median, 95.5 days). Reasons for repetition included obtundation and inability to test for memory lateralization (32), inability to test for language lateralization (13), no hemiparesis during first test (two), no aphasia during first test (one), atypical vessel filling (one), and bleeding complications from the catheter-insertion site (one). Language lateralization was reproduced in all patients. Memory improved after left injection in seven of 45 patients and deteriorated in one. After right-sided injection, one of 24 patients improved, and two deteriorated. Pearson's correlation coefficient between the first and second memory test was low (left r, 0.147; right r, 0.155). Bilateral repeated memory testing was available in 19 patients. In two patients, memory dominance switched sides. Seven patients again showed bilateral memory representation, five pa-

tients went from bilateral memory representation to unilateral dominance, and five patients with an initally lateralized memory showed bilateral memory on the second test. **Conclusions:** In 4% of patients, the IAT was repeated to deliver satisfactory information on either language or memory lateralization. Obtundation and inablility to test for memory or language were the usual reasons for repetition. Speech lateralization of the IAT was always reproduced. Repeated memory test results did not correlate as well, and memory lateralization was unreliable in 63% of the patients. Memory improvement was more likely to occur with left- than right-sided injection. Test results were limited by a varying dose of amobarbital, crossover of amobarbital from one side to the other, testing of both hemispheres on the same day, practice effects, unblinded observers, fluctuating cooperation of the patients, and a biased sample of patients. Gain of reliable information versus the risks of complications and failed tests has to be considered when a patient is subjected to an IAT. [Supported by Innovative Medizinische Forschung, WWU Münster (FoeKz. LO 610101) and NRW-Nachwuchsgruppe Kn2000, Federal Ministry of Education and Research (Foe.1KS9604/0), Interdisciplinary Center of Clinical Research Münster (IZKF Project NWG2).]

B.02

NEUROPSYCHOLOGICAL, MAGNETIC RESONANCE IMAGING HIPPOCAMPAL VOLUMETRY, AND WADA TEST RESULTS AS PREDICTORS OF MEMORY OUTCOME AFTER TEMPORAL LOBECTOMY: A MULTIFACTORIAL MODEL FOR PREDICTING MEMORY OUTCOME USING STATE-OF-THE-ART ASSESSMENT TECHNIQUES

Tara T. Lineweaver, Harold H. Morris, Beate Diehl, Imad M. Najm, Richard I. Naugle, Cynthia S. Kubu, and William Bingaman (Psychiatry and Psychology, Neurology, and Neurosurgery, The Cleveland Clinic Foundation, Cleveland, OH)

Rationale: Anterior temporal lobectomy (ATL) is an effective intervention for treating medically refractory temporal lobe epilepsy, but patients who undergo this procedure may be placed at risk for postsurgical memory decline. This study is designed to demonstrate that noninvasive, state-of-the-art assessment techniques are sufficient to maximize the accurate prediction of postsurgical memory decline after ATL, potentially rendering relatively higher-risk procedures obsolete for this purpose. The objective of this presentation is to provide clinicians with information about predictive relations between preoperative evaluations and postoperative memory outcome for use when counseling patients about potential risks of ATL. **Methods:** This IRB-approved study involved a retrospective analysis of data archived as part of the standard clinical care of 22 left ATL and 29 right ATL patients. Patients were administered the Wechsler Memory Scales–Third Edition (WMS-III) before and ~6 months after surgery. All 51 patients evidenced left-hemisphere language dominance, and 78% were seizure free after surgery. Patients were divided into two groups: those demonstrating memory decline (test–retest scores below the 15th percentile of nonsurgical epilepsy controls) versus those with stable memory. A series of exploratory logistic regression analyses with side of surgery, preoperative neuropsychological data, volumetric analyses of MRI scans, and Wada test results entered as dependent variables determined the relative contributions of these factors to the accurate prediction of memory decline. **Results:** In contrast to previous findings in the literature, side of surgery was not a significant predictor of memory outcome as measured by the WMS-III; right-ATL and left-ATL patients demonstrated similar rates of memory decline. For verbal memory measures, hippocampal atrophy contralateral to the seizure focus, and poor memory scores on the Wada test after ipsilateral injection were associated with memory decline after surgery. For visual memory measures, strong baseline visual memory was associated with postoperative memory decline, but a poor memory score on the Wada test after ipsilateral injection predicted a good memory outcome after surgery. **Conclusions:** Contrary to expectation, the Wada procedure predicts memory outcome after ATL above and beyond side of surgery, MRI volumetric analyses, and baseline memory. The ability of the contralateral hemisphere to independently support memory is significantly related to postoperative memory decline. Hippocampal volumes also help to predict verbal memory outcome, whereas preoperative neuropsychological measures are associated with visual memory changes. These exploratory results support recent research in the literature that suggests that both the functional adequacy and functional reserve models may contribute to understanding memory decline after ATL. Results also indicate that findings based on previous neuropsychological test measures may not be generalizable to newer methods of assessing memory. (Supported by the Epilepsy Foundation.)

B.03

PSYCHIATRIC COMORBIDITY IN PATIENTS WITH THE SYNDROME OF MESIAL TEMPORAL LOBE EPILEPSY: A CONTROLLED STUDY

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Rationale: Mesial temporal lobe epilepsy (MTLE) is a surgically remediable syndrome associated with considerable psychosocial, neuropsychological, and psychiatric comorbidity. The relative risk of DSM-IV–defined psychiatric comorbidity compared with control populations has yet to be fully characterized. This investigation conducted standardized psychiatric interviews of patients with MTLE and familial controls to characterize the nature and degree of risk of current and lifetime-to-date psychiatric comorbidity. **Methods:** Subjects included patients with complex partial seizures of definite or probable temporal lobe origin and mesial temporal atrophy determined by quantitative magnetic resonance imaging (MRI) volumetrics (MTLE, $n = 37$) and healthy familial controls of the patients (siblings, spouses, parents, or children, $n = 24$). All subjects underwent a standardized psychiatric interview (SCID-CV) to characterize current and lifetime-to-date rates of DSM-IV Axis 1 disorders. To characterize current psychiatric symptoms, subjects completed the Beck Depression Inventory (BDI) and Symptom Checklist-90–Revised (SCL-90-R). **Results:** The MTLE and control groups were comparable in gender (59.5 vs. 53.5%) and age (35.2 vs. 36.8 years). There were no significant differences ($p > 0.10$) between the MTLE and control groups in the overall rate of lifetime-to-date [50 vs. 40%; OR, 1.5 (95% CI = 0.53–4.27)] or current [30.3 vs. 29.2%; OR = 1.1 (0.33–3.3)] Axis I disorders. Among specifc lifetime-to-date Axis I disorders, Mood Disorders were more common in MTLE [41.2 vs. 20%; $p = 0.085$; OR = 2.8 (0.85–9.2)] in general, with more lifetime-to-date Major Depressive Episodes (MDE) in particular [27.3 vs. 12%; $p = 0.16$; OR = 2.8 (0.66–11.5)]. Current MDE was uncommon in this sample (5.8% vs. 0), but occurred significantly ($p = 0.03$) more often in MTLE. Examining self-report symptom inventories, MTLE patients were significantly more likely to score in the clinically elevated range on both the BDI (>11) [$p = 0.002$; OR = 14.8 (1.8–122.5)] and the SCL-90-R ($T > 63$) [$p = 0.001$; OR = 6.7 (1.9–22.9)]. Among MTLE patients, there was no significant relationship between gender or laterality of MTLE and the risk of lifetime-to-date Axis I disorders overall or MDE in particular. **Conclusions:** The following are the major findings: (a) Overall rates of current and lifetime-to-date Axis 1 disorders occurred with similar frequency in both MTLE and familial controls and reflected the general U.S. population rates reported by the National Comorbidity Survey (Kessler et al., 1994); (b) Lifetime-to-date and current MDE were more frequent in MTLE compared to familial controls; (c) Self-report symptom inventories revealed very significantly elevated rates of distress including depression; (d) The discordance between the rates of DSM-IV diagnoses versus depressive symptoms endorsed on self-report measures may suggest the presence of subsyndromal depressive episodes. (Supported by NIH NS RO1 37738.)

B.04

DEPRESSION IS ASSOCIATED WITH 18-FLUORODEOXYGLUCOSE–POSITRON EMISSION TOMOGRAPHY ABNORMALITIES IN A LARGE EPILEPSY OUTPATIENT SAMPLE

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Rationale: Depression is a common comorbid condition in patients with epilepsy, and substantially contributes to disability and poor

health outcomes. However, the association of depression with brain dysfunction in epilepsy (vs. social and vocational disability) is not definitively established. The purpose of this study was to evaluate the relation between depressive symptoms and brain dysfunction based on 18-fluorodeoxyglucose positron emission tomography (18FDG-PET) in persons with epilepsy. **Methods:** We prospectively evaluated 200 consecutive patients in our epilepsy clinic for depression. All patients gave consent through a document approved by our IRB. The Beck Depression Inventory (BDI) was used to assess depressive symptoms. Sixty-two of these patients had 18 FDG-PET scans as part of their clinical evaluation. This subset consisted of our study sample. Standard (47-slice) 18 FDG-PET imaging with a mathematical attenuation correction was performed. Scores and demographic data were stored and independent *t* test and analyses of variance were performed using SPSS. All analyses controlled for age, gender, and seizure frequency. **Results:** Of the 62 evaluated patients with 18 FDG-PET, 55 had abnormal and seven had normal scans. The mean BDI score was 9.7 (SD, 8.5) in the group with abnormal 18 FDG-PET scans and 1.8 (SD, 2.6) in the group with normal scans ($p = 0.01$). Fifty-two 18 FDG-PET scans had abnormalities involving the temporal lobes. Patients with right temporal lobe abnormalities ($n = 28$) had a mean BDI score of 11.6 (SD, 9.2). This value was significantly higher than the mean BDI score of 6.6 (SD, 5.8) in patients with left temporal lobe abnormalities ($n = 24$; $p = 0.02$). **Conclusions:** After controlling for gender, age, and seizure frequency, depressive symptoms were significantly more severe in pateints with 18 FDG-PET abnormalities than patients with normal 18 FDG-PET. Right temporal lobe dysfunction was associated with worse depressive symptoms than left temporal lobe dysfunction, based on 18 FDG-PET hypometabolism. These findings suggest that cerebral dysfunction is a contributing cause of depression in epilepsy, and also that further research is needed to more fully understand the complex interactions of brain dysfunction, depression, and seizures. (Supported by NIH grant NS01794-01, NIH grant NS40808, and a grant from GlaxoSmithKline.)

B.05

PREVALENCE OF DEPRESSION IN PERSONS WITH EPILEPSY, AND ASSOCIATED FINDING FROM THE EPILEPSY IMPACT PROJECT

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Rationale: The prevalence and implications of depression in epilepsy are not well known. Problems with some earlier studies include selection bias (tertiary centers), ascertainment method concerns, and lack of control groups. Large community-based studies are needed. **Methods:** We mailed a survey to persons with epilepsy (PWE) and to persons with asthma, depression, and no chronic ailments (NoProb). Subjects had been identified from a prior survey of 180,997 individuals from the National Family Opinion (NFO) database. The survey included demographic factors, questions about seizures and functional status, and the Center for Epidemiological Studies–Depression (CESD) inventory. Results were balanced to the U.S. Census. **Results:** We identified 775 persons with epilepsy, 395 with asthma, and 341 with NoProb. A diagnosis of depression was reported by 30.3% of PWE, 21% of persons with asthma, and none of NoProb. Diagnostic threshold on the CESD for major depression was reached in 24.9% of PWE, 18.4% of asthma, and 2.7% of NoProb. Of the PWE who had been diagnosed with depression, 73.1% showed CESD scores consistent with ongoing moderate or major depressive symptoms. Of the PWE who had not been diagnosed with depression, 13.3% showed CESD scores consistent with ongoing moderate or major depression. PWE had worse scores on all of the subitems on the CESD questionnaire compared to asthma sufferers, except for sleep disturbance. The most recent seizure occurred more than a year ago in 28.6% of PWE with depression compared to 41.0% of PWE without depression. Visits to psychiatrists and/or psychologists were reported in the past 12 months by 6.3% of asthma, 10.1% of PWE, and 2.3% of NoProb. Psychotherapeutic drug use was 6.9% for asthma and 10.6% for PWE. Delays in taking medication for their major health problem due to concerns about side effects was reported by 30.0% of asthma, 19.2% of PWE without depression, and 43.6% of PWE with depression. At least partial employment status was seen in 46.7% of PWE, 38.4% of PWE with depression, 60% of depression alone, 68% of asthma, and 76.4% of the NoProb population. **Conclusions:** In this large, population-based survey, depression is more frequent in persons with epilepsy than in persons with asthma or in persons with no chronic ailments. Epilepsy patients were more likely to take antidepressant medications and to visit a psychiatrist/psychologist. Epilepsy with depression, compared to epilepsy without depression, was associated with poor seizure control, increased health care utilization, noncompliance, and unemployment. A significant number of patients who had not been diagnosed with depression showed CESD scores suggestive of significant depressive symptoms. (Supported by GlaxoSmithKline Pharmaceuticals.)

B.06

RECURRENT SEIZURES AND TEACHERS' RATINGS OF BEHAVIOR PROBLEMS

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Rationale: Seizures have been found to be associated with behavior problems in children with new-onset seizures. Most past studies have used parents' ratings of behavior, and little is known about teacher's ratings of behavior. The purpose of this study was to explore the association of seizures and behavior problems in children with new-onset seizures using teachers' ratings of behavior. Data were collected 3 times over 24 months to determine differences between children: with recurrent seizures, without recurrent seizures, and with new-onset asthma. At the end of this presentation, participants will be able to discuss differences in behavior problems at school among three groups of children: those with recurrent seizures, those without recurrent seizures, and those with new-onset asthma. **Methods:** Subjects were 209 children with new-onset seizures and 93 subjects with new-onset asthma. During the 2-year period, 155 (74%) had at least one additional seizure, and 54 (26%) children had none. Data were analyzed using repeated-measures analysis of variance to compare differences in behavior problems across 3 times. Covariates were study site, age at onset, gender, race, caregiver education, and AEDs. **Results:** Children experiencing recurring seizures had higher total, internalizing, and externalizing behavior problems scores than children not experiencing recurring seizures ($p < 0.05$). Children without recurrent seizures did not differ from the asthma sample. Within the seizure sample, children taking antiepileptic drugs (AEDs) had significantly more behavior problems than children not taking AEDs ($p = 0.21$) after controlling for all covariates. **Conclusions:** The association between seizures and behavior problems was supported using behavior ratings of teachers. Children with new-onset seizures who are receiving AEDs should be assessed for behavior problems in the school setting. (Supported by NS22416.)

B.07

THE INTERACTION OF GENDER AND IQ IN BEHAVIOR AND SELF-CONCEPT IN CHILDREN WITH EPILEPSY

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Rationale: Children with both chronic epilepsy and low IQ are at increased risk for behavioral and mental health problems. It is not

known if gender has an effect on these outcomes. The purpose of this study was to describe the Gender × IQ interaction in children with low IQ and epilepsy in the areas of behavior and self-concept. At the end of this presentation, participants will be able to discuss gender by IQ interactions in this population. **Methods:** The sample of 164 children were diagnosed with epilepsy for ≥6 months. They were placed into one of three IQ groups; (a) IQ between 56 and 84 (n = 48), (b) IQ between 85 and 100 (n = 58), and (c) IQ between 101 and 130 (n = 58). Parents completed telephone interviews to measure behavior problems using the Child Behavior Check List (CBCL). Children completed the Piers Harris Self-Concept Scale via telephone to measure seven domains of self-concept: Total Self-Concept, Anxiety, Behavior, Happiness, Physical Appearance, Popularity, and School. Individual neuropsychological evaluations provided assessment of IQ. Gender interactions with IQ group were analyzed by fitting two-way analysis of variance (ANOVA) models with main effects for IQ group and gender and an IQ group × Gender interaction for continuous outcomes. Logistic regression was used for the binary outcomes (at-risk, yes or no) with main effects for IQ group and gender and an IQ group × Gender interaction. If the interaction was significant in the ANOVA models, we used the Tukey–Kramer method to test for pair-wise differences across the six gender and IQ groups. **Results:** On the CBCL, there was one significant interaction. The percentage at risk for Attention problem in boys showed little variability across the three IQ groups. In contrast, for girls, 82% in the Low-IQ group were at risk compared to 65% in the Middle-IQ group and only 17% in the High-IQ group. Girls in the low-IQ group had a signficantly poorer mean score for Total Self-concept and Anxiety Self-concept than the other five groups. For Happiness Self-concept, girls in the Low-IQ group had significantly poorer mean scores than all other groups except boys in the Low-IQ group. Physical Appearance Self-concept scores for girls in the Low-IQ group were significantly poorer than for girls in the High-IQ group and boys in the Low-IQ group. Finally, for School Self-concept, scores for the girls in the Low-IQ group were significantly poorer than for girls or boys in the High-IQ group. **Conclusions:** The findings from this study indicate a significant interaction between gender and IQ. In general, girls with low IQ were at greater risk for both self-concept and attention problems. Findings from this study suggest girls with low IQ and epilepsy are at heightened risk for problems and should be assessed for behavior and mental health problems in the clinical setting. (Supported by grant PHS RO2 NR04536 from the National Institute of Nursing Research to Joan K Austin.)

B.08

THE ASSESSMENT OF AN INSTRUMENT TO MEASURE PERCEIVED STIGMA AMONG ADULTS WITH EPILEPSY

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Rationale: The purpose of the present study, part of a larger study of self-management in people with epilepsy, was to examine the reliability and validity of a 10-item self-report instrument to measure perceived stigma among adults with epilepsy. The scale was originally designed for parents of children with epilepsy and revised to measure perceived stigma among adults with epilepsy. **Methods:** Participants for the study were recruited from two epilepsy centers—one in Atlanta and one in Boston—and a neurology clinic in Atlanta. Participants completed three assessments each 3 months apart. At each assessment, they completed the stigma scale along with psychosocial measures and measures of self-management and personal characteristics. A total of 321 adult men and women with epilepsy were enrolled in the study. The responses of the participants to the items on the stigma scale were first assessed for internal consistency and test–retest reliability. Construct validity was assessed using factor analysis and hypothesis testing. Item-response theory (IRT) techniques were used to assess the adequacy of the items in measuring the full range of the construct of stigma. **Results:** Participants range in age from 19 to 75 years with a mean of 43 years; 50.5% were women, and 80.4% were white. The mean age when seizures began was 22 years, and 76% of participants reported having a seizure within the past year. The results of these analyses demonstrated that the internal consistency was quite high, as evidenced by a Cronbach's alpha coefficient of 0.91. The test–retest reliability coefficients for two 3-month periods were 0.83 and 0.85. For a 6-month period, the test–retest reliability coefficient was 0.77. These coefficients provide evidence for moderate to high stability. Principal component analysis yielded one factor with factor loadings ranging from 0.637 to 0.830. The stigma scale also demonstrated evidence of construct validity. As predicted, perceived stigma was negatively correlated with depression, patient satisfaction, attitudes toward treatment and seizures, medication management, social support, and self-efficacy. Participants who reported seizures within the past year, less control of their seizures, and more seizure severity expressed higher levels of stigma. As expected, levels of perceived stigma were similar for men and women and across ethnic and age groups. A unidimensional IRT model was fit to the data. The item discrimination parameters ranged from 0.74 to 1.61. The threshold parameters ranged from –1.40 to –0.206 for the lowest category and from 1.24 to 2.43 for the highest category. **Conclusions:** The results of the study suggest that the Stigma Scale demonstrates acceptable reliability and validity for use among adults with epilepsy. The set of analyses, in particular the IRT analysis, provides useful information for the further development of the scale. (Supported by a grant from the National Institute of Nursing Research R01 NR04770.)

December 9, 2002
Platform Session C: Clinical Neurophysiology and Neuroimaging
3:30 p.m.–5:30 p.m.

C.01

PREICTAL STATE DETECTION IN CONTINUOUS INTRACRANIAL EEG RECORDINGS BASED ON DECREASED PHASE SYNCHRONIZATION: PROBLEMS AND PITFALLS

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Rationale: An important issue in epileptology is the question whether epileptic seizures can be anticipated. Recent studies have shown that certain measures derived from the theory of nonlinear time series analysis are to some extent capable of extracting information from the EEG that allows the characterization of a preictal state and its distinction from the interictal state. In particular, we have shown a significant loss of phase synchronization to be a characteristic feature of the preictal state. In the present study we investigated some problems and pitfalls that can arise when applying an anticipation technique based on this preictal drop in phase synchronization to the EEG recorded continuously over several days. **Methods:** Showing exemplary segments of the synchronization profiles calculated from the continuous EEG recordings from our patients, we first describe characteristic features of the preictal state and try to distinguish this state from the interictal state. We put a particular emphasis on phenomena occurring during sleep. These segments are then compared to the entire profiles, which in turn are scanned for correlation to changes in antiepileptic drug (AED) level and vigilance states during this period. Finally, the possible influence of a priori knowledge such as best channel selection is examined. **Results:** Examination of sleep phases revealed an increase in phase synchronization during slow-wave sleep (as determined by elevated delta power). Furthermore, certain epochs of distinct anticorrelation appeared to occur predominantly during sleep. Regarding the entire recording length, there appears to be an influence of AED levels on the general level of phase synchronization. All of these phenomena are likely to result in a decrease in sensitivity and/or specificity of an

anticipation technique. In addition, the performance of such an algorithm seems to heavily rely on the a priori knowledge of a best channel combination. **Conclusions:** Findings indicate that a number of phenomena (slow-wave sleep, anticorrelation epochs, AED levels, and selection of channels) may have a strong influence on phase synchronization levels and predictive performance, respectively, that needs to be taken into account when designing an algorithm for seizure anticipation. (Supported by the Deutsche Forschungsgemeinschaft.)

C.02

VERY SLOW EEG RESPONSES DISCLOSE THE LATERALITY OF TEMPORAL LOBE SEIZURES: A DC-EEG STUDY

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Rationale: New technology and methods were used to perform long-term scalp recordings to localize direct current (DC) EEG shifts during spontaneous temporal lobe seizures. The objective of the study was to define how consistently scalp-detected ictal DC-shifts lateralize to the side of onset in focal epilepsy as defined by routinely used noninvasive and invasive methods. **Methods:** DC-EEG recordings were performed on seven patients with temporal lobe seizures for periods from 1.5 to 24 h, capturing 35 seizures in seven patients at bedside. All recordings were performed simultaneously with conventional video-EEG (from scalp in five, and intracranial in two patients). Seizures in four of these patients were demonstrated by subdural electrodes to arise in the mesial temporal lobe. Ictal DC-shifts were evaluated by comparing them to the temporal evolution of ictal discharges, and by comparing the lateralizing information of DC-shifts to all the other clinical information used for presurgical evaluation. The side of origin of each patient's seizures was determined by consensus at epilepsy conference on the basis of the conventional EEG, neuroimaging, and the other presurgical diagnostic tests, with participants blinded to the DC-EEG results. Six of the seven patients went on to neurosurgical treatment. **Results:** We observed DC-shifts of considerable amplitude (30–150 μV relative to vertex) beginning within few seconds after every seizure. Ictal DC-shifts lasted for the whole seizure, or until the recording was obscured by movement artifacts. In seizures with mesial temporal lobe onset ($n = 7$) the polarity of the DC-shift was initially positive, changing to negative after spread of the seizure to lateral temporal regions. In every case, the side of the initial DC-shift was the same as the lateralization of the seizures determined at epilepsy conference. **Conclusions:** To our knowledge this is the first study in which noninvasive, scalp-recorded DC-EEG techniques have been used to record focal seizures in humans. We demonstrate that by using appropriate recording techniques, DC-shifts are consistently observed. The lateralization of these DC-shifts agree with that obtained from conventional EEG and other parts of the presurgical evaluation. The slow shifts seen during mesial temporal lobe seizures indicate that scalp-recorded DC-EEG might be particularly helpful in lateralizing seizures of hippocampal origin. This method warrants further study to determine if it might reduce the need for invasive monitoring in patients where ictal lateralization on conventional scalp monitoring is equivocal. (Supported by Finnish Academy, Finnish Cultural Foundation, Arvo and Lea Ylppö Foundation, and the Regional Epilepsy Center.) (Discussion of Unlabeled/Unapproved Uses: This study uses an investigational device that is not FDA approved, under an approved Human Studies Protocol. No pharmaceutical agents are discussed.)

C.03

INTERICTAL EPILEPTIFORM DISCHARGES DURING SLEEP IN EPILEPSY PATIENTS; A QUANTITATIVE APPROACH

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Rationale: Consideration of the effects of sleep stage on interictal epileptiform discharge (IED) rate and field may enhance the value of IEDs in the epilepsy surgery evaluation. Non–rapid-eye-movement (NREM) sleep may increase IED rate and field beyond the epileptogenic zone, whereas REM sleep may limit both the frequency and distribution to the region of interest. Therefore, the effect of sleep stage on IEDs in the epilepsy surgery evaluation may be useful, confounding, or both. The objective of this study was to develop a method of quantifying the frequency and field of IEDs during different stages of sleep to better study the effects of sleep on the localizing value of IEDs. The first four subjects in whom this method was applied are reported here. **Methods:** Three patients with unilateral temporal lobe IEDs and Engel class I outcome and one patient unilateral temporal lobe IEDs with class II outcome after anterior temporal lobectomy underwent overnight EEG-polysomnography during their presurgical evaluation. C.M. visually detected IEDs utilizing referential and bipolar montages while blinded to sleep staging. A second examiner (B.A.M.) reviewed these IEDs. Studies were scored for sleep by M.M. IEDs were classified into subtypes based upon distribution of electrode involvement. Each IED subtype was given a variance score based upon distance of involved electrodes from the three anterior temporal electrodes (F7/8, Sp1/2, and T3/4), closest to the location of the presumed epileptogenic zone. Rate of each IED subtype in NREM stage 1/2, NREM 3/4, and stage REM sleep was tabulated. Rate-weighted variance in IED field was calculated for NREM1/2, NREM 3/4, and REM sleep by multiplying rates for each IED subtype by their variance score and summing these values for each sleep stage. Paired *t* tests were performed comparing rate-weighted IED field variance in NREM 1/2 with that in NREM 3/4 and each of these sleep stages to REM sleep. Statistical significance was set at $p < 0.05$. **Results:** Paired *t* tests demonstrated that IED field variance was significantly higher in NREM 3/4 as compared to stage NREM 1/2 sleep ($p = 0.01$). IED field variance was higher in NREM 3/4 ($p = 0.04$) and NREM 1/2 ($p = 0.04$) as compared to REM sleep. Overall, relatively few IEDs were observed during REM sleep. However, when present, they were restricted to the presumed epileptogenic zone. In addition, as compared to stage 1/2 sleep, NREM stage 3/4 sleep was associated with new IED subtypes with wider distributions and new maxima at frontopolar and posterior temporal electrodes. **Conclusions:** More accurately to use the sleep EEG in the epilepsy surgery evaluation, we are developing a method to quantify IED frequency and distribution. Our preliminary results demonstrate a quantitative difference in IED variance between NREM sleep stages 1/2 and 3/4 and REM sleep. Further directions of this work will be to apply our method to larger numbers of patients with both temporal and extratemporal epilepsy syndromes. In addition we will compare this method to automated techniques evaluating IED frequency and topography. [Supported by NIH/NINDS NRSA NS07222-19 (C.M.), NINDS KO2 NS02099 (B.A.M.).]

C.04

INTRACRANIAL EEG SUBSTRATES OF SCALP EEG ICTAL PATTERNS

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Rationale: The character of cerebral sources of scalp EEG ictal rhythms has seldom been directly confirmed. Misconceptions are therefore likely regarding the extent of cortical activity required to generate seizure patterns, such as those in temporal lobe epilepsy. **Methods:** We recorded simultaneously 26 channels of scalp EEG and 46 to 98 channels of intracranial EEG in 16 epilepsy surgery candidates. Cerebral ictal discharges and interictal spikes with and without a scalp EEG correlate were identified, and the area of the cortical generator was estimated from the spatial extent of electrode contacts demonstrating concurrent depolarization. **Results:** Only a fraction of intracranial EEG spikes were associated with recognizable scalp potentials. Similarly, ictal discharges, when restricted to a few electrode contacts, often resulted in no scalp EEG rhythms. Synchronous or at least temporally overlapping activation of 10–20 cm^2 of gyral cortex was a common substrate for scalp-recordable spikes and ictal patterns. Cerebral generators with areas of less than ~6 cm^2 did not produce scalp potentials.

The onset of cerebral ictal activity was usually not reflected on scalp EEG until sufficient cortex was recruited into ictal activity. This commonly took several seconds. Propagation most often appeared as a moving patch of cortical depolarization. The changing geometry of the activated cortex was reflected in evolving scalp voltage topography. **Conclusions:** Brain sources of scalp EEG ictal rhythms are larger than commonly thought. A large area of cortex must be recruited into synchronous activity for scalp potentials to be evident. Accordingly, scalp EEG ictal onset seldom reflects intracranial EEG ictal onset. Propagation further obscures the actual ictal origin. Any analysis of ictal rhythms to define seizure origin should be performed on the earliest scalp EEG ictal pattern.

C.05

CELLULAR GLUTAMATE, γ-AMINOBUTYRIC ACID, AND GLUTAMINE CONTENT OF THE EPILEPTOGENIC HUMAN HIPPOCAMPUS

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Rationale: In vivo microdialysis studies show that seizure-associated glutamate release is doubled in the epileptogenic human hippocampus despite significant neuron loss and gliosis. A semiquantitative study reported significantly lower cellular glutamate content in the "sclerotic–gliotic" hippocampi compared to the "histologically unremarkable" ones. We measured the effects of neuron loss and gliosis on the cellular glutamate, γ-aminobutyric acid (GABA), and glutamine content of the epileptogenic human hippocampus. **Methods:** Twenty patients (eight men) with temporal lobe epilepsy selected for resection of the hippocampus were invited to participate in this project, which was approved by the Yale University Human Investigations Committee. With the blood supply intact (posterior circulation), a sample of the pes of hippocampus was removed and frozen in carbon dioxide snow. Perchloric acid extracts of the small metabolites were prepared and analyzed by proton magnetic resonance spectroscopy at 11.8 Tesla. Adjacent samples were used for cell counts. **Results:** Our data, measured in the epileptogenic human hippocampus resected at surgery, were quite remarkable in that they failed to show any significant relation between the degree of neuronal loss and the cellular content of glutamate, GABA (both major neuronal metabolites), and glutamine (a major glial metabolite). Rank-order regression showed that <2% of the variability in cellular metabolite content was accounted for by the fourfold difference in the degree of neuron loss. Mean cellular content of glutamate, GABA, and glutamine was the same in biopsies of hippocampi with the least and most severe neuron loss. Similarly, rank-order regression showed that <4% of the variability in cellular metabolite content was accounted for by the twofold difference in the glial density. Hippocampal glutamate content was above normal in 40% of patients. Above-normal glutamate concentrations were measured in hippocampi with the most severe neuron loss and greatest glial density, as well as those with the least neuron loss and gliosis. **Conclusions:** Our findings suggest that cellular glutamate content is increased, probably to above normal levels, in the epileptic human hippocampus. Intracellular glutamate concentrations must be exceedingly high in the remaining glutamatergic neurons or above normal glutamate content must be present in the remaining nonglutamatergic neurons or glia. The high glutamate content would be expected to contribute to the epileptic state by increasing network excitability and promoting excitotoxicity. (Supported by NIH-NINDS NS39092.)

C.06

CEREBRAL DAMAGE IN EPILEPSY: FINDINGS OF A LONGITUDINAL COMMUNITY-BASED QUANTITATIVE MRI STUDY

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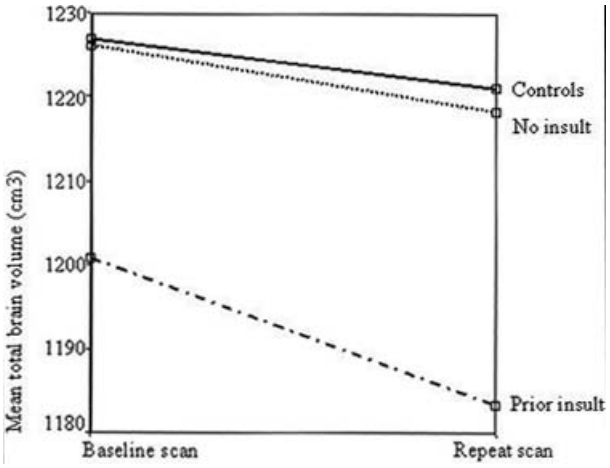
Rationale: Cerebral damage is a common finding in patients with epilepsy, yet the timing and pathogenesis of these changes are poorly understood. We report on the first longitudinal population-based quantitative magnetic resonance imaging (MRI) study to investigate the effect of epilepsy on the hippocampus, cerebellum, and neocortex over 3.5 years. **Methods:** The 122 patients with chronic active epilepsy, 68 patients with new onset seizures, and 90 age- and sex-matched controls were prospectively scanned 3.5 years apart on the same MRI scanner using identical acquisition sequences. Hippocampal, cerebellar, and fully automated measures of total brain, grey matter, white matter, and intracranial volume were performed on coregistered images and correlated with clinical risk factors. The investigator was blinded to scan order and all clinical information. Difference images were obtained by subtracting the matched repeated image from the baseline image and filtered against a structured noise map. Focal necortical changes were quantified using a normalised regional brain atlas. **Results:** Baseline hippocampal and cerebral volumes were reduced in the epilepsy groups that had had antecedent neurologic insults. Longitudinal volume losses were primarily determined by age and not seizure frequency. A history of a prior neurologic insult was associated with a significantly increased rate of cerebral and cerebellar atrophy. Epilepsy duration, antiepileptic drug (AED) use, status epilepticus, and gender were not associated with volume loss. There were significant hippocampal volume losses in one of 90 controls, two of 68 newly diagnosed patients, and six of 122 patients with chronic epilepsy. No patients developed hippocampal sclerosis de novo. After excluding changes due to artefact and confounding factors (e.g., surgery), areas of neocortical loss developed in 21 of 82 controls, 17 of 43 newly diagnosed patients, and 50 of 96 patients with chronic epilepsy. **Conclusions:** Hippocampal, cerebellar, and global volume reduction is not an inevitable consequence of epilepsy, but the cumulative effect of an initial insult and ageing. Individuals with a history of prior neurologic insults had increased susceptibility to cerebral damage. Patients with chronic epilepsy were more likely to develop significant hippocampal and focal neocortical loss than controls and newly diagnosed patients. The patterns of loss were heterogeneous, and in some individuals were remote from the putative epileptic focus (Fig. 1). (Supported by The Wellcome Trust and The National Society for Epilepsy.)



C.07

IMAGING ABSENCE SEIZURES USING FUNCTIONAL MAGNETIC RESONANCE IMAGING

Afraim Salek-Haddadi, Louis Lemieux, Martin Merschhemke, John S. Duncan, and David R. Fish (Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, United Kingdom)

Rationale: To identify and study the neural correlates of generalized spike–wave discharges (gSW) in man using simultaneous and continuous EEG-correlated functional magnetic resonance imaging (Fmri). **Methods:** We studied a patient with intractable idiopathic generalised epilepsy using a 35-min continuous whole-brain fMRI time series during which 10 channels of scalp EEG were recorded simultaneously.

This was enabled by an MR-compatible setup with postprocessing techniques to remove pulse (cardiobalistogram) (Allen PJ, Polizzi G et al., 1998) and imaging (Allen et al., 2000) artefact from the EEG. Four prolonged runs of 3-Hz gSW (absence seizures) were fortuitously captured in their entirety. Fourier analysis was used to derive a running estimate of power spectral density at 3 Hz, which was convolved with an HRF to provide a regressor for statistical parametric mapping using the SPM99 Software. **Results:** There were two distinct and highly significant patterns of blood oxygen level–dependent (BOLD) change, time-locked to gSW. Activation was seen exclusively within the thalami bilaterally, whilst profound deactivations were evident outside, symmetrically, and over large areas of cortical grey matter with a midline frontal emphasis. All changes were consistent across seizures. Activations (red–yellow) and deactivation (cyan–purple) are shown in Fig. 1 as thresholded at the $p < 0.05$ level corrected for multiple comparisons, using separate colour scales overlaid onto the structural EPI image. **Conclusions:** Despite an extensive body of work demonstrating thalamocortical mechanisms in animal models of gSW, surprisingly little has been established in humans. Positron emission tomography and Doppler studies of cerebral blood flow and glucose metabolism during GSWD are conflicting, although reductions in both have been described (Theodore et al., 1985; Nehlig et al., 1996). Our results provide direct evidence for a downregulation of cortical activity during gSW, suggesting a key role for the thalamus. Moreover, the pattern of cortical involvement was in keeping with current density source reconstructions of gSW, suggesting frontal and occipital centres of gravity (Rodin, 1999). [Supported by Medical Research Council (U.K.).]

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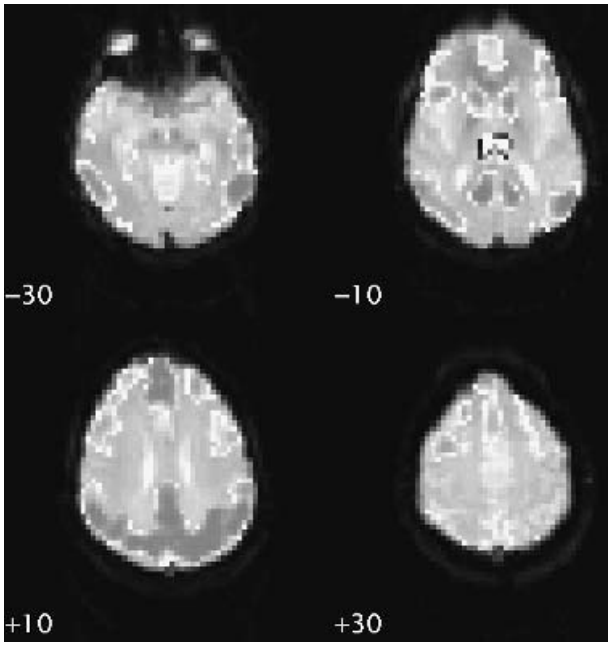

C.08
FALSE LOCALIZING ICTAL SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY: CLINICAL AND NEUROPHYSIOLOGICAL ANALYSIS
Ki Hyeong Lee, Yong D. Park, Don W. King, Kimford J. Meador, and Joseph R. Smith (Neurology, Medical College of Georgia, Augusta, GA; Neurosurgery, Medical College of Georgia, Augusta, GA)

Rationale: The development of computer-aided subtraction single-photon emission computed tomography (SPECT) technique has enhanced the usefulness of SPECT as a presurgical evaluation tool. False localizing ictal SPECT is often attributed to the postictal injection or rapid spreading of the epileptic discharges from the epileptogenic zone to secondary symptomatogenic zone. Even though many clinical studies on the value of ictal SPECT have been published, a systematic evaluation of the clinical and neurophysiological characteristics of nonconcordant or false-localizing ictal SPECT has not been performed. **Methods:** Two of the authors (Y.D.P. and D.W.K.) reviewed the results of the SISCOM (subtraction ictal SPECT co-registered to MRI) in 107 patients who underwent presurgical evaluation for intractable epilepsy at the Medical College of Georgia epilepsy program from 1998 to 2001. We defined nonconcordance or false-localizing SISCOM when (a) the injection of radioisotope (^{99m}Tc-ECD) was clearly done during the patients' habitual seizure confirmed by the review of ictal video/EEG; (b) the primary focus of ictal hyperperfusion on SISCOM was not concordant with other localizing methods such as magnetic resonance imaging (MRI) and video/EEG findings; and (c) other technical variants such as movement artifacts, scan time were excluded. The primary focus on SISCOM was based on the intensity and the volume of the hyperperfusion. Patient's clinical, radiologic, and neurophysiological data were reviewed by a separate author who was blinded to the results of SISCOM. **Results:** Among 107 patients, 35 patients (21 male and 14 female subjects; age, 1–55 years; mean, 23 years) were classified as having nonconcordant SISCOM. The time of radioisotope injection and the duration of seizures from the nonconcordant group were not different from the concordant group. Developmental malformation was the most common etiology for the false-localizing group (10 of 35, 29%), followed by head trauma (nine of 35, 26%). More than half of the nonconcordant group had true epileptogenic foci in either frontal (13 of 35) or temporal lobe (12 of 35). Common location of false localization was in wrong temporal lobe (eight of 35, 23%) (contralateral to true epileptogenic zone) followed by wrong occipital lobe (five of 35, 15%) (contralateral to true epileptogenic zone) and wrong orbitofrontal lobe (three of 35, 9%). Scalp EEG monitoring demonstrated the rapid spread of the epileptic discharges to the contralateral hemisphere before the radioisotope injection in 54% (19 of 35). Subclinical epilepsia partialis continua during the interictal SPECT was implicated in three patients with Rasmussen encephalitis and false-localzing SISCOM (9%, three of 35). Seven of the eight false-localizing temporal lobe SISCOM patients had bilateral independent temporal lobe onset seizures during the video/EEG monitoring. More than half (18 of 35) of the patients underwent subsequent intracranial EEG monitoring, and resective surgery was performed in 14 patients: extratemporal resection, nine; temporal lobectomy, three; and hemispherectomy, two. Their surgical outcome (class I, nine; II, two; II-I,two; IV, one, by Engel's classification at 1 year postop) was comparable to the concordant SISCOM group (class I, 22; II, seven; III, four; IV, one; n = 34). **Conclusions:** Our study suggests that the subraction SPECT could be falsely localizing in some partial seizures. Careful clinical and neurophysiological correlation is warranted in these patients.

December 9, 2002
Platform Session D: Pediatric Epilepsy and Genetics
3:30 p.m.–5:30 p.m.

D.01
ANGELMAN SYNDROME: DIFFICULTIES IN EEG PATTERN RECOGNITION AND POSSIBLE MISINTERPRETATIONS
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Rationale: EEG may have a cardinal importance in the diagnosis of Angelman syndrome (AS) patients with a milder phenotype, as infants

and patients without Chr deletion. Recent reports have agreed with the presence of a suggestive EEG, but there are many discrepancies among their descriptions. This study aimed to (a) evaluate the sensibility of EEG; (b) verify the age at onset of suggestive EEG; and (c) study EEG patterns, analyzing possible variations, and comparing our findings with descriptions and nomenclature used in other reports, in an attempt to organize and compile the distinct descriptive terms previously used. **Methods:** The 70 EEG and 15 VEEGs of 26 patients were analyzed, and suggestive EEG patterns of AS were classified according to Boyd et al. (1988): (a) Delta pattern (DP): runs of generalized, rhythmic delta activity, usually with frontal emphasis, and of high amplitude; (b) Theta pattern (TP): high amplitude, 4- to 6-Hz activity, generalized or over posterior regions; (c) posterior discharges (PD): spike and sharp waves mixed with high-amplitude 3- to 4-Hz activity, over posterior regions, triggered by eye closure. Generic terms, as delta pattern, were preferred instead of lengthy descriptions. **Results:** EEG patterns of AS were observed in 25 patients (96.2%). DP occurred in 22 patients and presented variations, classified as (a) hypsarrhythmic-like variant: resembling a hypsarrhythmic pattern with predominance of slow waves over epileptiform discharges (EDs); (b) Slow variant: high-amplitude, generalized, delta activity with no or rare ED; (c) Poorly defined slow spike-and-wave variant: regular, high-amplitude, generalized delta activity with superimposed ED forming a complex characterized by a slow wave, with notched appearance; (d) triphasic-like variant: monomorphic, rhythmic, moderate-amplitude delta waves over anterior regions with low-amplitude ED, on the descending phase of the slow wave. None of the DP variants presented changes during sleep. TP was observed in eight patients and presented a variable distribution, being observed as generalized in three patients, and over the posterior regions, in eight patients (three asymmetric). Morphology, distribution, frequency, and occurrence were not related to sleep/wake cycle, and not blocked by eye-opening. PD were seen in 19 patients and were observed as runs of rhythmic 4- to 6-Hz sharp waves in 13 and runs of high-amplitude slow waves, with superimposed ED in 16 patients. DP and PD were observed in all ages, and in all genetic groups. TP was age related (up to 8 years), and only in patients with DEL. In the 22 patients with genetic confirmation, EEG patterns preceded the genetic diagnosis in 16 (72.7%). In all patients without genetic confirmation, EEG was able to corroborate the diagnosis **Conclusions:** Although every author describes EEG findings of AS in a slightly different manner, there is obviously a common denominator. In this context, EEG seems to be a sensitive method for the diagnosis of AS, anticipating this diagnosis. On the other hand, we do not believe that these patterns may be accounted as specific, except for the delta pattern, which seems to be extremely unusual in other syndromes. Other EEG patterns observed in AS, such as theta activity, and posterior discharges, occur in a wide variety of disorders. (Supported by FAPESP.)

D.02

MUTATIONS OF THE SODIUM CHANNEL α1 SUBUNIT GENE IN JAPANESE PATIENTS WITH SEVERE MYOCLONIC EPILEPSY IN INFANCY

Goryu Fukuma, Shinichi Hirose, and Akihisa Mitsudome (Department of Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Fukuoka, Japan)

Rationale: To identify genetic abnormalities underlying severe myoclonic epilepsy in infancy (SMEI) in Japanese. Recently, mutations of the neuronal voltage-gated Na^+ channel α1 subunit gene (*SCN1A*) and γ-aminobutyric acid $(GABA)_A$ receptor γ2 subunit gene (*GABRG2*) have been identified as a cause of SMEI. *SCN1A* and genes encoding other components of Na^+ channels in the brain such as α2, β1, and β2 subunits (*SCN2A, SCN1B* and *SCN2B,* respectively) and *GABRG2* can be candidate genes for SMEI. **Methods:** Our study recruited 54 unrelated individuals whose clinical manifestations were consistent with SMEI and 96 healthy volunteers. Each participant or a responsible person signed an informed consent form approved by the Ethics Review Committee of Fukuoka University or similar committees of the participating institutions. Genetic abnormalities of *SCN1A, SCN2A, SCN1B, SCN2B,* and *GABRG2* were sought in genomic DNA using a direct sequencing method with an ABI 3700 sequencer. **Results:** In *SCN1A,* eight heterozygous nonsense, 23 missense, and three frame-shift mutations resulting in a premature stop were found in 44 individuals with SMEI. The mutations identified in the patients were not found in 96 healthy volunteers and hence considered to be disease-causing mutations. No mutation was found within the examined region of *SCN2A, SCN1B, SCN2B,* and *GABRG2.* **Conclusions:** In the first report made by Claes et al., mutations of *SCN1A* were found in all patients they studied, while only 44 of 54 patients bore causative mutations in *SCN1A* in our subjects. The relation between phenotype and genotype of SMEI should be further delineated. (Supported by The Ministry of Education, Culture, Sports, Science, and Technology of Japan, The Epilepsy Research Foundation, The Clinical Research Foundation, The Foundation for the Advancement of Clinical Medicine, and The Central Research Institute of Fukuoka University Ministry of Education Science and Culture of Japan.)

D.03

DISTINCT GENETIC INFLUENCES ON MYOCLONIC AND ABSENCE SEIZURES

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Rationale: The relationships among epilepsy syndromes and seizure types and their underlying genetic mechanisms are poorly understood. We have previously found evidence for distinct genetic contributions to generalized and localization-related epilepsy. Here we use similar methods to examine the shared versus distinct genetic contributions to two generalized seizure subtypes: absence and myoclonic seizures. At the end of this activity the participants should be able to understand the role of family studies in examining genetic contributions to different seizure types and the genetic influences on myocolonic and absence seizures in particular. **Methods:** We examined concordance of myoclonic and absence seizures in families containing multiple individuals with idiopathic generalized epilepsy. To evaluate whether or not the number of concordant families exceeded that expected by chance, we compared the observed number with the number expected from the distribution of absence and myoclonic seizures in the study families, using a permutation test. The rationale for this test is that if some of the genetic influences on myoclonic and absence seizures are distinct (i.e., they raise risk for one seizure type without raising risk for the other), familial concordance is expected to exceed that expected by chance, whereas if none of the genetic influences is distinct (i.e., each raises risk for both seizure types to the same degree), concordance is expected to be consistent with that expected by chance. **Results:** The analysis included 24 families containing 63 individuals with either myoclonic seizures alone ($n = 27$, 43%), absence seizures alone ($n = 18$, 29%), or both seizure types ($n = 18$, 29%). Overall, 15 of the 24 families (63%) were concordant for seizure type. In nine families, all individuals with generalized epilepsy had absence seizures only; in three families, all had myoclonic seizures only; and in three families, all had both absence and myoclonic seizures. The observed number of concordant families was significantly greater than that expected (15 vs. 6; $Z = 4.508$; $p < 0.0001$). To evaluate evidence for independent genetic effects on myoclonic seizures occurring alone and absence seizures occurring alone, we excluded the individuals with both seizure types. In this analysis, the observed number of concordant families remained greater than expected (14 vs. 7.87; $Z = 2.946$; $p < 0.0016$). **Conclusions:** These results provide evidence for distinct genetic effects on absence and myoclonic seizures. The approach used here can be used to guide linkage analysis by allowing rational subdivision of epilepsy syndromes into groups likely to share susceptibility genes. This may help solve the problem of phenotype definition in linkage studies of the idiopathic generalized epilepsy syndromes, suggesting that a focus on seizure type rather than syndrome may be fruitful. The results also give insight into the mechanisms by which genes cause epilepsy—raising

the risk not only for epilepsy overall but for its specific clinical features. (Supported by NIH grants R01 NS20656 and K23 NS02211.)

D.04
FUNCTIONAL CHARACTERIZATION OF THE D188V MUTATION IN SCN1A CAUSING GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS

Patrick Cossette, Andrew Loukas, Ronald G. Lafreniere, Daniel Rochefort, David S. Ragsdale, Robert J. Dunn, and Guy A. Rouleau (Neurology, McGill University Health Center, Montreal, Quebec, Canada; Neurology, Montreal Neurological Institute, Montreal, Quebec, Canada)

Rationale: Mutations in the α1 subunit of the voltage-gated sodium channel (SCN1A) have been increasingly recognized as an important cause of epilepsy in humans, with mutations found in patients with generalized epilepsy and febrile seizure (GEFS), febrile seizures associated partial epilepsy, and severe myoclonic epilepsy of infancy. However, functional consequences of these mutations remain largely unknown. The aim of this study is to determine the effects of the D188V mutation on voltage-gated sodium channel function in vitro. **Methods:** We identified a mutation (D188V) in the SCN1A gene segregating with GEFS in a large kindred. We used site-directed mutagenesis to introduce this mutation into cDNA encoding rat SCN2A. We coexpressed wild-type or mutant α subunits along with the auxiliary β1 subunit in human embryonic kidney (HEK 293) cells. Functional properties of the sodium channels were examined by whole-cell patch-clamp recording. **Results:** The D188V mutation does not affect the voltage dependence of SCN1A activation, steady-state availability, or inactivation time course. In turn, mutant channels have shown a decreased in channel refractoriness during high-frequency activation compared with the wild-type. Whole-cell sodium currents normally decrease in amplitude progressively over the course of high-frequency trains of channel activity, and this frequency-dependent current rundown is thought to play a significant role in dampening hyperexcitability associated with seizures. Therefore, this decreased sodium current rundown caused by the D188V mutation is expected to increase neuronal excitability. **Conclusions:** In vitro analysis of D188V mutation expressed in HEK cells have shown a reduction in frequency-dependent rundown of voltage-gated sodium currents, compatible with an increase in membrane hyperexcitability. This mechanism could be central in the pathophysiology of the epilepsies caused by mutations in sodium channels in humans. (Supported by Canadian Institute for Health Research, Xenon Genetics.)

D.05
REPEATED REMISSION AND RELAPSE IN CHILDHOOD-ONSET EPILEPSY

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Rationale: Most studies consider remission as the ultimate and final seizure outcome in epilepsy. In fact, seizure outcome, especially early in the course of the disorder, is far more complicated and varied. We examined the phenomenon of repeated remission and relapse to better characterize this pattern of seizure outcome and factors associated with it. **Methods:** A prospectively identified cohort of children (0–15 years) with newly diagnosed epilepsy (initial $n = 613$) is being intensively followed up. The probability of 1-year remission and subsequent relapse was examined for up to three remission periods per child. Product-limit and Cox methods were used for analysis. Cases were censored if they had insufficient follow-up (from study entry for the first remission or previous relapse for subsequent remissions) to achieve 1y remission. **Results:** During a median 6-year follow-up, 524 of 602 (87%) of those followed up for ≥1 year achieved a 1-year remission, and 231 (44%) then relapsed. Of 206 followed up ≥1 year after the first relapse, 163 (79%) had a second remission, and 64 (39%) of those relapsed again. Thirty-five of 45 (78%) followed up ≥1 year after the second relapse attained a third remission, of whom 16 (46%) relapsed. To facilitate comparisons across outcomes assessed over varying follow-up periods, product-limit (Kaplan–Meier) estimates were calculated. The probability of attaining a 1-year remission within 2 years of diagnosis was 64% (95% CI, 62–66), but 23% (21–25) relapsed within 1 year of remission. Within 2 years of the first relapse, 75% (69–81) entered a second remission, but 25% (18–32) relapsed again within 1 year of attaining the second remission. Finally, 81% (67–95) attained a third remission within 2 years of the second relapse, but 34% (17–51) relapsed for a third time within 1 year of attaining the third remission. In a Cox model of all possible remission episodes and relapses, those with cryptogenic (rate ratio (RR) = 0.84; $p = 0.04$) and symptomatic (RR = 0.53; $p < 0.0001$) etiology were less likely to enter remission than those with idiopathic etiology. Compared to a first remission, a second remission (RR = 1.23; $p = 0.02$) and a third remission (RR = 1.48; $p = 0.03$) were achieved more quickly. After adjusting for the effect of tapering medication, symptomatic etiology (RR = 1.84; $p = 0.0001$), family history of epilepsy (RR = 1.40; $p = 0.05$), and age at onset >12 years (RR = 2.03; $p < 0.0001$) were associated with an increased risk of relapse. Compared to relapse after a first remission, relapse may be more likely after a third (RR = 1.65; $p = 0.06$) but not after a second (RR = 1.11; $p = 0.48$) remission. **Conclusions:** One-year remission is common in childhood-onset epilepsy; however, relapses are also common. A repeated remitting–relapsing pattern is not unusual. Etiology, family history, and age at onset explain some of this variation. The current findings suggest that there may be a group that is prone to repeated remission and relapse during the first several years after initial diagnosis. The long-term significance of such a pattern of outcome can only be appreciated with prolonged follow-up. (Supported by NIH-NINDS grant RO1-NS 31146.)

D.06
α[^{11}C]METHYL-L-TRYPTOPHAN (AMT) POSITRON EMISSION TOMOGRAPHY CAN DETECT RESIDUAL EPILEPTIC CORTEX AFTER FAILED CORTICAL RESECTION IN CHILDREN WITH INTRACTABLE EPILEPSY

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Rationale: Cortical resection can alleviate seizures in children with intractable epilepsy. However, despite presurgical application of advanced imaging and electrophysiological techniques, seizures recur in ≥30% of such patients. Further resection of remaining epileptic cortex may ultimately lead to seizure freedom, but accurate delineation of the epileptogenic region is often difficult in these patients. The clinical usefulness of glucose metabolism positron emission tomography (PET) is limited in such cases since glucose hypometabolism often occurs in areas of diaschisis and in nonepileptic damaged tissue surrounding the resection. Previous studies have shown that increased cortical uptake of the PET tracer α[^{11}C]methyl-L-tryptophan (AMT; a tracer for tryptophan metabolism via the serotonin or kynurenine pathways) is very specific for epileptogenic cortex and can even differentiate between epileptogenic and nonepileptogenic lesions (e.g., in tuberous sclerosis). The goal of the present study was to assess whether AMT PET is able to detect residual epileptic cortex after failed cortical resection. **Methods:** AMT PET scans were performed in 30 children (aged 2.1–19 years) from several institutions with intractable epilepsy in whom seizures recurred after focal cortical resection, and further surgical resection was being considered. Five patients had a cortical lesion preoperatively, and the remaining 25 had normal magnetic resonance imaging (MRI) before surgery. All patients underwent further presurgical scalp EEG evaluation, and 11 children had intracranial EEG monitoring using subdural grid electrodes. On the PET scans, focal cortical increases of AMT uptake were identified, and their locations were correlated with electrophysiological findings. **Results:** Eleven

(36.7%) of the 30 patients had focal cortical increase of AMT uptake, typically close to the margin of the previous resection (locations: five frontal, three temporal, two parietal, and one parietotemporal). Increased AMT uptake was seen in seven of 25 patients (28%) with normal presurgical MRI, and in four of five patients (80%) with a previous lesion (two of these had dysembryoplastic epithelial tumor, which was incompletely resected, one had posterior megalencephaly with cortical dysplasia, and one child from another institution had a lesion of unknown etiology). Six patients with increased AMT uptake had intracranial EEG monitoring, which showed ictal onset consistent with the PET findings in all cases. Resection of this epileptogenic cortex resulted in seizure-free outcome in five of these six children. **Conclusions:** AMT PET can delineate residual epileptic cortex in patients with intractable epilepsy who continue to have seizures after cortical resection. The sensitivity of AMT PET appears to be particularly high in patients with preoperative lesions, but AMT PET may also identify residual epileptic cortex in more than one of four children with a normal MRI before the first resection. Cortical areas showing increased AMT uptake close to the resection margin show a good correspondence with the seizure focus delineated by intracranial EEG, and resection of these areas results in good outcome in most cases. [Supported in part by NIH grants NS 34488 and NS/RR 38324.)

D.07

BEHAVIORAL DISORDERS IN PEDIATRIC EPILEPSY; UNMET PSYCHIATRIC NEED

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Rationale: This study determined if children with complex partial seizures (CPSs) and primary generalized epilepsy with absence (PGE), who have a psychiatric diagnosis, received psychiatric treatment. It also examined the demographic, cognitive, linguistic, behavioral, and seizure-related variables associated with psychiatric treatment in those children with a psychiatric diagnosis. At the end of this activity, the participants should be able to discuss unmet mental health needs in pediatric epilepsy. **Methods:** The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), the Child Behavior Checklist, the Test of Language Development, and the WISC-R were administered to 62 CPS and 52 PGE children aged 5–16 years. A DSM-IV diagnosis and information regarding psychiatric treatment were derived from the K-SADS. **Results:** Although ~60% of the subjects had a DSM-IV psychiatric diagnosis, >60% received no psychiatric treatment. Absence of psychiatric care was associated with younger age, female gender, less parental education, shorter duration of epilepsy, and the presence of a single psychiatric diagnosis or an affective/anxiety diagnosis. **Conclusions:** This is the first study to demonstrate unmet mental health need in a large sample of CPS and PGE children. The findings underscore the importance of making parents and clinicians aware of the mental health needs of children with epilepsy, particularly if they are girls, younger children, or have recent onset of their seizure disorder. [Supported by NINDS grant 1 RO1 NS 32070 (R. C).]

D.08

WAVELET ANALYSIS CAN PREDICT WHETHER NEONATES WITH ELECTROGRAPHIC SEIZURES WILL DEVELOP POSTNEONATAL SEIZURES

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Rationale: The clinical outcome of neonatal seizures has been studied with some success. Combinations of EEG, clinical findings, and neuroimaging studies are useful predictors of developmental outcome, but do not correlate well with postneonatal seizures (PNSs). Wavelet transform is an analysis of nonstationary EEG signals. Using Wavelet, we analyzed the time course of the frequency components in neonatal EEG seizures to investigate whether we could predict PNSs. **Methods:** We reviewed the medical records of all neonates admitted to the Hospital for Sick Children (HSC), from 1996 to 1997, who had documented electrographic seizures and had ≥18 months of clinical follow up at HSC. Digital EEG system was used to record 16 channels of bipolar neonatal EEG and extracerebral monitoring channels, including eye movements, electrocardiogram, electromyogram (EMG), and thoracic (respiratory) movements. Minimum of 30-min recording was done at a sampling rate of 200 Hz. We reviewed the EEG seizures and selected a pair of electrodes with a 20-s epoch of preictal and ictal EEG. Gaussian Wavelet analysis was applied. We analyzed the following frequency bands: 1–10 Hz, 5–15 Hz, 10–25 Hz, and 20–40 Hz. **Results:** There were 70 neonates with documented electrographic seizures; 18 of them had clinical follow-up for ≥18 months at HSC. Fourteen of the 18 neonates had continuous high-intensity tracing at lower frequency: 13 in the delta range and one in the theta range. Thirteen of these 14 patients have PNS ($p < 0.01$) and are taking antiseizure medications (AEDs); one is seizure free and is not taking an AED. The remaining four patients, who did not have continuous high-intensity tracing in their Wavelet analysis of EEG seizure, remain seizure free and do not require AEDs. **Conclusions:** Our study shows that when Wavelet analysis reveals continuous high-intensity low-frequency tracing in the neonatal EEG seizures, the neonates are highly prone to developing PNSs. In addition, absence of continuous high-intensity tracing in the Wavelet analysis predicts seizure-free outcome. Wavelet analysis can be recommended for the neonates with seizures to predict the development of epilepsy.

December 10, 2002
Plenary Session 1: Parahippocampal Networks in Mesial Temporal Lobe Epilepsy
8:30 a.m.–11:00 a.m.

PL1.01

PARAHIPPOCAMPAL NETWORKS AND MESIAL TEMPORAL LOBE EPILEPSY

Massimo Avoli, Marco de Curtis, Jerome Engel, and Asla Pitkanen (Montreal Neurological Institute, McGill University, Montreal, QC, Canada; IRCCS Neuromed, Pozzilli, Italy; Istituto Neurologico, Carlo Besta, Milano, Italy; Departement of Neurology, UCLA, Los Angeles, CA, U.S.A.; Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland)

Mesial temporal lobe epilepsy (MTLE) is characterized by seizure discharges that involve the temporal neocortex and limbic areas such as the hippocampus, the entorhinal cortex, and the amygdala, and is associated with a typical pattern of brain damage known as mesial temporal sclerosis. Remarkable progress has been recently made in understanding the pathophysiogenesis of MTLE. However, these studies were often made in isolated hippocampal slices maintained in vitro, and thus the role(s) of other limbic structures, which are vital in MTLE, remains unclear. In addition, MTLE is a chronic condition involving neuronal damage and sclerosis, yet most studies have been carried out in tissue from unlesioned brains made epileptogenic by short-term convulsant treatment. This has been the standard although mesial temporal sclerosis can be reproduced in animals. In this symposium we will review data that address both of these issues. First, we will analyze the interactions between parahippocampal regions (e.g., perirhinal and entorhinal cortices and temporal neocortex) under conditions of normal excitability; these data indicate that the propagation of neuronal activity to and from the hippocampus is under a strong inhibitory control largely exerted by the perirhinal cortex. Second, we will focus on experimental and human data about the distribution of extrahippocampal damage in the epileptic brain; such a condition is associated with destruction of some of the major pathways between these limbic areas. Third, we will analyze interictal and ictal recordings performed in vivo

from hippocampus and parahippocampal structures in patients with MTLE and in a chronic animal model. These studies reveal the anatomical and pathophysiological substrates of limbic epileptogenesis. Finally, we will overview how hippocampal and parahipoccampal areas interact in an in vitro brain-slice preparation from nonepileptic and pilocarpine-treated epileptic animals. In particular, these experiments emphasize the control of hippocampal output activity on epileptiform synchronization and the possibility that seizure-induced damage uncovers epileptogenic interactions between the entorhinal cortex and the subiculum.

December 10, 2002
Poster Session 2
11:00 a.m.–5:00 p.m.

Nonhuman Mechanism Studies

2.001
PHARMACOLOGIC PROPERTIES OF EPILEPTIFORM SYNCHRONIZATION IN AMYGDALA/ENTORHINAL CORTEX NETWORKS IN VITRO

Ruba Benini, Margherita D'Antuono, and Massimo Avoli (Department Neurology & Neurosurgery, and Physiology, Montreal Neurological Institute/McGill University, Montreal, Quebec, Canada; IRCCS Neuromed, Pozzilli, (Isernia), Italy

Rationale: The amygdala is involved in some of the behavioral manifestations observed during seizures in temporal lobe epilepsy patients where it is often a primary focus of seizure activity. Here we used horizontal rat brain slices maintained in vitro to understand its involvement in epileptiform synchronization. **Methods:** Field potential and sharp-electrode intracellular recordings were obtained from rat brain slices that included the hippocampus, a portion of the basolateral/lateral nuclei of the amygdala (BLA), and the entorhinal cortex (EC) during bath application of the convulsant drug 4-aminopyridine (4-AP, 50 μM). **Results:** CA3-driven interictal discharges occurred in all structures at intervals of 1.2–2.8 s during 4-AP application. These discharges had duration of 310 ± 40 ms (n = 14) when measured in CA3, spread to the EC and BLA, and were abolished in these parahippocampal areas by cutting the Schaffer collaterals. This procedure induced the appearance of ictal (duration, >10 s) discharges along with slower interictal events that originated in either EC or BLA. In intact slices, the specific *N*-methyl-D-aspartate (NMDA) antagonist CPP increased the rate of occurrence and decreased the duration of CA3-driven interictal discharges in all areas. Moreover, the effects of CPP were not seen in CA3 when it was isolated from the EC/BLA. In Schaffer collateral lesioned slices, CPP abolished ictal discharges and reduced the duration of the slow interictal activity recorded in EC and BLA; moreover, application of the γ-aminobutyric acid $(GABA)_A$ receptor antagonist picrotoxin to Schaffer collateral lesioned slices made ictal discharges disappear and be replaced by a continuous pattern of robust interictal activity. **Conclusions:** In the presence of 4-AP, CA3 outputs entrain EC and BLA networks into a pattern of interictal activity that inhibits the occurrence of NMDA receptor–dependent ictal discharges resembling electrographic limbic seizures. Moreover, occurrence of these ictal events in BLA and EC requires the function of $GABA_A$ receptor–mediated mechanisms. (Supported by Canadian Institutes of Health Research and Savoy Foundation.)

2.002
INITIATION OF ELECTROGRAPHIC LIMBIC SEIZURES BY NEURONAL NETWORKS IN ENTORHINAL AND PERIRHINAL CORTICES

Philip de Guzman, Margherita D'Antuono, Jean Gotman, Francois Dubeau, and Massimo Avoli (Neurology & Neurosurgery, Montreal Neurological Institute/McGill University, Montreal, Quebec, Canada)

Rationale: The hippocampus proper is often identified as a major player in mesial temporal lobe epilepsy. However, emerging clinical and experimental evidence indicates that parahippocampal territories, such as the perirhinal cortex (PC) and entorhinal cortex (EC), may contribute to seizure initiation and perhaps epileptogenesis. Because there is limited information regarding the involvement of different parahippocampal cortices in the initiation of limbic seizures, we addressed this issue by using horizontal rat brain slices containing both EC and PC along with the hippocampus. **Methods:** Three simultaneous field potential recordings were placed within the medial EC (ECm), lateral EC (ECl) and PC in slices superfused with the convulsant drug 4-aminopyridine (4-AP, 50 μM). **Results:** The predominant pattern of epileptiform activity recorded in connected slices consisted of CA3-driven interictal discharges (duration, 0.29 ± 0.01 s; interval of occurrence, 0.3 ± 0.02 Hz). Abating the propagation of this interictal pattern to EC and PC, by cutting the Schaffer collaterals, disclosed slow interictal (duration, 0.47 ± 0.08 s; interval, 0.09 ± 0.01 Hz), and ictal-like discharges (duration, 30 ± 3.27 s; interval, 0.008 ± 0.001 Hz); the latter was associated with *N*-methyl-D-aspartate (NMDA)-receptor mechanisms. Simultaneous recordings performed in the ECm and ECl and in PC demonstrated bidirectional propagation of slow interictal and ictal discharges; time-delay measurements from PC to ECl or from ECl to PC revealed delays of 11.2–50.4 ms and 7.6–66.2 ms, respectively. Interictal and ictal events most often initiated in the ECm and PC, respectively. Physical separation of the connections between the ECm, ECl, and the PC, or functional inactivation of defined cortical areas by focal application of glutamatergic receptor antagonists resulted in independent epileptiform activity. **Conclusions:** This evidence indicates that all parahippocampal networks analyzed in this study can generate epileptiform synchronization that sustains limbic seizures. Further, the results indicate the PC exhibits a preference for ictogenesis in vitro. (Supported by Canadian Institutes of Health Research and Epilepsy Canada.)

2.003
ADENOSINE RELEASE IN THE HIPPOCAMPUS IS DEPENDENT ON INTRACELLULAR pH

Chris G. Dulla, Susan A. Masino, and Kevin J. Staley (Neuroscience Program, UCHSC, Denver, CO; Pharmacology, UCHSC, Denver, CO; Pediatrics, UCHSC, Denver, CO)

Rationale: Adenosine is a neuromodulator in the CNS that decreases both presynaptic release of neurotransmitter and postsynaptic excitability via the adenosine A_1 receptor. While endogenous levels of adenosine inhibit synaptic transmission tonically, during times of metabolic stress (hypoxia/anoxia, ischemia, seizure, etc.), large amounts of adenosine are released. The profound inhibitory influence of this additional adenosine is thought to be neuroprotective. All of these metabolically stressful conditions, known to release adenosine, are also associated with a decrease in intracellular pH. Here we used electrophysiological recordings to test the hypothesis that intracellular pH changes cause adenosine release in the CA1 region of rat hippocampal slices. **Methods:** Hippocampal slices were prepared from 6- to 8-week-old Sprague–Dawley rats; 400-μm slices were cut in ice-cold artificial cerebrospinal fluid (aCSF) bubbled with 95% oxygen/5% carbon dioxide. Field excitatory postsynaptic potentials (fEPSPs) were evoked by stimulation of Schaffer collateral axons with a bipolar stimulating electrode, and the fEPSP slope was measured with a recording electrode placed in the stratum radiatum of area CA1. **Results:** Under control conditions, decreasing intracellular pH with 20 mM propionic acid did not appear to cause an increase in extracellular adenosine as measured by either the amplitude or slope of fEPSPs. Interestingly, however, when neuronal excitability was increased [such as during γ-aminobutyric acid $(GABA)_A$ receptor blockade with picrotoxin], a decrease in intracellular pH with propionic acid increased the release of adenosine and inhibited excitatory neurotransmission. This effect was blocked by theophylline, a nonselective adenosine antagonist, and was

not present in adenosine A_1 receptor knock-out mice. To try to limit the pH-altering effect of propionic acid, we used a higher buffering capacity aCSF (52 m*M* Na bicarbonate bubbled with 90% O_2/10% CO_2). This completely blocked the effect of propionic acid when applied during $GABA_A$, providing further evidence that it is the pH change that causes the adenosine-mediated decrease in synaptic transmission. A dose–response curve for 2-chloroadenosine, a nonmetabolizable adenosine analogue, was performed under control conditions and in the presence of propionic acid, which showed that the pH effects could not be explained by changes in binding or receptor coupling. **Conclusions:** We conclude that intracellular pH causes adenosine release in area CA1 of the hippocampus during $GABA_A$ receptor blockade. This suggests that pH changes must occur in conjunction with other cellular events, such as increased cytosolic calcium levels, electrical activity, or reduced chloride shunting of excititory inputs, to release adenosine. This has implications regarding the brain's ability to regulate excitability during seizures and other types of heightened neuronal activity. (Supported by NIH grants R01 29173 and T32 HD41697-01.)

2.004

TOPIRAMATE SELECTIVELY BLOCKS GLuR5 KAINATE RECEPTOR–MEDIATED EXCITATORY SYNAPTIC TRANSMISSION IN AMYGDALA: EVIDENCE FOR INDIRECT ACTION VIA MODULATION OF PROTEIN KINASE A–DEPENDENT PHOSPHORYLATION

Divina S. Gryder and Michael A. Rogawski (Epilepsy Research Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD)

Rationale: Although the mechanism of action of the anticonvulsant (AED) topiramate (TPM) is poorly understood, there is evidence that the drug may affect glutamatergic excitatory neurotransmission though an interaction with AMPA/kainate receptors. We have demonstrated that GluR5 kainate receptors mediate a portion of the synaptic excitation of basolateral amygdala (BLA) principal neurons evoked by external capsule (EC) stimulation. In this study, we used selective antagonists to isolate the AMPA and GluR5 kainate receptor components of the EC-evoked excitatory synaptic current (EPSC) and compared the effects of TPM on these two distinct EPSC components. We also examined the possibility that TPM acts indirectly via effects on protein phosphorylation. **Methods:** Whole-cell patch recordings were carried out from visually identified BLA principal neurons in 450-μm coronal slices of rat amygdala. Synaptic currents were evoked with 100-μs monophasic stimuli applied via a tungsten bipolar electrode placed on the EC. Mixed AMPA and GluR5 kainate receptor responses were isolated by perfusion with 100 μ*M* D-AP5, 10 μ*M* bicuculline methiodide, and 10 μ*M* SCH 50911 to block the *N*-methyl-D-aspartate (NMDA), γ-aminobutyric acid $(GABA)_A$ and $GABA_B$ receptors, respectively. AMPA receptor currents were further isolated by addition of 10 n*M* LY 293558, which at these low concentrations selectively blocks GluR5 kainate receptors. Conversely, the GluR5 kainate receptor component was isolated with 50 μ*M* GYKI 52466, a selective AMPA-receptor antagonist. **Results:** TPM perfusion caused a concentration-dependent reduction in the amplitude of the GluR5 response, with nearly complete block at 10 n*M*. The blocking action of TPM was uncharacteristically slow, suggesting that the drug may not directly interact with GluR5 kainate receptors. In contrast, the AMPA receptor-mediated component of the response was much less sensitive to TPM, with only minimal block at concentration as high as 10 μ*M*. The effect of TPM was mimicked by the protein kinase A (PKA) inhibitor H-89 (1 μ*M*), consistent with the possibility that TPM may selectively block GluR5 kainate receptors by modulating PKA-dependent phosphorylation of GluR5 kainate receptors or related proteins. **Conclusions:** The ability of TPM to selectively block kainate receptors and not AMPA receptors could contribute to its unique anticonvulsant properties and its relatively few side effects compared with other types of glutamate-receptor antagonists. Our preliminary studies support the view that TPM acts via a nonconventional modulatory mechanism. (Supported by NINDS-NIH.)

2.005

DOPAMINE ALTERS THRESHOLD FOR INITIATION OF EPILPTIFORM ACTIVITY IN RAT NEOCORTEX

John J. Hablitz and Carlos Gonzalez-Islas (Department of Neurobiology, University of Alabama at Birmingham, Birmingham, AL)

Rationale: Dopamine (DA) is believed to be an endogenous neuromodulator in the cerebral cortex and to be important for normal brain function. Clinical and experimental studies have also implicated DA in the pathogenesis of a number of neurologic and psychiatric disorders, including epilepsy. DA has been shown to be an important modulator of epileptiform discharges in vivo and in vitro. The mechanisms underlying these effects are unclear. We have examined the effect of DA on excitatory postsynaptic currents (EPSCs) and the spatial–temporal spread of activity in neocortex. **Methods:** Experiments were performed in slices of rat neocortex maintained in vitro. Epileptiform activity was induced by bath application of bicuculline. Whole-cell voltage-clamp recordings were used to study synaptic activity evoked by intracortical stimulation. The voltage-sensitive dye RH 414 and a diode recording array was used to study the spatial–temporal spread of activity. Threshold for evoking epileptiform activty was assesed before and after bath application of 20 μ*M* DA or 10 μ*M* SKF 38393. **Results:** Weak intracortical stimulation did not evoke epileptiform activity under control conditions. Bath application of 20 μ*M* DA had two effects in pyramidal cells. EPSC amplitude was increased by 16%. This was accompanied by the appearance of late epileptiform discharges of variable latency and amplitude. This activity presumably represents activity in recurrent excitatory pathways. Epileptiform discharges are generally thought to represent the synchronous discharge of a local population of neurons. The factors that determine whether a discharge stays localized or spreads are poorly understood. The spatial–temporal extent of neocortical activation was studied with voltage-sensitive dyes in 17 slices from nine animals. DA enhanced the spatial extent of neocortical activation in response to subthreshold stimulation in four slices. The width of cortical area activated increased from 653 to 1,586 μm. DA also increased the probability of evoking epileptiform discharges in nine slices. In the presence of DA, previously subthresold stimuli triggered epileptiform discharges that could propagate throughout the slice. Similar results were obtained with the specific D1-receptor agonists SKF 38393, suggsting involvement of D1-like receptors. **Conclusions:** DA enhanced the formation of dynamic assemblies of synchronized neurons in neocortical slices. This increased the initiation of propagating epiletiform discharges. It appears that activation of D1-like receptors can have a proconvulsant effects, altering the threshold for epileptiform activity and increasing the probability of spread of paroxysmal activity. These results suggest that treatment of other neurologic disorders with DA agonists and antagonists could potentially affect patients with epilepsy. (Supported by NS18145 and NS22373.)

2.006

LOW-FREQUENCY STIMULATION OF AMYGDALA INHIBITS ICTOGENESIS IN THE PERIRHINAL CORTEX

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Rationale: Low-frequency (0.5–1 Hz) electrical stimulation of hippocampal outputs controls ictogenesis in the limbic system maintained in vitro in a slice preparation (Barbarosie and Avoli, 1997). This procedure may have potential therapeutic implications. Hence, we studied whether similar low-frequency stimuli delivered in the basolateral amygdala (BLA) could inhibit ictal discharges generated by perirhinal cortex (PC) netwoks. **Methods:** Field potential and sharp-electrode intracellular recordings were conducted within horizontal rat brain slices containing the PC and a portion of the BLA. Connections with the hippocampus proper were surgically separated. Epileptiform activity was induced by bath applying the convulsant drug 4-aminopyridine (4-AP, 50 μ*M*). Electrical stimuli were delivered in BLA through bi-

polar tungsten electrodes. **Results:** Electrical stimuli applied to the BLA under control conditions elicited monosynaptic excitatory responses in neurons recorded in the middle layers of the PC. After addition of 4-AP to the bathing medium, ictal discharges (duration, ≤40 s) appeared in both BLA and PC. This epileptiform activity was characterized by prolonged, *N*-methyl-D-aspartate (NMDA) receptor-dependent depolarizations in regularly firing PC neurons. Moreover, cutting the connections between PC and BLA made independent interictal and ictal discharges occur in both structures. In PC/BLA-connected slices, after addition of 4-AP, repetitive stimulation at frequencies ≥0.5 Hz decreased and eventually blocked the ictal activity recorded in PC. **Conclusions:** These results show that reciprocally connected BLA/PC networks generate ictal discharges in response to bath application of 4-AP. These events, which resemble the electrographic limbic seizures seen in mesial temporal lobe epilepsy patients, can originate independently in either BLA or PC. Moreover, we have demonstrated here that repetitive, low-frequency activation of BLA outputs directed to the PC can control ictogenesis in this limbic area. (Supported by Canadian Institutes of Health Research and Savoy Foundation.)

2.007

INTRAHIPPOCAMPAL *N*-METHYL-D-ASPARTATE PRODUCES AGE- AND TIME-DEPENDENT NEUROTOXICITY IN RATS

Jaspreet Kaur and Linda K. Friedman (Depatment of Neuroscience, Seton Hall University, South Orange, NJ)

Rationale: Clinical studies and experimental models of epilepsy have shown that the immature brain is highly susceptible to seizures and status epilepticus compared with the mature brain. However, the immature brain is relatively resistant to seizure-induced damage. *N*-methyl-D-aspartate (NMDA) induces seizures and plays a predominant role in neurotoxicity. Maturational effects of NMDA on the hippocampus have not been previously explored. Therefore, we microinjected varied doses of NMDA into the hippocampus of mature and immature rats. **Methods:** Rat pups (P13) and adults were anesthetized with a mixture of ketamine and xylazine and then stereotactically implanted with a cannula/electrode assembly in the CA1 region of the hippocampus. After 24-h postoperative rest, different doses of NMDA (2.5, 15, 25, 50 nmoles) were delivered with a microinfusion pump and 5-μl syringe. EEG recordings were obtained using Datawave acquisition software interfaced to an IBM computer. The animals were killed at 1 and 5 days after intrahippocampal NMDA. Classic histologic stains were used to assess the cell injury. and the lesion area was quantified with Scion Image software. **Results:** At low doses, both adult and rat pups manifested similar behavior within 20 min that included scratching, running, hyperactivity, wet-dog shakes, and body stiffness. At high doses, the adults showed additional behavior that included violent running, shrill vocalization, frothing, and occasional forelimb clonus, but the rat pups showed behavior similar to that observed at low doses. In adults, 1 day after intrahippocampal NMDA at 15 nmol, histologic damage was preferential to the CA1 subregion. Many cells were lost, and the lesion was similar at 1 and 5 days. In contrast, at higher doses (25–50 nmol), the lesion volume was greater and showed a spread to other hippocampal subfields (DG, hilus, and CA3). In rat pups at 1 day, no damage was detected after 2.5 or 25 nmol of NMDA. However, at 5 days, pups showed a similar pattern of generalized cell loss (15 nmol, 0.535 mm^3; 25 nmol, 4.34 mm^3) but to a lesser degree than adults (15 nmol, 2.77 mm^3; 25 nmol, 5.16 mm^3). **Conclusions:** The NMDA infusion data suggest that the immature hippocampus is more susceptible to seizures but resistant to neuronal damage induced by NMDA relative to the mature brain, somewhat similar to other convulsants (e.g., kainic acid, pilocarpine). However, NMDA is not acutely toxic to the immature hippocampus at doses that induce seizures, suggesting differential and age-specific mechanisms of toxicity. Although NMDA produced dose-dependent hippocampal damage in adults and pups, the cell loss was significantly delayed and less extensive in rat pups, suggesting that there is an increased window of therapeutic intervention in developmental epilepsy. (Supported by Supported by NIH-NS-38069 and NJ Neuroscience Institute.)

2.008

EFFECTS OF NITRIC OXIDE ON CORTICAL EXCITATORY POSTSYNAPTIC POTENTIALS IN THE THALAMIC RETICULAR NUCLEUS: IMPLICATIONS FOR ABSENCE EPILEPSY

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Rationale: The corticothalamic feedback projection from layer VI of the cerebral cortex converges onto both thalamic relay cells (TC) and thalamic reticular nucleus (TRN) cells. The degree of cortical feedback directly AFFEcts the generation of spike–wave discharges within thalamic networks. Much like those seen in TC cells, corticothalamic synapses within the TRN also contain AMPA and *N*-methyl-D-aspartate (NMDA) receptors. The object of this study was to delineate how brain nitric oxide synthase (bNOS) containing terminals from the brainstem parabrachial region (PBR), which pervade both the LGN and TRN, influence corticothalamic feedback. We have previously shown (Kurukulasuriya et al. *Epilepsia* 2001;42:6) that nitric oxide, NO released from the PBR, enhances corticothalamic excitatory postsynaptic potentials (EPSPs) in the LGN. This effect was further shown to be largely mediated through a cyclic guanosine monophosphate (cGMP)-mediated NO-NMDAR interaction. Because TRN cells are a preferential target for corticothalamic fibers (Steriade. *Proc Natl Acad Sci U S A* 2001;98:3625–7; Golshani et al. *Proc Natl Acad Sci U S A* 2001;98: 4172–7), the effect of NO on EPSPs within the TRN is of particular significance. We hypothesized that NO influences corticothalamic EPSPs in the TRN. **Methods:** We tested this with intracellular recordings in adult ferret (>P35) TRN/LGN slices. We evoked EPSPs in the TRN via a bipolar stimulating electrode (1-mA, 0.1-ms pulses) placed in the optic radiations. γ-Aminobutyric acid $(GABA)_A$ and $GABA_B$ IPSPs were blocked with 50 m*M* bicuculline methiodide and 200 m*M* 2-OH-Saclofen, respectively. Pharmacologic agents including the NO donor S-nitroso-N-acetyl-DL (SNAP, 2 m*M*) were bath applied using a computer-controlled superfusion system. **Results:** As with TC cells, CT EPSPs in hyperpolarized TRN cells were rapid, whereas a slower component appeared at depolarized potentials (n = 24). Paired-pulse facilitation of the CT EPSPs in the TRN was apparent (n = 10). The delayed EPSP in the TRN was shorter compared to those seen in the LGN. The rapid component was DNQX (30 m*M*) sensitive and AMPAR mediated (n = 3), whereas the delayed component was APV (150 m*M*) sensitive and NMDAR mediated (n = 3). Application of the NO donor SNAP (2 m*M*) selectively enhanced the NMDAR component of the TRN CT EPSP (n = 5), sometimes transforming the EPSP into a burst. Voltage isolation of the AMPA component revealed that NO did not significantly alter AMPA transmission (n = 6). **Conclusions:** The NO mediated increase in NMDAR activity within the TRN may result in greater synaptic activation of TRN cells, which in turn could increase inhibition of TC cells, promoting rebound bursts. This finding suggests a brainstem/PBR contribution to the relative strength of corticothalamic excitatory input in the TRN. We speculate that controlling the nitrergic influence at the cortico-TRN synapse could affect the generation of thalamic spike-and-wave discharges. (Supported by EY11695.)

2.009

THE ROLE OF GLUTAMATE TRANSPORT IN TUMOR-INDUCED EPILEPTOGENESIS

Jamie L. Maguire, Stephen H. Williams, and Margaret L. Sutherland (The Department of Pharmacology, The George Washington University, Washington, DC)

Rationale: Epilepsy is a condition in which the brain is rendered electrically unstable because of a genetic abnormality or an underlying derangement, such as major head trauma, stroke, or benign and malignant gliomas. Approximately 75% of patients with CNS gliomas develop seizures. The hyperexcitable state of the epileptic brain results

from a disruption in the balance between excitation and inhibition. Glutamate transporters involved in glutamate clearance out of the synatptic cleft have been implicated in the manifestation of seizures. Expression of the glutamate transporter EAAT2 is decreased in the brains of epilepsy patients as well as in experimental models of epilepsy. Glutamate transporters function to maintain extracellular concentrations of glutamate below neurotoxic levels and prevent neurotoxicity. Neuronal cell loss accompanies and may contribute to glioma-related epileptogenesis. However, it remains controversial whether cell death precedes seizure activity or if cell death is a consequence of seizures. We hypothesize that increased glutamate transport will decrease glioma-associated seizure activity and provide neuroprotection against neuronal cell death. **Methods:** Recently our laboratory established a transgenic mouse model that overexpresses the glutamate transporter, EAAT2. Seizures were induced in wild-type and EAAT2-overexpressing mice by injection of 2 million C6 glioma cells into the motor cortex. Epileptiform activity was assessed in vivo by EEG recording and in vitro by extracellular recording in the hippocampal slice model. Cell death was analyzed over the course of tumor progression by TUNEL analysis and neuronal cell counts. **Results:** Using this model, we demonstrate that increased glutamate uptake attenuates glioma-associated epileptiform activity both in vivo and in vitro. In addition, the slow onset of seizure activity in the glioma model enables us to analyze cell death over the course of seizure induction. Here we demonstrate that cell death occurs in the cortex and bilaterally in the hippocampus before seizure onset, and increased glutamate transport decreases the extent of neuronal cell loss. **Conclusions:** These findings suggest a model for glioma-induced epileptogenesis in which cell death shifts the balance between excitation and inhibition, resulting in glutamatergic overexcitation. Glutamate transport may be a therapeutic target for the treatment of glioma-induced neurologic damage and secondary epileptogenesis. (Supported by NINDS-NS042854 and the John F. Annegers Pre-doctoral Research Fellowship from the Epilepsy Foundation.)

2.010

_N_-METHYL-D-ASPARTATE APPLICATION CHANGES THE MEMBRANE PROPERTIES FROM REGULAR SPIKING INTO BURSTING IN A SUBPOPULATION OF CORTICAL NEURONS

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Rationale: Many studies have focused on understanding the role of *N*-methyl-D-aspartate (NMDA) receptors in mediating synaptic transmission, but little is known about their role in modulating voltage-dependent membrane properties. The objective of the present study was to investigate how NMDA alters voltage-dependent membrane properties in cortical neurons as a potential mechanism for the generation of epileptic seizures. **Methods:** Experiments were performed on male and female mice (P8–P13) that were deeply anesthetized with ether. The cortex was isolated in ice-cold artificial CSF containing (in m*M*): 118 NaCl, 3 KCl, 1.5 $CaCl_2$, 1 $MgCl_2$, 25 $NaHCO_3$, 1 NaH_2PO_4, and 30 D-glucose at a pH of 7.4 bubbled with carbogen (95% oxygen and 5% CO_2). The cerebral hemispheres were separated at the midline. Slices (500 μm thick) were sectioned 1,500 μm from the frontal pole and were immediately transferred into a recording chamber, which was maintained at a temperature of 29°C. After 30 min, the potassium concentration was raised from 3 to 5 m*M* to obtain spontaneous rhythmic activity. Population activity recordings were obtained with suction electrodes positioned onto the surface of cortical layers 4 and 5. Intracellular whole-cell patch-clamp recordings were obtained from cortical neurons using the blind-patch technique. Cell layer and cell type were identified by staining each neuron with biocytin. **Results:** Intracellular and extracellular recordings were simultaneously obtained from the motor cortex. The majority of slices spontaneously generated population activity occurring in slow (<1 Hz) recurrent oscillations, which changed into higher frequency (>3 Hz) epileptiform population activity after the bath application of NMDA (5–10 μ*M*). Associated with the induction of epileptiform activity was a change in the intrinsic membrane properties of individual cortical neurons. Under control conditions, depolarizing current injections evoked tonic regular spiking activity, which linearly increased in frequency when increasing the amplitude of current injections. The same neurons generated rhythmic burst activity in the presence of NMDA. Brief current pulses reset the rhythmic burst activity, long depolarizing current injections increased, and hyperpolarizing current injections decreased the frequency of intrinsically generated pacemaker activity. This bursting activity persisted in the absence of extracellular population activity, which was eliminated by blocking calcium currents and synaptic transmission with Cd^{2+} (200 μ*M*). The NMDA-induced bursts depended on the activation of the persistent sodium current and were blocked by riluzole (20 μ*M*). **Conclusions:** We conclude that NMDA induces in a subpopulation of cortical neurons intrinsic bursting properties, which depend on the activation of the persistent sodium current. This change in the intrinsic membrane properties could be a possible cellular mechanism that leads at the network level to the transformation from slow recurrent oscillations to high-frequency epileptiform activity. [Supported by Falk Foundation (C.J.M., W.vD., K.E.H.); Rett Syndrome Research Foundation (J.M.R.); and NIH HL60120 (J.M.R.).]

2.011

PROCONVULSANT EFFECTS OF A LOW-AFFINITY GLUTAMATE ANTAGONIST

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Rationale: Periodic population bursts in the CA3 area of the hippocampus are an in vitro model of interictal activity. These discharges are thought to be triggered by spontaneous glutamate release at recurrent collateral synapses. Low concentrations of quinoxaline AMPA kainate receptor antagonists increase the time interval between bursts by diminishing the excitatory effects of the released glutamate. To determine the dose–response relation between AMPA/kainate antagonism and burst interval, we used the water-soluble, low-affinity glutamate antagonist kynurenic acid (KYNA). **Methods:** Hippocampal coronal slices were prepared from adult (4–6 weeks) Sprague–Dawley rats. A stimulating electrode and an extracellular recording electrode were placed in the stratum pyramidale layer of the CA3. Bursting was induced by a tetanus protocol (100 Hz for 1 s); 100 μ*M* picrotoxin blocked γ-aminobutyric acid $(GABA)_A$ receptors; 10 μ*M* glycine was added to the bath to avoid interactions at the glycine site of the NMDA receptor. Evoked responses were established by stimulating for 20 μs every 20 s. Then 20 μ*M* KYNA was added to the bath once a baseline response was established. **Results:** After development of spontaneous bursting of the cell body layer of the CA3, addition of 20 μ*M* KYNA increases the frequency of interictal events by 25% ($n = 3$). The same concentration of KYNA does not affect the amplitude of evoked responses in this area of the CA3 ($n = 6$). **Conclusions:** Low concentrations of KYNA decreased the interval between bursts. This effect is opposite to previous observations using higher-affinity quinoxaline AMPA/kainate antagonists. Our observations support the hypothesis that low-affinity AMPA/kainate-receptor competitive antagonists decrease the postburst level of receptor desensitization at the glutamatergic synapses that initiate CA3 bursting. (Supported by NIH.)

2.012

L-CYSTEINE SULFINIC ACID, A POTENTIAL NOVEL ANTIEPILEPTOGENIC AGENT

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Rationale: Both (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) and (S)-3,5-dihydroxyphenylglycine (DHPG) convert interictal bursts into ictal-length discharges, suggesting a role for group I metabotropic glutamate receptors (mGluRs) in the interictal-to-ictal transition. However, only DHPG elicits persistent prolongation of epileptiform bursts. Whereas both ACPD and DHPG activate group I

mGluRs, there are reported differences in their ability to activate phospholipase D (PLD)-coupled receptors. We therefore examined whether this distinction accounts for the differences in effect of group I mGluR activation via ACPD versus DHPG. **Methods:** Transverse 400-μm guinea pig hippocampal slices were perfused with artificial CSF, oxygenated with 95% O_2/5% CO_2 and maintained at 35.5–36.0°C. Intracellular recordings were obtained from CA3 stratum pyramidale using thin-walled glass microelectrodes. Drugs were applied via continuous bath perfusion. In all experiments, baseline interictal bursts (350–475 ms) were elicited with picrotoxin, an antagonist of γ-aminobutyric acid $(GABA)_A$ receptor–mediated inhibition (50 μ*M*). **Results:** Both ACPD (100 μ*M,* 40 min) and DHPG (50 μ*M,* 40 min) converted picrotoxin-induced interictal bursts into 1.5- to 2.5-s discharges (1,940 ± 72 ms; n = 5, and 1,886 ± 61 ms; n = 6, respectively). ACPD-induced prolonged bursts returned to interictal burst length (461 ± 23 ms, n = 5) within 10 min of agonist washout, whereas DHPG-induced prolonged bursts persisted for hours after washout (1,305 ± 104 ms at 2-h washout, n = 6). ACPD-induced reversible burst prolongation proceeded unaltered in the presence of L-cysteine sulfinic acid (L-CSA 100 μ*M*), an agonist at PLD-coupled receptors (1,761 ± 27 ms, n = 4). In contrast, L-CSA when coapplied with DHPG prevented the induction of prolonged bursts (505 ± 10 ms, n = 7). Nevertheless, maintenance of the prolonged bursts after DHPG washout was not significantly affected by L-CSA application: at 1-h washout, burst length was 1,007 ± 32 ms; after 30-min L-CSA, burst length was 1,016 ± 84 ms (n = 4). **Conclusions:** Previous work from this laboratory has demonstrated that the selective group I mGluR agonist DHPG elicits persistent burst prolongation, suggesting a role for these receptors in some forms of epileptogenesis. Although the induction process appears to be independent of NMDA-receptor activation (Galoyan and Merlin, 2000) or ongoing bursting activity (Merlin, 1999), it is strongly suppressed by protein synthesis inhibitors (Merlin et al., 1998). L-CSA, an agonist at PLD-coupled receptors, has a similar effect to the protein-synthesis inhibitors in that it prevents induction of prolonged bursts without suppressing the DHPG-mediated increase in interictal burst frequency. Furthermore, both types of agents have no effect on the maintenance of prolonged bursts once they have been fully induced. These data suggest that L-CSA may be useful as a novel antiepileptogenic agent. (Supported by NIH NS40387 to L.R.M.; SFN MNFP to M.J.R.)

2.013

METABOTROBIC GLUTAMATE RECEPTOR INVOLVEMENT IN EPILEPTIFORM ACTIVITY PRODUCED BY HIGH POTASSIUM IN HIPPOCAMPAL SLICES

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Rationale: Previous work has indicated that the nonspecific metabotropic glutamate receptor (mGluR) antagonist S-a-methyl-4-carboxyphenylglycine (MCPG) suppresses epileptiform activity produced by elevated potassium in the hippocampal slice (McBain. *J Neurophysiol* 1995). We evaluated the effect of selective mGluR-receptor antagonists on epileptiform discharges produced by elevated extracellular potassium ($[K^+]_o$). **Methods:** Hippocampal slices were prepared from young adult rats and exposed to an artificial cerebrospinal fluid with a $[K^+]_o$ of 7.5 m*M*. Extracellular recordings were made in the CA3 region to monitor spontaneously occurring epileptiform discharges. The rate of discharges was determined and changes produced by MCPG, 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester (CPCCOEt, an mGluR1 antagonist), LY367385 (an mGluR1 antagonist), 2-methyl-6-(phenylethynyl)pyridine (MPEP, an mGluR5 antagonist), and LY341495 (mGluR2 and 3 antagonist at concentrations <100 n*M*) were assessed. **Results:** MCPG (250 μ*M*) decreased the rate of high $[K^+]_o$ epileptiform discharges from 0.37 ± 0.05 to 0.175 ± 0.07 Hz ($p < 0.05$; n = 43). Neither the selective mGluR1 antagonist CPCCOEt (30 μ*M*) nor the selective mGluR5 antagonist MPEP (10 μ*M*) changed the rate of discharges. Coapplication of both mGluR1 and five noncompetitive antagonists (100 μ*M* CPCCOEt and MPEP) actually increased the rate of discharges from 0.16 ± 0.05 to 0.26 ± 0.07 Hz ($p < 0.05$; n = 5). The competitive mGluR1 antagonist LY367385 depressed the rate of discharges at concentrations >3 μ*M* (0.38 ± 0.05 vs. 0.21 ± 0.04 Hz; $p < 0.05$; n = 28). The selective group II antagonist LY341495 (10 n*M*) stopped discharges in eight of 10 slices with 30 n*M* stopping the discharges in the two slices that continued to have spontaneous activity **Conclusions:** Group I agonists produce epileptiform activity in the hippocampal slice, and we expected the suppression of high $[K^+]_o$ discharges by MCPG to be a result of group I antagonism. Surprisingly, selective mGluR1 or five noncompetitive antagonists did not alter the rate of high $[K^+]_o$ epileptiform discharges, although the competitive mGluR1 antagonist LY367385 depressed the discharge rate. Group II mGluR antagonism suppressed discharges completely. These results suggest that elevation in $[K^+]_o$ activates mGluR1 and group II mGluR and that these receptors contribute to the generation of high $[K^+]_o$-induced epileptiform discharges. (Supported by Veterans Administration Research.) (Disclosure: Salary: Veterans Administration; Grant: Veterans Administration.)

2.014

ANTICONVULSANT EFFECTS OF ENDOGENOUS CANNABINOIDS IN VITRO

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Rationale: Although only one cannabinoid receptor (CB1), located on γ-aminobutyric acid (GABA)ergic terminals, has been identified in the brain, its absence does not eliminate cannabinoid signaling at glutamatergic synapses. Cannabinoid pharmacology at excitatory synapses is not well characterized. Current evidence indicates that postsynaptic calcium entry is required for cannabinoid synthesis and release. Because CA3 interictal activity results in a large postsynaptic calcium influx in CA3 cells, we investigated the effects of cannabinoid signaling in our preparation. **Methods:** We tested the effects of cannabinoid antagonist AM251 (2 μ*M*), and of cannabinoid uptake inhibitor AM404 (20 μ*M*), on the CA3 synchronized network activity using extracellular and intracellular recordings. Hippocampal coronal slices were prepared from 4- to 6-week-old Sprague–Dawley rats. Spontaneous bursting of the CA3 network was induced by blockade of $GABA_A$ and $_B$ conductances with 100 μ*M* picrotoxin and 1 μ*M* CGP55845A, respectively. **Results:** Cannabinoid antagonism increases the frequency of CA3 interictal activity by 30% (n = 4). Additionally, cannabinoid uptake inhibition results in large decreases in the duration of CA3 bursts (30%, n = 5), paired in 40% of cases with large decreases in CA3 burst frequency. Comparison of mEPSCs amplitude distributions before and after application of the cannabinoid uptake antagonist AM404 indicates that endogenous cannabinoids selectively affect the probability of multivesicular release but not univesicular release at recurrent collateral synapses. **Conclusions:** These data suggest that endogenous cannabinoids have an anticonvulsant effect on CA3 synchronized activity. By selectively affecting the probability of multivesicular glutamate release but not univesicular release at recurrent collateral synapses, endogenous cannabinoids decrease the extent of synchronized CA3 network activity. (Supported by NIH.)

2.015

ELECTROPHYSIOLOGIC EVIDENCE OF FORMATION OF NEW LOCAL EXCITATORY CIRCUITS AMONG CA1 PYRAMIDAL NEURONS IN THE KAINATE MODEL OF EPILEPSY

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Rationale: Local excitatory circuits are thought to synchronize neuronal activity during seizures. Formation of new local excitatory circuits has been proposed to be one major contributor to epileptogenesis. This hypothesis was tested in the hippocampal CA1 area of the kainate-treated rat model of temporal lobe epilepsy. **Methods:** Whole-cell recordings of CA1 pyramidal neurons, with flash photolysis of caged glutamate as a focal excitant, were used to study local excitatory connections in CA1. Kainate-treated rats (n = 15, 3–9 months after treat-

ment), which had been observed to have spontaneous motor seizures, and saline-treated or age-matched control rats (n = 6) were studied. All experiments were done in isolated CA1 minislices, and in the presence of bicuculline (30 μ*M*) to block γ-aminobutyric acid $(GABA)_A$-receptor–mediated inhibition. **Results:** Spontaneous excitatory postsynaptic currents (sEPSCs) were observed in 69% (27 of 39 neurons) from kainate-treated rats and in 55% (11 of 20) of the controls. Although the sEPSC amplitude of the two groups was similar, the sEPSC frequency in the kainate group was considerably higher than in the controls. The sEPSC frequency, but not amplitude, in kainate-treated animals was correlated with their seizure frequency. Local excitatory interactions between CA1 pyramidal neurons were detected with focal photolysis of caged glutamate in 31% (12 of 39) of neurons from epileptic animals, but only in one of 20 neurons (5%) from the control group. Within the kainate group, the rats that showed excitatory synaptic interactions had a higher sEPSC frequency than those rats that did not. Those rats with excitatory interactions also had a higher seizure rate. **Conclusions:** Rats with kainate-induced epilepsy exhibited enhanced sEPSCs and increased connectivity among hippocampal CA1 neurons, which suggests that the formation of new local excitatory circuits was associated with recurrent seizures. (Supported by NS 16683.)

2.016

INCREASED GLUTAMATE TRANSPORTER ACTIVITY IS NEUROPROTECTIVE IN A TEMPORAL LOBE EPILEPSY MODEL

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Rationale: Recent evidence suggests that temporal lobe epilepsy is associated with changes in the level of expression of EAAT2 (Glt-1), the predominant CNS glutamate transporter. Similar findings have been made in experimental models of temporal lobe epilepsy. One important role the transporters may play is to prevent glutamate levels from rising to neurotoxic levels during seizure activity. This could be particularly important in temporal lobe epilepsy, where cell loss from the hippocampus can occur (Ammon's horn sclerosis). We tested the hypothesis that enhanced glutamate transporter activity might subserve a neuroprotective role under seizure conditions with a mouse EAAT2 overexpression model. **Methods:** To examine the role of glutamate transporters in a temporal lobe epilepsy model, we generated a transgenic murine model of EAAT2 glutamate transporter overexpression. In the EAAT2 transgenic model, overexpression of EAAT2 was driven by the astrocyte-specific promoter glial fibrillary acidic protein (GFAP) and resulted in a three- to fivefold increase in cortical and hippocampal synaptosomal glutamate uptake. **Results:** Transgenic animals exhibited higher survival rates after i.p. injection of 30 mg/kg kainic acid than age-matched wild-type littermates. Histologic analysis, 7 days after seizure induction, indicated that in both EAAT2 transgenic lines, increased glutamate uptake resulted in a 70–80% reduction in latent excitotoxic cell death compared with wild-type animals, as determined by TUNEL analysis. Immediate-early gene induction and inhibition of astrogliosis were also significantly reduced in EAAT2 transgenic animals compared to wild type. To determine if electrical activity was affected, we recorded surface cortical EEG activity before and during seizures. In two independently derived lines of EAAT2 transgenic mice, seizure activity after administration of 30 mg/kg kainic acid was reduced by 80% compared with recordings from age-matched wild-type animals. **Conclusions:** Our results suggest that increased glutamate uptake can have both short- and long-term effects in the seizure sequelae. We find that EAAT2 overexpression significantly reduces excitotoxicity in the kainic acid model. Interestingly, overexpression of the glutamate transporter also reduces the severity of the paroxysmal electrical events that occur during the seizure, suggesting that glutamate may play a role in controlling excitability in glutamatergic circuits during hypersynchronous activity. [Supported by grants from NINDS (NS042854) and MDA (M.L.S.).]

2.017

***N*-METHYL-D-ASPARTATE RECEPTOR ACTIVATION PRODUCES HYDROGEN PEROXIDE AS DETECTED BY IN VIVO ELECTRON SPIN RESONANCE**

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Rationale: Injury to hippocampal structures during epileptogenesis is associated with the excitotoxic effects of glutamate, especially through activation of *N*-methyl-D-aspartate (NMDA) receptors (NMDA-R). Such NMDA-R activation results in phospholipase A2 (PLA2)-mediated generation of superoxide (O_2^-). Both enzymatic dismutation and spontaneous disproportion rapidly convert superoxide into hydrogen peroxide (H_2O_2). Although H_2O_2 is an important reactive oxygen species related to initiation of lipid peroxidation, there is no direct evidence that NMDA-R activation actually mediates H_2O_2 generation. **Methods:** After placement of a hippocampal probe in rats designed to allow in vivo microdialysis, hydrogen peroxide was generated by coperfusion of 10 m*M* NMDA for 10 min. Electron spin resonance (ESR) spectroscopy was used to measure formation of stable nitroxide radicals in the perfusate. Spin traps included *p*-acetamidophenol (p-AP) and 4-hydrazonomethyl-1-hydroxy-2,2,5,5,-tetramethyl-3-imidazoline-3-oxide (HHTIO). To confirm whether H_2O_2 generation was derived from PLA2 activation, an experimental group was given 250 m*M* quinacrine (QA,PLA2 inhibitor). **Results:** During perfusion with 10 m*M* NMDA, measurement of the appearance of stable nitroxide radicals with ESR showed a rapid increase in the generation of H_2O_2. After QA coperfusion, NMDA failed to induce the appearance of H_2O_2 in the perfusate. Lipid peroxidation is initiated by hydrogen abstraction from polyunsaturated lipid acids by hydroxyl radicals that are formed by the transformation of H_2O_2 and O_2^- and catalyzed by transition metals. Neural injury during seizures generates lipid peroxidation products. This study of in vivo changes demonstrated that NMDA-R activation induces H_2O_2 generation. Further PLA2 activation appears to be an important pathway involved in seizure-related neurotoxicity through lipid peroxidation. **Conclusions:** Kindling-induced epileptogeneisis depends upon changes modurated through NMDA receptors. While calcium-mediated neurotoxic effects involve glutamate effects on NMDA-R, we have shown that in freely moving rats, NMDA-mediated PLA2 activation will generate H_2O_2, leading ultimately to lipid peroxidative injury as well. [Supported by a Grant-in-Aid for Encouragement of Young Scientists (12770537) from the Ministry of Education, Science, Sport and Culture, Japan (to Y.U.).]

2.018

GluR5 KAINATE RECEPTOR–MEDIATED EPILEPTIFORM BURSTING IN RAT BASOLATERAL AMYGDALA IN VITRO

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Rationale: The excitatory neurotoxin kainate induces seizure activity, but whether this occurs through its actions on AMPA or kainate receptors is uncertain. We used ATPA, a selective GluR5 kainate-receptor agonist, to determine if activation of kainate receptors alone can induce epileptiform activity. Our experiments were carried out with field-potential recording in slices of the rat basolateral amygdala (BLA). We have previously shown that GluR5 kainate receptors, a member of the ionotropic glutamate receptor family, mediate a portion of synaptic excitation in the BLA. Moreover, in situ hybridization and immunocytochemical studies have confirmed that GluR5 kainate receptors are localized to BLA synapses. **Methods:** Coronal amygdala slices (500 μm) were vibratome cut from brains of 50–100 g male Sprague–Dawley rats and placed in a submerged recording chamber with oxygenated artificial CSF flowing at 2–3 ml/min (31°C, pH 7.4). After equilibration, an insulated bipolar stimulating electrode was po-

sitioned in the external capsule (EC), and a glass recording micropipette (5–10 MΩ) placed in the BLA. The specific GluR5 agonist (*RS*)-α-amino-3-hydroxy-5-*tert*-butyl-4-isoxazolepropionic acid (ATPA) was bath applied at concentrations from 1 to 10 μ*M*. In control experiments, molar equivalent concentrations of AMPA were used. In some experiments, the GluR5-specific antagonist LY 293558 was also added to the superfusion solution. The EC-evoked population and spontaneous extracellular field responses were amplified and stored in digital form. **Results:** In nine of 10 slices, bath application of ATPA (10 μ*M*) elicited spontaneous epileptiform bursts within 5–10 min of the onset of drug perfusion. Ordinarily, the bursts consisted of a fast negative-going wave followed by a slower positive wave with an overall amplitude <0.5 mV. The frequency varied greatly by slice, but generally was <1 Hz. Occasionally, slices manifested prolonged seizure-like discharges composed of multiple bursts in rapid succession. An increase in the number of waves in the EC-evoked field response was also sometimes seen with ATPA. Bursting terminated within 5 min after removal of ATPA from the perfusion medium. Coadministration of LY 293558 at concentrations of 100–250 n*M* markedly reduced the frequency of ATPA-induced bursting and terminated bursting at 500 n*M*. ATPA concentrations <10 μ*M* generally did not cause large-amplitude bursts, although an increase in noise was apparent. Spectral analysis revealed a concentration-dependent increase in power at frequencies of 5–100 Hz with ATPA (threshold concentration, 2.5 μ*M*). Bath application of AMPA at similar concentrations usually led to immediate termination of all activity including the "population spike" in the EC-evoked response, but occasionally did induce some bursting at concentrations of ≤1 μ*M*. **Conclusions:** Selective activation of the GluR5 receptors in the BLA leads to spontaneous epileptiform activity. In contrast, activation of AMPA receptors generally suppresses epileptiform activity, presumably because of neuronal overdepolarization. These results provide strong support for the concept that the seizure-inducing properties of kainate, at least in the amygdala, result from its ability to activate kainate receptors and not AMPA receptors. (Supported by NINDS.)

2.019

NR2B-SELECTIVE *N*-METHYL-D-ASPARTATE RECEPTOR ANTAGONISTS SUPPRESS DENTATE GRANULE CELL SEIZURES AND MOSSY FIBER SPROUTING IN VITRO

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Rationale: N *N*-methyl-D-aspartate (NMDAR) antagonists inhibit epileptogenesis in animal models, but high-affinity competitive NMDAR antagonists exacerbate seizures in some epilepsy patients. Similarly, we showed previously that prolonged treatment of hippocampal slice cultures with the high-affinity competitive NMDAR antagonist, D-APV, enhanced electrographic granule cell seizures (Bausch and McNamara, 2001). Seizure enhancement was associated with mossy fiber sprouting (MFS), a synaptic rearrangement postulated to contribute to epileptogenesis. **Methods:** To examine whether other classes of NMDAR antagonists inhibit epileptogenesis and whether the effects of these antagonists on epileptogenesis are linked to MFS, hippocampal slice cultures were treated long-term with vehicle; APV (high-affinity competitive); Ro 25-6981, or ifenprodil (NR2B-selective); memantine (moderate-affinity uncompetitive), or DCKU (glycine site). At 17–21 DIV, electrographic granule cell seizures were recorded extracellularly, and MFS was detected by Timm stain. **Results:** In response to γ-aminobutyric acid $(GABA)_A$ receptor blockade with bicuculline (BMI), vehicle-treated cultures exhibited multiple recurrent seizures. In comparison with vehicle-treated cultures, total BMI-induced seizure durations were increased by 28.44%, 88.44%, and 82.87% in memantine-, DCKU-, and APV-treated cultures, respectively. In contrast, total BMI-induced seizure durations were reduced by 65.8% and 67.31% in Ro 25-6981- and ifenprodil-treated cultures, respectively. In parallel, moderate MFS was observed in memantine-, DCKU-, and APV-treated cultures, whereas only minimal MFS was noted in vehicle-, Ro 25-6981-, and ifenprodil-treated cultures. **Conclusions:** These results indicate that NR2B-selective antagonists inhibit epileptogenesis and support the hypothesis that MFS contributes to epileptogenesis. (Supported by USUHS C075HK and the Defense Brain & Spinal Cord Injury Program.)

2.020

IMMUNOELECTRON MICROSCOPIC LOCALIZATION OF KAINATE RECEPTOR SUBUNITS GluR5 AND KA2 IN THE RAT BASOLATERAL AMYGDALA

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Rationale: There is emerging evidence that kainate receptors play a role in seizure generation and epileptogenesis in the amygdala. Physiological studies have demonstrated that GluR5 kainate receptors mediate a portion of excitatory transmission in the basolateral amygdala (BLA) and also contribute to seizure induction in response to kainate-receptor agonists. Presynaptic kainate receptors, which regulate excitatory and inhibitory transmitter release in other brain areas, could also play a role in amygdala seizures. We used immunoelectron microscopy with subunit-specific antibodies to define the pre- and postsynaptic localization of GluR5 at synapses. We also examined the distribution of KA2, which may be an auxiliary subunit in heteromeric GluR5-containing kainate receptors. **Methods:** Brain sections from adult male Sprague–Dawley rats were processed for immunocytochemistry with affinity-purified polyclonal antibodies raised against synthetic peptides corresponding to sequences in the carboxy termini of human/rat GluR5 (18-mer) and KA2 (20-mer). Specific labeling was determined by preadsorption of the antisera with the synthetic peptides. The antibody was visualized with the immunoperoxidase method at the light- and electron-microscopic levels. **Results:** GluR5 immunocytochemistry at the light level revealed specific labeling of neuronal somata and processes in the BLA. Electron microscopy revealed a nonuniform distribution of labeling, with a predominance of labeling confined to dendrites and spines. Of 511 synapses examined, 164 exhibited postsynaptic labeling. Labeling over presynaptic terminals and axons was rare (fewer than five synapses). Similarly, the KA2 antibody was highly localized to postsynaptic structures and was generally distributed in a similar fashion to GluR5. **Conclusions:** Our results indicate that the GluR5 and KA2 kainate-receptor subunits are primarily located on postsynaptic elements in BLA, consistent with physiological studies supporting a role for these receptors as mediators of synaptic excitation in the amygdala. The similar overall pattern of immunostaining with the GluR5 and KA2 antibodies is consistent with the existence of GluR5/KA2 heteromers. Presynaptic GluR5 and KA2 receptors, if they occur, are infrequent. (Supported by National Institute of Neurological Disorders and Stroke.)

2.021

GLUTAMATE TRANSPORTERS EXPRESSION IN THE RAT HIPPOCAMPUS AFTER Y1 OR Y2 RECEPTOR ANTAGONIST INJECTION

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Rationale: Recently, neuropeptide Y (NPY) has become the focus of much attention for its possible involvement in epilepsy. Selective Y1 antagonist, administered intrahippocampally, had an anticonvulsant effect in rats. Excitatory glutamatergic neurotransmission affects the regulation of expression of NPY. On the other hand, NPY suppresses glutamate release by activating Y2 receptors. We administered Y1 or Y2 antagonists to the lateral ventricle and measured the glutamate transporters (GLAST, GLT1, and EAAC1) in the rat hippocampus. The purpose was to determine if Y1 or Y2 antagonists affect expression of glutamate transporters. **Methods:** Experimental animals, Sprague–Dawley rats, were injected to the lateral ventricle with BIBO3304TF (Y1 antagonist) (10^{-6} *M*), 5 μl, or BIIE0246TF (Y2 antagonist) (10^{-6}

M), 5 μl. Control rats were injected with an equal volume of 0.9% NaCl. The animals were killed at designated times, either at 2, 4, or 24 h after the injection, and the hippocampus were removed. We used Western blots to measure levels of glutamate transporters (EAAC1, GLT1, GLAST) with each antibody. **Results:** We observed that GLAST was increased in the hippocampus 4 h after the injection of a Y2 antagonist but not a Y1 antagonist. **Conclusions:** A Y2 antagonist affected expression of GLAST. Suppression of glutamate release is reduced by a Y2 antagonist in hippocampal slices in vitro. The levels of GLAST expression can be increased by activation of glutamate receptors and by coculturing with neurons. It is possible that the Y2 antagonist increased the release of glutamate and after the activation of glutamate receptors increased the expression of GLAST. It is postulated that the increase of GLAST levels works as a compensatory mechanism during excess excitation. [Supported by NIH (to Dr. Westfall).]

2.022

AGE DEPENDENCE OF SEIZURE-INDUCED MITOCHONDRIAL OXIDATIVE STRESS

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Rationale: Prolonged seizures can cause brain damage in all animals regardless of age. However, the degree of seizure-induced brain damage is highly age dependent. The mechanisms underlying the decreased vulnerability of the immature brain to seizure-induced brain damage remain unknown. It is hypothesized that mitochondrial oxidative stress is an important underlying mechanism by which aging influences the occurrence of seizure-induced brain damage. **Methods:** Using aconitase inactivation and 8-hydroxyguanosine (8OhdG) as indices of steady-state mitochondrial superoxide production and oxidative DNA damage, respectively, we asked whether kainate-induced seizures in developing (postnatal days 12–21) and adult (postnatal days 30–60) animals increased oxidative stress and whether this correlated with cell damage. **Results:** Mitochondrial aconitase inactivation and 8OHdG formation were increased in the hippocampus and piriform cortex by kainate administration in adult (postnatal days 30–60), but not young rats (postnatal days 12 and 21). The absence of oxidative injury to cellular macromolecules correlated with the minimal neuronal loss and microglial activation observed in the young animals. The absence of mitochondrial oxidative stress in young animals was not due to a selective induction of MnSOD, a critical mitochondrial antioxidant enzyme. **Conclusions:** The age-dependent increase in mitochondrial superoxide production and oxidative DNA damage suggests that oxidative mechanisms play a key role in the resistance of the immature brain to seizure-induced neuronal death. The inability of the developing brain to succumb to mitochondrial oxidative injury after seizures may render it resistant to seizure-induced brain damage. [Supported by Parents Against Childhood Epilepsy (PACE).]

2.023

CA1 INHIBITORY INTERNEURONS UPREGULATE METABOTROPIC GLUTAMATE RECEPTOR 1 PROTEIN AFTER REPETITIVE EPISODES OF STATUS EPILEPTICUS IN PREPUBERTAL RATS

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Rationale: The paradoxical mechanisms underlying a reduced seizure threshold during the first 2 weeks of postnatal (P) life and increased threshold during weeks 3 and 4 are unknown. In adult rats, kindled seizures increase metabotropic glutamate receptor (mGluR) I mRNA expression of hippocampal pyramidal cells, whereas mGluR II subtype hyperpolarizations are reduced, possibly leading to a reduction in the seizure threshold and development of spontaneous seizures in the mature brain. After postnatal week 2, mGluR1 specific agonist, 3,5-DHPG, induces seizures and preferential CA1 injury. However, maturational expression of mGluR proteins in response to a varied seizure history has not been previously explored. **Methods:** To study the consequences of sustained recurrent seizures on maturational expression of mGluR proteins and the seizure threshold over time, a series of kainic acid (KA) seizure episodes was induced either once or 3 times on P6, P9, and P14 or P21. Animals were killed 48 h after 1xKA or 3xKA at the four ages. Brains were examined with specific group I and group II antibodies. Electrographic activity (EEG) was recorded in the P14 and P21 rats. **Results:** In PBS-injected age-matched controls, mGluR1 hippocampal immunolabeling patterns were developmentally regulated. At P6, pyramidal and dentate granule layers were labeled uniformly. At P9, mGluR1 intense labeling occurred only within inhibitory interneurons of the subiculum/CA1 stratum oriens molecular layer. At P14 and P21, interneurons were also labeled in other regions, and CA3 pyramidal cells were faint. In adults, as previously reported, neuropilar staining of the CA3 and dentate hilus was robust, and CA1 interneurons continued to label. In contrast, mGluR2 and mGluR5 protein patterns were mature by P14. After 1xKA, there was no apparent change in the expression of group I or group II antibody-labeling intensities or patterns at the young ages examined. In contrast, P14 rats with 3xKA showed selective increases in mGluR1 protein within inhibitory interneurons of the CA1 stratum oriens and subiculum, particularly within the dendritic network. Interestingly, in the EEG, the appearance of long high-synchronous events and frequency amplitude were significantly increased in animals at P14 but reduced at P20 although they had the same history of perinatal seizures. **Conclusions:** Maturational differences in mGluR1 expression may influence the endogenous switch in seizure susceptibility. Upregulation of mGluR group I receptors within CA1 hippocampal inhibitory interneurons induced by repetitive perinatal seizures may provide an adaptive mechanism by increasing the inhibitory drive of the hippocampus after a certain age via increased interneuronal release of GABA due to repeated seizure-induced glutamate stimulation. (Supported by NIH-NS-38069.)

2.024

ALTERATIONS IN GLUTAMATE TRANSPORTER PROTEIN EXPRESSION AND ACTIVITY IN CULTURES OF ASTROCYTES AFTER TOPIRAMATE TREATMENT

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Rationale: Topiramate (TPM) has multiple mechanisms of action, which may contribute to its antiepileptic efficacy. For example, it has recently been demonstrated that TPM can interfere with excitatory events by inhibition of AMPA/kainic acid (KA)-subtype receptors as assessed by Co^+-influx in cultured neurons. Glutamatergic neurotransmission is preferentially terminated by the astroglial glutamate transporters (GluTs), GLT-1 and GLAST. These transporters are highly regulated by several factors participating in the neuron–glia crosstalk, including growth factors and glutamate itself acting on the glial KA- and mGluR3 and -5 glutamate receptor subtypes. Moreover, GluT activity is modulated by cell-surface trafficking, and the GluT expression level can be altered by downstream effectors of glutamate transporter gene regulation. It is hypothesized that TPM can interfere with the GluT regulatory machinery in astroglia and thus indirectly modulate the excitatory tone by altering the availability of extracellular glutamate. **Methods:** Primary cultures of neocortical astrocytes were established from neonatal mice and cultured for 3 weeks before use. The last week of culturing, 0.25 m*M* N^6,2′-*O*-dibutyryladenosine 3′:5′ cyclic monophosphate (dbcAMP) was added to obtain a shift in astrocyte morphology that resembles differentiation. Subsequently, TPM was added directly to the culture medium to final concentrations of 1–100 μ*M* for 48 h. GluT activity was measured by uptake of the GluT substrate [^{3}H]-D-aspartate. Expression levels of the glutamate transporters GLT-1 and GLAST were measured by Western blotting using specific affinity-purified polyclonal antibodies raised against synthetic peptides corresponding to the amino acid residues 493–508 or amino acid residues 522–541, respectively. **Results:** The protein expression level of GLAST was markedly altered by >25% after 48-h exposure to 30 μ*M* TPM. The expression level of GLT-1 did not seem to be influenced by TPM, which is consistent with the fact that GLT-1 and

GLAST expression is differentially regulated. In line with the altered expression level, the transport activity was also altered by >30% after 48-h TPM treatment (30 μ*M*). The effect of TPM on the level of expression and the modulation of glutamate uptake were apparently highly susceptible to the general status of the astroglial cell population, because the expression level of GLAST could be both increased and decreased. We are currently investigating whether this effect is dependent on the phosphorylation status of various kinases that in turn can modulate the GluT regulatory machinery. **Conclusions:** We have found that TPM appears to modulate astroglial glutamate uptake and alter the expression of GLAST in cultures of astrocytes. Because astroglial GluT activity is the major determinant for the termination of glutamatergic neurotransmission, the effect of TPM may indirectly change the availability of extracellular glutamate that in turn could influence neuronal excitation. (Supported by The R.W. Johnson Pharmaceutical Research Institute.) (Disclosure: Grant: The R.W. Johnson Research Institute.)

2.025

THE LACK OF SEIZURE ACTIVITY IN EAAC1-DEFICIENT MICE MAY BE A RESULT OF COMPENSATORY INCREASE IN GLUTAMATE UPTAKE

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Rationale: We have previously shown that reduced expression of EAAC1 in adult wild-type rats by antisense treatment (knockdown), led to behavioral abnormalities including staring/freezing episodes and EEG seizures. This effect was specific to EAAC1 (as compared to sense EAAC1, GLT-1, and GLAST antisense), and caused a 50% loss of hippocampal γ-aminobutyric acid (GABA) levels. Newly synthesized GABA from extracellular glutamate was also significantly impaired by reduction of EAAC1 expression. In contrast, EAAC1-deficient mice, as reported by Peghini et al., had no seizure activity by observation (no EEG recorded) and no compensatory change in the expression of other glutamate transporters. We hypothesized that due to the deficit of the transporter protein during ontologic development, a compensatory mechanism may protect the deficient mice from epilepsy. **Methods:** In the current study we examined the same EAAC1-deficient mice and investigated the effect of EAAC1 abolishment on spontaneous seizure activity and seizure susceptibility using a seizure behavioral scale, EEG recording, and pentylenetetrazol (PTZ) test. We used Western blot analysis to compare the expression levels of the other glutamate transporters. We have also compared functional glutamate uptake (total and DHK sensitive) between the EAAC1-deficient mice and wild-type controls. **Results:** The null mice did not show any freezing/staring episodes, nor did they display any other epileptic activity. Furthermore, EEG recording was normal, and the seizure susceptibility as measured by PTZ test was not different from controls (wild-type mice of the same background). In a Western blot analysis, we found no change in the expression levels of the other glutamate transporters. However, measurements of transport activity (done by glutamate-uptake assays) revealed a striking increase in the null animals transport activity, as compared to controls. **Conclusions:** We postulate that during development, a compensation process takes place, which leads to an elevation in other transporters' glutamate-uptake activity, while not affecting their expression levels. The hippocampal GABA levels, as well as the rate of its production in the EAAC1 null mice, are under investigation. The ability to modify glutamate transporter EAAC1 activity may be an important mechanism of preventing/treating some types of epilepsy. [Supported by NIH (Jeff Rothstein) and EFA (Jehuda Sepkuty).]

2.026

TOPIRAMATE ATTENUATES POTASSIUM- AND KAINATE-INDUCED INCREASE IN INTRACELLULAR CALCIUM IN RAT CORTICAL AND HIPPOCAMPAL CELL CULTURES

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Rationale: Numerous in vivo and in vitro studies have demonstrated the neuroprotective properties of topiramate (TPM). An increase of intracellular calcium has been implicated in the process of cell death. Electrophysiological experiments have demonstrated that TPM affects the function of several ion channels including kainate receptors and voltage-gated calcium channels. Therefore, we hypothesized that the neuroprotective effect of TPM may be related to an attenuation of the rise of intracellular calcium concentration ($[Ca^{2+}]_i$) after excitatory amino acid application. **Methods:** Populations of cells (mixed neuronal and glial) from cortical and hippocampal regions were isolated from E18 rat pups. Cells were cultured at a density of 30 K/well in 96-well plates and maintained for 8 and 9 days before the day of experiments. Ca^{2+} imaging experiments were performed using a fluorescence-imaging plate reader (FLIPR) assay kit and protocol. Cells were pre-incubated for 10 min with TPM (1–100 μ*M*) before the addition of glutamate (1–100 μ*M*), AMPA (3–300 μ*M*), kainate (10–1,000 μ*M*), NMDA (3–300 μ*M*), or KCl (10 and 50 m*M*). **Results:** TPM failed to reduce the increases of $[Ca^{2+}]_i$ evoked by glutamate, AMPA, and NMDA. However, TPM did attenuate kainate- and KCl-induced increases of $[Ca^{2+}]_i$. Increasing the concentration of KCl and kainate decreased this effect of TPM. For example, in cortical cells maintained 8 days in culture, 100 μ*M* TPM reduced peak increases of $[Ca^{2+}]_i$ evoked by 10 and 50 m*M* KCl to 68 ± 4 and 85 ± 6% of control, respectively. Also, TPM effects on increases of $[Ca^{2+}]_i$ differed slightly between cortical and hippocampal cultures and 8- and 9-day-old cultures. For example, in hippocampal cells maintained 8 days in culture, 100 μ*M* TPM reduced peak increases of $[Ca^{2+}]_i$ evoked by 30, 100, 300, and 1,000 μ*M* kainate to 41 ± 8.7, 65.9 ± 16, 80 ± 4, and 69 ± 14% of control, respectively, whereas in cortical cells maintained 8 days in culture, 100 μ*M* TPM reduced peak increases of $[Ca^{2+}]_i$ evoked by kainate to 47.7 ± 7.8, 89.3 ± 6.4, 89.2 ± 4.3, and 96 ± 4.3% of control, respectively. **Conclusions:** These results suggest that TPM may reduce excitability and excitotoxicity by attenuating increases of $[Ca^{2+}]_i$. The precise mechanism through which TPM exerts these effects has not been established; however, it is hypothesized that the demonstrated inhibitory activity of TPM at non-NMDA receptors and voltage-gated calcium channels contributes to its efficacy in this study. (Supported by Johnson & Johnson Pharmaceutical Research and Development, LLC.) (Disclosure: Salary: Johnson & Johnson Pharmaceutical Research and Development, LLC; Grant: Johnson & Johnson Pharmaceutical Research and Development, LLC.)

2.027

GABAERGIC SYNAPTIC DIVERSITY AND ITS POSTSYNAPTIC EFFECTS: REGULATION OF NEURONAL EXCITABILITY BY CHANGES IN INHIBITORY POSTSYNAPTIC CURRENT VARIANCE

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Rationale: γ-Aminobutyric acid (GABA)ergic synaptic inputs to principal cells are heterogeneous in terms of their anatomic, molecular, and physiological properties. Whether diversity in GABAergic synaptic inputs affects the efficacy of GABAergic inhibition is not understood. Here we show that alterations in the heterogeneity of inhibitory postsynaptic currents (IPSCs), even without alteration in the mean amplitude or kinetics of IPSC populations arriving at single cells, can significantly modify the effects of GABAergic inputs on neuronal excitability. Following this presentation the participants will be able to discuss the role of changes in variability in GABAergic synaptic inputs as a possible mechanism underlying inhibitory control of principal cells. **Methods:** The effects of IPSC diversity were examined in a computational model that incorporated experimentally measured values for spontaneous IPSCs and CA1 pyramidal cell electrophysiologic properties (Chen et al. *Nat Med* 2001; Aradi and Soltesz. *J Physiol* 2002). **Results:** The simulations showed that increased variance in the conductance or decay of IPSCs, even without changes in the mean,

could potently modulate the firing rate of the postsynaptic cells. The actual direction of the IPSC variance-induced modulation in postsynaptic cell discharges depended on the mean conductance and mean decay time constant of the IPSCs, as well as on the degree of depolarization and firing of the postsynaptic cell. Further analysis of the underlying mechanisms determined that these effects of IPSC variance on neuronal excitability could be entirely predicted from the nonlinear actions of IPSCs on action-potential generation. **Conclusions:** These data show that the degree of heterogeneity of the GABAergic synaptic inputs to principal cells can modulate the efficacy of GABAergic inhibition. Therefore, modified variability of inhibitory inputs (e.g., after interneuron loss) may constitute a novel factor in the generation of seizures. The results have interesting implications for our understanding of the evolution of the diversity of interneurons in cortical and hippocampal circuits, as well as for the unraveling of novel forms of GABAergic plasticity that may take place in epilepsy. [Supported by NIH (NS35915) to I.S.]

2.028

FUNCTIONAL AUTAPTIC TRANSMISSION IN FAST-SPIKING INTERNEURONS: A NOVEL FORM OF FEEDBACK INHIBITION IN THE NEOCORTEX

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Rationale: Cortical interneuronal activity plays important roles in epileptogenesis and in generation of network oscillations that may underlie several brain functions. Reductions in γ-aminobutyric acid (GABA)ergic output from interneurons, resulting from increased inhibition or decreased excitation of these cells, might be an important factor in the development or spread of epileptogenic discharge in cortical networks. There is extensive morphologic evidence that neocortical interneurons can synapse on themselves; however, a functional role for such autaptic innervation has not been established, raising the possibility that these anatomically defined autapses are nonfunctional. We therefore tested the hypothesis that autaptic contacts on interneurons are functional and that their activity can modulate interneuronal excitability. **Methods:** We obtained whole-cell recordings from fast-spiking (FS) and low-threshold spike (LTS) layer V interneurons in sensorimotor cortical slices from P13–20 rats. Cells were identified as multipolar neurons lacking apical dendrites, and electrophysiologically characterized in current-clamp. **Results:** Brief command steps applied to voltage-clamped FS neurons elicited an escaped action current followed by an inward current that proved to be GABAergic, as it was completely and reversibly blocked by 10 μM gabazine, a $GABA_A$ receptor blocker, and was enhanced by the $GABA_A$ receptor modulator clonazepam. Application of either extracellular Cd^{2+} or intracellular BAPTA, two manipulations known to prevent the release of neurotransmitter from presynaptic terminals, blocked these GABAergic currents, thus indicating their synaptic origin. Autaptic GABAergic responses were common in FS interneurons (48 of 57 cells; 84.1%), highly reliable (failure rate = 0.03 ± 0.001; n = 20), and large (peak current amplitude, –352.3 ± 70.9 pA; n = 20). In contrast, no action-current evoked, gabazine-sensitive response was detectable any of 25 recorded LTS interneurons, indicating that this interneuronal subtype has few, if any functional autaptic contacts or that they are present at remote locations. The autaptic activity in FS cells substantially changed action-potential waveform, particularly during spike afterhyperpolarization, and played a crucial role in repetitive firing. **Conclusions:** These results indicate that autaptic interneuronal innervation is functional and is selectively present in FS interneurons, where it modulates the pattern of spiking. The activation of an autaptic conductance during neuronal firing is of particular interest because it is a mechanism that would regulate interneuronal output, particularly during spike trains, such as those occurring during epilepsy. Modifications of autaptic synaptic efficacy might give rise to long-term alterations in interneuronal firing properties. Moreover, the amount of cortical self-innervation, either excitatory or inhibitory, may be enhanced in epileptic tissue, which has been shown to undergo intense axonal sprouting and de novo synaptogenesis, thus leading to a possible change in the amount of either excitatory or inhibitory autaptic connections. (Supported by NIH grant NS 12151 from the NINDS and the Pimley Research and Training Funds.)

2.029

LOSS OF INTERNEURONS AND GRANULE CELL INHIBITION IN A MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: Patients with temporal lobe epilepsy display neuron loss in the hilus of the dentate gyrus. Some missing cells are interneurons. Whether dentate granule cells are less inhibited is an important but unresolved issue. **Methods:** Rats experienced pilocarpine-induced status epilepticus when they were 51 ± 3 (mean ± SEM; n = 25) days old. They were video-monitored for seizure activity 40 h/week. Their first observed spontaneous seizure occurred 26 ± 3 days after status epilepticus, and they were used in an experiment 28 ± 4 days later. Control animals included age-matched naive controls (n = 15) and pilocarpine-treated rats that did not have status epilepticus and did not develop epilepsy (n = 17). We found no differences in the results from the two types of controls. Horizontal slices were prepared from the temporal hippocampus. Immediately after slicing, the first and last slice were fixed for Nissl staining and somatostatin and parvalbumin immunocytochemistry. Intracellular recordings were obtained in an interface recording chamber (30–32°C) with sharp electrodes. The outer molecular layer was stimulated at an intensity that evoked a maximal-amplitude inhibitory postsynaptic potential (IPSP) at 150 ms latency. To visualize biocytin-labeled neurons, slices were fixed, sectioned, and processed using the ABC method. **Results:** In epileptic rats, Nissl staining revealed a loss of hilar neurons. The density of parvalbumin- and somatostatin-immunoreactive interneurons was 36–37% of controls ($p < 0.0001$). The density of somatostatin-positive neurons in 3- to 7-day post–status epilepticus rats (35 ± 6 cells/mm^2, n = 15) was similar to that of chronically epileptic rats (33 ± 4 cells/mm^2, n = 25). Stimulation of the outer molecular layer revealed hyperexcitability of granule cells in epileptic rats. The maximum number of action potentials discharged per stimulus was higher in epileptic rats (1.4 ± 0.1, n = 84 cells) compared to controls (0.7 ± 0.1, n = 74 cells; $p < 0.0001$). At stimulation intensities below spike threshold, prolonged depolarizations were evident in epileptic rats. None of the granule cells from control or epileptic rats responded to current step injection with a burst of action potentials, and resting membrane potential and input resistance were similar in both groups. Basal dendrites were evident in 31% of 108 labeled granule cells in epileptic rats and in only 5% of 58 cells in controls ($p < 0.005$). At least one axon collateral from a biocytin-labeled granule cell projected into the molecular layer in 91% of 34 slices from epileptic rats and in only 19% of 27 slices from controls ($p < 0.005$). In normal aCSF, the average synaptic conductances at 20- and 150-ms latencies in epileptic rats were lower than those of controls (74 and 77% of controls, respectively), but the differences were not significant. The reversal potential at 20 ms was more depolarized in epileptic rats ($p < 0.001$). Monosynaptic IPSPs recorded in CNQX/D-APV in control and epileptic rats had similar reversal potentials, but in epileptic rats, the mean conductances of fast and slow IPSPs were reduced to 23 and 32% of control values, respectively ($p < 0.03$). **Conclusions:** Granule cells in epileptic rats receive less inhibitory synaptic input than controls. However, that change alone appears to be insufficient to cause epilepsy, because interneuron loss is present 3–7 days after status epilepticus when rats do not appear to experience spontaneous seizures. (Supported by NINDS.)

2.030

INHIBITORY SYNAPTIC TRANSMISSION IN RODENTS GRAFTED WITH NEURONAL PRECURSORS FROM THE MEDIAL GANGLIONIC EMINENCE

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Rationale: Recent studies suggest that neuronal precursors from the medial ganglionic eminence (MGE) tangentially migrate to neocortex and differentiate into a stable population of γ-aminobutyric acid (GABA)-, parvalbumin-, or somatostatin-expressing interneurons. Previous work has shown that grafted MGE cells can also migrate and differentiate into interneurons throughout the cortical plate in the host animal. However, it is not known whether newly integrated inhibitory interneurons make functional synaptic connections with existing neurons in neocortex. To address this issue we examined GABAergic function in rodents receiving grafted MGE neuronal precursors. **Methods:** For transplantation, MGE regions were dissected from green fluorescent protein (GFP) mice at embryonic day 14. After mechanical dissociation, cells were loaded into a glass micropipette and stereotactically grafted into brains of 1-day-old rats. Animals were killed at postnatal days 7, 14, 21, and 28. For immunohistochemistry, staining was performed on free-floating 50- to 100-μm vibratome brain slice sections using antibodies against GABA, somatostatin, parvalbumin, calretinin, calbindin, and GFP. For elecctrophysiology, IR-DIC visualized whole-cell voltage-clamp recordings were performed on neocortical brain slices from grafted rodents at three different ages (P14, P21, P28; hp, 0 mV). To isolate GABAergic synaptic currents, slices were perfused with nACSF supplemented with CNQX and APV. Spontaneous and evoked IPSCs (sIPSCs- eIPSCs) were recorded from neocortical pyramidal cells in layers II/III. All cells were filled with Lucifer yellow and analyzed post hoc. **Results:** MGE GFP-positive grafted cells migrated from injection sites to the ipsilateral neocortex. At P7, GFP+ cells exhibited the typical migratory morphology expected for MGE neurons and were located mainly in cortical layers II/III. From P14 to P21, grafted cells began to differentiate, reaching a mature morphology by postnatal day 28. Grafted GFP+ cells stained with standard interneuron markers including GABA, somatostatin, parvalbumin, calretinin, and calbindin. Spontaneous and evoked IPSCs could be recorded from neocortical pyramidal cells in layers II/III of slices from grafted animals. IPSCs were abolished by the addition 10 μ*M* bicuculline to the bathing medium, suggesting that they were mediated by GABA-A receptors. Initial analysis of sIPSC kinetics at P14 revealed a frequency ~0.8 Hz and an amplitude ~21 pA (n = 20). At P28, closer to a mature adult time point and nearly a month after grafting, sIPSC kinetic analysis indicated a frequency of ~1.3 Hz and an amplitude of ~21 pA (n = 10). **Conclusions:** Our results suggest MGE precursors grafted into a host animal differentiate into cells with the anatomic and physiologic properties of GABAergic interneurons. If MGE grafted cells can be used to increase the functional level of inhibition in the host animal, then this type of strategy could prove extremely beneficial for the treatment of epilepsy. [Supported by Parents Against Childhood Epilepsy (P.A.C.E.).]

2.031

ZINC FACILITATES HYPEREXCITABILITY IN THE HIPPOCAMPUS OF EPILEPTIC RATS

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Rationale: At the end of this activity you should be able to describe the potential role of zinc in dentate gyrus disinhibition during epilepsy. Feed-forward inhibition in the dentate gyrus (DG) is normally able to subdue synchronous activity entering the hippocampus via the perforant path. In temporal lobe epilepsy, zinc co-released from recurrent mossy fibers is hypothesized to disrupt this inhibition, reducing the DG ability to protect downstream targets, particularly CA3. This hypothesis hinges on two points: in epilepsy, recurrent mossy fiber connections onto granule cells are prevalent, and synaptic γ-aminobutyric acid $(GABA)_A$ receptors become zinc sensitive. It is not known if zinc can affect DG function or whether these effects are specific to changes in the DG associated with epilepsy. We therefore tested zinc's ability to disrupt DG gatekeeper function in control and epileptic animals and compared these results to partial disinhibition with the $GABA_A$ antagonists picrotoxin or bicuculline. **Methods:** Adult epileptic rats were generated using a pilocarpine model, with epilepsy defined as at least two observed seizures. Hippocampal slices (400 μm) were stained with the voltage-sensitive dye RH-795, and placed in an interface chamber at 34°C. Imaging DG and CA3 activity in response to perforant path stimulation was recorded with a 6,400 pixel CCD camera at 0.2–2 kHz. Concurrent electrophysiologic field responses were also recorded from the dentate or CA3. Pharmacologic disinhibition was generated with 3–5 μ*M* picrotoxin or 20 μ*M* bicuculline. **Results:** In normal conditions, stimulation of the perforant path produced a decrease in fluorescence over the whole molecular layer of the DG, indicating a strong depolarization throughout the synaptic field of the perforant path. This stimulation generated little or no activity from the CA3 in slices from either group, showing that, under normal conditions, gatekeeper function of the DG remains intact even in epileptic animals. The presence of 0.3 m*M* zinc significantly increased CA3 activity following perforant path stimulation, but only in slices from epileptic animals, with zinc having no effect on slices from control rats. In contrast, directly disinhibiting the DG by applying $GABA_A$ antagonists allowed robust CA3 responses to be evoked in both groups. **Conclusions:** These data show that zinc can act to specifically increase DG excitability in the DG of epileptic animals. Because synaptic $GABA_A$ receptors on granule cells are not normally zinc sensitive but become so in epilepsy, and zinc effects are mimicked by partial disinhibition, these data suggest that these epilepsy-associated zinc effects are due to disinhibition in the DG. This further supports the hypotheis that endogenous release of zinc in epilepsy may disrupt gatekeeper function of the DG. (Supported by NIH-NIMD grants NS-32403 and NS-38572.)

2.032

CALCINEURIN MEDIATES EARLY DOWNREGULATION OF γ-AMINOBUTYRIC ACID SUBTYPE A RECEPTOR FUNCTION AFTER PERINATAL SEIZURES

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Rationale: Hypoxic encephalopathy is the most common cause of neonatal seizures and can be associated with long-term neurocognitive deficits and epilepsy. In our perinatal rodent model, hypoxia-induced seizures result in an increase in hippocampal network excitability and increase long-term seizure susceptibility. We have previously reported a decrease in γ-aminobutyric acid $(GABA)_A$ inhibitory postsynaptic potentials (IPSCs) in hippocampal CA1 observed at 96 h after hypoxia. As the phosphatase calcineurin (CaN) can regulate $GABA_A$ receptor ($GABA_AR$) function, the goal of this study was to examine the role of CaN in hypoxia-induced hyperexcitability. We evaluated CaN expression in hippocampus after hypoxia-induced seizures. We examined the role of CaN in hypoxia-induced hyperexcitability by evaluating the effect of the CaN inhibitor FK-506 on the altered IPSCs in hippocampal slices in vitro and on seizure incidence in the in vivo animal model. **Methods:** Rat pups at postnatal day (P) 10–11 were placed in 4–7% of O_2 for 15 min for induction of seizures. For Western blot analysis, blots from whole-cell hippocampal protein samples (removed at 24 h after hypoxic seizure or from littermate controls) were incubated with the CaN A antibody. For electrophysiology, hippocampal slices were removed at 1 h after hypoxia-induced seizures. Whole-cell patch-clamp studies were made in CA1 pyramidal neurons from hypoxia-treated and age-matched control rats. Spontaneous ISPCs (sIPSCs) mediated by $GABA_AR$ were recorded as index for GABAergic neurotransmission. IPSC frequency was compared at baseline and after addition of CNQX (20 μ*M*), APV(50 μ*M*), or FK-506 (10 μ*M*). To study the effects of FK-506 in vivo, FK-506 (10 mg/kg, i.p.) was administered 30 min before hypoxia, and seizure frequency was compared to that of hypoxic vehicle-treated controls. **Results:** Western blots showed that CaN A protein was significantly increased 24 h after hypoxia ($p < 0.04$). Both the frequency and amplitude of CA1 pyramidal neuronal sIPSCs mediated by $GABA_AR$s were significantly decreased as early as 1 h after hypoxia (n = 5) compared to control slices (n = 5; $p < 0.01$). Subsequent application of FK-506 in slices from hypoxic rats significantly

reversed this decrease in sIPSCs ($n = 4$; $p < 0.001$). Similarly, application of CNQX and APV also reversed this decrease ($n = 5$; $p < 0.001$). Finally, rats treated with FK-506 before hypoxia ($n = 12$) exhibited significantly fewer hypoxia-induced seizures compared to vehicle-treated hypoxic control littermates ($n = 11$; $p < 0.0001$). **Conclusions:** These data support the hypothesis that early increases in CaN activity may play a role in the impaired $GABA_AR$ signaling seen in area CA1 after hypoxia-induced seizures, and may contribute to hypoxia-induced neuronal hyperexcitability. The action of FK-506 to reverse hypoxia-induced IPSC downregulation was similar to the effect of glutamate-receptor blockade, suggesting that CaN may be activated by glutamate receptors after hypoxic seizures. The anticonvulsant effect of FK-506 in our rodent model indicates that FK-506–like agents may have clinical potential in the treatment of refractory perinatal seizures. [Supported by NINDS RO1 NS31718-10 (F.E.J.).]

2.033

INHIBITORY POSTSYNAPTIC CURRENTS OF HIPPOCAMPAL NEURONS IN RATS WITH KAINATE-INDUCED EPILEPSY

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Rationale: An imbalance of synaptic excitation and inhibition in the hippocampus has been hypothesized to contribute to epilepsy. Hypotheses about loss or dormancy of inhibitory interneurons, and the consequences of synaptic reorganization, have been debated. In this preliminary study, we examined inhibition with whole-cell recordings from hippocampal slices in the kainate-treated rat model of temporal lobe epilepsy. **Methods:** Hippocampal slices were prepared 5–9 months after kainate treatment, when rats were observed to have a high frequency of spontaneous motor seizures. Spontaneous inhibitory postsynaptic currents (sIPSCs) from dentate granule cells and CA1 pyramidal neurons were recorded using: (a) CsCl-containing pipets and holding potential at –70 mV in DNQX (50 μM) and AP-5 (50 μM), and (b) Cs-gluconate–containing pipets and holding potential at 0 mV in aCSF. Miniature IPSCs (mIPSCs) were obtained by adding tetrodotoxin (TTX; 1 μM). **Results:** In preliminary data, all 14 granule cells from kainate-treated rats recorded with CsCl pipets invariably exhibited large (up to hundreds pA) and frequent sIPSCs. Application of TTX revealed highly frequent mIPSCs with medium-to-large amplitudes. Similarly, seven granule cells recorded with Cs-gluconate also expressed large and frequent sIPSCs both in aCSF and in DNQX (50 μM) plus AP-5 (50 μM). The mIPSCs were also frequent. In CA1, most pyramidal neurons (11 of 12, from the same rats used for granule-cell recordings) also exhibited frequent sIPSCs, but their amplitudes were considerably smaller than those of granule cells. In nine of 11 neurons, the mIPSCs were small but frequent. **Conclusions:** These preliminary data, based on sIPSCs and mIPSCs, suggest a vigorous hippocampal inhibition (at least in the dentate gyrus) of rats with kainate-induced epilepsy. The properties of this inhibition and its hypothetical role in epilepsy remain to be explored. (Supported by NS 16683.)

2.034

SOMATIC VERSUS DENDRITIC INHIBITION OF DENTATE GRANULE CELLS

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Rationale: The excitability of granule cells (GC) in dentate gyrus is regulated by diverse γ-aminobutyric acid (GABA)ergic interneurons that can be divided into two groups, either anatomically (somatic vs. dendritic innervation of GCs) or physiologically [fast-spiking (FS) vs. non–fast-spiking (NFS)]. Our objective was to examine the anatomy, spiking properties, and synaptic physiology of these interneurons, to better understand their different roles in hippocampal network dynamics. **Methods:** Paired whole-cell patch-clamp recordings were made from synaptically coupled interneurons and granule cells, in hippocampal slices from 12- to 20-day-old rats, using standard solutions, at room temperature. Biocytin was included in the pipette solutions for subsequent anatomic characterization. Spikes evoked in the presynaptic interneuron under current clamp produced inhibitory postsynaptic currents (IPSCs) in the postsynaptic granule cell, voltage clamped at –60 mV. All data are mean ± SEM, with values for FS given first. Statistical significance ($p < 0.05$) was judged by two-tailed unpaired *t* tests. **Results:** Interneuron types were distinguished by their responses to current injection (1 s, +1 nA). FS neurons ($n = 16$–20) responded with a continuous spike train (72 ± 5 spikes; 81 ± 4 Hz mean rate) with modest accommodation. NFS neurons ($n = 5$–14) accommodated rapidly and completely (14 ± 3 spikes, 65 ± 4 Hz mean). FS and NFS neurons had similar resting potentials (FS, 58 ± 1; NFS, 55 ± 1 mV), but significantly different input resistances (105 ± 6 vs. 202 ± 16 Mohm), membrane time constants (33 ± 3 vs. 49 ± 2 ms), first spike amplitudes (114 ± 4 vs. 125 ± 2 mV), and spike widths (0.9 ± 0.08 vs. 1.42 ± 0.18 ms). Both FS and NFS somata were located at the GC layer–hilus border with dendrites in the hilus and molecular layer. All FS cell axons arborized extensively in the GC body layer as expected for basket or axo-axonic cells, whereas all NFS axons arborized exclusively in the molecular layer where GC dendrites lie. Measures of presynaptic function revealed that NFS cells had longer synaptic latencies (1.1 ± 0.1 vs. 1.7 ± 0.1 ms), greater paired-pulse depression (14 ± 2 vs. 21 ± 3%; 100-ms intervals), and a higher failure rate (48 ± 6 vs. 69 ± 4%). However, IPSCs mediated by FS and NFS cells were similar in conductance (2.0 ± 0.5 vs. 0.95 ± 0.17 nS) and mean decay-time constant (23 ± 0.9 vs. 24 ± 1.3 ms), differing mainly in their rise time constants (0.9 ± 0.1 ms, 1.8 ± 0.2), possibly due to dendritic filtering. **Conclusions:** Somatic and dendritic inhibition are mediated by interneurons with distinct electrical and presynaptic properties, whereas individual IPSCs mediated by the two classes are remarkably similar. Thus, differences in the character of somatic versus dendritic inhibition will depend on how these interneurons are driven within the network, rather than on postsynaptic differences at the synapses they form with GCs. [Supported by the Epilepsy Foundation (M.V.J.).)

2.035

ANTIEPILEPTIC EFFECT OF ELECTRICAL STIMULATION OF UNILATERAL SUBTHALAMIC NUCLEUS ON EXPERIMENTAL NEOCORTICAL SEIZURES (1): ELECTROPHYSIOLOGICAL STUDY

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Rationale: Evidence from animal studies suggests the existence of a nigral control system of epilepsy, and the subthalamic nucleus (STN) is considered to be a target site to activate this seizure inhibitory system. In previous studies, chemical or electrical inhibition of bilateral STN suppressed seizures, but the unilateral procedures showed no effect. We hypothesized unilateral STN inhibition suppressed the ipsilateral neocortical seizures and examined the antiepileptic effect of STN inhibition on a neocortical seizure model. **Methods:** A cannula was implanted into the left motor cortex in eight male Wistar rats. The animals were implanted with monopolar electrodes in bilateral motor cortices for EEG recording and a bipolar electrode in bilateral STN for electrical stimulation. Focal motor seizures were induced by an infusion of 2.0 μg of kainic acid via the cannula. During the seizure status, continuous STN stimulation for 40 min was performed repetitively, with a resting interval of 20 min. The stimulation parameters were biphasic square pulse with 0.1-ms width and 130 or 500 Hz frequency. The intensity was set to 70% of the threshold of motor symptom. The antiepileptic effect was analyzed by changes in seizure frequency and spike frequency calculated using a video-EEG system. The data were compared between the stimulation period and the resting intervals. In another experiment, the animals were implanted with a cannula into the left STN in exchange for the stimulation electrode. During seizure status, 200 ng of muscimol was infused into the STN, and the effect on seizures was studied. The behavior of the animal was observed for 7

days after the procedures, and then the animals were killed and examined histopathologically. **Results:** Three of the eight animals were removed from this study because of incorrect location of the electrodes or different parameters of the stimulation. In five animals, the seizure frequency decreased during the STN stimulation period compared with that during the nonstimulation interval. When the stimulation was stopped, seizures occurred frequently. The seizure frequency during ipsilateral STN stimulation of 130 Hz was only 55% of the nonstimulation intervals, and ipsilateral stimulation of 500 Hz also reduced seizure frequency to 66%. Bilateral stimulation of 130 Hz reduced seizure frequency to 60%. There was no remarkable difference between the frequencies of interictal spikes in the stimulation and nonstimulation periods. None of the animals showed abnormal behavior during or after STN stimulation. Infusion of muscimol into STN rapidly inhibited the seizure status. EEG became to show only interictal spikes, and neither clinical nor electrographic seizures occurred thereafter. However, behavioral change of the animals was observed, in that they were circling to the right backward and then searching. These abnormal behaviors lasted for 3–6 h. **Conclusions:** Our results revealed that not only bilateral but also unilateral inhibition of STN could suppress focal neocortical seizures. STN stimulation may be useful as a new therapeutic procedure not only for primary generalized seizures but also for unilateral focal seizures elicited from the surgical unresectable cortex.

2.036

PEAK OF EPILEPTOGENESIS COINCIDES WITH EXCITATORY ACTION OF γ-AMINOBUTYRIC ACID IN THE POSTNATAL RAT HIPPOCAMPUS

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Rationale: The immature brain is prone to seizures, but the underlying mechanisms are poorly understood. We explored the hypothesis that increased susceptibility of the developing brain to seizures is due to the excitatory action of γ-aminobutyric acid (GABA) on the immature neurons. **Methods:** Extracellular and patch-clamp recordings from CA3 pyramidal cells were performed on 500-mm-thick hippocampal slices from Sprague–Dawley rats. **Results:** Under control conditions, slices from the postnatal days P0–13 rats displayed spontaneous epileptiform activity in the form of spontaneous population bursts (SPBs) that coincided with giant depolarizing potentials on the cellular level. Exposure of slices to high-potassium (7.5–8.5 m*M*) solution induced various epileptiform patterns at various ages: during the first postnatal week, an increase in the frequency of SPBs; during the second postnatal week, multiple population spikes or tonic–clonic discharges; and starting from the third postnatal week onward, only SPBs-like events. Epileptiform events were scored, and gaussian fit of age-dependence of the high-potassium–induced epileptiform activity revealed a peak of epileptogenesis at P10 ± 2. In the second experiment, we determined the time course of the developmental change in the effect of GABA(A) receptor activation on the pyramidal cells using noninvasive extracellular recordings from CA3 pyramidal cells. Activation of GABA(A) receptors by the selective agonist isoguvacine induced an increase in the frequency of extracellular spikes during the first 2 postnatal weeks and inhibition later on in development. Boltzman fit of the age-dependence of the GABA(A) effect on neuronal activity revealed that the developmental switch from excitation to inhibition occurs at P14 ± 1. **Conclusions:** Thus, the critical period of highest epileptogenesis in the developing rat hippocampus coincides with the late phase of the excitatory action of GABA, and it is terminated by the transition of GABA from excitatory to inhibitory. We therefore suggest that excitatory action of GABA via GABA(A) receptors is an important factor contributing to epileptogenesis during the critical period, in addition to other factors such as the development of recurrent collateral synapses between the pyramidal cells. Excitatory action of GABA is also responsible for generation of "physiological" precocious epilepsy during the 2 first postnatal weeks in the rat hippocampus that is reminiscent of the immature "trace alternant" pattern in human EEG. [Supported by NINDS (NS27984), Ligue Francaise contre l'Epilepsie, and the French Medical Research Council.]

2.037

PLASTICITY OF SYNAPTIC γ-AMINOBUTYRIC ACID SUBTYPE A RECEPTORS PRESENT ON DENTATE GYRUS GRANULE CELLS IN THE LITHIUM–PILOCARPINE MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: Most epileptic disorders described so far are associated with a dysfunction in γ-aminobutyric acid (GABA)ergic neuronal inhibition. In particular, postsynaptic $GABA_A$ receptors ($GABA_A$Rs) present on dentate gyrus granule cells (DGCs) undergo drastic changes in their biophysical and pharmacologic properties during the epileptogenic process. This point has been illustrated in several studies and can be summarized as follows : $GABA_A$R currents recorded from "epileptic" DGCs become sensitive to zinc but are less potentiated by zolpidem (type I benzodiazepine) or allopregnanolone (neurosteroid). These observations likely indicate implication of $GABA_A$Rs composed of α4 and δ subunits that have been described in DGCs but are only located at extrasynaptic sites. Indeed, the expression of these two subunits are thought to increase in "epileptic" DGCs. To further analyze this phenomenon, we chose to study the pharmacologic alterations exhibited by $GABA_A$Rs at DGC synapses during the chronic phase of epilepsy in rats rendered spontaneously epileptic after experiencing a sustained episode of status epilepticus induced by lithium and pilocarpine (Li-Pilo). **Methods:** Whole-cell patch-clamp recordings of DGCs were performed at room temperature (20–23°C) in horizontal hippocampal slices from 6-month-old control (Li-saline) and epileptic (Li-Pilo) rats that exhibited spontaneous seizures for 3–4 months. Spontaneous $GABA_A$R–mediated inhibitory synaptic currents ($GABA_A$R sIPSCs) were isolated by blocking ionotropic glutamate receptors with steady-state concentrations of kynurenic acid. The sIPSCs recorded in control conditions were compared to those obtained with perfusion of allosteric modulators of $GABA_A$R function in both Li-Pilo and Li-saline hippocampal slices. **Results:** When compared to control conditions, $GABA_A$R sIPSCs recorded in GCs from Li-Pilo rats exhibited several differences in their kinetic parameters and frequency of occurrence. They had increased mean peak amplitude (40%), time to peak (45%), deactivation time (20%), and frequency of occurrence (65%). Whereas perfusion of 1 μ*M* diazepam prolonged the mean time to peak (17%) and deactivation time (89%) of $GABA_A$R sIPSCs recorded from Li-saline DGCs, $GABA_A$R sIPSC parameters remained unchanged in Li-Pilo DGCs. Interestingly, perfusion of the benzodiazepine antagonist flumazenil (10 μ*M*) significantly accelerated the time to peak and deactivation time of a fraction of $GABA_A$R sIPSCs recorded in Li-Pilo DGCs (40–60%). **Conclusions:** In summary we have shown significant differences in the biophysical and pharmacologic properties of synaptic $GABA_A$Rs present in "epileptic" DGCs. These changes that have been described initially early after status epilepticus seem to persist during the chronic phase in this model. Although sIPSCs were apparently not modulated by acute perfusion of diazepam in Li-Pilo rats, our results suggest that benzodiazepine-sensitive $GABA_A$Rs (non-α4βnδ) may still be present at DGC synapses. It is therefore tempting to speculate that these receptors may be composed of other subunits but had "masked" or uncoupled benzodiazepine binding sites. (Supported by INSERM U398 ULP/CNRS UMR7519.)

2.038

ANTIEPILEPTIC EFFECT OF ELECTRICAL STIMULATION OF UNILATERAL SUBTHALAMIC NUCLEUS ON EXPERIMENTAL NEOCORTICAL SEIZURES (2): METABOLIC STUDY

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Rationale: There is some evidence from experimental animal studies that high-frequency subthalamic nucleus (STN) stimulation suppress substantia nigra pars reticulata (SNr), and it leads to suppress seizures. However, it is not well documented how SNr suppresses the

seizure. In this study, we analyzed the changes in cerebral glucose metabolism of during high-frequency STN stimulation in kainic acid–induced seizures using autoradiography. **Methods:** Male Wistar rats weighing between 260 and 320 g were used. They were stereotactically implanted with a stainless-steel cannula (0.6 mm in diameter) into the left motor cortex and a bipolar electorode (0.2 mm in diameter) into the ipsilateral STN under halothane anesthesia. Seven days after the surgery, kainic acid (2.0 μg) was microinjected into the motor cortex via the cannula to induce seizure. The stimulation was started when the rat developed to seizure status clinically and continued to the end of the experiment. The stimulation parameters were biphasic square pulse; pulse width, 0.1 ms; and frequency, 130 Hz. The intensity was set to 70% of the threshold of motor symptom in each animal. The [^{14}C]-2-deoxy-D-glucose ([14C]-2-DG) (25 μCi) was intravenously injected 10 min after the beginning of the stimulation. Arterial blood was sampled over the subsequent 45 min. The rats were killed as soon as the last blood sampling was finished, and then the brain was quickly removed and frozen. The autoradiogram was made with the coronal section of the brain. Changes in local cerebral metabolism were compared between the rat with STN stimulation and the control. **Results:** Seizures were induced by kainic acid in all rats, and the seizures were suppressed by high-frequency STN stimulation. In STN-stimulation rats, seizure-induced hypermetabolism was suppressed in the thalamus, substantia nigra, and caudate-putamen. In control, local glucose utilization was increased not only in the site of kainic acid–injected cortex but also in the various structures including the SNr. **Conclusions:** Unilateral STN stimulation led to inhibition of the seizure-induced hypermetabolism in the ipsilateral SNr, thalamus, and caudate-putamen. This result supports that STN stimulation can activate the nigral control system in epilepsy, and suggests that antiepileptic mechanism of STN stimulation may correlate with the inhibition of neuronal activities in the thalamus and caudate-putamen.

2.039

ALTERATIONS OF INHIBITION OCCUR EARLY DURING STATUS EPILEPTICUS AND INCLUDE INTERNALIZATION OF γ-AMINOBUTYRIC ACID SUBTYPE A RECEPTORS

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Rationale: Reduction in the effect of γ-aminobutyric acid (GABA) ergic agents as status epilepticus (SE) proceeds is well known (Treiman et al., 1998; Kapur & Macdonald, 1997). We hypothesisze that a reduction in postsynaptic $GABA_A$ receptors occurs during SE with physiologic consequences on GABA inhibition. The participants should appreciate a relation between status epilepticus, $GABA_A$ receptor internalization, and altered $GABA_A$ synaptic physiology at the end of the presentation. **Methods:** Immunocytochemistry was performed on 6- to 8-week-old Wistar rats who had intracardiac perfusion with paraformaldehyde after 1 h of lithium (3 mEq/kg, i.p.)–pilocarpine (40 mg/kg, i.p.)–induced SE. Brain slices through hippocampus were double labeled with antibodies for β2/β3 subunits and synaptophysin and viewed by confocal micropscopy. Visualized granule whole-cell patch-clamp recordings of mIPSCs (using tetrodotoxin) were performed in hippocampal slices from SE and control animals. **Results:** $GABA_A$ receptor internalization occurs by 1 h of SE. Dentate granule cells, hilar interneurons, and CA3a pyramids demonstrate colocalization of the β2/β3 subunits with synaptophysin on the surface of soma and proximal dendrites in controls with internalization of those subunits in SE. Initial results show 12% of β2/β3 subunits are internalized in controls compared to 47% in rats in SE for 1 h with the lithium–pilocarpine model. mIPSCs recorded from dentate granule cells in acute slices prepared 1 h after pilocarpine SE show a decrease peak amplitude to 61.8% (±11.9%) of control values. With an intermittent perforant-path stimulation (PPS) model of SE (20 Hz, 10 s/min and 2-Hz continuous pulses, 0.1-ms duration, 20 V), we noted sustained loss of inhibition of paired-pulse responses after even brief periods of stimulation. With only 1–3 min of stimulation, loss of inhibition lasted 43 (±15) min in the dentate in vivo [as measured by increase paired-pulse ratio (P2/P1 ISI, 40 ms) from 0.25 (±0.27) pre- to 1.02 (±0.18) poststim ($p < 0.001$)] and in hippocampal slice preparations (where it is mimicked by low-dose $GABA_A$ antagonists). **Conclusions:** The immunocytochemical findings of $GABA_A$ receptor internalization and peak amplitude decrease of mIPSCs after 1 h of SE suggest that a reduction of cell-surface $GABA_A$ receptor numbers has early effects on synaptic inhibition and may herald the transition to self-sustaining SE. In addition, the sustained loss of paired-pulse inhibition to very brief perforant-path simulation suggests a profound and rapid onset of alteration in GABAergic inhibition to mild convulsant stimuli. The early effects on inhibition may serve as an initial events or triggers to seizure onset. [Supported by a VA Career Development Award (to D.N.) and by research grant N13515 from NINDS (to C.W., H.L.).]

2.040

ALTERATIONS IN γ-AMINOBUTYRIC ACID (A) RECEPTOR FUNCTION IN HIPPOCAMPAL DENTATE GRANULE NEURONS OF ADULT RATS WITH TEMPORAL LOBE EPILEPSY AFTER EARLY-LIFE STATUS EPILEPTICUS

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Rationale: Seizures occur commonly in early childhood, and prolonged seizures have been associated with an increased incidence of temporal lobe epilepsy (TLE; Cendes et al. *Ann Neurol* 1993;34:795–801). However, potential mechanisms linking early-life seizures to the subsequent development of epilepsy are not well understood. Previous studies from our laboratory suggest that 65% of rats will develop spontaneous seizures after lithium–pilocarpine–induced status epilepticus (SE) at postnatal day 20 (P20), but only a small fraction of these epileptic animals show structural changes in the hippocampus such as cell loss and mossy fiber sprouting. Previous studies in animals with TLE after SE in adulthood support the importance of hippocampal γ-aminobutyric acid (GABA)(A) receptor alterations. We therefore examined the functional properties of GABA(A) receptors in acutely isolated hippocampal dentate granule neurons (DGNs) of adult rats with spontaneous seizures after SE at P20. These studies should help elucidate potential mechanisms of epileptogenesis after early-life seizures. **Methods:** Sprague–Dawley rat pups at P19 were injected with 3 mEq/kg lithium chloride and on P20 with 60 mg/kg pilocarpine. Occurrence of SE in pilocarpine-treated pups was confirmed by EEG and behavioral monitoring. Rats were video-EEG monitored in adulthood (>P90) to identify animals with spontaneous seizures. DGNs were acutely isolated from epileptic and age-matched, sham-treated littermate control rats, and GABA(A) receptor currents were recorded at GABA concentrations of 3–1,000 μM using a whole-cell patch-clamp technique. **Results:** GABA efficacy was significantly lower at concentrations of 30–1,000 μM ($p \leq 0.02$). Maximal GABA evoked current (at 1,000 μM) in epileptic DGNs was 42% of that seen in DGNs from age-matched, sham-treated littermate controls (382 ± 96 pA in epileptic DGN vs. 910 ± 155 pA in control DGN; $p \leq 0.01$). **Conclusions:** Our earlier studies showed that morphologic changes in the hippocampus were not a necessary prerequisite for occurrence of spontaneous seizures after pilocarpine-induced SE at P20. The present study suggests that long-term changes in GABA(A) receptor function in DGN occur after SE at P20 and could contribute to epilepsy development. Further, these data indicate that SE-induced GABA(A)-receptor changes are markedly age dependent. Previous studies of rats who develop TLE after SE in adulthood have demonstrated increased maximal GABA currents (Brooks-Kayal et al. *Nat Med* 1998;4:1166–72), in contrast to the decreased GABA maximal currents seen after early-life SE. (Supported by NIH NS38595 and Epilepsy Foundation of America to A.B.K.)

2.041

HYPEREXCITABILITY CAUSED BY CHANGES IN THE VARIANCE, WITHOUT CHANGES IN THE MEAN, OF INTERNEURONAL PARAMETERS

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Rationale: Interneurons are important regulators of neuronal excitability. The conventional approach to describing interneuronal properties is to focus on the mean values of various parameters. Here we tested the hypothesis that changes in the variance of interneuronal properties (e.g., in the degree of scattering of parameter values of individual cells around the population mean) may modify the neural activity in networks of inhibitory and excitatory cells. **Methods:** Biophysically realistic multicompartmental models of principal cells and interneurons were constructed that incorporated experimentally determined values of parameters measured from hippocampal interneurons and CA1 pyramidal cells. Inhibitory synaptic inputs to principal cells and excitatory inputs to interneurons were described by using exponentials to reproduce the amplitudes and kinetics of inhibitory postsynaptic potentials (IPSPs) and excitatory PSPs (EPSPs) (Chen et al. *Nat Med* 2001; Aradi and Soltesz. *J Physiol* 2002). **Results:** The results showed that changes in the variance in the electrophysiologic (i.e., adaptation properties, resting membrane potential) and anatomic properties (axonal arborization) of interneurons significantly alter the input–output functions, rhythmicity, and synchrony of principal cells, even if the mean values were unchanged. In most cases, increased heterogeneity in interneurons resulted in stronger inhibition of principal cell firing. However, there were parameter ranges where increased interneuronal variance decreased the inhibition of principal cells. These simulation results showed that the degree of interneuronal variability can be an important factor in controlling neuronal excitability. Electrophysiologic recordings showed that the variance in the resting membrane potential of CA1 stratum oriens interneurons persistently increased after experimental complex febrile seizures in developing rats, without a change in the mean resting membrane potential. These experimental findings indicate that lasting alterations in interneuronal heterogeneity can take place in real neuronal systems. **Conclusions:** These computational and experimental data demonstrate that modifications in interneuronal population variance influence the excitability of neuronal networks, suggesting a physiologic role for interneuronal variability. Furthermore, the results indicate that interneuronal heterogeneity can change in seizure models, and raise the possibility that neuromodulators may act by regulating the variance of different properties in interneuronal populations. [Supported by NIH (NS35915) to I.S. and Fellowship of the Epilepsy Foundation of America to I.A.]

2.042

THE γ-AMINOBUTYRIC ACID SUBTYPE A RECEPTOR MUTATION γ2 (R43Q), FOUND IN HUMANS WITH EPILEPSY, SLOWS CURRENT DECAY AND INCREASES DESENSITIZATION

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Rationale: An arginine-to-glutamine mutation at position 43 within the γ-aminobutyric acid (GABA) γ2 subunit has been identified in patients with childhood absence epilepsy and febrile seizures (Wallace RH, et al. Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. *Nat Genet* 2001;28:49–52). Our objective was to explore the possibility that the γ2(R43Q) mutation contributes to epileptogenesis via alterations in the kinetics of inhibitory postsynaptic currents (IPSCs). We mimicked synaptic receptor activation by applying brief pulses of GABA to outside-out patches containing wild-type $\alpha1\beta2\gamma2$ or $\alpha1\beta2\gamma2$(R43Q) receptors. **Methods:** Recordings were made from outside-out patches excised from HEK-293 cells that were transiently transfected with recombinant α1, β2, and γ2 subunits. Patches were voltage clamped at –60 mV and placed in the stream of a multibarrel flowpipe array mounted on a piezoelectric bimorph. Solution exchange times were typically <200 μs. **Results:** After a 2-ms pulse of 10 mM GABA, currents from mutant receptors deactivated significantly more slowly than currents from wild-type (wt) receptors. Weighted time constants determined from multiexponential fits to the time courses of deactivation (τ_w) were 46 ± 12 ms (wt) and 98 ± 12 ms (mutant, mean ± SEM). When mutant receptors were presented with a 500-ms step of saturating GABA, slowed deactivation was also accompanied by a markedly increased fast component of desensitization (τ_w-wt = 371 ± 31 ms, τ_w-mutant = 74 ± 12 ms). Paired-pulse experiments demonstrated that increased fast desensitization of $\alpha1\beta2\gamma2$(R43Q) receptors caused a profound increase in paired-pulse depression from which the receptors were slow to recover. Currents from patches containing both wt and mutant receptors were relatively insensitive to block by 10 μ*M* zinc, confirming that the γ subunit was efficiently expressed in both instances. **Conclusions:** During inhibitory synaptic transmission, the slow deactivation caused by the γ2(R43Q) mutation predicts that IPSCs would be prolonged. However, the mutation also greatly increases the rate and extent of desensitization, and dramatically slows the recovery from desensitization after a brief GABA pulse. Therefore, rapid and repetitive stimulation of inhibitory synapses may cause $\alpha1\beta2\gamma2$(R43Q) receptors to accumulate in desensitized states, resulting in a progressive loss of inhibition and possibly leading to epileptiform activity. [Supported by grants from the Epilepsy Foundation (D.W. and M.V.J.), the National Health and Medical Research Council of Australia, and Bionomics Ltd.]

2.043

THE BASELINE BURST PROBABILITY INFLUENCES ANTICONVULSANT ACTION IN CA3

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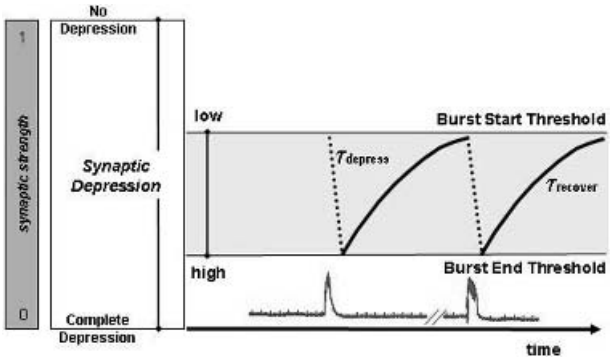
Rationale: Barbiturate anticonvulsants (AEDs) have been used in severe epileptic conditions including those associated with EEG findings termed periodic lateralizing epileptiform discharges (PLEDs). In the presence of PLEDs, barbiturates may be ineffective in stopping seizures or abnormal epileptiform discharges. We have described a model in which synaptic depression governs the transition between epileptiform activity and quiesence. Using this model, we are able to examine conditions in which seizure probability can be varied. When the seizure probability is high, our model predicts that barbiturate AEDs will be ineffective. After this presentation, the participants will be able to discuss a physiologic explanation for the apparent ineffectiveness of barbiturates for the treatment of PLEDs. **Methods:** To address this paradox, we extended a model of CA3 bursting in the in vitro slice preparation. Thresholds for burst initation and termination were calculated using experimentally obtained burst duration and interburst interval before and after application of barbiturate AEDs. Baseline burst probability, a measure of CA3 network excitability, was also evaluated. **Results:** (a) The thresholds for burst initiation (burst start threshold) and burst termination (burst end threshold) were calculated from experimentally obtained burst duration and interburst intervals; (b) When burst probability was low, pentobarbital (PTB) increased the burst-start threshold by 17 ± 3% and burst-end threshold by 66 ± 7% (n = 10); (c) however, when burst probability was high, the burst-start threshold was unchanged, and the burst-end threshold increased by 8 ± 3% (n = 10). **Conclusions:** (a) In high-burst probability, the effects of barbiturate AEDs on the bursting thresholds are attenuated compared to low-burst probability; (b) this occurs because the threshold shift caused the synapses to oscillate in a region of the synaptic recovery curve where the rate of recovery was much slower. Synapses operating in high-burst probability recover from synaptic depression partially and quickly, whereas synapses operating in lower burst probability recover more completely and slowly from synaptic depression; (c) this model of CA3 bursting, based on recovery from synaptic depression, provides one explanation for the apparent ineffectiveness of barbiturate AEDs

under conditions of high burst probability such as PLEDs (Fig. 1). (Supported by AES and NIH.)



2.044

PRESYNAPTICALLY MEDIATED COMPROMISE IN INHIBITION ELICITED BY DECREASED EXPRESSION OF GAT-1 AND EAAC-1, BUT NOT VGAT IN CA1 INHIBITORY TERMINALS OF EPILEPTIC RATS

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Rationale: At the end of this activity, the participants should be able to discuss potential novel mechanisms meditating disinhibition in the epileptic hippocampus. Inhibition is compromised in area CA1 of rats with temporal lobe epilepsy (TLE). Similar decreased inhibition occurs in animals in which expression of the neuronal glutamate transporter, EAAC-1, is reduced by antisense oligonucleotide administration (Cohen et al. SFN Abstracts 25, 1224, 1999). These animals also exhibit seizures. EAAC-1 is enriched in inhibitory synaptic terminals, potentially providing glutamate as a substrate for local γ-aminobutyric acid (GABA) synthesis. We therefore hypothesized that epilepsy-associated decreases in inhibition in area CA1 may be secondary to reductions in levels of GABA in the presynaptic terminal. **Methods:** To test this hypothesis, expression levels of EAAC-1, the GABA transporter, GAT-1, and the vesicular GABA transporter, VGAT, were examined using Western blotting and immunocytochemistry in adult rats with TLE induced by pilocarpine, compared to age-matched controls. TLE animals were injected with scopolamine, followed by pilocarpine (380 mg/kg, i.p.), which triggered status epilepticus. This was terminated within 3 h with diazepam (DZP; 4–10 mg/kg). Animals were used for experimentation 3–9 months after pilocarpine, and all exhibited spontaneous seizures. Western blots were run using 50 μg per lane of isolated fresh frozen CA1 protein. The same primary antibody was used for both techniques. **Results:** Western blot analysis of CA1 protein isolated from TLE animals (n = 3) demonstrated a significantly decreased expression of both EAAC-1 and GAT-1, but not VGAT relative to controls (n = 3). In immunocytochemical studies, distinct VGAT, GAT-1, and EAAC-1 immunoreactive punctate staining within stratum pyramidale of area CA1 was observed. A significant decrease in both the numbers of immunoreactive puncta and intensity of staining within puncta was observed for both EAAC-1 and GAT-1 in TLE animals. VGAT immunoreactivity did not change in number of puncta or intensity of puncta stained between the control and TLE animals (n = 3 each). **Conclusions:** Because VGAT levels were not altered in Western blots, or in numbers or intensity of VGAT immunoreactive puncta, we conclude that the numbers of inhibitory terminals within stratum pyramidale of CA1 were not altered in epileptic animals. However, both EAAC-1 and GAT-1 levels were significantly decreased, suggesting decreased levels of glutamate as a local precursor for GABA synthesis and decreased recycling of GABA in inhibitory terminals, respectively. This could combine to reduce the amount of GABA available for release in inhibitory terminals, and disrupt inhibition in area CA1 of epileptic animals via a presynaptic mechanism. (Supported by NIH-NINDS grants NS-32403 and NS-38572.)

2.045

Ca^{2+}/CALMODULIN KINASE II PHOSPHORYLATION OF γ-AMINOBUTYRIC ACID SUBTYPE A RECEPTOR SUBUNITS IS SIGNIFICANTLY INHIBITED DURING PROLONGED STATUS EPILEPTICUS

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Rationale: Status epilepticus (SE) is a serious medical emergency affecting thousands of people annually and has potentially devastating short- and long-term consequences. Many current drugs, which are initially effective at treating SE, lose efficacy as SE duration progresses. Because many first-line medications target the γ-aminobutyric acid $(GABA)_A$ receptor, maintenance of GABAergic function is important in treating SE. CaM kinase II activation has been shown to positively modulate both receptor binding and agonist-induced currents at $GABA_A$ receptors. Because CaM kinase II function is sensitive to SE, this study examined the effect of prolonged SE on CaM kinase II–dependent $GABA_A$ receptor subunit phosphorylation. **Methods:** The rat pilocarpine model was utilized to study the effect of SE on CaM kinase II–dependent phosphorylation of GABA-receptor subunits. Cortical tissue was isolated from pilocarpine-treated and sham-treated animals. Crude synaptic membrane (SPM) fractions were isolated by differential centrifugation. CaM kinase II–dependent phosphorylation reactions were performed, and reactions terminated by detergent solublization to extract receptor subunit protein from membrane fractions. Specific receptor subunits were immunoprecipitated from the detergent soluble fraction, resolved on sodium dodecylsulfate–polymerase chain reaction (SDS-PAGE) and subjected to Western analysis. Phosphate incorporation in specific GABA subunits was measured directly using in Instant Imager (Packard Instruments) with a counting efficiency of 25%. **Results:** Under basal conditions for CaM kinase II activation, the $GABA_A$ α1 subunit was minimally phosphorylated (10.6 ± 0.4 amol/mm^2/min). Maximal activation of CaM kinase II resulted in an ~160% increase in phosphate incorporation into the $GABA_A$ α1 subunit (27.8 ± 0.7 amol/mm^2/min). The activation-dependent increase in phosphate incorporation could be blocked by the coincubation of KN-93 during the phosphorylation reaction. Prolonged SE did not affect phosphate incorporation into the $GABA_A$ α subunit under basal conditions for kinase activation. However, SE did significantly inhibit the CaM kinase II activation–dependent phosphorylation of the $GABA_A$ α1 subunit (16.6 ± 0.7 amol/mm^2/min). In addition to the GABA-A α1 subunit, SE significantly affected the CaM kinase II–dependent phosphorylation of coprecipitating $GABA_A$ β2/3 subunits. As observed for the $GABA_A$ α1 subunit, SE did not affect the phoshorylation of $GABA_A$ β2/3 subunits under basal conditions. However, SE resulted in a 37% inhibition of phosphate incorporation under conditions maximal for CaM kinase II activation (12.8 amol/mm^2/min, control vs. 7.99 amol/mm^2/min, SE). **Conclusions:** The phosphorylation state of the $GABA_A$ receptor has been shown to be important for receptor function by multiple investigators. CaM kinase II–dependent phosphorylation has been shown to augment both agonist and allosteric modulator binding, as well as agonist-evoked currents. Therefore, the SE-induced inhibition of CaM kinase II–dependent phosphorylation of GABA-A receptor subunits may represent a cellular mechanism that results in loss of drug efficacy in prolonged SE. (Supported by RO1-NS39970, PO1-NS25630.)

2.046

NEUROPROTECTIVE EFFECTS OF GROUP I METABOTROPIC GLUTAMATE ANTAGONIST ON KAINIC ACID–INDUCED SEIZURES IN THE MATURE RATS

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Rationale: In previous studies, we have shown that in immature rats, kainic acid (KA)-induced seizures lead to a selective loss of CA1 interneurons in the oriens/alveus layer. This was associated with a loss of hippocampal function as shown with the Morris Water Maze test. The selective mGluR1 antagonist 1-aminoindan-1,5-dicarboxylic acid (AIDA) was able to reverse the effects of KA on hippocampal functions and limit the loss of interneurons. In mature rats, KA-induced seizures lead to a similar loss of hippocampal functions but with extensive loss of both interneurons and principal cells. The present study was undertaken to evaluate the neuroprotective effects of AIDA on the anatomic and cognitive consequences of the KA-induced seizures in mature rats. **Methods:** Sprague–Dawley rats aged postnatal day 60 (P60) were given two subconvulsive doses of KA (8.0 mg/kg) intraperitoneally (i.p.) at 1-h intervals. Another group received two doses of KA plus simultaneously AIDA (1.8 mg/kg) i.p. Control rats received an equivalent volume of either AIDA (1.8 mg/kg) alone or a saline solution. Initial and recurrent seizures were monitored using daily videorecordings. Hippocampal function was tested 45 days after the KA-induced prolonged seizures with the Morris Water Maze test. In this procedure, we measured the latency for the rats to escape from the water onto a hidden platform. Morphologic changes were assessed 60 days after injection. In one hemisphere, cresyl violet staining was performed. The other hemisphere was stained for immunofluorescence with anti-parvalbumin (PV) polyclonal and anti-somatostatin (SS) monoclonal antibodies to label inhibitory interneurons. **Results:** In the Morris Water Maze test, the KA rats took more time to reach the platform than the KA+A group. But KA+A rats still performed worse than controls. Cresyl violet staining revealed a complete loss of CA1 and CA3 pyramidal cells in the KA rats and a marked thickening of the granule cell layer. This was associated with a marked sclerosis of all the hippocampal structures. In KA+A rats, most of the CA3 pyramidal and hilar cells were lost, but the anatomic landmarks were still recognizable. In CA1 pyramidal cells, neuronal loss was partially blocked by AIDA. Immunofluorescence staining also showed a marked reduction in the number of PV- and SS-containing cells in both the CA3 pyramidal cell layer and in the CA1 oriens/alveus strata in the KA rats. **Conclusions:** The metabotropic glutamate receptor antagonist AIDA limits some of the cognitive and morphologic impairments of the KA-induced seizures in mature rats. This neuroprotective effect appears, however, to be less robust than in the immature rat. This would be consistent with the developmental profile of class I metabotropic glutamate receptors. (Supported by Savoy Foundation for Epilepsy.)

2.047

GONADAL HORMONES REGULATE KCC2 EXPRESSION IN RAT SUBSTANTIA NIGRA RETICULATA

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Rationale: The γ-aminobutyric acid (GABA)(A) responsive neurons of the rat substantia nigra pars reticulata (SNR) have sex- and age-specific effects on seizures, which are organized by the early postnatal presence of testosterone. The neuron-specific potassium chloride cotransporter KCC2 mediates the functional switch of GABA(A) receptors from depolarizing to hyperpolarizing. We have recently provided evidence that high levels of KCC2 mRNA expression in SNR neurons may be required for the development of SNR-mediated seizure suppression in response to GABA(A) agonists. In this study, we have investigated whether (a) gonadal hormones also regulate KCC2 expression in rat SNR, and (b) whether their effects may explain the sexually dimorphic and age-specific patterns of KCC2 expression and GABA(A) receptor function in seizure control. **Methods:** KCC2-specific in situ hybridization on sagittal SNR sections from PN15 male and female rats was used to determine the effects of 17β-estradiol (5 μg s.c. per rat), testosterone propionate (100 μg s.c. per rat), or dihydrotestosterone (180 μg s.c. per rat) or oil on the expression of KCC2 mRNA in rat SNR. Comparisons of the cellular signal densities of KCC2-positive SNR neurons were performed among the different experimental groups. **Results:** Both short- (4 h) and long-term (52 h) exposure to 17β-estradiol decreased KCC2 mRNA in male SNR neurons. 17β-estradiol did not change KCC2 mRNA expression in females. Both short- and long-term exposure to either testosterone or dihydrotestosterone augmented the neuronal expression of KCC2 mRNA in both male and female SNR. **Conclusions:** (a) Estradiol downregulates KCC2 mRNA expression in infantile male SNR, and may thus promote the appearance of the muscimol-sensitive proconvulsant region of the male PN15 SNR; (b) estradiol has no effect on the expression of KCC2 mRNA in the female SNR, and this may explain the lack of muscimol-sensitive proconvulsant SNR region in females; and (c) androgens elevate KCC2 mRNA expression in rat SNR of both sexes and may be involved in the prepubertal upregulation of KCC2 and thus the development of GABA(A)-sensitive SNR-mediated seizure-suppressing systems. (Supported by EFA grant and RO1 NS20253.)

2.048

SEX- AND AGE-RELATED DIFFERENCES IN γ-AMINOBUTYRIC ACID IMMUNOREACTIVITY IN THE SUBSTANTIA NIGRA PARS RETICULATA

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Rationale: The substantia nigra pars reticulata (SNR) plays a critical role in the control of seizures. The SNR effects on flurothyl seizures are sex and age specific. Pharmacologic studies revealed that, in postnatal day (PN)30 rats, there are two distinct γ-aminobutyric acid $(GABA)_A$-sensitive regions within the SNR: the anterior region (SNRanterior) and the posterior region (SNRposterior). In male rats, infusions of muscimol into these two regions have opposite effects on flurothyl seizures. In female rats, infusions of muscimol in the SNRanterior are anticonvulsant, but infusions in the SNRposterior have no effect. There is only one functional region at PN15. Nigral infusions of muscimol at PN15 are proconvulsant in males but have no effect on seizures in females. The aim of this study was to determine whether there are sex- and age-specific differences in the distribution and expression of GABA in the SNR. **Methods:** Free-floating sagittal sections of the SNR were processed for immunohistochemistry with GABA antibody in male and female rats at PN30 and PN15. Immunoreactive (ir) neurons were counted. We used optical density (OD) measurements to determine the level of immunoreactivity in the SNRanterior and SNRposterior. **Results:** In both age groups and sexes, there were fewer GABA-ir neurons in the SNRanterior compared to SNRposterior. In both sexes at PN30, neurons in the SNRanterior had higher ODs than neurons in the SNRposterior. At PN15, there were no regional differences in the ODs. However, in each age group, the female SNR had more GABA-ir cells, and higher ODs than the male SNR. **Conclusions:** The data support the notion that the SNR is a sexually dimorphic structure. Sex- and age-related differences in the SNR in GABA immunoreactivity support the findings of sex- and age-specific effects of GABAergic drug infusions in the SNRanterior and the SNRposterior in the control of seizures. [Supported by Mario Negri Institute for Pharmacological Research Grant, Milano (T.R.), NS-36238 (J.V.), and NS-20253 (S.L.M.).]

2.049

QUANTITATIVE REVERSE TRANSCRIPTASE–POLYMERASE CHAIN REACTION OF γ-AMINOBUTYRIC ACID SUBTYPE A α1, β1, AND γ2S SUBUNITS IN EPILEPTIC RATS AFTER PHOTOTHROMBOTIC INFARCTION OF NEOCORTEX

Kathy L. Schmitt, Jiangping Liu, Elena A. Kharlamova, Carol J. Stolarski, Dennis R. Grayson, and Kevin M. Kelly (Neurology, Allegheny-Singer Research Institute, Allegheny General Hospital, Pittsburgh, PA; Medicine, Allegheny-Singer Research Institute, Allegheny General Hospital, Pittsburgh, PA; Psychiatry, The Psychiatric Institute, University of Illinois, Chicago, IL)

Rationale: Photothrombotic brain infarction can result in altered expression of cortical γ-aminobutyric acid (GABA)A receptors and in epileptic seizures in adult rats. We sought to determine whether infarct size and/or epileptic seizures resulted in a differential expression of cortical GABAA receptor α1, β1, and γ2S subunit mRNA both ipsilateral and contralateral to the lesion. At the end of this activity the participants should be able to discuss photothrombotic brain infarction and the potential role of GABAergic mechanisms in neocortical epileptogenesis. **Methods:** Photothrombosis was performed to create 2- to 3-mm diameter cortical lesions that extended approximately halfway to (small lesions) or fully to (large lesions) the subcortical–cortical interface. Fourteen young adult male rats were used in these studies: eight animals underwent photothrombotic brain infarction (three with small lesions, no epilepsy; three with large lesions, no epilepsy; and two with large lesions, epilepsy), and six animals were used as controls. Animals were monitored for seizure activity using continuous video-EEG monitoring techniques before killing and removal of hemispheric cortices. A reverse transcription–polymerase chain reaction (RT-PCR) was used with internal standards for GABAA receptor subunits to quantitate mRNA expression in cortex ipsilateral (left) and contralateral (right) to the infarct for α1, β1, and γ2S subunits in nonepileptic animals with small or large infarcts, epileptic animals with large infarcts, and young adult controls. Analysis of variance and Student's *t* test were performed for group comparisons ($p < 0.05$). **Results:** Significant alterations in GABAA receptor subunit mRNA expression was seen for α1 ipsilaterally in animals with large infarcts and epilepsy (increased 284% compared to control; increased 184% compared to contralateral side) and for β1 ipsilaterally in animals with large infarcts and epilepsy (decreased 120% compared to control), and no epilepsy (decreased 152% compared to control). The only other intragroup variation of significance was for β1 in animals with small lesions where mRNA values were different for ipsilateral and contralateral cortices but not different compared to controls. **Conclusions:** These results indicate that GABAA receptor subunit mRNA is differentially expressed in neocortex after photothrombotic brain infarction due to the effects of large cortical infarcts, acute seizures, and/or the epileptic state. Alteration in cortical GABAergic systems after photothrombotic infarction appears to be a complex phenomenon that primarily involves tissue ipsilateral to the lesion. Potential changes in the subunit composition of expressed GABAA receptors could result in altered receptor pharmacologic sensitivity and gating kinetics and decreased postsynaptic inhibition, thereby contributing to the mechanisms of poststroke epileptogenesis. (Supported by American Heart Association Grant-In-Aid to K.M.K.)

2.050

SYNAPTIC AND EXTRASYNAPTIC DISTRIBUTION OF γ-AMINOBUTYRIC ACID TYPE A RECEPTOR SUBUNITS IN RAT HIPPOCAMPAL DENTATE GRANULE CELLS

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Rationale: Dentate granule cells gate the propagation of paroxysmal activity through hippocampal circuits. However, the gating function of the dentate gyrus can collapse during status epilepticus and in temporal lobe epilepsy. This is in part due to altered properties of γ-aminobutyric acid type A ($GABA_A$) receptors, which depends on their subunit composition. More than 10 $GABA_A$ receptor subunits are expressed in dentate granule cells, but their subcellular distribution has not been described. **Methods:** The subcellular distribution of $GABA_A$ receptor subunits (α1, α2, α4, β1, β2/3, γ2, δ) in adult rat dentate granule cells was investigated by immunohistochemistry for subunit protein and for the GABAergic presynaptic marker glutamic acid decarboxylase(GAD) or postsynaptic marker gephyrin. Confocal laser scanning microscopy was used to study the sections. **Results:** The α1, α2, β1, β2/3 and γ2 immunoreactivity (IR) was in form of clusters that outlined the granule cells. Clusters of α2 IR were more frequently present on the hilar pole of granule cells. Analysis of 385 α1 subunit clusters revealed that they ranged in size from 0.05 to 0.3 μm^2, with a skewed distribution toward larger size clusters. More than half the clusters were small (< 0.1 μm^2). The size distribution of γ2 subunit clusters was similar. Double labeling experiments revealed that the large clusters frequently colocalized with synaptic markers while the small clusters rarely did so. Only 6.7% of 0.05 μm^2 α1 subunit IR clusters colocalized with GAD IR while 75 % of 0.16 μm^2 size clusters, and 100% of 0.22 μm^2 clusters colocalized with GAD. The rate of colocalization with synaptic markers correlated well with the cluster size (spearman correlation $r = 0.92$, $p < 0.0001$). The results were similar when α1 cluster colocalization with gephyrin was studied or that of γ2 subunit with GAD or gephyrin. Some of the clusters for γ2 and α1 IR colocalized with NMDAR1 clusters. The α4 and δ subunit IR was diffusely distributed throughout the granule cell body and did not colocalize with synaptic markers. **Conclusions:** The $GABA_A$ receptor subunits are distributed in synaptic and extrasynaptic compartments of dentate granule cells. Large clusters of α1, α2, β1, β2/3, γ2 subunits are frequently present at synapses. Small clusters may be extrasynaptic, or present at excitatory synapses, or belong to the trafficking pool. The α4 and δ subunits are diffusely distributed in extrasynaptic compartment. (Supported by NINDS grants NS 02081 and NS 40337 and the Epilepsy Foundation through the generous support of the American Epilepsy Society and the Milken Family Foundation.)

2.051

ANTIKINDLING PROPERTY PRESENT IN POSTICTAL HUMAN CEREBROSPINAL FLUID

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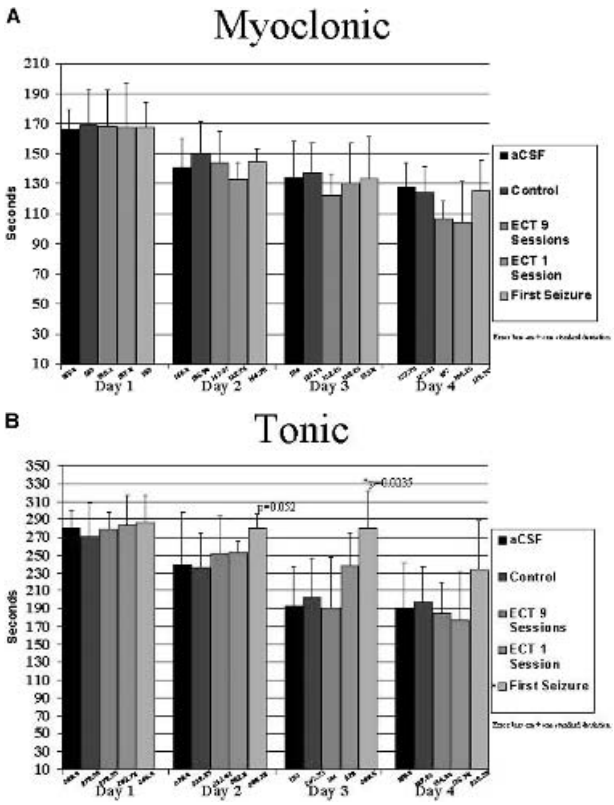
Rationale: The mechanism of action of electroconvulsive therapy (ECT) is unknown; however, THE ECT anticonvulsant effect has been proposed to play a roll. Seizure threshold increases during the typical course of ECT, and animal studies have suggested an anticonvulsant property of the CSF after electroconvulsive shock. The present study investigated whether this property exists in human CSF after one ECT treatment, nine ECT treatments, or a spontaneous first seizure. **Methods:** Male Sprague–Dawley rats were placed in a sealed 12.6-L plastic container. Flurothyl was infused into the container on to a piece of filter paper at the rate of 0.1 ml/min using an infusion pump. A timer was begun at the start of flurothyl infusion, and the time was recorded at two points: (a) when the rat started to have myoclonic jerks, and (b) when there was a generalized tonic seizure. The infusion was then immediately stopped, and the animal removed from the container. This process was repeated once per day for ≤4 consecutive days. There were five experimental groups: Group 1 ($n = 5$) artificial CSF (aCSF) intraventricular injected; Group 2 ($n = 9$) control human CSF intraventricular injected; Group 3 ($n = 9$) after nine sessions ECT, human CSF intraventricularly injected; Group 4 ($n = 4$) after one session ECT, human CSF intraventricularly injected; and Group 5 ($n = 5$) after first seizure, human CSF intraventricularly injected. Data were analyzed using analysis of variance with repeated measures and *t* tests. **Results:** Decrease in seizure threshold over time (4 days) was highly significant ($p < 0.001$) for all groups, for both myoclonic and tonic seizures, demonstrating a kindling effect. For myoclonic seizures, latencies to seizure onset were not significantly different than control in

any of the four treatment groups verses control. For the tonic seizures, the first seizure group ($F = 15.19$; $p = 0.001$) was significantly different from control CSF group over time (4 days). Additionally, on day 3, the first seizure group was significantly different from control CSF ($p = 0.024$) when measuring the onset of tonic seizure. There was no significant Group × Time interaction compared to control CSF for any of the four groups versus control for either myoclonic or tonic seizures (Figs. 1A and B). **Conclusions:** The results of this first study ever to assess human postictal CSF for an anticonvulsive property suggest that there is no anticonvulsant property in the CSF of humans after ECT. Human CSF after a first generalized seizure may have a neuroprotective property that prevents kindling. [Supported in part by the National Institutes of Mental Health (MH57980).]



2.052

UPREGULATION OF TrkA AND PROTEIN TYROSINE PHOSPHORYLATION AFTER ELECTROCONVULSIVE SHOCK TREATMENT IN RATS

Giuseppe Conti, Dawn Selby, Karen Gale, and Alexei Kondratyev (Department of Pharmacology, Georgetown University, Washington, DC)

Rationale: Brief repeated noninjurious seizures evoked by minimal electroconvulsive shock (ECS) have been shown to decrease vulnerability to neuronal cell death in limbic system regions, while inducing sustained increases in the expression of nerve growth factor (NGF) in some of these same regions, including hippocampus and rhinal cortex. Thus, the induction of NGF is a potential mechanism for the neuroprotective action of ECS treatment. The activation of the tyrosine protein kinase activity of the TrkA receptor for NGF is a key mediator of the neuroprotective action of this neurotrophin. The purpose of this study was to determine whether ECS treatment causes an increase in TrkA protein expression and/or an increase in protein tyrosine phosphorylation. To determine the functional significance of changes in these parameters, we also compared the effects of a neuroprotective prolonged ECS treatment with the effects of a short-term ECS treatment that was not neuroprotective. **Methods:** Minimal ECS was administered via corneal electrodes (200 ms, 35 mA). A single ECS treatment session consisted of three ECS seizures, given at 30-min intervals (i.e., at 0, 30, and 60 min). Control (sham) animals received the same handling and contact with the electrodes, but no current was passed. Animals were behaviorally observed to ensure that minimal limbic motor seizures (clonic movements of the face and forelimbs) lasting 5–10 s occurred after each ECS. Short-term treatment consisted of a single ECS treatment session. Prolonged ECS consisted of daily treatment (one session per day given in the morning) for 7 days. TrkA and tyrosine phosphorylation were measured immunohistochemically using specific antibodies. **Results:** In rats treated with prolonged ECS, upregulation of TrkA receptors was found in rhinal cortex and in several hippocampal areas (CA1, CA2, CA3, and polymorph layer dentate gyrus) by 4–7 h. This increased expression of TrkA was still observed in CA2 and CA3 at 24 h after the last seizure. Moreover, these same rats also showed upregulation of TrkA in the anterior olfactory nucleus (medial part) after 4, 6, 7, and 24 h after the last seizure. Short-term treated rats exhibited a transient increase in TrkA expression that was present in rhinal cortex and hippocampus only during the first 7 h. In addition, upregulation in TrkA immunoreactivity was colocalized with increased tyrosine phosphorylation levels. **Conclusions:** Our results demonstrate that prolonged ECS causes a sustained upregulation of TrkA expression and tyrosine phosphorylation in several limbic areas in which neuroprotective effects are observed. These results are consistent with the hypothesis that NGF contributes to ECS-evoked neuroprotection. (Supported by NIH grants NS 20576, MH 02040, and by the Epilepsy Foundation.)

2.053

EFFECTS OF STATUS EPILEPTICUS ON MECHANISMS OF DNA REPAIR

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Rationale: Excitotoxicity associated with status epilepticus (SE) leads to severe DNA damage, which is the cause of death in a significant population of neurons. Studies of the mechanisms of DNA damage after excitotoxic insults have been extensive, but very little is known about the competing function of DNA repair under these conditions. We hypothesized that the up- or downregulation of DNA repair mechanisms may be an important determinant of vulnerability to excitotoxic neuronal death. In this study we examined changes in the levels of subunit of DNA-dependent protein kinase, Ku70, after 2 h of continuous SE in rats. This subunit is considered to be responsible for binding to double strand breaks in the DNA and thereby mobilizing DNA repair activity. In addition, we evaluated DNA repair activity in the same tissue using an in vitro assay system. We also determined protein levels of p21/waf (a p53-dependent mediator of DNA repair) after SE. **Methods:** SE was induced in adult male Sprague–Dawley rats by kainic acid (12 mg/kg, i.p.) and terminated after a 2-h duration with diazepam (DZP; 30 mg/kg, i.p.). Protein levels of Ku70 and p21 were determined by Western blotting at several times during the 72 h after seizure termination. In addition, at selected times, we performed an in vitro end-joining assay for DNA repair activity. **Results:** In the hippocampus, a 36% decrease in Ku70 protein level was found at 48 h, and this decrease remained significant up to 72 h after SE termination. At 24 h, there was an increase in DNA end-joining activity, but no change in Ku70 protein level. SE resulted in four- to fivefold upregulation of p21/waf protein at 24–72 h after seizure. **Conclusions:** Our results indicate that components of the DNA repair cascade are activated shortly after SE-evoked injury with subsequent depletion as the injury progresses toward cell death. This provides initial evidence that regulation of DNA repair mechanisms may represent a target for manipulating the vulnerability of neurons to excitotoxic insults. The possibility that neuroprotective strategies may activate DNA repair is now under

investigation. (Supported by NIH grants NS 20576, NS041231, MH 02040, and by the Epilepsy Foundation.)

2.054
DIFFERENTIAL EXPRESSION OF C-JUN AND ATF-2 TRANSCRIPTION FACTORS IN IMMATURE AND ADULT RAT HIPPOCAMPUS AFTER LITHIUM–PILOCARPINE STATUS EPILEPTICUS

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Rationale: The activating transcription factor 2 (ATF-2) protein, a constitutively expressed transcription factor, is essential for the normal development of mammalian brain. ATF-2 is activated by c-Jun N-terminal kinase (JNK) and modulates both the induction of the c-jun gene and the function of the c-Jun protein, a mediator of neuronal death and survival. Lithium–pilocarpine–induced status epilepticus (LPSE) causes neuronal cell death that has features of both necrosis and apoptosis. Because LPSE-induced neuronal death is both selective and age-dependent, we investigated the expression of the c-Jun and ATF-2 protein in the immature and adult rat hippocampus to begin to understand their roles in LPSE-induced neuronal death. **Methods:** Lithium chloride (3 mEq/kg) followed 24 h later by pilocarpine (35 mg/kg) was administered intraperitoneally in the 10-day (P10), 21-day-old (P21), and adult Sprague–Dawley rats. Saline-injected animals served as control. The expression of c-Jun and ATF-2 protein was assessed by immunohistochemistry ($n = 3$, each group) and Western blot ($n = 3$, each group) in the hippocampus isolated at various times (4, 24, 72 h) after LPSE. Neuronal injury was assessed by silver stain and cresyl violet stain ($n = 6$, each group). **Results:** The early induction of c-Jun measured at 4 h after the onset of seizures was present in dentate gyrus, CA1, and CA3 of hippocampus in all age groups studied, but c-Jun immunoreactivity was most robust in adults and weakest in P10. The late induction of c-Jun measured at 24 h was absent from the P10 and weakly present in CA1 and CA3 of the hippocampus of P21 and adult rats. The expression of ATF-2 at 4 h after seizure was slightly increased in dentate gyrus, CA1, and CA3 of hippocampus in all age groups. ATF-2 immunoreactivity of adult rats at 24 and 72 h was significantly more decreased in CA3 and CA1 of hippocampus than that in P10 or P21 rats. Western blot revealed that c-Jun and ATF-2 immunoreactivity were both increased at 4 h after seizure and returned to basal level by 24 h in all three age groups. C-Jun protein expression was the highest in adult rats, but ATF-2 protein expression was highest in P10 rats. The severity of neuronal injury by silver stain and cresyl violet stain at 72 h after the LPSE was in the following order: CA1CA3dentate gyrus; and adultsP21P10 (no damage). **Conclusions:** C-Jun immunoreactivity increases but ATF-2 immunoreactivity decreases as the brain matures. P10 rats that had the highest ATF-2 and lowest c-Jun expression showed no neuronal damage, whereas the adult rats with the lowest ATF-2 and highest c-Jun expression had the most neuronal damage. Because c-Jun and ATF-2, both activated by JNK, are targets and competitors in the same signal-transduction cascade, one could speculate that ATF-2 may be competing with c-Jun for JNK phosphorylation. These results suggest a neuroprotective role of ATF-2 in this maturation-related evolution of neuronal cell death from SE. (Supported by NS37125 and Mayo Foundation.)

2.055
A NEURAL NETWORK MODEL OF NEOCORTICAL EPILEPTIC FOCI

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Rationale: Determinations of the localization of neocortical epileptic foci are limited by the spatial resolution of existing methods. High temporal resolution methods are needed to differentiate ictal onsets from areas of early regional spread to facilitate localization in patients undergoing presurgical evaluations. We developed a computational model of epileptic foci in simulated neural networks with the goal of modeling difficult-to-localize clinically relevant events associated with seizure origination from areas with rapid regional spread. **Methods:** Our model incorporates (a) an array of excitatory neurons capable of reproducing the spread of bursting activity and (b) a small subpopulation or subnetwork that triggers the activity in the network array. Neurons are modeled using a conductance-based model, and realistic synaptic connections are simulated. Connections between neurons in the array are local (e.g., each neuron receives inputs from neighboring neurons only). This network is capable of reproducing the spread of bursting activity. To simulate the epileptic focus, an additional subpopulation of neurons is incorporated into the network array. This subnetwork comprises neurons capable of generating endogenous bursts (model 1) or has the built-in structures of connections capable of maintaining self-sustained oscillations (model 2). **Results:** In both types of models of the epileptic focus, we observed recurrent waves of bursting activity spreading through the network array. In the first model, when intrinsically bursting neurons stimulate with the same period and phase postsynaptic neurons in the array, we observed strictly periodic waves of bursting activity spreading through the network array. The frequency of propagating waves is determined by the recovery time of neurons from afterhyperpolarization and by the frequency of burst occurrence in intrinsically bursting neurons in the triggering subpopulation. When the number of intrinsically bursting neurons involved in triggering of the activity increases (e.g., the area of projection increases), the spatiotemporal pattern of activity is recurrent. In instances of activation of the network array by an "epileptic circuit" (model 2), single-pulse stimulation of one neuron in the triggering network produces persistent activity in this network, which drives the postsynaptic neurons in the network array. The number of active postsynaptic neurons in the area of the projection of the focal ictal activity changes in time. In this type of focus (model 2), induced spatiotemporal patterns of activity in the network array are sensitive to oscillations in the area of projection from the focus. **Conclusions:** The presented model can clearly reveal differences in the pattern of activity in the triggering zone (model epileptic focus) and in the surrounding network. This model reproduces synchronous bursting events in network arrays when the population of neurons in the focus (participating in the origination of ictal events) is relatively constant (model 1) or varies from moment to moment (model 2). These models can be helpful in investigations of the nature of ictal or nonictal events near the region of ictal onset. (Supported by NIH grant NS38958.)

2.056
REGULATION OF PROTEIN L-ISOASPARTYL METHYLTRANSFERASE IN THE HIPPOCAMPUS OF PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: Protein L-isoaspartyl methyltransferase (PIMT) is implicated in the repair of damaged proteins that have accumulated abnormal aspartyl residues (L-isoaspartyl) during cell aging. Gene targeting has elucidated a physiologic role for PIMT by showing that mice lacking PIMT died prematurely of fatal epileptic seizures. Here we investigated the role of PIMT in human epilepsy. **Methods:** We used surgical specimens of hippocampus and neocortex from patients with temporal lobe epilepsy and from control patients to investigate the expression, activity, and mRNA of PIMT, as well as the accumulation of proteins damaged by abnormal aspartyl residues in these tissues. **Results:** We showed that PIMT activity and expression were 50% lower in epileptic hippocampus than in controls but were unchanged in neocortex. Although the protein was downregulated, PIMT mRNA expression was unchanged in epileptic hippocampus, suggesting post-translational regulation of the PIMT level. Moreover, several proteins with abnormal aspartyl residues accumulate in epileptic hippocampus. Microtubules component tubulin, one of the major PIMT substrates,

had an increased amount (twofold) of L-isoaspartyl residues in the epileptic hippocampus. **Conclusions:** These results demonstrate that the downregulation of PIMT in the hippocampus of patients with temporal lobe epilepsy leads to a significant accumulation of damaged proteins such as tubulin that could contribute to neuron dysfunction in human epilepsy. (Supported by The National Sciences and Engineering Research Council of Canada, the Savoie Foundation, the Claude Bertrand Foundation, and the FRSQ-FCAR-Sante.)

2.057

CASPASE-3 AND APOPTOTIC PROTEASE-ACTIVATING FACTOR-1: INCREASED EXPRESSION OF mRNA AFTER STATUS EPILEPTICUS IN RATS

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Rationale: Status epilepticus (SE) induced neuronal death in selected populations of neurons in hippocampus and rhinal cortex involves caspase-3–dependent mechanisms although the adult brain has very low expression levels of caspase-3. Moreover, caspase-3 activation can be elicited by apoptotic protease-activating factor-1 (APAF-1), a factor that is constitutively expressed at extremely low levels in the adult brain. We therefore reasoned that both caspase-3 and APAF-1 would be upregulated by SE. **Methods:** SE was induced in adult male Sprague–Dawley rats by kainic acid (12 mg/kg, i.p.) and terminated after a 2-h duration with diazepam (DZP; 30 mg/kg, i.p.). Total RNA was extracted from rhinal cortex at 2, 4, 8, 24, and 48 h after termination of SE and analyzed by semiquantitative reverse transcriptase–polymerase chain reaction for mRNA encoding caspase-3, caspase-9, and APAF-1. **Results:** A significant increase in caspase-3 mRNA levels was found at 4, 8, 24, and 48 h after SE termination as compared with control animals, with maximum levels reached by 24 h. APAF-1 mRNA levels were also significantly elevated, with maximum at 48 h after SE. In contrast, caspase-9 mRNA levels remained unchanged at all times examined. **Conclusions:** These results demonstrate that prolonged injurious seizure activity induces both caspase-3 and APAF-1 genes, allowing the initiation of a caspase-dependent apoptotic cascade. Interestingly, these genes are highly downregulated in the adult brain, as compared with the immature brain (before postnatal day 7 in rat). This raises the possibility that SE-induced injury reengages the cellular machinery characteristic of programmed cell death during development. (Supported by NIH grants NS 20576, NS 38941, NS041231, MH 02040, and by the Epilepsy Foundation.)

2.058

SEIZURE-INDUCED PRODUCTION OF INTERLEUKIN-6 IN HUMAN AND EXPERIMENTAL EPILEPSY

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Rationale: We have previously reported that Interleukin-6 (IL-6) levels are increased in CSF and plasma in patients after single tonic–clonic seizures. Present study was carried out to determine whether the increase in IL-6 levels is correlated to the duration or type of seizures. Localization and time course of seizure-induced IL-6 production was studied in kainic acid–injected rats. **Methods:** We determined the levels of IL-6 in CSF and serum samples from healthy controls (n = 17) and from patients after a single tonic–clonic seizure (n = 16), after prolonged tonic–clonic seizures (n = 10), and after prolonged partial seizures (n = 7). Samples after seizures during video-EEG recordings were studied (n = 12). To study the time course and localization of seizure-induced IL-6 expression, in situ hybridization and Northern blot analysis was performed in rats after kainic acid–induced status epilepticus. **Results:** After seizures, IL-6 levels were increased in the patient group when compared to controls in CSF (median, 10.6 pg/ml, and 2.5 pg/ml) and serum (median, 5.4 pg/ml and 1.2 pg/ml). These changes were more prominent after prolonged tonic–clonic seizures when compared to a single tonic–clonic seizure in CSF (median, 58.0 pg/ml and 9.25 pg/ml), as well as in serum (median, 19.5 pg/ml and 3.35 pg/ml). In addition, more robust changes in serum IL-6 levels were evident after prolonged tonic–clonic seizures than prolonged partial seizures (median, 19.5 pg/ml and 4.0 pg/ml). After seizures during video-EEG recordings, IL-6 levels were increased at 6–12 h, especially after generalized seizures. Northern blot analysis revealed increased IL-6 expression at 3–24 h after SE, which was localized in temporal lobe structures and adjacent meninges. **Conclusions:** These results indicate that IL-6 is expressed in the brain parenchyma and meninges after seizures, followed by increased CSF and serum levels of IL-6. This increase in IL-6 levels is dependent on duration and generalization of seizures, indicating that IL-6 production is caused by seizure activity per se. Because IL-6 is also known as neurotrophic factor, IL-6 may therefore contribute to seizure-induced neuronal plasticity. (Supported by Tampere University Hospital Medical Research Fund.)

2.059

THE DYNAMIC CHANGES OBSERVED IN HIPPOCAMPAL PYRAMIDAL CELL FUNCTION DURING DEVELOPMENT

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Rationale: Prior studies from our laboratory have revealed that status epilepticus on postnatal day 20 (P20) results in abnormal place cell function and spatial learning in the adult rat (P75-90). As a first step in understanding the time course of the changes in place cell physiology that occurred after status epilepticus, we have systematically studied the dynamic changes of hippocampal pyramidal cell activity that occur during development in male Sprague–Dawley (SD) rats not subjected to status epilepticus. **Methods:** Four tetrodes consisting of 16 insulated nichrome wires were implanted into the CA1 region of the right hippocampus of P23 rats (n = 6). The tetrodes were implanted ~300 μm above the CA1 region and then advanced 80 μm/day starting with the first recording session on P25. Once a place cell was isolated, the tetrode was no longer advanced until that cell was no longer well isolated. During a recording session, the rat was free to move within a cylinder (diameter, 76 cm) surrounded by a 2.5-m-long curtain for ≤16 min per session. Similar to our previous studies, rats were subjected to four recording sessions/24-h period divided into two pairs separated 4–6 h with 2–3 min separating each session in a pair. During a recording session, the rats would chase 20–30 food pellets that were dropped at random times at random positions in the recording cylinder. **Results:** Twenty-one hippocampal pyramidal cells in the CA1 region with complex spikes and peak-to-peak amplitude of 150 μV were recorded. No place cell was isolated before P32. Place cell fields were relatively stable during the period of cell isolation. Place cells isolated before P55 tended to have a higher average firing frequency and a larger average firing area, and the information content and coherence were lower than the place cells in adult control SD rats. Place cells isolated on P55 and after were similar to those isolated in adult control rats of age P75 and older. **Conclusions:** This study demonstrates (a) the place cells can be recorded from the hippocampal pyramidal cells in the freely moving developing rat, (b) the developing place cells offer less information content and coherence than the mature place cell, and (c) an adult place cell profile is obtained just before the end of postnatal month 2. Our failure to isolate place cells before P32 may result from the recording technique. These findings suggest that place cell function in the developing rat will be a useful measure in assessing seizure-induced injury. [Supported by the Emily P. Rogers Research Fund, a grant to G.L.H. from the NINDS (NS27984), and a Mental Retardation Research Center Grant from NIH (HD18655-19). X.Z.L. was supported by a fellowship from the American Epilepsy Foundation. H.P.G. received support from the NIH (32NS07473).]

2.060

CONCENTRATIONS OF PLASMA AND CEREBROSPINAL FLUID AMINO ACIDS IN PATIENTS WITH SEIZURES

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Rationale: The concentrations of amino acids have been shown to change during epileptic activity in the human brain, leading to an imbalance between excitatory and inhibitory amino acids. These alterations are also discernible in the CSF and blood. Many antiepileptic drugs (AEDs) also affect the amino acid levels in the brain. We compared amino acid levels in different epileptic syndromes and also after acute seizures. **Methods:** In the first experiment we studied 37 patients with localization-related epilepsy; 20 of them had temporal lobe epilepsy with hippocampal sclerosis. Twenty-five patients had juvenile myoclonic epilepsy (JME). In second experiment, 22 patients were studied immediately after generalized tonic–clonic seizure, and in these patients also, CSF samples were drawn. The results were compared with the data from 40 healthy control subjects matched for age and sex. All samples were stored at 20°C until analyzed **Results:** The plasma levels of glutamate were not altered in epilepsy patients, except only after the seizures ($p = 0.04$). In the CSF, there were no changes in the levels of glutamate. Plasma levels of taurine were decreased in patients with JME when compared to healthy controls ($p = 0.03$), and after these acute seizures, taurine levels were decreased in CSF also ($p = 0.028$). The glycine levels in plasma were elevated in patients with JME ($p = 0.007$), but the levels of aspartate were reduced in patients with localization-related epilepsy ($p = 0.014$). γ-Aminobutyric acid (GABA) levels were below the detection level in the plasma, and in the CSF, there were no changes when compared to controls. **Conclusions:** The plasma levels of amino acids are altered differently in idiopathic and localization-related epilepsy syndromes. Seizures also affect directly the amino acids levels. The medication used may have also affected the results obtained. The glutamate levels were raised immediately after tonic–clonic seizures, but the interictal plasma levels of glutamate were unaltered in patients with localization-related epilepsy. (Supported by the Medical Research fund of Tampere University Hospital and Tampere University Brain Research Center.)

2.061

SIMULATION OF NEOCORTICAL ACTIVITY

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Rationale: Epilepsy in children often involves pathologic activity in the neocortex. Clinical recordings during seizures and interictal spikes show the overall electrical activity of the affected cortex, without revealing details of the underlying functions. One method of exploring these underlying mechanisms is to perform computer simulations of the activity of coupled neural elements. Current studies focus on properties of individual elements or thalamocortical loops. Our objective was to use large-scale simulations of the microcircuitry of the neocortex to examine the role of different neural elements in the initiation and propagation of synchronized bursts as a model for epileptiform activity. **Methods:** A scalable network model was built on the GENESIS neural simulator (Bower and Beeman, 1998). The simulation software runs on the Chiba City cluster of Linux-based PC′s at Argonne National Laboratory. Our approach is based on the canonical circuit first proposed by Douglas and Martin (1990); a cortical unit consists of a superficial and deep pyramidal cell plus of inhibitory elements. The inhibitory cells in our model are basket cells that inhibit the pyramidal cell soma and receive inputs from the pyramidal cells, and chandelier cells that inhibit the initial segment of the pyramidal cells. Although the input to these cells is unknown, in our model we follow the speculation that association fibers form these connections. The local excitatory connections are summarized in Fig. 1A, the inhibitory contacts, in Fig. 1B. An EEG signal was calculated by using the procedure described by Wilson and Bower (1992). **Results:** Activity in the network was initiated by a current injection into one of the elements. The elicited activity patterns were studied in networks of different size and with a different ratio between excitation and inhibition. Individual neurons in the network responded with a regular firing pattern to a depolarizing current injection. Interestingly, the activity in the network as a whole displayed a bursting pattern. The frequency of the bursts decreased with increased inhibition and depended on network size. **Conclusions:** Bursting behavior of a population of neurons without intrinsic bursting properties, is influenced by network parameters. Simulated neural activity of neocortical networks can therefore provide a useful tool for the exploration of neural network mechanisms of ictogenesis. (Supported in part by the Falk Grant, and in part by the Mathematical, Information and Computational Sciences Division subprogram of the Office of Advanced Scientific Computing Research, U.S. Department of Energy, under contract W-31-109-ENG-38.)

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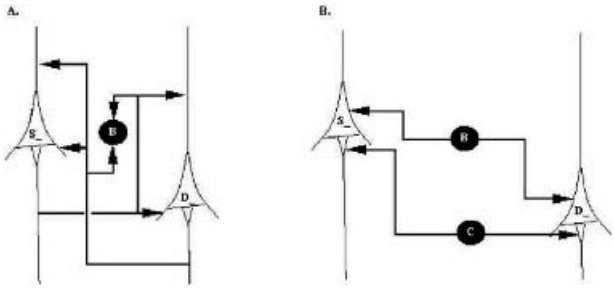

2.062

THE INFLUENCES OF γ-AMINOBUTYRIC ACID TYPES A AND B INHIBITION IN BURSTING ACTIVITY IN A MODEL OF PYRAMIDAL CELLS

Keun-Hang Yang, Piotr J. Franaszczuk, and Gregory K. Bergey (Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD)

Rationale: γ-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian brain. GABA inhibition via interneurons, which synapse on the dendritic trees and soma, can offset neuronal excitation occurring during epileptic seizures. We have demonstrated in previous studies that the inhibitory interneurons can regulate neuronal bursting activity and that the pattern of bursting behavior depends on the synaptic weight and delay of the inhibitory connection, as well as the location of the synapse. In this study, two types of GABA receptors, $GABA_A$ and $GABA_B$, are investigated at several locations of the inhibitory synapse using a multicompartmental pyramidal neuron model. We also investigated the role of $GABA_A$ and $GABA_B$ inhibition in the pattern of bursting activity. **Methods:** We build a multicompartmental pyramidal model of synaptically connected neurons using the simulation software GENESIS. Three simplified pyramidal neurons and an interneuron are modeled in this study: two neurons are synaptically connected with excitatory synapses forming a loop, a neuron where random input is applied to generate action potentials, and an inhibitory interneuron, which synapses on $GABA_A$ or $GABA_B$ recep-

tors of one of the modeled pyramidal neurons, in a negative feedback loop. We investigate the influences of $GABA_A$ and $GABA_B$ inhibition on the pattern of bursting activity in model pyramidal neurons. The inhibitory interneurons have inputs on $GABA_A$ or $GABA_B$ receptors at the soma, main dendrites, or branch dendrites of the modeled pyramidal neurons. The values of median and standard deviation in interspike interval (ISI) analysis are used for examination of bursting patterns. **Results:** Simulations show that $GABA_B$ inhibition is stronger than $GABA_A$ inhibition when inhibitory interneuron synapses on the soma, main dendrites, or branch dendrites of the modeled pyramidal neurons. When the inhibitory interneuron synapses on $GABA_A$, rather than $GABA_B$, receptors of any locations of the modeled pyramidal neurons, larger synaptic weight is needed to block bursting activity. The inhibitory action of $GABA_A$ as well as $GABA_B$ is stronger when the inhibitory interneuronal synapse is close to the soma. The synaptic weight of the inhibitory interneuron has to be increased to prevent bursting activity when the interneuron synapses on a branch dendrite. **Conclusions:** GABA inhibition regulates the bursting behavior in a multicompartmental pyramidal model. $GABA_B$ inhibition is stronger than $GABA_A$ inhibition on any location of inhibitory synaptic connections in a multicompartmental pyramidal neuron model. Both $GABA_A$ and $GABA_B$ inhibition are stronger when the inhibitory interneuronal synapse is close to the soma of the modeled pyramidal neurons. The potential for $GABA_B$ inhibition to play an important modulatory role is supported by these findings. (Supported by NIH grant NS 38958.)

2.063

FLUORESCENT LABELING OF HIPPOCAMPAL CELLS IN KINDLED RATS

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Rationale: This study investigated if hippocampal cells in kindled rats take up and metabolize 5-aminolevulinic acid (5-ALA) more readily than hippocampal cells in nonkindled rats. 5-ALA is a component of the heme synthesis pathway and is FDA approved for use in photodynamic therapy for certain tumors. It is converted in the mitochondria to protoporphyrin IX (PpIX), a fluorescent and photosensitizing agent. We speculate that 5-ALA is selectively taken up by cells involved in seizure generation, in vivo, and converted to PpIX, based on similarities to uptake determinants for tumors: pH, metabolism, and blood–brain barrier changes. Currently, EEG is used to localize seizure-initiation sites in epileptic brains. A fluorescent-labeling technique would provide clinicians with another and perhaps more specific method of defining the area of seizure generation. **Methods:** We compared PpIX fluorescence in three groups of Sprague–Dawley rats: (a) fully kindled rats with elicited seizures on the day of 5-ALA infusion, (b) fully kindled rats without elicited seizures on the day of 5-ALA infusion, and (c) implanted controls. Brains were flash frozen in isopentane at –40°C and sliced into 20-μm sections. The slices were excited at 405 nm, and the red-wavelength emissions were captured with a SPOT digital camera. Images were analyzed after being converted to gray scale using Image-Pro software. Relative fluorescence was quantified as mean optical density of the gray scale images. **Results:** Preliminary data with a small number of animals suggest that fully kindled rats with elicited seizures show greater 5-ALA uptake in hippocampal cells compared with both fully kindled rats without elicited seizures and the implanted controls. Our initial results also suggest that kindled rats without elicited seizures show more fluorescence than implanted controls. **Conclusions:** Preliminary evidence indicates that cells involved in seizure generation take up more 5-ALA compared to nonseizure controls. Kindling itself may also enhance 5-ALA uptake, because a kindled animal without seizures showed more uptake than nonkindled controls. These initial results provide a first step toward using 5-ALA in visualization of epileptic foci and applying photodynamic therapy to epilepsy. (Supported by C.U.R.E and Bronte Foundation.)

Clinical Epilepsy—Adult

2.064

THE INTRACTABLE IDIOPATHIC GENERALIZED EPILEPSIES

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Rationale: The idiopathic generalized epilepsies (IGEs) include a wide range of syndromes with heterogeneous pathophysiologic mechanisms. Seizures in most IGE patients are readily controlled by appropriate anticonvulsants (AEDs), but some patients have an unfavorable course and drug resistance. The objective of this study was to further define the causes of medical intractability in IGE patients. This may be helpful in devising optimal therapeutic strategies. **Methods:** Twenty-seven patients fulfilling the major diagnostic criteria for IGE but who were medically intractable were studied. Clinical, EEG, neuroradiologic, and neuropsychological data were reviewed. **Results:** Seventeen patients were women, mean age at seizure onset was 9 years (range, 3–17 years), and mean duration of disease was 25 years (range, 7–46 years). A family history of epilepsy with affected first- or second-degree relatives was present in 16 (58%) patients. An antecedent of febrile convulsions was reported in two, and seven had a history of risk factors such as head trauma, encephalitis, and meningitis. All patients had more than one seizure type except three who had only absences. Two seizure types were reported in 13, three in nine, and four in two patients. The first seizure type at onset of disease was absence in 19, generalized tonic–clonic seizures in four, and myoclonus in four patients. Five patients had other types of seizure as well, including petit mal status (two), atonic seizures (two), and seizures with focal features (one). All patients received polytherapy with valproate (VPA) or lamotrigine (LTG), the drugs most frequently taken at last follow-up. Initial treatment with phenytoin (PHT), carbamazepine (CBZ), or gabapentin (GBP) was reported in 20 patients. Precipitating seizure factors were found in 17 patients: sleep deprivation (10), fatigue (three), poor compliance (three), alcohol (two), and drug intoxication (one) were reported in 17 patients. EEG background activity was normal, and all had generalized epileptiform discharges ranging from 2.5 to 5 Hz. Only two patients showed photosensitivity. Additional focal epileptiform (nine) and nonepileptiform (two) abnormalities were found in 11 cases. Magmetic resonance imaging study was normal in 21 (78%) patients; the remaining patients had subcortical atrophy (two), limited encephalomalacia (two), hippocampal atrophy (one), and asymmetry of insular cortex (one). Neuropsychological examination showed generalized or bifrontal dysfunction in 12 of 19 (63%) patients, and one had temporal lobe dysfunction. **Conclusions:** Reasons for intractability were inadequate initial AED treatment (74%) and presence of precipitating factors (63%). Focal features also contributed to intractability (52%). Control was difficult to reestablish once lost, even with adequate drug regimen. Complete investigation of intractable patients and elimination of correctable aggravating factors should reduce intractability and provide clarification of the apparent increased severity in some patients. [Supported by Canadian Institutes of Health Research (CIHR).]

2.065

ACTION MYOCLONUS–RENAL FAILURE SYNDROME: A STUDY OF 15 PATIENTS FROM THREE CONTINENTS AND CHARACTERIZATION OF THE COLLAPSING GLOMERULOPATHY

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Rationale: Action myoclonus–renal failure syndrome (AMRF, OMIM 254900) is a distinctive form of progressive myoclonus epilepsy associated with renal failure. The syndrome was not recognized before the advent of dialysis and renal transplantation because of its rapidly fatal course if renal failure is untreated. The first description of AMRF was in four French–Canadian patients (*Adv Neurol* 1986;43: 87–103). We now describe 15 patients from five countries, allowing a more complete characterization of AMRF. **Methods:** The 15 patients (nine families) consisted of 11 additional individuals (from Australia, Canada, Cuba, Germany, and United States), and the original four described in 1986. Clinical phenotype and disease history of each patient were characterized. Genealogic history was obtained on each family. Pedigrees were constructed with Cyrillic 2.1. Statistical data were analyzed with SPSS software. Brain and renal pathology were reviewed. **Results:** The findings show that AMRF can present with either renal or neurologic features. Tremor onset ranged from 17 to 26 years (mean, 19.8 years). Onset of action myoclonus was from 19 to 29 years (mean, 21.7 years). Convulsive seizures occurred in 11 of 15 patients (73%); onset ranged from 20 to 28 years (mean, 22.7 years). Ataxia and dysarthria were observed in all as the disease progressed. There was no intellectual deterioration. Proteinuria detected at ages 10–30 years in all cases progressed to renal failure in 12 of 15 patients within 0–8 years (mean, 3.8) after proteinuria detection. Brain autopsy (two patients) revealed extraneuronal storage. Renal biopsy specimens showed focal sclerosing glomerulonephritis with features of collapsing glomerulopathy. Autosomal recessive inheritance was determined in all nine families based on absence of affected cases in previous generations; two or more affected siblings (four families); verified parental consanguinity (three families); and parental origins from the same rural area (six families). **Conclusions:** This study extends the original AMRF phenotype, and demonstrates a more extensive ethnic and geographic distribution of a rare and probably underdiagnosed syndrome. Our results show that the renal lesion in AMRF is a recessive form of collapsing glomerulopathy. Genes already identified for focal segmental glomerulosclerosis involved with the glomerular basement membrane and related proteins are thus candidates for AMRF. Moreover, the independent progression of the neurologic and renal disorders in AMRF suggests pleiotropic effects of a unitary molecular lesion. Storage in the brain and lack of kidney storage leads to the hypothesis that the mutant protein is also expressed in brain but cannot be effectively cleared, leading to the extraneuronal brain storage. Treatment with antimyoclonic drugs (valproic acid, clonazepam, piracetam, or levetiracetam) and effective dialysis or transplantation can improve quality of life, because AMRF patients can survive for a number of years with retained intellect. (Supported by Canadian Institutes of Health Research.)

2.066

THINKING-INDUCED EPILEPSY IN KOREA: THE DIFFERENCES FROM THE PREVIOUS LITERATURES

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Rationale: Reflex epilepsy induced by thinking and spatial tasks has been reported to have the clinical characteristics similar to those of idiopathic generalized epilepsy. However, we recognized that the clinical and electrophysiologic findings in Korean patients with thinking-induced epilepsy were different from the previous literatures. **Methods:** Clinical features of the 14 patients were collected via detailed interview with each patient by one of the authors. Brain imaging findings and routine EEG data including sleep activation, hyperventilation, and photic stimulation were obtained from the patients' charts. In 12 of the 14 patients, EEG activations were carried out by means of the actual task simulation and the neuropsychological tests for various mental activities. **Results:** All patients were male. The mean age at onset of seizures was 38.1 years (range, 13–65 years). The median age at onset was 47 years. Two patients had a family history of epileptic seizures. All patients except one had no spontaneous seizures. The reported stimuli that evoked seizures were playing Korean cards (so-called flower cards) in nine, playing the game of "go" in four, making complex decisions in two, and playing cards in one. Only two patients had more than one effective trigger. Reflex seizures usually occurred after a period of 5–24 h of mental activity with sleep deprivation. All patients had generalized tonic–clonic seizures, which were often preceded by prodromal symptoms including recurrent absence, visual illusion, mental cloudiness, fragmentation of thinking, febrile sensation, dizziness, nausea, and headache. There were no patients reporting myoclonus. On routine EEG, all patients except one showed no epileptiform discharges. Neither neuropsychological testing nor the actual task simulation activated epileptiform discharges in all patients. Brain imaging was normal in eight, abnormal in five, and no images was performed in one patient. **Conclusions:** Compared with the previous literatures, thinking-induced epilepsy in Korean patients had some different clinical characteristics including adulthood onset of seizures, few spontaneous seizures, reflex precipitation of generalized tonic–clonic seizures preceded by absence but not myoclonus, and a few epileptiform discharges on routine and activation EEGs.

2.067

ANTERIOR TEMPORAL LOBE ABNORMALITIES ASSOCIATED WITH HIPPOCAMPAL SCLEROSIS IN TEMPORAL LOBE EPILEPSY PATIENTS

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Rationale: Anterior temporal lobe abnormalities (TLAs) associated with hippocampal sclerosis (HS) are more frequently recognized as a result of the use of high-resolution magnetic resonance imaging (MRI) in temporal lobe epilepsy patients. The aim of the study was to compare patients with HS and patients with HS plus TLA (HS Plus) to find out if they belong in two different groups. At the end of this activity, the participants should be able to identify this kind of abnormalities on the MRI and their clinical differences. **Methods:** We selected, retrospectively, patients with temporal lobe epilepsy diagnosed on the basis of clinical and EEG data and HS on their MRI. They were divided in two groups: patients with only HS (group 1) and patients with HS Plus (group 2). We analyzed side affected, average age (AA), time of evolution (TE), age at onset (AO) of the epilepsy, febrile convulsions (FCs), status epilepticus (SE), family history (FH) of epilepsy, monthly seizure frequency (SF), interictal epileptiform abnormalities on the EEG (IEA), and their coincidence with the side affected on the MRI (CSA), and response to treatment. **Results:** We included 83 patients. Group 1 ($n = 62$), 26 males (41.9%). Left side affected in 23 cases (37.1%), right in 30 (48.4%), and bilateral in nine (14.5%). AA 38 ± 10 years, TE 25 ± 12.2, AO 12.7 ± 10.3, 14 (22.5%) with FC, four (6.4%) with SE, 17 (27.4%) with FH, SF 7 ± 9.5 (range, 0–60). EEG showed IEA in 43 cases (69.3%) and CSA in 24 cases (38.7%). Refractory patients were 45 (72.5%); 18 were operated on, and 14 (77.7%) are in class I of Engel. Group 2 ($n = 21$), 12 males (57.1%). Left side affected in 17 cases (80.9%), right in four (19.1%). AA 35.6 ± 13.6 years, TE 27 ± 11.7 years, AO 8 ± 7.2 years, six (28.5%) with FC, six (28.5%) with SE, three (14.3%) with FH, SF 5 ± 6.5 (range, 0–30). EEG showed IEA in 18 cases (85.7%) and CSA in 16 cases (76.2%). Refractory patients were 16 (76.2%), four patients were operated on, and all of them (100%) are in class I of Engel. There were statistically significant differences in the side affected, more frequent on the left in group 2 ($p < 0.01$), AO, lower in group 2 ($p = 0.05$), SE more frequent in group 2 ($p = 0.01$), and CSA, higher in group 2 ($p < 0.01$). **Con-**

clusions: Our results suggest that HS Plus patients may be different from cases that show only HS.

2.068

ACCURACY OF SEIZURE IDENTIFICATION BY CLINICAL HISTORY IN PATIENTS WITH SUSPECTED TEMPORAL LOBE EPILEPSY

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Rationale: Technical advances have not erased the value of seizure description by clinical history. It is still one of the most important tools in the evaluation of patients with epilepsy. There has not been a formal comparison of the accuracy, sensitivity, and specificity of seizure identification by history alone, versus the gold standard, seizure identification by long-term video-EEG monitoring. We performed this analysis in patients with suspected temporal lobe epilepsy. At the end of this activity, participants will have an evidence-based notion of the accuracy of epileptologists' assessment of the clinical history to correctly identify seizures in patients with probable temporal lobe epilepsy. **Methods:** The clinical and EEG monitoring data of 88 patients with suspected temporal lobe epilepsy were reviewed. Detailed descriptions of the different types of clinical events reported by these patients were registered in a database. All events were also classified according to the International League Against Epilepsy seizure classification. The EEG telemetry monitoring data of all recorded, seizure-like events in these patients were extracted and classified as a seizure or not a seizure. Seizure origin and seizure type were noted. Each clinical event reported by history was matched with the corresponding clinical event recorded in the epilepsy unit (gold standard). Each clinical event was adjudicated by three blinded (no access to EEG data), independent epileptologists as being a seizure or not. Sensitivity, specificity, overall accuracy, and interrater agreement for the clinical assessment were obtained. **Results:** Of 361 clinically different events described by 88 patients (average, four per patient), 175 (48.4%) were recorded in the epilepsy unit. Forty (23%) were simple partial seizures, 97 (55%) complex partial seizures, 28 (16%) primarily or secondarily generalized seizures, and 10 (6%) nonepileptic events. Only 10 events (6%) were misidentified as a seizure or not by blinded epileptologists, resulting in an overall clinical accuracy of 94%. Epileptologists' sensitivity for seizure identification was 96% [95% confidence intervaI (CI), 94–99%], but their specificity was only 50% (95% CI, 15–85%). Raw agreement among the three epileptologists was 90%. Agreement beyond chance was good, with a κ of 0.7 for paired evaluations. **Conclusions:** The overall clinical accuracy of epileptologists in identifying an event as a seizure or not by clinical semiology alone was high in patients with suspected temporal lobe epilepsy. Epileptologists rarely missed a seizure (high sensitivity, 96%), but they often overcalled nonseizures as seizures (low specificity, 50%). Agreement among different epileptologists was good. Features that influence clinical accuracy and implications for research and clinical practice are discussed. [Supported by University of Sherbrooke, Quebec, Canada, and The Physicians Services Incorporated Foundation (Canada).]

2.069

A NORTH AMERICAN KINDRED WITH FAMILIAL ADULT MYOCLONIC EPILEPSY

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Rationale: Clinically, familial adult myoclonic epilepsy (FAME) is defined by an autosomal dominant inheritance pattern, adult-onset myoclonus, rare generalized tonic–clonic seizures, and a nonprogressive course. Generalized spike or polyspike-and-wave complexes are seen on EEG. Fatigue, insomnia, repetitive photic stimulation, and stress have all been reported to precipitate the myoclonus. The geographic distribution of these families was recently expanded to include cases in Europe, in addition to the originally identified Japanese families. Linkage analyses in the European kindred excluded the genetic locus for FAME that had previously been identified (8q23.3-q24.1), thus confirming the genetic heterogeneity of the syndrome. **Methods:** A three-generation North American family with four symptomatic members is described. We report the clinical and EEG findings from two affected members. **Results:** All of the symptomatic members of this family met clinical criteria for the diagnosis of FAME. Pedigree analysis suggested autosomal-dominant inheritance. In each case, the onset of myoclonus occurred during the fourth decade. Each patient also had rare generalized tonic–clonic seizures. Prolonged EEG monitoring on two members documented generalized spike or polyspike-and-wave ictal discharges. Fatigue, photic stimulation, and eye closure were all confirmed as precipitants of myoclonic seizures during the EEG monitoring. **Conclusions:** The geographic occurrence of families with FAME can now be extended to include North America. This is the first report of eye closure acting as a seizure precipitant in this group of patients.

2.070

THE VALUE OF INVASIVE PRESURGICAL ELECTROPHYSIOLOGIC RECORDING IN PATIENTS WITH ORBITOFRONTAL LESIONS AND MEDICALLY REFRACTORY PARTIAL SEIZURES

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Rationale: Orbitofrontal seizures are often clinically indistinguishable from complex partial seizures of temporal lobe origin. We review an approach to presurgical evaluation of three patients with orbitofrontal lesions and partial seizures with uncertain noninvasive localization. **Methods:** We reviewed charts of three patients (A, B, C) with orbitofrontal lesions (hamartoma, cortical dysplasia, trauma). All patients had gross lesions on magnetic resonance imaging (MRI) with normal-appearing temporal lobes. Patient A had a history of partial seizures and had been seizure free after removal of a left orbitofrontal hamartoma; 5 years after the surgery, she developed seizures of a different semiology with nonlocalizing scalp frontotemporal changes ipsilateral to the lesion. Patient B had partial seizures of two distinct semiologies and MRI evidence of right orbitofrontal cortical dysplasia, with scalp recordings showing ipsilateral, nonlocalizing frontotemporal changes. Patient C had a history of multiple seizure types after head trauma, with MRI evidence of right orbitofrontal encephalomalacia; surface recording revealed seizures that appeared to arise from the right temporal lobe. However, invasive monitoring was pursued in light of the orbitofrontal lesion. All patients underwent invasive electrophysiologic monitoring. In cases A and B, recordings were obtained using a six-contact depth electrode placed in the superior frontal gyrus directed inferiorly into the lesion, a lateral frontal six-contact strip electrode inserted from the same burr hole, and two depth electrodes directed orthogonally into the amygdala and pes hippocampus. In case C, recordings were made using two medial and lateral frontal strip electrodes placed via a superior approach, and one laterally placed subtemporal strip electrode with distal contacts approximating mesial temporal structures. **Results:** An independent temporal focus was found in all cases. In addition, there were coexisting orbitofrontal seizures in two of the three (B, C); patient A had distant orbitofrontal seizures based on the previous evaluation and outcome from frontal resection. After surgical intervention (selective amygdalohippocampectomy in case A, orbitofrontal resection in case B targeting the predominant seizure type, multilobar resection in case C), there was complete seizure control in cases A and B and a significant reduction (Engel 2) in case C. Of note, the recurrent seizures in case C were mainly simple partial seizures, all of extratemporal semiology. The pathology was mesiotemporal sclerosis in case A, cortical dysplasia in case B, and old hemorrhage (orbitofrontal) with normal temporal lobe in case C. **Conclusions:** In patients with independent orbitofrontal and temporal lobe seizures, multilobar resection can effectively control

seizures without significant adverse neuropsychological consequences. Invasive video-EEG telemetry was necessary in the evaluation of our patients with orbitofrontal lesions and partial seizures of unclear localization. This was especially helpful in the case in which recurrence was shown to be from a focus independent of the orbitofrontal lesion.

2.071
A STANDARD TESTING SYSTEM TO IMPROVE THE COLLECTION OF SEIZURE DATA DURING EPILEPSY LONG-TERM MONITORING

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Rationale: Epileptic seizures and their postictal periods are rich sources of information about the nature of epilepsy, but patients are rarely examined systematically during and after attacks in a way that is consistent from one patient to the next, even during long-term EEG monitoring. We present a standard procedure that can be done quickly and consistently, and one that covers areas providing much information about the underlying seizure disorders. After training with the materials we have developed, epilepsy long-term monitoring staff are able to consistently test EEG-monitored seizures using this uniform approach. **Methods:** An interdisciplinary team of nurses and psychometrists, with input from neuropsychologists and physicians, identified essential functions requiring testing during and after epileptic seizures. Mindful of the often very limitied time available to gather data during and immediately after a seizure, we developed a short, standard seizure-testing system to assess orientation, ability to name objects, ability to read a sentence and follow directions, and to assess short-term memory and motor function. The set of materials consists of a series of two-sided, laminated cards with pictures and print for patients to view during testing, with cues for staff on the reverse sides of the cards. To assure standardized administration of the testing, all staff were trained with a 10-min video demonstration, a one-page sheet of instructions, and individual training from charge nurses and supervisors. **Results:** The standard testing protocol has been used on our inpatient unit since September 2001. A set of testing cards is kept on a shelf by each monitored patient's bed and in each of the neuropsychology testing rooms. This testing protocol is routinely used to test each monitored seizure on the inpatient unit. For >8 months, with an estimated minimum of 50 monitored, tested seizures per month, we have evaluated >400 seizures thus far using this uniform seizure-testing system. Nurses now report more confidence in undertaking the procedure, and there is less delay in beginning testing after a seizure has begun. Physicians have stated that testing during seizures is more consistent, and that the information it generates is more useful in helping to arrive at correct diagnoses and appropriate treatment plans. Furthermore, with each seizure videotaped, a research tool is now in place that did not previously exist. **Conclusions:** The standard seizure-testing system has improved the consistency and quality of information available to neurologists, neurosurgeons, and neuropsychologists, and we believe that it has also improved our ability to develop care plans for our patients. The system can be used for a variety of research projects in the future.

2.072
MALFORMATIONS OF CORTICAL DEVELOPMENT AS A CAUSE OF ADULT-ONSET EPILEPSY

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Rationale: Malformations of cortical development (MCDs) are recognized as a relatively common cause of epilepsy. Approximately 20% of adults and 50% of children treated with epilepsy surgery have MCDs as their pathologic substrate. MCDs are usually associated with childhood or adolescent-onset epilepsy; it has been infrequently described with adult-onset epilepsy. A recent report showed heterotopias as a cause of adult-onset epilepsy. We describe patients with adult-onset epilepsy associated with a variety of MCDs **Methods:** In the University of Michigan Epilepsy Clinic, we identified 17 patients with adult-onset epilepsy, defined as epilepsy onset after age 20 years. For all patients, the following clinical information was collected: age at onset, seizure type, localization, magnetic resonance imaging (MRI) classification of the MCD, and seizure outcome with medical therapy. MRIs were reviewed by D.G.H. and E.A.P. and classified according to the classification system of Barkovich and Kuzniecky (2001). **Results:** Seventeen patients (six women/11 men) were identified with adult-onset epilepsy associated with an MCD. The mean age at onset of epilepsy was 29 years (range, 23–37 years). The MCD location was diffuse (three); frontal (three); temporal (seven); occipital (three), and parietal (one). Two of the patients with temporal MCDs had mesial dysplasia, and five had cortical dysplasia. All patients had partial-onset seizures with infrequent secondarily generalized tonic–clonic seizures. The following MCDs were identified on MRI: mesial dysplasia (two); cortical dysplasia (10); polymicrogyria (two), and heterotopia (three). Nine of 17 patients were not controlled with antiepileptic drugs. **Conclusions:** MCDs can be a cause of adult-onset partial epilepsy. A wide range of MCDs cause epilepsy in adults, with cortical dyslasia as the most common type. High-resolution MRI with epilepsy protocol and multiplanar reformatting is necessary to identify these MCDs. Temporal lobe location is most common, and in some patients, the MCD can be diffuse (i.e., PMG and heterotopias), and in most, it is focal (i.e., cortical dysplasia). Identification of these MCDs is important in that it could have implications for long-term prognosis for seizure control. Future studies are necessary to understand why the epileptogenicity of MCDs is expressed in childhood and adolescence in most patients and in adulthood in others. (Supported by Paul Cumbo Fund.)

2.073
TONIC-ABSENCE SEIZURES: AN UNDERRECOGNIZED SEIZURE TYPE

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Rationale: To characterize an underrecognized seizure type. The individual electroclinical patterns–tonic seizures with generalized paroxysmal fast activity (GPFA, activity >13 Hz), and absence seizures with generalized slow spike-and-wave activity (GSS&W, <3 Hz)–have been extensively described in the literature. However, there has been only passing reference to the pattern of GPFA followed by GSS&W. In addition, these descriptions were formulated in the pre-EMU era, without benefit of video/clinical correlation. **Methods:** We retrospectively reviewed the data from eight patients with seizures that demonstrated this stereotyped EEG and clinical pattern. **Results:** We identified eight patients (six female; age 6–29 years; age at seizure onset, neonate to 10 years) who were evaluated at the Columbia Presbyterian Epilepsy Monitoring Units between 1993 and 2002. All eight carried an International League Against Epilepsy (ILAE) diagnosis of symptomatic generalized epilepsy, with six of eight manifesting multiple seizure types, six of eight with mild mental retardation, and two with normal cognition. A total of 29 electroclinical seizures of this pattern were recorded. Twenty-six of 29 seizures demonstrated GPFA (frequency between 14 and 30 Hz, lasting 2–8 s) followed by GSS&W (frequency range between 1 and 2 Hz, lasting 3–50 s). The predominant clinical correlate was bilateral tonic activity followed by a period of inattentiveness. In general, these seizures were differentiated from the patient's typical tonic seizures by this protracted period of impaired attentiveness. **Conclusions:** We describe a heretofore underrecognized and poorly characterized seizure type in patients with symptomatic generalized epilepsy, which we have termed "tonic-absence" seizures. Clinically and electrographically, this consists of a tonic seizure with GPFA followed by an absence seizure with GSS&W.

2.074

ICTAL MANIFESTATION OF ALIEN-LIMB SYNDROMES

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Rationale: Alien-limb syndromes are characterized by seemingly purposeful limb movements, which are subjectively experienced as alien induced and beyond the patient's voluntary control. According to the localization of the underlying lesion, three subtypes of alien-limb syndromes have been described: (a) frontal type, (b) frontocallosal type, and (c) posterior type. Usually, alien-limb syndromes remain stationary but can also occur ictally, as shown in our cases. The phenomenon is supposed to reflect a disconnection of interhemispheric pathways or unilateral projection fibers. **Methods:** Case 1: A 43-year-old patient with temporal lobe epilepsy due to left mesial temporal sclerosis had episodic involuntary abduction movements of her alienized right arm. The episodes lasted only a few minutes while the patient tried to resist the movement by pulling back the arm with her unaffected left hand. Case 2: This 16-year-old patient with a focal epilepsy due to cortical dysplasia in the right cingulate gyrus experienced paroxysmal involuntary anteversion movements of his alienized left leg. **Results:** In both cases, video-EEG monitoring revealed these episodic phenomena to be of ictal origin. Case 3: In this 16-year-old patient with left-sided tumoral parietal lobe epilepsy, paroxysmal alien-limb symptoms with involuntary movements and estrangement of his right arm could be elicited by electrical stimulation of the left postcentral cortex. **Conclusions:** Epileptic seizures can cause a variety of focal neurologic symptoms by episodic activation or inhibition of cortical areas with certain functional eloquence. As our cases show, this is also true for complex phenomenona like the alien-limb syndromes. Analogous to the stationary types, we suspect a functional disconnection of sensory and motor cortex, limited to the duration of the seizure.

2.075

VIDEO-EEG EVIDENCE THAT PRIMARY GENERALIZED SEIZURES ARE ACTUALLY SECONDARILY GENERALIZED

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Rationale: Whether the cerebral cortex or subcortical structures, specifically the thalamus, play the dominant role in generating primary generalized seizures has been the subject of long debate. Most experimental data support a predominant role for cerebral cortex in generation of the spike-and-wave activity, with the thalamus quickly recruited to sustain generalized spike-and-wave oscillations in a reverberating thalamocortical network. A focal cortical generator or a multifocal cortical "hyperexcitability" has been postulated to underlie the presumed cortical initiation. There is little clinical evidence to support either of these hypotheses. We present video-EEG recordings of six generalized tonic–clonic seizures in three patients with proven primary generalized epilepsy (PGE), all of whom showed a consistent pattern of lateralized seizure onset compatible with a unifocal frontal lobe generator. **Methods:** Among 300 patients referred for video-EEG monitoring, three were found to have PGE with tonic–clonic convulsions. All had a family history of epilepsy and no other epilepsy risk factors. Epilepsy onset was during childhood (one) or adolescence (two): duration was 35, 19, and 5 years. All had absence spells and tonic–clonic convulsions; one had occasional myoclonic absences accompanying daily morning myoclonic jerks. Patients were taking one to four antiepileptic drugs (AEDs) at admission, none of which was valproic acid (VPA). Two of three are now seizure free with VPA monotherapy (f/u, >12 months). One patient refused VPA but has improved with lamotrigine (LTG) and phenobarbital (PB). **Results:** Interictal EEG showed very active bilaterally synchronous generalized spike-and-wave or polyspike and slow wave discharges between 2.5 and 4.5 Hz, maximal over the midfrontal structures symmetrically in all patients. Coherence analyses showed no hemispheric time leads. Ictal EEG showed a generalized tonic recruiting pattern maximal over the anterior hemispheres without lateralization. Surprisingly, in all six recorded tonic–clonic seizures, there was a distinct, stereotyped, sustained (10–15 s) clinical lateralization at onset, which took the form of a tonic "fencing posture" in two patients (three seizures) and forced head/eye/torso version in the third (three seizures). **Conclusions:** Tonic–clonic seizures are presumed to be generalized from onset in patients with PGE. However, because patients with PGE are not surgical candidates, video-EEG is rarely performed, and the clinical features of primary generalized seizures are likely underappreciated. The findings of distinct and sustained lateralization at onset, with features clinically indistinguishable from focal-onset frontal lobe seizures, is compatible with the hypothesis of a focal region of cortical "hyperexcitability," situated in the frontal lobes of patients with PGE. Whether this cortical generator is autonomous or "triggered" by ascending, possibly normal, thalamocortical volleys is unresolved, but a cortical predominance for the generation of tonic–clonic seizures in PGE appears evident. [Supported by Bloorview Epilepsy Research Program (P.C., R.W.).]

2.076

INTRACRANIAL EEG CORRELATES OF POSTICTAL NOSEWIPING

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Rationale: Postictal nosewiping (PINW) is a common feature in temporal lobe epilepsy (TLE), occuring in ~50–60% of patients with TLE, and in only 10–33% of those with extratemporal epilepsy (ETE). PINW is performed with the hand ipsilateral to the epileptogenic zone in the majority of patients, thus providing localizing and lateralizing indications with respect to seizure onset. The physiopathology of PINW remains unknown. To date, the relation between PINW and intracerebral EEG data has been reported in only one patient, in whom PINW correlated with an amygdala discharge (Wennberg et al., 2000). We have therefore undertaken a retrospective study in 33 patients who underwent intracranial EEG monitoring, to correlate PINW with the ictal involvement of the amygdala. **Methods:** Thirty-three patients with refractory partial epilepsy who underwent an intracranial EEG investigation in our institution were included in this study. Video and intracranial EEG data of 204 seizures were reviewed independently by two different observers who respectively studied the occurrence of ictal or postictal nosewiping, and the time of onset, duration, and origin of ictal EEG discharges. These different analysis used the same time reference, allowing calculation of the delay separating each nosewiping from the seizure onset and termination. Only PINW occurring during the 2 min after the latter were taken into account. We evaluated the ratio of seizures with at least one PINW for each individual, and compared this ratio between patients with TLE and ETE. In a subset of 49 temporal lobe seizures, we evaluated the type (low-voltage fast activity vs. other types of ictal discharge), duration and earliness of an amygdala discharge, and looked for an association between these parameters and the occurence of PINW. **Results:** Twenty-four patients had TLE, whereas nine patients had ETE. PINW was observed in 51% of temporal lobe seizures, and in only 3% of extratemporal seizures ($p = 0.0001$); 88% of TLE and 33% of ETE patients had at least one seizure associated with PINW ($p = 0.0075$), whereas 79% of TLE and no ETE patients showed PINW in at least one third of their recorded seizures ($p = 0.0002$). All selected TLE patients had ictal discharges that involved the amygdala at some point. The occurrence of PINW did not correlate with the type or the duration of that discharge. However, there was a weak association between the likelihood of observing PINW and the involvement of the amygdala at seizure onset, which approached significance ($p = 0.0732$ for $\chi 2$ with continuity correction; $p = 0.0358$ without correction). **Conclusions:** This intracranial EEG study has confirmed that postictal nosewiping is significantly more frequent in TLE than in ETE, and has a strong localizing value when occuring in $\geq 33\%$ of recorded seizures. The role of an amygdala dysfunction in generating PINW is mildly supported by the association found between PINW and the earliness of the amygdala discharge. (Supported by University Claude Bernard Lyon 1.)

2.077

CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS IN 17 PATIENTS WITH HYPOTHALAMIC HAMARTOMAS

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Rationale: This study was designed to analyze the clinical spectrum of epilepsy in a large number of patients with hypothalamic hamartomas. **Methods:** Data from 17 patients (aged 5–45 years) with a hypothalamic lesion found on magnetic resonance imaging (MRI) were analyzed. The clinical course of epilepsy, seizure semiology, and electrophysiologic findings were correlated with size and site of lesion. **Results:** Laughing as a prominent symptom occurred in 14 of 17 patients, usually as part of a seizure with psychomotor or tonic semiology. The remaining three patients had an ictal grin or an aura consisting of an urge to laugh or smile. All patients had focal seizures (tonic, eight; psychomotor, 11; generalized tonic–clonic, four; with an aura in seven patients). Only one patient had a normal interictal EEG; of the remaining patients, six had generalized and regional slowing over one or more cerebral regions; seven had regional slowing, which was unilateral in three. In these three patients, unilateral slowing was always ipsilateral to the side of lesion, and in our sample, always over the right hemisphere. Fifteen of 17 patients had regional epileptiform potentials (temporal only, one; extratemporal only, four) or seizure patterns, occurring in two patients exclusively unilaterally, in seven patients bilateral regional, and in six patients, additionally generalized. Two patients with generalized epileptiform potentials also had a photoparoxysmal response in EEG. Mild to severe mental impairment was present in eight, and pubertas praecox in two of 17 patients. Neurologic examination revealed no focal abnormality except a facial nerve palsy in one patient. No patient became seizure free through medication. **Conclusions:** This study demonstrates that the clinical spectrum of this disease ranges from isolated laughing attacks without any further impairment to severely handicapped patients with additional significant mental impairment and endocrine dysfunction. Despite the characteristic symptoms, diagnosis was delayed for years in several of our patients for various reasons, indicating that the incidence of this condition is probably underestimated.

2.078

GRASPING DURING "FRONTAL HYPERMOTOR" SEIZURES: A RELEASE OF INNATE BEHAVIOR?

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Rationale: Two-fold purpose: (a) to quantify and analyze repetitive grasping, which we observed during the complex motor sequences, characterizing "hypermotor" (Luders et al., 1998), "frontal" (Williamson et al., 1985) seizures; (b) to ascertain whether grasping can occur in seizures types other than the hypermotor frontal one. **Methods:** Thirty hypermotor seizures, lasting >30 s, were video and polygraphically recorded in 12 patients. Off-line frame-by-frame video-analysis was performed. Frequency, side, and site of grasping and latency from seizure onset were evaluated. Occurrence of grasping was also analyzed in a control group of 41 consecutive patients, who had 193 video-polygraphically recorded seizures, without the hypermotor manifestations, according to Luders (1998) semiologic definition. **Results:** Grasping was observed in 29 hypermotor seizures of 30 (96.66%); the total number of grasping phenomena, recorded in all seizures, was 117 (mean value, 6.7 repetitive events per seizure), with a mean latency of 3 s from clinical onset. Grasping was mainly directed to bed equipment, genitals, thigh, gluteus; it often appeared to have function of steadying point for "pedaling–bicycling–rocking" movements. During the same seizure, both arms could perform the grasping, which was generally preceded by reaching and followed by holding or pulling, as in the case of voluntary physiologic prehension (Rizzolatti et al., 1993). Grasping was not observed in 193 seizures without hypermotor behaviors (control group). We can conclude that repetitive grasping is quite specifically related to the complex motor manifestations characterizing the hypermotor seizure. **Conclusions:** Our data shows that forced prehension (grasping) is a frequent and, in our experience, specific manifestation in frontal hypermotor seizures. Grasping can be considered as an innate motor behavior (Grillner and Wallen, 1985), physiologically present in newborn and lately occurring in pathologic conditions related to dysfunction of frontal lobe. According to Denny Brown (1960), "instinctive tactile grasping and placing are related to mesial frontal lesion....and disturb the balance in favor of exaggeration of grasping." Therefore, the seizure event can trigger hypermotor clinical manifestations as well as interfere with inhibitory frontal function, leading to a release of grasping innate behavior.

2.079

SEIZURE SEMIOLOGY IN TEMPORAL LOBE EPILEPSY: HIPPOCAMPAL SCLEROSIS VERSUS HIPPOCAMPAL SCLEROSIS PLUS

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Rationale: At the end of this activity the participants should be able to discuss if patients with pure hippocampal sclerosis (HS) and patients with HS associated with abnormalities on the temporal pole belong to different subgroups. To compare ictal and postictal clinical symptoms in patients with temporal lobe epilepsy (TLE) and pure hippocampal sclerosis (HS), and patients with TLE and HS associated with abnormalities on the temporal pole (HS-Plus), diagnosed by magnetic resonance imaging. **Methods:** Blinded to clinical details, we reviewed preoperative ictal video-EEG recordings from patients with TLE and HS, and from patients with TLE and HS-plus, who underwent temporal lobectomy. We analyzed ictal and postictal symptoms, and the order of appearance of the manifestations in the first 30 s of the seizures. **Results:** We analyzed 56 seizures in 21 patients. Patients were differentiated in two groups: group 1, HS (16 patients, 36 seizures); and group 2, HS-plus (five patients, 20 seizures). The most frequent auras were in group 1, epigastric sensation (50%) and fear (25%), and in group 2, epigastric sensation (40%), fear (40%), and "déjà vu" (40%). The most frequent clinical symptoms were in group 1, staring (88%), behavioral arrest (86%), oroalimentary automatisms (72%), and repetitive hand automatisms (67%); and in group 2, oroalimentary automatisms (65%), repetitive hand automatisms (55%), and staring (45%). The symptom "déjà vu" was more frequent in group 2 ($p < 0.001$), and the clinical manifestation "behavioral arrest" was more frequent in group 1 ($p < 0.001$). The most common sequence of symptoms in group 1 was behavioral arrest > staring > oroalimentary automatisms > repetitive hand automatisms; we did not find any specific sequence of symptoms in group 2 ($p < 0.001$). **Conclusions:** These observations suggest that patients with HS and HS-plus belong to different subgroups of patients. The presence of a specific sequence of symptoms may be useful in discriminating seizures of pure HS from HS-plus seizures. (Supported by Epilepsy Center, Department of Neurology, Ramos Mejía Hospital.)

2.080

ICTAL SPITTING: CLINICAL AND ELECTROENCEPHALOGRAPHIC FEATURES

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Rationale: Semiologic features of seizures are helpful in lateralizing the epileptogenic zone. Ictal spitting is a rare event during focal seizures. The goal of our study was to identify clinical and EEG correlates of ictal spitting and assess their lateralizing value. **Methods:** The epilepsy-monitoring database of The Cleveland Clinic Foundation (CCF) was searched for patients with history of ictal spitting. The charts of the patients and their original video and EEG data were reviewed. **Results:** Nine of ~5,000 patients who underwent long-term video-EEG monitoring at the CCF between 1990 and 2001 had a clear

history of ictal spitting. In five of them, a total of 13 seizures with ictal spitting automatisms could be recorded. All seizures started with an aura or arousal out of sleep. In two seizures, the aura consisted of intense fear. In five seizures, ictal spitting was not preceded by any motor features. Before the spitting, oral automatisms were seen in three seizures, staring in two seizures, and whole-body automatisms in four seizures. Ictal spitting was followed by retching and nausea in two seizures, by oral automatisms in two seizures, by hand or whole-body automatisms in five seizures, and by dystonic posturing of the right hand in one seizure. In five seizures, there were no other clinical features after the spitting. In four of the five patients (10 of 13 seizures), EEG onset was clearly lateralized to the right, nondominant hemisphere. Spitting occurred 21 s (median) after EEG seizure onset. At that time high-amplitude theta was seen in the hemisphere of seizure onset, maximum temporal. In seven seizures, there was no significant ictal EEG activity in the hemisphere contralateral to seizure onset at that time. Total duration of the EEG seizures was 61 s (median). In one patient (three seizures), left temporal and parietal depth electrodes were implanted. His seizures started in the left posterior hippocampus. At the time the spitting occurred, discharges had spread to the amygdala and anterior hippocampus, without change in surface EEG in two of the three seizures. He became seizure free after left anterior temporal lobectomy. Six of the total of nine patients had the seizure onset in the right, nondominant hemisphere. In two patients, seizure onset was bilateral independent, and no spitting automatism could be recorded during the stay. One patient had seizure onset in the left, language-dominant hemisphere. **Conclusions:** Ictal spitting occurs predominantly in the first half of a seizure, usually preceded by an aura. Oral, manual, or whole-body automatisms may occur before or after the spitting. Seizure onset is from the nondominant hemisphere in the majority of the cases, and ictal EEG activity often is confined to this hemisphere at the time of the spitting automatisms. However, there was one carefully documented case with the seizures arising from the left, dominant hemisphere. Therefore, this clinical sign should be interpreted with caution.

2.081

COMPARISON OF CLINICAL PROFILES BETWEEN CONVENTIONAL CRYPTOGENIC MTLE AND SYMPTOMATIC MTLE DUE TO PRECEDING CNS INFECTION

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Rationale: Mesial temporal lobe epilepsy (MTLE) is a well-known clinical syndrome in electroclinicopathologic point of view. However, there are no plasuable preceding causes leading to mesial temporal sclerosis (MTS) except for the history of febrile convulsion. Occasionally we have met intractable epilepsy patients with MTS and only a history of CNS infection. We investigated the clinical profiles of MTLE patients with CNS infection as another cause of MTS to delineate the clinical differences between conventional MTLE and MTLE due to preceding CNS infection. **Methods:** Clinical data of TLE patients with unilateral MTS in magnetic resonance imaging (MRI) were thoroughly reviewed from patients registered at Yonsei University Severance Hospital for last 12 years. T1 axial and T2-weighted oblique coronal image including fluid-attenuated inversion recovery (FLAIR) images were taken for evaluation of hippocampal morphology. Cases with clear unilateral MTS without additional lesions in MRI were divided into cryptogenic (conventional) MTLE group and symptomatic (CNS infection–related) MTLE. We compared the clinical data including sex, age at onset, semiology, frequency of seizure, laterality of MTS, presence of secondarily generalized seizure, and prognosis. We decided the prognosis to be poor if the reduction of seizure frequency was less than half and good if seizure free or aura only. **Results:** Total enrolled cases were 126 in the cryptogenic MTLE and 22 in the symptomatic MTLE group. Conventional cryptogenic MTLE showed statistically significant preponderance ($p < 0.05$) in febrile convulsion and accompaniment of secondarily generalized tonic–clonic (SGTC) seizures. In contrast, symptomatic MTLE was statistically significant higher ($p < 0.05$) in male preponderance, family history, daily attack, and nocturnal GTC. Clinical semiology including aura and automatism was not different between two groups, and overall prognosis was same with >5 years' follow-up duration. **Conclusions:** Our data showed prominent preponderance of febrile convulsions in the conventional MTLE group as expected, but family history was not. In consideration of no differences of ictal semiology such as aura and automatism despite minor differences in these results, the mesial temporal location of ictal onset does not seem to have an effect on the semiology, depending on the underlying etiology.

2.082

ELECTROGRAPHIC VARIATION OF SEIZURES ARISING FROM THE SAME ICTAL ZONE IN PATIENTS WITH MULTIFOCAL EPILEPSY

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Rationale: We have previously shown that in patients with multifocal epilepsy, seizures arising from the same ictal zone (as determined by intracranial EEG) often have dissimilar clinical semiologies (*Neurology* 2002;58(suppl 2):40) and hypothesize that there may be more than one focus for generating seizures within a single ictal zone. **Methods:** We performed blinded reviews of the intracranial EEGs of 17 multifocal epilepsy patients. Two seizures arising from the same ictal zone were reviewed in each patient (total of 34 seizures reviewed). Video and EEG recordings were reviewed separately and blinded from each other, and without prior knowledge of the clinical history or neuroimaging findings. The morphology of EEG discharge at seizure onset was compared between pairs of seizures with dissimilar and pairs with similar semiology. **Results:** Seizures in 13 of the 17 patients (76.5%) had dissimilar semiology. Seizures in the other four patients (23.5%) were similar in semiology. EEG discharge morphology at seizure onset was different in seven of 13 patients (54%) whose seizures were dissimilar in semiology despite the same intracranial ictal zone localization. In contrast, morphology of the EEG discharge was the same in all patients whose seizures were similar in semiology. In the 13 patients with dissimilar seizure semiology, differences observed in their EEG discharge morphology could be divided into the following four categories: (a) rhythmic beta discharge in one seizure and 3- to 5-Hz spike–waves in the other seizures (four patients); (b) rhythmic beta discharge in one seizure and rhythmic theta discharge in the other seizure (one patient); (c) rhythmic beta discharge/electrodecrement in one seizure and electrodecrement only in the other seizure (in one patient); (d) electrodecrement in one seizure and 4-Hz spike–wave in the other seizure (in one patient). **Conclusions:** Our study suggests that subpopulations of seizure foci may exist within a single ictal zone in patients with multifocal epilepsy. The findings may explain our initial observation that seizures arising from the same ictal zone can have dissimilar semiology. (Supported by Mayo Foundation for Research and Education.)

2.083

ELECTROCLINICAL FEATURES OF EPILEPSY ASSOCIATED WITH BILATERAL FRONTAL POLYMICROGYRIA

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Rationale: Bilateral frontal polymicrogyria (BFP) is a recently described malformation of cortical development, characterized by symmetrical polymicrogyria of both frontal lobes back to precentral sulcus (Guerrini et al., 2000). The main clinical features are developmental delay, spastic quadriparesis, impaired language development, mental retardation, and epilepsy. Epilepsy can show variable ages at onset and severity. We report the electroclinical features of two adult patients with BFP and severe drug-resistant epilepsy. **Methods:** Patient 1 was

a 24-year-old woman. Maternal toxoplasmosis at 3 months of pregnancy was diagnosed. The patient had bilateral glaucoma and cataract, mental retardation, mild bilateral pyramidal syndrome. At age 10 years, she had a drug-resistant epilepsy characterized by partial seizures with automatisms, tonic seizures, and frequent episodes of partial status. Patient 2 was a 30-year-old man with mild mental retardation and psychotic disturbances. At age 6 years, learning difficulties and behavioral disorders were noted. At 7 years, he started to have daily seizures characterized by loss of consciousness, and massive tonic contraction; motor manifestations could often follow. Occasional tonic–clonic seizures could also occur. The seizures were poorly controlled by antiepileptic (AED) treatment. Both patients underwent awake and sleep video-EEG/polygraphic recording, computerized video-EEG monitoring, brain magnetic resonance imaging (MRI), and interictal single-photon emission computed tomography (SPECT; in patient 1). **Results:** In both patients, interictal EEG was characterized by diffuse, with frontal predominance, paroxysmal activities; in patient 1, multifocal (left frontal and asynchronous bilateral temporal) spikes were present as well. In patient 1, ictal video-EEG showed seizures characterized by a massive tonic contraction, followed by left head version and mild pedaling movement of the lower limbs; in the EEG, an initial diffuse flattening was observed, followed by diffuse rhythmic spike activity, with maximal amplitude over the frontocentral regions, and then anteriorly predominant spike–wave complexes appeared. In patient 2, video-EEG allowed the recording of seizures with a diffuse tonic contraction followed by hypermotor phenomena. Ictal EEG showed an initial diffuse slow-wave complex, that preceded a low-amplitude fast rhythmic activity that was followed by diffuse slow spike-and-wave abnormalities. In both patients, brain MRI showed BFP, in patient 1 associated with cerebellar vermis agenesia. In patient 1, interictal SPECT showed bilateral frontal hypofixation. **Conclusions:** The electroclinical features of epilepsy associated with BFP has been not clearly described. A spectrum of epileptic disorders has been reported. Both adult cases that we observed showed similar electroclinical epileptic features, suggesting the involvement of frontal structures. Neurologically, they differed from the data of the literature for the mild (patient 1) or absent (patient 2) motor impairment.

2.084

ICTAL URINATION DURING FOCAL EPILEPTIC SEIZURES IN FOUR PATIENTS

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Rationale: Only a few studies have dealt with the physiology of perictal urination. To determine the localizing value of this symptom, we report on four cases explored in our epilepsy unit. **Methods:** Ictal urination was defined as an urination experienced by the patients during their seizures. Four patients were selected : three men and one woman. They were examined in a presurgical unit for drug-resistant epilepsy. All patients' urination is documented by video-EEG monitoring. Interictal and ictal single-photon computed tomography (SPECT) and high-resolution magnetic resonance imaging (MRI) were performed in every patient, and a depth electrode exploration (stereo-electroencephalography; SEEG), in three patients. Epileptic zone (EZ) was mainly determined by the ictal correlations made with video-EEG, SEEG, and SPECT. **Results:** In three patients, the EZ was located in the orbital part of the right frontal lobe. In one patient with depth electrodes, the EZ is localized in the left temporal lobe, the seizure involved secondarily the insular cortex and the opercular part of the frontal lobe, whereas slow waves were recorded in the orbital region in the same side. **Conclusions:** Ictal urination seems to be trigged by ictal involvement of the orbital frontal region, mainly in the right hemisphere; this could reflect the primary EZ or a propagation. Insular cortex may be also involved, as some temporal lobe seizures may provoke urination. This part of the insular cortex could be equivalent to a primary viscerosensory area responsible for a filled-bladder sensation (Baumgartner et al., 2000).

2.085

ICTAL APROSODIA IN NONDOMINANT TEMPORAL LOBE EPILEPSY

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Rationale: Previous studies have reported that lesions in the right cerebral hemisphere can be associated with aprosodia. No study to our knowledge that has described aprosodia as an ictal manifestation during an epileptic seizure. **Methods:** This is a case review of two patients admitted to our video-EEG epilepsy monitoring unit for the presurgical evaluation of epilepsy surgery who exhibited ictal aprosodia during seizures. We compared their baseline speech prosody with that during their seizures. We differentiated speech during seizures from that of epileptic auras by the presence of other clinical manifestation of seizures such as amnesia, focal motor activity, automatisms, or some alteration of awareness. **Results:** Patient 1 is a 23-year-old right-handed man. He had no risk factor for epilepsy. His seizure started at 2 years of age. The seizures were preceded by an olfactory aura. His seizures evolved into a stare with an arrest of activity and had some chewing movements of the jaw. During monitoring, his typical seizures were recorded. His mother had described his speech during his seizures as "like a robot." The ictal EEG revealed regional seizure onset from the right temporal region. He was diagnosed with right temporal lobe epilepsy based on EEG findings and a lesion in the right mesial temporal lobe on MRI. Patient 2 is a 54-year-old right-handed woman. Her seizures started at age 42 years. Small hemorrhage from an arteriovenous malformation (AVM) in the right posterior operculum region was found. Subsequently she underwent surgery for removal of an AVM. Eighteen months later, she started to have seizures again. The seizures started with an aura of strange feeling, followed by rapid deep breathing, goose bumps, tachycardia, and urinary urge. During two monitorings, her typical seizures were recorded. She was completely aware of her surroundings, and her speech was fluent, but she talked as if she were lacking an affect. During these seizures, she had other ictal manifestations including right-eye blinking, urinary urge, goose bumps, and oral automatism. The invasive ictal EEG revealed focal ictal onset from right mesial temporal region. She was diagnosed with right temporal lobe epilepsy based on invasive EEG findings. In these two cases, affective prosody was disturbed during ictal period, while speech fluency was preserved. This characteristic of speech is considered to be aprosodia. The lateralization of the epileptogenic zone in these two cases was suspected to be in the language nondominant hemisphere, although a Wada test was not performed. **Conclusions:** To our knowledge, this is the first report of ictal aprosodia during epileptic seizures. This ictal aprosodia was seen in the two patients with right temporal lobe epilepsy. Several lesion studies suggest that affective prosody is lateralized to the right hemisphere. Ictal aprosodia may be a lateralizing sign, which suggests that the seizures arise from nondominant hemisphere. (Supported by The Japan Epilepsy Research Foundation.) (Disclosure: Grant: The Japan Epilepsy Research Foundation.)

2.086

ICTAL HAND ATAXIA AS INITIAL MANIFESTATION OF PARIETAL LOBE SEIZURES

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Rationale: Parietal lobe seizures are rarely reported. Clinical manifestations are heterogeneous including somatosensory (paresthetic, painful), apraxia, and disturbances of body image. Ictal symptoms reflect often a propagation to central (asymmetric tonic or clonic phenomena), temporal (dialeptic, automotor, auditory hallucinations), occipital regions (visual hallucinations or illusions). We report two patients with ictal ataxia as initial signs of parietal lobe seizures documented by EEG-video. **Methods:** Two patients aged 12 and 15 years with refractory partial epilepsy were studied. Video-EEG, morpho-

logic, and functional neuroimaging were performed as presurgical investigations. **Results:** Ten seizures were recorded. Paroxysmal left-hand ataxia was the initial predominant sign, followed by painful paresthesia in one case. No tonic or clonic motor phenomena were observed, suggesting central seizure propagation. Interictal and ictal EEG features were consistent with parietal origin. Magnetic resonance imaging in one patient suggested underlying focal cortical dysplasia. **Conclusions:** Our cases point out the existence of ictal hand ataxia as initial sign of parietal lobe seizure onset. Such sign should be identify before invasive SEEG-video investigations in presurgical drug-resistant epilepsies.

2.087

MECHANISMS OF ICTAL SPEECH ARREST IN LANGUAGE-DOMINANT–ONSET TEMPORAL EPILEPSY

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Rationale: Ictal speech with automatism and preserved responsiveness (APR) has been proposed as a reliable lateralizing sign with possible 100% specificity in non–language-dominant onset (NLDO) temporal lobe epilepsy (TLE). In our experience, similar semiology may be present in patients with language-dominant onset (LDO) TLE. Possible mechanisms of impaired ictal speech are explored here by studying cases with fluent ictal speech. **Methods:** We reviewed clinical semiology and intracranial video-EEGs of 46 adult patients for whom language dominance had been determined by Wada testing. Between January 1999 and March 2002, these patients were evaluated by bilateral depth with scalp electrodes or unilateral grids ± subdural strips. During ictal events, patients were tested for orientation, ability to count, and ability to follow commands. **Results:** Fourteen patients had extratemporal foci and are not discussed. Of the 32 patients with TLE, nine had left, 17 right, and six bilateral onsets. The cerebral dominance for language was left hemisphere in all patients. Among the 15 patients with unilateral left-onset or bilateral temporal onset seizures, two patients had ictal speech with APR during LDO seizures. For patient A, who had similar semiology in either left- or right-onset hippocampal (hc) seizures, the presence of propagated epileptiform activity in the ipsilateral temporal cortex did not consistently abolish her ictal speech. Patient B, with a left-onset hc epileptic focus, maintained his baseline mentation and speech throughout seizures. With these seizures, there was no propagation of epileptiform discharges to ipsilateral neocortex. However, he did completely lose responsiveness in seizures with secondary generalization to the contralateral hemisphere. **Conclusions:** Fluent ictal speech in TLE is not a pathognomonic lateralizing sign for NLDO seizures. It may occasionally be seen in patients whose focus is within the language-dominant hemisphere. Propagation of epileptiform activity to the ipsilateral temporal neocortex may impair responsiveness but may not necessarily impair fluency. Distribution or rhythmicity and morphology of epileptiform activity in the temporal neocortex may be associated with varying degrees of ictal aphasia in LDO TLE.

TABLE 1. *Focus sites and the presence of ictal speech and preserved responsiveness*

Focus site	No. (patients)	No. (patients with ictal speech and APR)
L-hippocampus	3	1 (patient B)
L-lateral temporal	6	0
B hippocampus + lateral temporal	6	4-R only and 1 (patient A)-L&R[a]
R-hippocampus	9	2
R-lateral temporal	8	3

R, right; L, left; B, lateral; APR, automatism and preserved responsiveness.

[a] Seizures of L or R onset did not occur simultaneously.

2.088

DEVELOPMENTAL RISKS IN PATIENTS WITH NONEPILEPTIC SEIZURES

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Rationale: Trauma histories have been consistently identified as a major risk factors for nonepileptic seizures (NESs). Far less is understood regarding the role of developmental and biologic substrates of NESs. Neuroimaging correlates of other psychiatric disorders, as well as other forms of conversion, suggest neurologic underpinnings of NESs may exist. The etiology is elusive, and there remains considerable symptom and risk overlap with epileptic seizures (ESs). Developmental vulnerabilities and other forms of neurologic compromise may provide fertile ground to the expression of NESs in later life. The purpose of this study was to compare patient self-report of developmental and select neurologic histories in patients with video-EEG confirmed NESs and ESs. Participants should be able to identify basic features, known and suspected risk factors of adult-onset NESs. **Methods:** Responses of 34 NESs patients to a comprehensive background history questionnaire were compared with age- and education-matched patients with ESs. All underwent diagnostic inpatient video-EEG monitoring to characterize the nature of spells and seizures. **Results:** There were no group differences in gender distribution, mean age, or education. Twenty-one percent of NES patients had a formal diagnosis of attention deficit disorder (ADD) or attention deficit–hyperactivity disorder (ADHD) while in school; no ES patient in this sample reported this history ($\chi 2 = 0.03$). Approximately one third of NES patients reported a childhood history of difficulty interpreting others' emotions, whereas <10% of ES patients endorsed this problem ($\chi 2 = 0.05$). Both family and personal history of severe headache or migraine were common in NES (62 and 82%, respectively). Comparatively fewer ES patients reported family or personal history of headache (41 and 25%; $\chi 2 = 0.01, \chi 2 = 0.002$, respectively). No statistically significant group differences emerged, however, in patients' self-report of developmental delays (e.g., walking, language), formal diagnosis of learning disability, or school failure. Although experiencing more difficulty interpreting others' emotions during childhood, NES patients did not perceive any greater childhood difficulty expressing their own emotional states and needs as compared to patients with ESs. **Conclusions:** Patients with NESs may possess vulnerabilities during childhood and adolescence that predispose expression of the disorder in a manner similar to that proposed by diathesis stress models. Neurologic underpinnings associated with ADD/ADHD, headache, and familial history of headache may play a meaningful role in the emergence of somatization disorders in adulthood. Review of such factors may be useful as part of a comprehensive clinical workup and may further guide therapeutic intervention.

2.089

PREDICTIVE VALUE OF THE PERSONALITY ASSESSMENT INVENTORY (CONVERSION SUBSCALE) FOR NONEPILEPTIC SEIZURES VERSUS ALCOHOL PATCH INDUCTION, USING CLOSED-CIRCUIT VIDEO-EEG

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Rationale: Of patients referred to epilepsy clinics with "blackouts," 25% have conversion disorder or some type of psychogenic event. Power of suggestion through use of the alcohol induction patch provides a way of determining whether the patient is experiencing nonepileptic seizures. The alcohol patch will normally produce only nonepileptic seizures. This procedure, however, sometimes fails to induce a nonepileptic seizure, even though the physician suspects that this is the case. **Methods:** The Personality Assessment Inventory (PAI) was randomly administered to first-time patients, at Epilepsy Institute of North Carolina, beginning in October 2001. A physician performed the alcohol induction patch protocol during video-EEG to induce seizures in patients whose psychosocial histories suggested conversion

disorder symptoms. PAI and inductions were performed in separate departments, and information was not shared. **Results:** As of May 1, 2002, the PAI had confirmed 60 conversion disorders. Alcohol patch inductions were subsequently administered to these patients. The "patch" provoked seizures in 42 (70%) of these patients. Of the remaining 18 (30%) patients, normal EEGs, background psychosocial histories, and medical histories indicated that 11 (61%) were experiencing nonepileptic seizures. **Conclusions:** The PAI Conversion Disorder subscale is a powerful tool to aid the physician to distinguish nonepileptic seizures in the absence of positive alcohol patch seizure induction on CCTV-EEG.

2.090

UNDERSTANDING THE PSYCHODYNAMICS OF PSYCHOGENIC PSEUDOSEIZURES IN PATIENTS WITH AND WITHOUT EPILEPSY

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Rationale: Patients with psychogenic pseudoseizures (PPs) frequently have affective disorders, anxiety disorders, and personality disorders. The global psychological distress experienced by epilepsy patients with/without PP is apparent, yet the premorbid personality disorders in PP patients that significantly impair coping skills in stressful situations is not fully understood. It is possible that certain Personality Disorder Clusters described in the DSM-IV could be used as a predictive factor for the diagnosis and prognosis of PPs. Therefore, we prospectively evaluated patients who were diagnosed with epilepsy in adulthood admitted for video-EEG monitoring for psychiatric symptoms. **Methods:** The psychiatric profiles of three groups of patients (i.e., patients with epilepsy, patients with pseudoseizures only, and patients with both epilepsy and pseudoseizures) were assessed using the Symptoms Checklist-104 and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders. **Results:** Eleven patients who were admitted with a preliminary diagnosis of epilepsy and/or pseudoseizures were included in this study. All subjects were women with a mean age of 40.6 years. Subjects by seizure group include group 1 (patients with epilepsy and PP), $n = 6$; group 2 (patients with PP only), $n = 3$; and group 3 (patients with epilepsy), $n = 2$. All 10 subgroups of symptoms assessed by the SCL-104 (including somatization, obsessive–compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychotic, and dissociative symptoms) did not show any statistically significance between the three groups. Among the patients with PPs (with or without epilepsy), four had cluster B Personality Disorders (Borderline PD, Histrionic PD, Antisocial PD, and Narcisstic PD); two had Cluster C Personality Disorder (Avoidant, Dependent, Obsessive–Compulsive PD); one had no Personality Disorder; one patient refused, and one patient was not able to complete testing. Patients with epilepsy only had no Personality Disorder. **Conclusions:** These results suggest that patients with epilepsy, PPs, or both have multiple psychiatric symptoms that cause global suffering. Our preliminary results suggest that in patients with PPs, there is a high prevalence of PD (particularly Cluster B and C), which imply persistent maladaptive coping mechanisms that need special attention as predictors of PP diagnosis and treatment.

2.091

MEMORY SYMPTOM VALIDITY PATTERNS IN PSEUDOSEIZURES AND EPILEPSY

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Rationale: Previous studies have shown psychological testing may differentiate patients with psychogenic, nonepileptic seizures (NESs) from those with epileptic seizures (ESs). The Minnesota Multiphasic Personality Inventory (MMPI) has received the most attention, as it commonly reveals an increased incidence of somatization, somatoform, and conversion profiles in NES patients. Other psychometric measures may further enhance diagnostic accuracy beyond the MMPI. Memory symptom validity testing, commonly used in neuropsychology, may help identify patients who exhibit suboptimal effort and motivation on neuropsychological examinations. Recent studies have shown patients with NESs may be more likely to perform poorly on such tests. The objective of this study was to evaluate performance on the Test of Memory Malingering (TOMM) in patients with NESs and ESs, and determine its contribution to differential diagnosis of NESs versus ESs. **Methods:** Subjects were drawn from a consecutive series of adults who underwent long-term video-EEG monitoring for purpose of differential diagnosis or to determine suitability for epilepsy surgery. Inclusion criteria were (a) definitive diagnosis of NESs or ESs made by a board-certified clinical neurophysiologist based on ictal EEG findings and clinical semiology of the seizures, and (b) completion of both the TOMM and MMPI-2 as part of a routine neuropsychological screening evaluation. Patients with both seizure types (comorbid NESs and ESs), only subjective spells, or no typical spells recorded were excluded. Ninety-one patients with NESs and 168 patients with ESs met these criteria. **Results:** Significant differences in performance were observed on the TOMM, with 9% of the NES group and 1% of the ES group scoring in the invalid range (<45) on trial 2 ($\chi^2 = 9.6$; $p = 0.002$). On the MMPI-2, mean scores of the NES group were significantly ($p < 0.05$) higher than the ES group on clinical scales 1 to 8, with the greatest differences on scales 1 ($p < 0.001$) and 3 ($p < 0.001$). Stepwise logistic regression was used to select scores from the MMPI-2 and TOMM that contributed independently to diagnostic classification. The following variables were identified as significant predictors: MMPI-2 Hysteria scale ($p < 0.001$), performance on trial 1 of the TOMM ($p < 0.01$), and MMPI-2 Hypochondriasis scale ($p < 0.05$). These combined measures contributed to an overall classification rate of 79% (89% of patients with ESs, and 60% of patients with NESs were correctly classified) **Conclusions:** Our findings reveal that the majority of patients with NESs or ESs demonstrate adequate effort and motivation on memory symptom validity tests. While an invalid TOMM performance indicating suboptimal effort or embellishment on neuropsychological examinations may be rare in patients with epilepsy, it occurs in a significant minority of those with NESs. Consequently, performance on symptom validity tests such as the TOMM may contribute to establishing a diagnosis in patients with seizures of unknown etiology.

2.092

TEMPORAL LOBE SEIZURES AND PSYCHOGENIC SEIZURES: COMPARISON OF PERSONALITY PROFILE AND PSYCHOSOCIAL ADJUSTMENT INDICATORS

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Rationale: This research identifies distinctions between the personality structure and psychosocial adjustment profile of psychogenic seizure patients, left temporal epilepsy patients, and right temporal epilepsy patients. **Methods:** We evaluated differences in personality organization and psychosocial adjustment in psychogenic seizure (PS) ($n = 10$), left temporal lobe (LTL) ($n = 14$), and right temporal lobe (RTL) ($n = 17$) seizure patients, utilizing the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) and Washington Psychosocial Seizure Inventory (WPSI). MMPI-2 high-point pairs were identified from standard scores (T-scores). Correlations between MMPI-2 mean subscale findings and WPSI mean subscale findings were determined by Spearman two-tailed tests. **Results:** PS and LTL groups were found to exhibit distinct MMPI-2 high-point pairs (Hypochondriasis-Hysteria and Schizophrenia-Depression) (T: 72.8–70.9 and 66.7–66.6, respectively), with no MMPI-2 mean elevations found for the RTL patient group. Significant correlations between personality traits and adjustment issues were distinct between groups, and minimal for the PS group (Hypochondriasis-Adjustment to Seizures, $p < 0.035$; Social Introversion-Financial Status, $p < 0.049$). RTL findings included four distinct correlations constellated around emotional adjustment, while LTL findings included 19 significant correlations across a broad spectrum. **Conclusions:** PSs represent the most frequent nonepileptic condition evaluated in epilepsy centers, constitutung ~20% of referrals

(Benbadis et al., 1996). The diagnosis rests primarily on prolonged EEG-video monitoring. In compartive analysis of PS and organic seizure patients, most studies exclude patients with TL abnormalities, because of associated psychological aberrations (Stewart et al., 1982). However, surgical settings have a particular interest in distinguishing PS from TLE patients. Our findings suggest that PS patients may be distinguished from TLE patients by the unique associations between their personality traits and issues of psychosocial adjustment. Future directions involve participation of our PS patients in a course of dialectic behavioral therapy, considered an efficacious therapeutic approach for psychiatric patients with disorders of personality.

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2.093

GENDER DIFFERENCES IN PSYCHOGENIC NONEPILEPTIC SEIZURES: MOTOR AND AFFECTUAL FEATURES

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Rationale: Previous research has shown gender differences in psychogenic nonepileptic seizures (NESs). Specifically, male subjects have been shown to have convulsive episodes, whereas female subjects have been shown to have nonconvulsive episodes. The purpose of this study was to examine gender differences in affect and motor expression during a psychogenic NES. Additional behaviors, crying and pelvic thrusting, were also examined. **Methods:** Subjects included 111 patients (29 men, 82 women) diagnosed with psychogenic NESs who were evaluated at the Regional Epilepsy Center in Seattle between 1993 and 2001. All patients had at least one documented psychogenic seizure with no coexisting epileptic seizures or interictal discharges documented by long-term EEG-video monitor studies. The patients had a total of 672 seizures. Two independent researchers reviewed videotapes from these studies to ensure reliability. Each patient was classified as having seizures with (a) motor components consisting of localized movements, repetitive movements, or tonic–clonic motor activity; (b) affectual changes consisting of crying, screaming, panic, or fear; (c) staring spells or subjective events in which no motor activity or affectual changes were noted. Patients were also categorized as exhibiting or not exhibiting crying or pelvic thrusting. **Results:** The proportion of women exhibiting affectual changes during a psychogenic NES was significantly greater than the proportion of men: $\chi 2(1, n = 111) = 6.477$, $p = 0.011$. Also, the proportion of women that cried during a seizure was significantly greater than the proportion of men: $\chi 2(1, n = 111) = 6.621$, $p = 0.01$. No significant gender differences were found in the incidence of seizures with a motor component, pelvic thrusting, or staring spells. **Conclusions:** Understanding the nature of and gender differences in psychogenic NESs can assist physicians in the diagnostic process and in treatment recommendations. This study provides evidence that women are more likely to exhibit an affectual change and/or cry during a psychogenic NES. Men and women were equally likely to exhibit pelvic thrusting, staring spells, or a motor component during the seizure.

2.094

NONEPILEPTIC SEIZURES IN MIDDLE-AGED MEN

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Rationale: Characteristically, nonepileptic seizures (NESs) occur in young adults and are disproportionately weighted toward young women. Our study examines the occurrence of NESs in middle-aged men and characterizes the clinical characteristics of their NES events. Methods of precipitating NESs are examined. Comparison is made with age-matched controls with epileptic seizures (ESs) in terms of education, employment status, and the effects of diagnosis on subsequent employment. All patients attended an outpatient epilepsy clinic at the Ralph H. Johnson DVA Medical Center, Charleston, SC. **Methods:** Video-EEG confirmed a diagnosis of NESs in 11 men. Demographic data from the study group and from consecutively derived, age-matched controls with ESs were compared. Methods of inducing NESs were noted, and behavioral characteristics of NES events were classified by type. Patients and sometimes eyewitnesses viewed V-EEG events to verify that the recorded events represented their characteristic attacks. **Results:** Men with NESs ranged from age 33–73 years (55 ± 12 years). The most common features of NESs were convulsive (bilateral in four and focal in three), followed by altered responsiveness (five cases). Other NES behaviors included tachypnea (three), visual hallucinations (one), and piloerection (one). Some patients had multiple NES types. Some attacks occurred spontaneously (four), whereas others were provoked by suggestion plus hyperventilation (three) or suggestion alone (two). Two cases were precipitated by reenactment of an inciting event. NES patients often had previous psychiatric diagnosis (55%) or a history of ethanol abuse (18%). ES patients had higher levels of educational attainment (11± 3 years vs. 9 ± 4 years for those with NESs). Those with ESs were also more likely to be employed (27%, vs. 18% for NESs). After the diagnosis of NESs, one additional man obtained employment. Patients with NESs continued to experience their typical attacks, but for the most part, they found the experience to be less distressing after the diagnosis was made and explained to them. **Conclusions:** Although adults with NESs are typically young women, middle-aged men also experience NESs. Convulsive events, either focal or generalized, are the most common manifestation of NESs in the latter group. Men with NESs have lower educational attainment and higher unemployment status than age-matched controls with ESs. Although diagnosis of NESs did not lead to cessation of the attacks, patients found them to be less distressing after they understood the diagnosis.

2.095

TEDDY BEARS AND OTHER WARM FUZZIES: AN INTERESTING OBSERVATIONAL FINDING IN PATIENTS WITH NONEPILEPTIC PSYCHOGENIC SEIZURES

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Rationale: The identification of clinical signs distinguishing nonepileptic psychogenic events (NEPs) from epileptic events have received considerable attention over the past few years. Studies have provided some evidence for differentiating the ictal and periictal manifestations between NEPs and epilepsy patients including particular motor manifestations, vocalizations, and emotionality. An interesting clinical observation noted over the years in our inpatient video-EEG seizure monitoring unit population, is that many nonretarded late adolescents and adults have various types of toy animals (e.g., teddy bears, dogs) in their rooms. Anecdotally, it has been the staff impression that when this behavior is present, they are inevitably diagnosed with NEPs. The present study intends to provide quantitative analysis of this clinical observation and find out whether this is unique to NEPs patients or a product of hindsight bias. **Methods:** The database and records of the University of Alabama at Birmingham–Epilepsy Monitoring Unit were reviewed from October 1, 1999, to December 31, 2001, identify patients with the diagnosis of exclusive NEPs or epileptic seizures. Over this 27-month period, 920 patients (older than 14 years) were admitted to the UAB inpatient video-EEG seizure-monitoring unit who either received a diagnosis of epilepsy (n = 470) or NEPs (n = 430). An information data card containing demographics, as well as medical information, was created for all patients admitted, by our clinical nurse coordinator at the time of admission. Information on the presence of objects deemed unusual for a neurologically intact late adolescent or adult-age patient to be possessing while in the hospital was recorded.

These items consisted primarily of toy animals. Those brought by others as gifts to the patients were not included. **Results:** A total of 23 patients (2.4%) was found with toy animals. Twenty were diagnosed with NEPs ($p = 0.0001$, Fisher's Exact test), and three with epilepsy. Sensitivity was found to be 0.02% and specificity to be 99%, with a positive predictive value of 87% and negative predictive value of 52%. Interestingly patients with epilepsy who had animal toys had history of a psychiatric disorder. **Conclusions:** Our results suggest that the presence of a toy animal (teddy bear, etc.) indicates a high likelihood diagnosis of NEPs. The clinical use of this finding is limited, because it cannot be used for routine diagnosis, but merely as an interesting observation. Etiology for such a behavior likely relates to the patient's psychiatric profile and dysfunctional interpersonal relationship patterns.

2.096

PREDICTION OF NONEPILEPTIC SEIZURES WITH THE PERSONALITY ASSESSMENT INVENTORY

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Rationale: The Minnesota Multiphasic Personality Inventory (MMPI) has been used extensively as an aid in distinguishing nonepileptic seizures (NESs) from epileptic seizures (ESs). The Personality Assessment Inventory (PAI) is a relatively new measure of personality, developed based on contemporary diagnostic theory. The PAI may be of greater value than the MMPI in developing a psychiatric treatment plan. We present the first reported application of the PAI to patients undergoing long-term video-EEG (VEEG) and will show the utility of the PAI in predicting ESs versus NESs as demonstrated by VEEG. **Methods:** Of 50 consecutive admissions for VEEG in which there was a complete data set, 18 patients were diagnosed as NESs and nine had ESs, based on VEEG findings. Cases of mixed NESs and ESs were excluded from study. All patients were adults with a mean age of 35.4 years. The PAI was administered to each patient and scored in conventional fashion. **Results:** T-test group comparisons showed no group difference on any of the validity scales. Group differences were found on the Depression ($p < 0.032$), Treatment Rejection ($p < 0.029$), and Dominance ($p < 0.043$) scales. While the Somatization scale showed no group differences ($p < 0.215$), the subscale Conversion Disorder showed large group differences ($p < 0.010$). For the NESs group, these results reflected greater physiologic signs of depression, greater willingness to endorse the need for personal psychological change, and a modest and retiring personality style. Most striking was the NES group tendency to endorse functional impairment due to symptoms associated with sensory and/or motor deficits (conversion). Using the Conversion subscale alone, a sensitivity of 67% and a specificity of 89% were found in classifying patients as NESs versus ESs. **Conclusions:** The PAI shows promise in making the distinction between NES and ES. Applied to patients with NESs, PAI may also assist in the formulation of psychiatric treatment, based on contemporary psychology theory.

2.097

ARE THERE PHYSICAL RISK FACTORS FOR PSYCHOGENIC NONEPILEPTIC SEIZURES IN PATIENTS WITH EPILEPSY?

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Rationale: Patients with epilepsy may have additional psychogenic nonepileptic seizures (PNESs). It has been suggested that PNESs are more common in patients with epilepsy who are female, develop epilepsy later in life, and who have right hemispheric brain lesions. This controlled study informs participants whether these or other physical parameters are risk factors for the development of additional PNESs in patients with epilepsy. **Methods:** In this study, 119 consecutive patients with PNESs and concurrent epilepsy and 119 consecutive patients with epilepsy alone were compared with regard to the variables sex, age at onset of epilepsy, epileptic seizure frequency, epilepsy type (focal/generalized), location and lateralization of epileptogenic zone, etiology of epilepsy, interictal epileptiform potentials, magnetic resonance imaging (MRI) abnormalities, neuropsychological (NPS) deficits, and intelligence quotient (IQ). **Results:** The factors female sex ($p < 0.001$), abnormal visual memory ($p = 0.009$), global NPS impairment ($p = 0.015$), and low-IQ category ($p = 0.008$) were associated with a higher risk of PNESs. Other variables did not differ between the groups. **Conclusions:** In patients with epilepsy, female sex, nondominant hemisphere, or global neuropsychological underperformance and low IQ are associated with an increased risk of PNESs. MRI changes, epileptiform EEG abnormalities, and location of epileptogenic zone did not show a predilection for the right hemisphere. Onset of epilepsy did not affect PNES risk. Physical factors do not fully explain the occurrence of PNESs in patients with epilepsy; additional psychological, personality, and biographical factors are likely to play an important role. [Supported by St. James's Hospital Nervous Diseases Trust Fund and the Special Trustees of the General Infirmary at Leeds, United Kingdom (M. Reuber).]

2.098

VAGUS NERVE STIMULATOR IMPLANTATION IN PATIENTS WITH NONEPILEPTIC EVENTS: A COSTLY RESULT OF MISDIAGNOSIS

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Rationale: Vagus nerve stimulation (VNS) has emerged as adjunctive therapy in the management of epilepsy. The use of VNS has expanded beyond epilepsy centers into general neurology practice because a comprehensive evaluation is not required before implantation. However, ~20–40% of patients with intractable seizures actually have nonepileptic events (NEEs). Clinical description of seizure activity by witnesses and patients form the basis of the diagnosis in the outpatient setting, the accuracy of which is limited. To increase awareness of the consequences of circumventing a comprehensive epilepsy evaluation in making these decisions, we present two patients with NEEs in whom VNS was initiated. **Methods:** After approval by the IRB, the EEG database at the Mayo Clinic was reviewed for all patients with VNS examined in the Epilepsy Monitoring Unit between 1998 and 2001, in whom NEEs were recorded. **Results:** Two patients were identified. The first patient reported daily spells over the last 5 years consisting of chest pain or headache, progressing to asynchronous limb shaking, with occasional tongue bite and incontinence. These were diagnosed as epileptic seizures elsewhere after video-EEG monitoring and remained refractory to multiple trials of antiepileptic drugs (AEDs). A VNS was placed in 1999 with complete control for 6 months. After January 1, 2000, seizures returned, attributed to Y2K effect by the patient. Subsequent AED and VNS adjustments were unsuccessful. After admission to the video-EEG monitoring unit, all of the patient's habitual events were recorded, which were clinically and electrographically consistent with NEEs. A comprehensive psychiatric evaluation diagnosed panic disorder and posttraumatic stress disorder (PTSD). Behavioral and medical therapy was successful. At 4 months' follow-up, she was event free with the device turned off. The second patient developed stereotyped events at age 14 described as generalized tonic–clonic seizures. They previously occurred 1 to 3 times per year, but increased to two per week at age 48 years, resulting in medical disability. AEDs were ineffective, and a VNS was placed elsewhere without prior video-EEG monitoring. This resulted in fewer generalized seizures, but a new spell type emerged, consisting of facial tingling, progressing to flaccid unresponsiveness, occurring several times a day. These were followed by extreme headache requiring narcotics. At age 54 years, the patient was admitted to our monitoring unit. All of his habitual events were recorded; they were clinically and electrographically consistent with NEEs. The patient did not accept the diagnosis and elected to continue his AED. **Conclusions:** VNS is increasingly used by general neurologists as well as epileptologists in the treatment of refractory epilepsy without standardized evaluation. These cases illustrate a pitfall of this

process. Requiring video-EEG monitoring before implantation may not ensure proper diagnosis. In light of the known limitation of the device, the decision to start VNS therapy is best made after comprehensive evaluation at an epilepsy center with large patient numbers, in which a variety of treatment options are available.

2.099

NONEPILEPTIC SEIZURES: ACUTE CHANGES IN SEIZURE FREQUENCY AFTER PRESENTATION OF THE DIAGNOSIS

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Rationale: Estimates of the prevalence of nonepileptic seizures (NESs) range from 3 to 20% of outpatient epilepsy populations. Simultaneous video-EEG monitoring has greatly facilitated the identification and diagnosis of NESs in recent years. Currently, there are few studies examining the treatment outcome of NESs. The first step in treating NESs is to present the diagnosis to patients and their families in a way that is understandable and facilitates treatment of the underlying disorder. Some literature suggests that after being presented with the diagnosis and some basic educational information, NESs resolve without further treatment in a portion of patients. Further study on how to present the diagnosis to patients, as well as the short and long-term outcome of NESs is needed. **Methods:** In the current study, we examined the frequency of seizures captured while individuals were hospitalized for video-EEG recording. We compared the number of NESs within the 24-h period before diagnosis, with the number of events that occurred within the 24-h period after patients have been presented with the diagnosis. The protocol used to present the diagnosis followed the detailed and comprehensive protocol developed by Shen et al. (*Neurology* 1990;40). **Results:** During the 24-h period before diagnosis, the individuals in this study had, on average, two to three NESs. Seven of nine patients had no further NESs within the 24-h period after they had been presented with the diagnosis. Our clinical findings demonstrate that there is a significant reduction in the number of NESs within the immediate 24-h period after presentation of diagnosis. **Conclusions:** Results suggest that at least immediately, the provision of a diagnosis of NESs using the Shen et al. protocol appears to be useful in reducng the frequency of NESs. The presentation of the diagnosis is likely to be an important first step in the long-term remediation of NESs. Future research should examine outcome on a more long-term basis and attempt to identify factors that distinguish individuals who continue having NESs versus those who do not.

2.100

LENGTH OF STAY OF MONITORED PSEUDOSEIZURE VERSUS SEIZURE PATIENTS

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Rationale: Patients are monitored to diagnose the nature of their events, to classify their seizure type, and to localize site of seizure onset. Because the diagnosis of pseudoseizures can be made after a single definitive episode, because the "common wisdom" is that pseudoseizure patients have episodes earlier in monitoring than patients with epilepsy (never documented), and because characterization of seizure type and localization of seizure onset require more episodes for a definitive judgment to be made, we expected that our monitored pseudoseizure patients would have a significantly shorter lengths of stay than our patients with epilepsy. Our objective was to verify this with a formal study. **Methods:** The University of Washington Epilepsy Center Clinical Data Base for l993 to the present was searched to identify those monitored patients who had only pseudoseizures and those with epileptic seizures only. The length of each patient's initial monitoring was determined. The distribution of the length of stay for each group was determined, and the two distributions were compared using analysis of variance. **Results:** We identified 208 patients with pseudoseizures and 641 patients with epileptic seizures. The pseudoseizure group contained more female subjects (70 vs. 54%), had a higher IQ (Full-Scale IQ, 90 vs. 83), and had a later age at onset (26 vs. 14.5 years). The average age of first monitoring at our center was the same for both groups (35 and 34 years). Mean length of stay was only slightly shorter for pseudoseizure patients (5.12 vs. 5.67 days), and this difference was not statistically significant. However, the distributions of length of stay for the two groups were significantly different ($p < 0.0001$). More pseudoseizure patients were discharged after short hospital stays. Cumulative percentages of pseudoseizure (and epilepsy) patients discharged after 2 days of monitoring were 12.0 (5.3), after 3 days, 26.9 (13.6), after 4 days, 37.0 (27.0), after 5 days, 48.6 (42.3), after 6 days, 66.8 (59.8), and after 7 days, 97.6 (93.6). Despite the earier discharge of many pseudoseizure patients, 30.8%, as opposed to 34.2% of epileptic patients, were discharged on day 7, our center's usual maximum length of stay. **Conclusions:** At our center, monitored patients are scheduled for 7 days and are discharged as soon as the questions being asked about them are answered. We expected that pseudoseizure patients would be much less likely to stay the maximum 7 days as compared to patients with epilepsy. Their mean length of stay, while shorter, was not statistically shorter. As a group, they tended to be discharged earlier but, almost as many, 30.8 versus 34.2%, stayed our usual maximum of 7 days. The reason appears to be that the goal in monitoring a patient who is shown to have pseudoseizures is not just to make that diagnosis, but also to exclude, as best we can, the possibility that they also have epilepsy. The longer the patient is monitored with no evidence of epilepsy, the lower the probability that they have epilepsy. The lack of evidence for epilepsy is helpful in convincing the patients that they have pseudoseizures, not epilepsy, and aids in planning their subsequent treatment.

2.101

PROFILE OF PSYCHOGENIC SEIZURES IN AN URBAN UNDERSERVED POPULATION

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Rationale: Profile of patients diagnosed with nonepileptic psychogenic seizures in an urban medically underserved population is presented to emphasize the necessity of availability of continuous video-EEG monitoring units for early diagnosis and to prevent potentially dangerous complications of antiepileptic drug (AED) use. **Methods:** Retrospective review of patients admitted to a recently established urban epilepsy monitoring unit for diagnosis of recurrent paroxysmal events between July 2000 and December 2001. Patients were included if they underwent continuous video-EEG monitoring for $\geq$24 h. Patients with physiologic nonepileptic events were excluded. **Results:** Forty-three patients were diagnosed with nonepileptic psychogenic seizures. This represented 15% of a total of 286 patients monitored during the same period and 21.8% of monitored patients older than 10 years. The male/female ratio was 1:5.4. More than 60% of patients were between the ages of 11 and 40 years; only five (11.6%) patients were older than 50 years, and three (6.9%), younger than 10 years. The mean duration of paroxysmal events before admission was 7 years, and the median duration was 3 years. Fifteen (35%) had had events for <1 year. Most patients were receiving AEDs at the time of admission: 51% were taking one AED, 42%, 2 or more AEDs, and 30.2%, both AEDs and psychopharmacotherapy. Mean duration of video-EEG monitoring was 4.5 days, with a range of 1–8 days. Four (9.3%) patients had concurrent epileptic and psychogenic seizures recorded during the monitoring. Seizure phenomenology in psychogenic seizures was predominantly generalized shaking (37.2%), asymmetric jerking (39.5%), and pelvic thrusting (14%). Sensory symptoms were present in 9.3%, and only one patient had urinary incontinence. Tongue injury did not occur in any patient. **Conclusions:** Psychogenic seizures were a common diagnosis in an intractable seizure population in this urban community. Early referral and establishment of diagnosis were accomplished in a relatively high percentage of patients. Many patients were taking multiple AEDs at admission and were exposed to the potential short-term and long-term side effects unnecessarily. This underscores the importance

of accessibility of epilepsy monitoring units in underserved areas for early diagnosis and treatment.

2.102
PROGNOSTIC PREDICTORS OF THE OUTCOME OF EPILEPSY SURGERY: A META-ANALYSIS

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Rationale: It is commonly accepted that ≥50% of patients who undergo temporal or extratemporal resections become completely seizure free. However, information is inconsistent on the role of the main prognostic predictors of treatment success. The aim of this study was to examine the existing literature and calculate the probability of seizure freedom after surgery in patients with selected prognostic indicators. **Methods:** A Medline search was made of English language original articles published since 1984 that addressed the outcome of epilepsy surgery. Criteria for inclusion were sample size >30, well-defined selection criteria, >90% of patients assessed by magnetic resonance imaging (MRI), follow-up >1 year, and outcome measure specified. Each article was reviewed independently by two of the authors. Any disagreement was resolved in conference. Data were recorded on patients and disease characteristics and a list of prognostic factors, including family history of epilepsy and/or febrile seizures, perinatal complications, etiology of epilepsy, MRI, and surgical and pathologic findings. The primary efficacy outcome was rated as complete versus incomplete seizure control. The probability of success in patients with specific prognostic indicators was quantified with the risk ratio (RR) with 95% confidence limits (CL). **Results:** In total, 374 articles were selected. Of these, 299 were excluded based on our exclusion criteria, and 48 articles (comprising 3,385 patients) have been completely reviewed. The review of the remaining 27 articles is under way. The sample included 3,292 adults and 93 children; 73% of cases underwent temporal lobe resection. Complete seizure control was obtained in 66% of cases. Significant predictors of treatment success, shown by univariate analysis, were history of febrile seizures (RR, 1.3; 95% CL, 1.1–1.4), mesial temporal sclerosis (RR, 1.2; 95% CL, 1.1–1.3), tumor (RR, 1.1; 95% CL 1.0–1.2), EEG/MRI concordance (RR, 1.6; 95% CL, 1.2–2.0), and large extent of surgical resection (RR, 1.5; 95% CL, 1.4–1.8). **Conclusions:** In this preliminary analysis, success of epilepsy surgery can be predicted by prior febrile seizures, the presence of mesial temporal sclerosis or other removable structural lesion, EEG/MRI concordance, and extensive resection. The independent role of each of these variables will be assessed by multivatiate analysis and the end of the review.

2.103
INCIDENCE OF HIPPOCAMPAL SCLEROSIS IN ROCHESTER, MINNESOTA, 1990–1996

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Rationale: To examine incidence of partial epilepsies and in particular temporal lobe epilepsy during a time period when magnetic resonance imaging (MRI) was available in a population-based sample. **Methods:** A population-based retrospective study was performed by the authors utilizing the Rochester Epidemiology Project Records-Linkage System to ascertain patients with a diagnosis of partial epilepsy seen at Mayo Clinic Rochester from 1990 through 1996. The 470 patients were identified and partial seizures were confirmed in 180 patients. Of the 180 patients with confirmed partial epilepsy, 98 had onset of their seizure disorder, while living in Olmstead County, between 1990 and 1996. MRI was performed in 75 of the 98 patients. Olmstead County population data were obtained from the U.S. Census Bureau. **Results:** Of the 98 patients with onset of their seizure disorder while living in Olmstead County between 1990 and 1996, a temporal lobe seizure disorder was present in 25 patients, and an extratemporal seizure disorder was present in 22 patients. Benign rolandic epilepsy was present in an additional seven patients. In the remaining 44 patients, there was insufficient information to determine location of seizure onset. The incidence of partial epilepsy was 13 per 100,000. Temporal seizure disorders had an incidence per 100,000 of 3.2 and extra-temporal seizure disorders of 2.8. The incidence of benign rolandic epilepsy was 0.9 per 100,000, or 4.5 per 100,000 for children aged 5–17 years. MRI imaging was performed in 20 of the 25 patients with temporal lobe seizures. Hippocampal atrophy was seen with an incidence of 0.3 per 100,000. **Conclusions:** The incidence of hippocampal atrophy was 10% of the total incidence for temporal lobe epilepsy. The reported incidence of partial epilepsy was comparable to previous studies, although lower than a previous epidemiologic study performed in Rochester, Minnesota. A difference in the methods is suggested as the cause for this discrepancy.

2.104
LONG-TERM PROGNOSIS AND PSYCHOSOCIAL OUTCOMES

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Rationale: To analyze the impact of seizures on everyday life and the long-term effects of epilepsy on health status and psychosocial outcomes. The nature of epilepsy, together with the associated stigma that is deeply rooted in history, gives rise to a variety of psychosocial difficulties. Results of the few studies that evaluate the long-term impact of epilepsy show that psychosocial adjustment and competence problems persevere into later life. We studied a large cohort of newly diagnosed patients with epilepsy with a mean follow-up of 34 years. **Methods:** Follow-up study of a cohort of 1,355 consecutive patients newly diagnosed with epilepsy, between 1953 and 1967. In 1995 a random sample of 333 patients received a questionnaire asking clinical and demographic information and validated measures for psychosocial outcomes. Comparisons were made with the general Dutch population, standardized for age, sex, and calendar period. **Results:** The response rate was 73% (116 men and 127 women), the mean age was 49.9 years (SD, ±11.2). Mean age at epilepsy onset was 15 years (SD, ±11), mean duration was 24.4 years (SD, ±13.1); 134 patients (46% women) were ≥5 years seizure free, and 81 patients (57% women) still had seizures in the last year. One hundred twenty-seven patients (54% women) were taking antiepileptic drugs (AEDs), of whom 51 (51% women) were receiving monotherapy. Epilepsy patients have a positive health evaluation, comparable to the general Dutch population ($p = NS$). Fewer epilepsy patients married or had children than the general Dutch population; more patients live at home with their parents, or in foster homes or institutions ($p < 0.001$). Having epilepsy at school age has a significant negative effect on learning achievement ($p < 0.01$). **Conclusions:** Epilepsy has a marked negative impact on education and achievement in later life, especially those with seizures at school age. [Supported by The Dutch "Nationaal Epilepsie Fonds (NEF)," subsidy: NEF/CLEO A-101.]

2.105
FAMILY HISTORY OF EPILEPSY IN PATIENTS WITH HIPPOCAMPAL SCLEROSIS

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Rationale: Hippocampal sclerosis (HS) is the most common cause of medically intractable temporal lobe epilepsy (TLE). Traditionally, HS has been considered to be a sporadic condition; a concept supported by studies on identical twins. However, the high incidence of the coexistence of HS with developmental lesions (dual pathology) raises the question of a possible familial component to this entity. In this study, we investigated the presence of a family history of epilepsy in patients with TLE due to HS. **Methods:** Fifty-five consecutive patients with TLE who met volumetric magnetic resonance imaging (MRI) criteria for the diagnosis of HS were studied. The patients and/or family members were contacted over the telephone, and a thorough family history of at least three generations was obtained. **Results:** Of the 55 patients, 22 (40%) reported having another family member with seizures. Seven patients had more than one affected family member. Of the 31 affected family members, seven (23%) had definite etiologies for their seizures, including one family member with bilateral HS. Thirteen family members (42%) had no apparent etiology for their seizures, and three (10%) were found not to have seizures. There was insufficient information about eight (26%) affected family members to determine if they had epilepsy. Therefore, of the 22 patients reporting family members with epilepsy, we were able to confirm a family history in 15 patients (27%). Both the reported (40%) and verified (27%) prevalence of epilepsy in family members of patients with HS were significantly different ($p < 0.01$) from that in the general population. **Conclusions:** Patients with HS have a high incidence (27%) of family members with epilepsy. This suggests that HS is found in individuals with an increased genetic susceptibility for seizures.

2.106

SEIZURE IN THE YOUNG WITH STROKE: A DECADE OF EXPERIENCE

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Rationale: The reported proportion of stroke patients who experience early seizures varies from 3.9 to 43%. Stroke is a common risk factor for seizures in elderly. However, there is little known about the epidemiology of seizure in the young adult population with stroke. Our objective was to study the occurrence of seizure in the young adult aged 15–45 years with acute stroke. **Methods:** Retrospective chart review was done in patients between ages 15 and 45 years who were admitted to the University of Alberta Hospital from January 1, 1990, to December 31, 1999, with acute ischemic or hemorrhagic stroke and who experienced seizure either at the presentation or during their hospital stay. The results of risk factors, etiology, morbidity, and mortality were entered into a database. **Results:** Acute stroke was diagnosed in 586 patients. Of those 383 (65%) were hemorrhagic, and 203 (35%) nonhemorrhagic. Seizures occured in 98 (17%) patients, 71 (73%) at the presentation, and 27 (27%) during hospitalization. Eighty-eight patients (90%) experienced generalized, and 10 (10%), partial seizures. From 98 patients with seizures, 84 (85%) had hemorrhagic, and 14 (15%), nonhemorrhagic strokes. From hemorrhagic stroke patients with seizure, 42 (50%) experienced subarachnoid hemorrhage, 24 (25%), lobar, 11 (11%), extradural hematoma, and seven (7%) deep brain, brainstem, or intraventicular hemorrhage. The most common causes of nonhemorrhagic stroke with seizures were venous sinus thrombosis, systemic lupus erythematosus, vasculitis, and cardioembolic. Patients with seizures had significantly higher rate of complications including stroke recurrence (52 vs. 24%), sepsis (20 vs. 6%), and aspiration pneumonia (52 vs. 24%). Twenty-eight patients with seizure (29%) died in hospital, which constituted 27% of the total mortality. **Conclusions:** Our experience with a large number of young adults with acute stroke shows that early seizure is a common occurrence in this population. Seizures in stroke patients were more commonly generalized and occurred more frequently at the presentation of hemorrhagic strokes. Young patients with stroke and seizure experienced significantly higher mortality and morbidity than their seizure-free counterparts. Further follow-up study is under way to see if early seizure in this young population is a predictor of developing epilepsy, and whether antiepileptic therapy is warranted.

2.107

THE IMPACT OF EPILEPSY ON ANNUAL HOSPITALIZATION RATES IN THE ELDERLY

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Rationale: As the prevalence of epilepsy increases with age, and elderly patients have multiple comorbid conditions, this study sought to assess the impact of epilepsy on annual hospitalization rates in the elderly. **Methods:** The 1999 5% SAF Medicare database is a nationally representative 5% sample of Medicare beneficiaries and includes the inpatient, outpatient, and physician/supplier Medicare claims of 1.2 million people aged 65 years and older. Patients with epilepsy are identified for analysis in this cross-sectional study using ICD-9 codes 345.x grouped according to the International League Against Epilepsy seizure-type classification. The prevalence of comorbid conditions in epileptics is compared to nonepileptics using $\chi 2$ test. Mean and median annual hospitalization rates are estimated for epileptic patients with and without comorbid conditions and compared using the $\chi 2$ test and the Mann-Whitney *U* test. Multiple logistic regression is performed to identify the odds of hospitalization in epileptics as compared to nonepileptics while adjusting for age, gender, ethnicity, and comorbid conditions. **Results:** Epilepsy patients have a higher prevalence of multiple comorbid conditions than nonepilepsy patients. In the univariate analysis, the mean annual hospitalization rate in epilepsy patients is 13.5 hospitalizations per 100 patients. This is substantially higher ($p < 0.001$) than the mean annual hospitalization rate in nonepilepsy patients (3.6 per 100 patients). The addition of epilepsy to any comorbid condition more than doubles the median annual hospitalization rate. Even after adjusting for age, gender, ethnicity, and multiple comorbid conditions, epilepsy patients have higher odds of hospitalization than nonepileptsy patients ($p < 0.05$). **Conclusions:** Elderly epilepsy patients are at higher risk for hospitalization and have higher rates of comorbid conditions as compared to nonepilepsy elderly patients. (Supported by The Robert Wood Johnson Foundation and Partnership for Solutions: Better Lives for People with Chronic Conditions.)

2.108

VAGUS NERVE STIMULATION IN PATIENTS OLDER THAN 60 YEARS: A MULTICENTER STUDY

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Rationale: Vagus nerve stimulation (VNS) has proven effective in a variety of seizure disorders in children and adults. However, its efficacy and side effects in the elderly remain uncertain. Antiepileptic drugs (AEDs) are often associated with more side effects and drug interactions in this population, and alternative therapies are desirable. At the end of this activity, the participants should be able to discuss the efficacy and tolerability of VNS in patients older than age 60. **Methods:** Medical records of all 152 patients treated with VNS at the three Mayo Clinic sites (Rochester, Scottsdale, and Jacksonville) were reviewed. Patients older than 60 years who were receiving VNS were selected, and their clinical course including duration of epilepsy, seizure type, etiology, and adverse effects was evaluated. Patients were contacted to ascertain the efficacy and tolerability of VNS. The seizure frequency at last visit was compared to preimplantation seizure frequency. **Results:** Nine patients receiving VNS at the three Mayo Clinic

sites older than 60 years were identified. There were five women and four men with a mean age of 65 at implantation (range, 57–82 years). Six patients had partial, two had partial and secondarily generalized, and one had primary generalized seizures. The etiologies were prior head trauma (three), encephalitis (three), idiopathic (two), and tuberous sclerosis (one). The duration of epilepsy before initiation of VNS ranged from 2 to 61 years. The duration of follow-up ranged from 12 to 40 months (mean, 25 months). At the last follow-up, two patients (22%) had a 100%, two (22%) had a 60–80%, and one (11%) had a 30% reduction in seizure frequency. One patient who benefited initially with an 80% reduction in seizures died 14 months after implantation during a seizure. Three patients had no significant benefit, and one patient had an increase in seizure frequency (44% nonresponders). Six patients had a reduction in the frequency and duration of seizure clusters. There were no incidents of intraoperative asystole, device failure, or wound complications. One patient experienced vocal cord paresis postoperatively, which resolved several months later. Medications were reduced in two patients. Side effects related to VNS occurred in five patients (55%), including dyspnea, hoarseness, dysphonia, and dysphagia, but these side effects did not result in discontinuation of treatment in any patient. **Conclusions:** VNS resulted in a significant improvement in seizure frequency in 44% of this elderly epilepsy population. VNS was well tolerated in this age group.

2.109

RECRUITING OLDER PATIENTS INTO RANDOMIZED CLINICAL TRIALS: AN UPDATE

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Rationale: Older adults are faced with significant economic, medical, and social difficulties associated with the aging process. These factors interfere with the mature adults' ability to participate in research studies. As an increasing amount of research studies are including this population, careful consideration of these factors should be addressed. **Methods:** This was a retrospective analysis of eligibility criteria from VA Coop Study 428, "Treatment of Seizures in the Elderly Population." Eighteen VAMCs are presently participating in a study to evaluate the efficacy and tolerability of gabapentin (GBP), lamotrigine (LTG), and carbamazipine (CBZ) in the treatment of seizures in individuals 60 years or older. Screening records were reviewed to determine reason(s) for ineligibility for the trial. Refusal forms were sent to all centers to determine the most common reasons for refusals. **Results:** 1,295 patients have been screened. Of these, 594 were enrolled and 701 were excluded. The number excluded is likely to be an underestimate because screening forms were not done on every potential patient. The most common exclusion reasons are no seizures in the last 3 months (24%), unstable medical disorders (16%), unable to give consent (15%), questionable compliance (14.6%), satisfied with current treatment (14.5%), and refused (10.4%). Other exclusions included treated with study drug (7.7%), alcohol withdrawal (4%), psychiatric disorder (3.8%), chronic barbiturates (3.6%), metabolic seizures (2.6%), street drugs (1.6%), enrolled in other research (1.4%), allergy (1.2 %), acute CNS infection (0.41%), human immunodeficiency virus (0.14%). Reasons for refusals included family member refusal (17%), denial of seizures (15%), too much medication (7%), travel (4.2%), nursing home (4.2%), and guinea pig (3.4%). The effects of age, gender, race, and level of education were not analyzed. **Conclusions:** Elderly patients are more likely to refuse participation in research than younger adults. Approval from family members/caregivers becomes more important in determining participation. Other demographic factors such as age, gender, race, and education may influence an older patient's decision to participate in a study. Cognitive impairment related to aging contributes to the inability of older patients to understand and give consent. Retrospectively, older patients might consider participation in clinical trials, if fewer visits were required. Participation of older adults may increase if the family members are actively included in the recruitment process. More attention should be placed on educating the family about the rationale for good, clinical research in this population of patients. Further scrutiny of the reasons for refusal is needed. (Supported by VA Cooperative Study Program.)

2.110

EFFICACY AND TOLERABILITY OF TOPIRAMATE IN THE ELDERLY POPULATION

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Rationale: Topiramate (TPM) is a novel anticonvulsant drug (AED) that has been approved as adjunctive therapy for patients with partial-onset seizures and/or generalized tonic–clonic seizures. The side-effect profile of this drug in monotherapy is favorable, and drug interactions appear to be few. Little is known about the optimal therapeutic approach for older patients with seizures. The increased hazards of seizures, comorbid conditions, polypharmacy, altered metabolism, and compliance argue for the need for safe, effective AEDs in the elderly population. Although little information exists on the tolerability and efficacy of TPM in older patients, TPM has several characteristics that suggest it may be a useful drug in this patient population. **Methods:** This was a 24-week, blinded, randomized, multicenter trial of TPM in patients 60 years and older diagnosed with epilepsy. Patients newly diagnosed as well as those with a history of partial seizures are eligible to participate. Patients taking either no AED or on a stable regimen of one AED who are not controlled can be included. Eligible patients must have had at least one seizure in the previous 6 months, two in the prior year, and have experienced sufficient side effects to warrant change in therapy. Patients are randomized to one of two target doses (50 or 200 mg/day).The current AED is tapered and discontinued. Initial dose is 25 mg/day in both treatment arms, and titration is by 25 mg/week until target dose is achieved or toxicity is encountered. At the end of the 24-week blinded phase, patients may enter a 4-month open-label phase. **Results:** Thirty-four patients have been enrolled in Miami. Mean age is 68.6 years, and 73.5% are males. Five patients were new onset. Prior AED therapy included phenytoin (PHT; $n = 25$), carbamazepine (CBZ; $n = 7$), phenobarbital (PB; $n = 3$), lamotrigine (LTG; $n = 3$), valproic acid (VPA; $n = 2$), and gabapentin (GBP; $n = 2$). The average seizure frequency in the 6-month retrospective baseline ranged from none to three per month. Average seizure frequency on treatment ranged from none to one per month. Seizure types are 33.3% SPS, 38.2% CPS, 70.6% GTC, and 35.3% mixed. Of the five new-onset patients, only two completed the study and were seizure free. Twenty-one patients have had reduction in seizure frequency. Of those who completed the blinded phase ($n = 17$), nine (41.2%) became seizure free; 61.8% reported overall improvement on patient global evaluation scale. Systemic toxicities reported were weight loss $\geq$2 lbs (38.2%) and weight gain (2.9%). Neurotoxicities consisted of dizziness, 2.9%; confusion, 5.9%; sweating, 2.9%. Only one patient reported word-finding difficulty. Fourteen patients were early terminators. Of these, only three exited because of side effects (one patient c/o dizziness and confusion and two patients c/o weight loss). Average weight loss for these two patients was 10 lbs. Four patients had uncontrolled seizures; two were noncompliant; and four voluntarily withdrew from the trial. No hematologic or serum chemistry abnormalities occurred during the study. **Conclusions:** TPM has been found to be effective and well tolerated in older adults with epilepsy. TPM as monotherapy in the treatment of seizures in the elderly is promising. Adverse cognitive effects were infrequently encountered at the doses of 50 and 200 mg. There were no reports of renal stones in these patients. (Supported by Ortho-McNeil Pharmaceutical, Inc.)

2.111

EPILEPSY IN OLDER ADULTS: UPDATE FROM VA COOPERATIVE STUDY 428

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Rationale: Few studies on the clinical management of seizures have specifically focused on the elderly population. It has been shown that this age group has the highest affliction rate of this disorder, yet little is known about the best approach and treatment for these individuals. The normal physiologic changes of aging, comorbid diseases, and polypharmacy all complicated potential therapies for older patients newly diagnosed with a seizure disorder. Exploring the differential effects of older antiepileptic drugs (AEDs) compared to newer agents may help shed some light on this complex matter. **Methods:** The 4-year enrollment phase of VA Cooperative Study 428 is now completed. This 18-center, parallel, double-blind trial compared gabapentin (GBP), lamotrigine (LTG), and carbamazepine (CBZ) in the treatment of new-onset partial seizures in patients aged 60 years or older. The primary outcome measure was retention at 12 months, a measure of efficacy and tolerability. Target doses were GBP, 1,500 mg/d; LTG, 150 mg/d; and CBZ, 600 mg/d. Dosage adjustments were allowed to ameliorate side effects or improve seizure control. Those patients experiencing side effects and inadequate seizure control exited from the trial. **Results:** The 594 patients were enrolled; for the 515 patients having data, the mean age is 72.0 years (median, 71.8 years). Presenting symptoms included memory disturbances (17.7%), confusion (36.7%), amyotropic lateral sclerosis (44.2%); 166 (32.5%) patients have completed 12 months, 243 (47.6%) have terminated early, and 101 (19.8%) are still in study. Twenty-two deaths, 88 adverse reactions, 63 "voluntary" withdrawals, and 16 uncontrolled by study drug have been reported. Only 13 (2.5%) withdrew because of rash. Although the study remains blinded, the DSMB and HSS have found no significant difference between treatment arms with regards to SAEs including death. If such a difference were evident, the problematic treatment arm(s) would have been terminated; 54.6% of completers were seizure-free. Seizure-free rate was 65% at 3 months and 56% at 6 months. Systemic toxicities were weight gain (53.6%), gastrointestinal problems (28.7%), weight loss (25.8%), hyponatremia (7.1%), impotence (6.2%), and both thrombocytopenia and neutropenia (0.2%). Sedation (42.5%), gait disturbance (28.3%), dizziness (29.5%), cognitive decline (25.9%), and change in mood/affect (26.8%) were the most common neurologic toxicities. Seizure types included 43% with CPS only, whereas 26.3% had GTC only. Most common etiology was cerebral infarction (34.1%), followed by unknown (24.6%), cerebral arteriosclerosis (14.9%), and head trauma (6.9%). Associated medical diseases included hypertension (67.7%), cardiac disease (49.6%), diabetes (28.1%), and cancer or history of cancer (22.2%). Mean blood levels at 12 weeks were GBP, 9.06; LTG, 3.37; and CBZ, 6.94 μg/ml. **Conclusions:** In the elderly, the misdiagnosis of epilepsy for other conditions represents a significant problem. Tolerability may be a key factor in selecting an appropriate AED for an older individual with epilepsy. Because most patients discontinue within the first 2 months, older patients can be controlled with relatively low plasma AED levels. Hematologic side effects were rarely encountered. Seizure-free rate was high in those completing 12 months. (Supported by VA Cooperative Study Program.)

2.112
OBSERVATIONS ON THE DELAY IN THE DIAGNOSIS OF SEIZURES IN THE ELDERLY: UPDATE 2

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Rationale: The onset of epilepsy often occurs in the elderly population. From our observations, the time to correct diagnosis is often delayed. Our interest is to investigate this phenomenon. **Methods:** We reviewed the charts of 128 patients enrolled in the Veterans Administration Cooperation Study of new-onset epilepsy in the elderly. No patients were profoundly demented or had known fatal illnesses. Concomitant medical diseases were permitted. **Results:** One hundred twenty-seven men and one woman aged 60–96 years (mean, 75 years) had a mean time to corrert diagnosis of seizures of 2.3 years (median, 1 year). Forty-seven individuals were diagnosed immediately. Forty-eight patients had generalized tonic–clonic seizures (GTCs), and two thirds were immediately diagnosed. Sixty-three patients had complex partial seizures (CPSs), one fourth had an immediate diagnoses. This was dependent on delays by the patient and the health care providers. If a history of cerebral vascular disease or arrhythmia was known, the correct diagnosis was significantly delayed. More severe concomitant medical disorders caused greater delays in the time to diagnosis. Thirty-five percent of patients with simple partial seizures (SPSs) were incorrectly diagnosed originally as having transient ischemic attacks (TIAs). Limbic SPSs occurred in six patients, and were initially ignored by all patients. Patients with SPSs tended to be self-referred, whereas those with CPSs or GTCs were mostly referred by family members or health care providers. **Conclusions:** We observed significant delays in the correct diagnosis of seizures in the elderly population. Two reasons we believe contribute to this problem are the lack of awareness of partial seizures by the public and health care providers, and an attempt to attribute all of a patient's symptoms to a single diagnosis. [Supported by a Veterans Administration (VA) Cooperative Study funded by the VA.]

2.113
POST–ISCHEMIC STROKE SEIZURES: INFLUENCES OF GENDER AND AGE OF THE PATIENT

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Rationale: Epileptic seizures are a common occurrence after ischemic cerebrovascular accidents (ICA). They are the most prevalent cause of epilepsy in adult populations older than 45 years, and stroke accounts for more than half of the newly diagnosed cases of epilepsy in the elderly. Seizures after ICA can occur during the acute phase of the insult or after an extremely variable latent period. Several experimental studies have reported the influences of gender and sex steroids on occurrence of spontaneous seizures. However, few clinical studies have addressed the influence of gender on remote symptomatic epilepsy. In the present study we evaluate, in patients with first-ever ICA, the influences exerted by both gender and age on the latent period needed to manifest the first remote epileptic seizure. **Methods:** Twenty-six (14 men) patients from private and outpatient clinic of the Federal University of Pernambuco Clinical Hospital-Recife were retrospectively evaluated. Information was obtained from medical records and from direct interviews with patients and their relatives. All patients had at least one seizure episode after an ICA. To avoid the inclusion of acute- and subacute-induced seizures due to postischemic reversible changes (electrolytic, metabolic, edema, etc.), we decided to include only cases in which seizures occurred later than 30 days after the ICA episode. **Results:** The duration of the latent period (in months) was significantly longer in men when compared with women (19.1 ± 4.6 vs. 7.7 ± 1.7, respectively; $p = 0.0389$). In the male group, six of 14 (42.9%) had a latent period >24 months, whereas all patients in the female group had a latent period <24 months (none of 12, 0%; $p = 0.0171$, Fisher's Exact test). When patients (both genders) were classified by categoric ages at the time of ICA (in years), no differences in the duration of latent period (in months) were found: 38–50 years = 9 ± 3 months; 51–60 years = 18 ± 8 months; 61–70 years = 9 ± 3 months; and 71–80 years = 20 ± 8 months, $p = 0.3788$, analysis of variance. **Conclusions:** The present study demonstrates that male patients have a longer latent period for the first remote epileptic seizure after an ICA than female patients. Conversely, the age of the patient at the moment of ICA does not seem to interfere with the period needed to manifest poststroke seizures. [Supported by CNPq, PRONEX and FAPESP (Proc. 99/11729-2, 00/12376-5); Brazil.]

Pediatric Epilepsy—Clinical

2.114
MONOSOMY 1p36 MICRODELETION SYNDROME ASSOCIATED WITH EPILEPSY AND POLYMICROGYRIA

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Rationale: Describe the epilepsy characteristics of 1p36 monosomy syndrome in the first patient also presenting with polymicrogyria and emphasize the importance of a clinical diagnosis for genetic counseling. **Methods:** To confirm the clinical hypothesis of monosomy 1p36 fluorescence in situ hybridization (FISH) using a subtelomeric probe 1p. **Results:** Monosomy 1p36 is a recently delineated microdeletion syndrome, characterized by moderate to severe mental retardation, growth delay, seizures, and distinct craniofacial features (large anterior fontanel, prominent forehead, horizontal eyebrows, deep-set eyes, flat nasal bridge, midface hypoplasia, ear asymmetry, and orofacial clefting). Congenital heart defects are also part of the microdeletion 1p36 syndrome. Other features include hearing loss and hypothyroidism. Incidence is estimated to be 1 in 5,000 births. The majority of the deletions are maternally derived. In some cases, the deletion is the result of a parental rearrangement. The deletion size is quite variable and appears to correlate with clinical complexity. Loss of the potassium channel b-subunit gene KCNAB2 has been recently reported in patients with 1p36 and intractable epilepsy. Our patient, the first child of nonconsanguineous parents, had hypotonia at birth and was initially followed up for an Ebstein anomaly. At age 4 months, she experienced four seizures described as tonic–clonic. A month later, she developed typical infantile spasms and hypsarrhythmia. Episodes limited to an upward eye deviation were also extremely frequent. Several antiepileptic drugs (AEDs), including vigabatrin, proved inefficient. Steroids allowed a transient control. At age 8 months, interictal EEG showed a very slow background activity and a right temporal spike–wave focus. Magnetic resonance imaging evidenced bilateral, predominantly frontoparietal, polymicrogyria. Complete metabolic screening was normal. A first routine chromosomal analysis was unrevealing. The diagnosis of monosomy 1p36 was primarily suggested on the basis of a distinct pattern of facial anomalies associated with a cardiac malformation (Ebstein anomaly). FISH using a subtelomeric probe 1p (Vysis) showed the lack of a signal on one chromosome 1. Parental chromosomes were normal. **Conclusions:** Polymicrogyria and related disorders are not uncommon findings in children with epileptic spasms, but genetic counseling is difficult on this sole element. To our knowledge this is the first reported case of polymicrogyria and spasms also with 1p36 monosomy. It illustrates that although routine karyotyping may be unrevealing, the syndrome is clinically recognizable. The subsequent use of the appropriate techniques may allow a chromosomal diagnosis, rendering genetic counseling possible.

2.115
ZONISAMIDE IN BENIGN FOCAL EPILEPSY OF CHILDHOOD

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Rationale: Benign focal epilepsy of childhood (BFECh) or rolandic epilepsy is a childhood syndrome seen between 3 and 10 years of age with seizures present in 70–80% of affected patients. Treatment choices vary, with some patients electing not to treat. Ease of dosing, lack of blood-test monitoring, and limited risk of severe side effects made us choose zonisamide (ZNS) to study as a once-daily dosing form of treatment. **Methods:** Pediatric patients seen regularly by our clinic, who had recurrent abnormal routine awake and asleep EEG with triphasic perirolandic spikes in drowsy and asleep states, were screened to try ZNS as monotherapy for BFECh. There were three girls and five boys screened. Sulfa allergies eliminated one patient, one patient chose another antiepileptic drug (AED), and one patient did not elect to start medication. Two patients failed one and three prior AEDs, respectively. Three patients had no prior treatment with AEDs. The five patients who continued on the ZNS were monitored for 2–12 months (average, 6.3 months). EEG studies were studied at 6 months into the study. Seizure diaries were recorded for the patients. All patients were started on 100 mg ZNS daily. **Results:** Tolerance of ZNS was seen in four of five patients. One patient had breakthrough seizures and also developed anhydrosis requiring stopping the ZNS. None of the remaining patients taking ZNS for 6 months had significant EEG improvement. Seizures were completely controlled in four of five patients. No significant appetite, sleep pattern, or behavioral problems occurred. **Conclusions:** ZNS appears to be well tolerated and provided good seizure control in BFECh. Further study in this common childhood epilepsy is warranted.

2.116
DO NOT RUSH TO REPLACE "CRYPTOGENIC" WITH "PROBABLY SYMPTOMATIC" IN PEDIATRIC FOCAL EPILEPSY: A STUDY OF 207 PATIENTS

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Rationale: Proposed revisions to the "Classification of Epileptic Disorders" would replace the term "cryptogenic" with the term "probably symptomatic." However, many pediatric patients with focal epilepsy have no clear etiology, no clear genetic predisposition, and normal magnetic resonance imaging (MRI) scans, so the term cryptogenic may still have value. Participants should be able to decide whether the term cryptogenic remains valuable in classifying children with focal epilepsy. **Methods:** The epilepsy classification of 207 consecutive outpatients seen by a pediatric epileptologist during 2001–2002 was reviewed. The newly proposed International League Against Epilepsy (ILAE) classification system was used. For patients who could not be classified as having a specific epilepsy syndrome, four categories were used: idiopathic, cryptogenic, probably symptomatic, or symptomatic. Idiopathic patients had a known or strongly suspected genetic predispostion; cryptogenic patients had no obvious etiology, no other neurodevelopmental problems, and normal MRI scans; probably symptomatic patients had learning, behavioral, or developmental disorders suggesting underlying brain dysfunction; and symptomatic patients had an obvious cause for their epilepsy. **Results:** The new classification system worked well for all pediatric patients except those with focal epilepsy. Easily classified were 52 children with generalized epilepsy (12 childhood absence, 12 other idiopathic generalized, one juvenile myoclonic, 11 infantile spasms, three Lennox–Gastaut, and 13 other symptomatic generalized); nine patients with both focal and generalized epilepsy (all symptomatic); and 37 patients with epileptic seizures but not a diagnosis of epilepsy (13 with acute reactive seizures, 11 with suspected seizures, eight with neonatal seizures, and five with a single seizure). In contrast, only eight of 109 children with focal epilepsy had a clear epilepsy syndome (five benign rolandic, two benign occipital, and one Rasmussen syndrome). The remaining 101 children with focal epilepsy were classified as follows: 0 idiopathic, 34 cryptogenic, 16 probably symptomatic, and 51 symptomatic. Response to treatment was favorable in the children with cryptogenic focal epilepsy, with 26 of 34 (79%) seizurefree after the first AED trial. In contrast, only five of 16 (31%) children with probably symptomatic focal epilepsy were seizure free after the first AED trial, and only 10 of 51 (20%) children with symptomatic focal epilepsy were seizure free after the first AED trial. **Conclusions:** Pediatric patients with cryptogenic focal epilepsy are very different in response to treatment frompediatric patients with probably symptomatic and symptomatic focal epilepsy. Proposed revisions to the Classification of Epileptic Disorders should retain the term cryptogenic because it describes a distinct subset of pediatric patients with focal epilepsy.

2.117
CLINICAL PRESENTATION OF EPILEPSY PATIENTS WITH HYPOTHALAMIC HAMARTOMAS

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Rationale: Epilepsy due to hypothalamic hamartomas is difficult to treat by medical or surgical approaches. We examined the clinical presentation, seizure semiology, and electrophysiologic findings in patients with hypothalamic hamartomas. **Methods:** We identified all patients with hypothalamic hamartomas from our database seen between 1994 and 2000. **Results:** Eleven patients (mean age at presentation, 12.3 years, seven males) with hypothalamic hamartomas were identified. Three other patients whose magnetic resonance imaging (MRI) films were unavailable are not included. Patients had gelastic (10) and bilateral asymmetric tonic (one) seizures. Other seizure types in the patient's history included dialeptic/absence (four), atonic (three), automotor (two), and bilateral asymmetric tonic seizures (one). Evolution to generalized tonic–clonic seizures was seen in three patients. Seven patients had a preceding aura (three cephalic, two abdominal, one psychic, one pleasant feeling). Other presenting features included developmental delay (10), behavioral difficulties (six), and precocious puberty (one). Interictal spikes were generalized (two), focal (five; three multiregional, one frontal, and one temporal), or both (three). In one patient, no spikes were found. Ictal EEG was generalized (four), lateralized (two), regional (one), and nonlocalizable (one). No EEG change was seen during clinical seizures in two patients. In one patient, no video-EEG monitoring was performed. The hamartomas were exophytic in seven and sessile in four. One patient had dual pathology (temporal malformation of cortical development). Positron emission tomography (PET) in two patients showed frontal and temporal hypometabolism. Ictal single-photon emission computed tomography (SPECT) in two patients demonstrated hyperperfusion over the frontotemporal and parietofrontal regions. Four patients received vagus nerve stimulation (VNS). One responded with >80% reduction of seizure frequency, and three patients did not show improvement. One patient was monitored with depth electrodes into the hypothalamic hamartoma, and in the right temporal lobe. No independent spikes arising from hypothalamus were recorded, and no localized EEG seizure pattern was seen. **Conclusions:** Patients with hypothalamic hamartomas frequently have pharmacologically intractable gelastic, dialeptic/absence, tonic, or atonic seizures. Associated features include precocious puberty, developmental delay, and behavioral difficulties. Interictal and ictal EEG activity related to hypothalamic hamartomas can be generalized, regional, multiregional, or normal. Localized abnormalities predominated over the temporal and frontal regions. [Supported by Innovative Medizinische Forschung, WWU Münster (FoeKz. LO 610101) and NRW-Nachwuchsgruppe Kn2000, Federal Ministry of Education and Research (Foe.1KS9604/0), Interdisciplinary Center of Clinical Research Münster (IZKF Project NWG2).]

2.118
ETIOLOGY AND RESPONSE TO THERAPY OF SEIZURES OCCURRING WITH CEREBRAL PALSY IN CHILDREN

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Rationale: At the end of this activity the participants should be able to discuss the etiology and response to therapy of seizures occurring with cerebral palsy in children . **Methods:** A search of a patient database of 527 children with seizures followed up in an academic pediatric neurology practice from December 1999 to April 2002 was made to identify children with both seizures and cerebral palsy (CP). All seizure types occurring at any time in life were included. CP was defined as a fixed motor deficit with onset early in life. An identified brain abnormality or insult was considered the cause of both the seizures and CP, and classified as either Intrauterine–Developmental, Secondary to Prematurity, Perinatal, Postnatal, or Unexplained. Response to therapy of seizures was considered excellent if a daily antiepileptic drug (AED) was not prescribed, good if only one AED was currently prescribed, moderate if two AEDs were prescribed, and poor if three AEDs were prescribed. **Results:** A total of 74 children were identified with both seizures and CP. Causes of CP and seizures in this patient group were 19 Intrauterine–Developmental, which includes cerebral anomalies, congenital hydrocephalus, TORCH infection, intrauterine stoke, or tuberous sclerosis; 19 Postnatal, which includes central nervous system infection with meningitis or encephalitis, toxic–metabolic, or trauma; 18 Seconday to Prematurity from intraventricular hemorrhage or periventricular leukomalacia; 11 Perinatal, which includes hypoxic ischemic encephalopathy from abruptio placenta or meconium aspiration and neonatal stroke; and seven Unexplained. Moderate to Severe mental retardation was present in 42 of the 74 patients and was considered a comorbid sign and not a cause for CP or seizures. Response to therapy for the 74 children was excellent in the 16 children who received no daily AED; good in 27 children receiving one AED; moderate in 22 children receiving two AEDs, and poor in 9 children receiving three AEDs. Prescription or use of a seizure-rescue medication (either an oral or rectal benzodiazepine) was not consistently recorded in the database to use as a measure for therapeutic response. **Conclusions:** In 74 children with both seizures and CP, a cause was identified in most, 67 (91%) of patients. In this patient sample, causes were about evenly distributed amoung Intrauterine-Developmental (26%), Prematurity (24%), and Postnatal (26%) events with fewer caused by Perinatal (15%) or Unexplained (9%). More than half of children with seizures and CP, 42 of 74 (57%) had an excellent to good response to therapy requiring zero or only one daily AED. In children with both seizures and CP, an evaluation of etiology and an attempt to optimize therapy is indicated.

2.119
MIGRATING PARTIAL SEIZURES IN INFANCY: SIX NEW CASES

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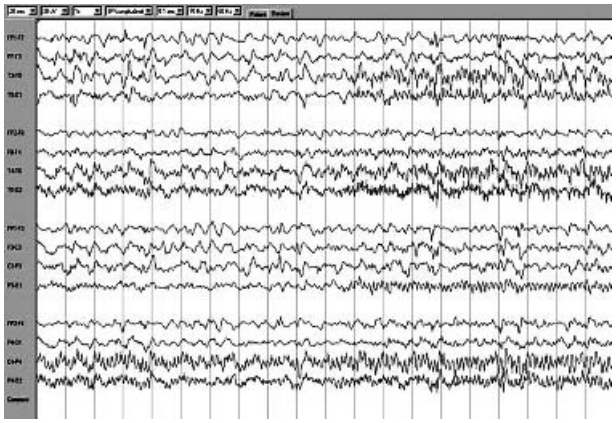
Rationale: In 1995 Coppola et al. (*Epilepsia* 1995;36:1017–24) described 14 epilepsy infants with unidentified cause whose clinical and EEG features were similar to each other but dissimilar from any of the previously described epilepsy syndromes. They named this newly categorized disorder migrating partial seizures in infancy (MPSI). Only seven additional cases of MPSI have since been reported in literature. We present six additional patients who fit the diagnostic criteria for MPSI and further substantiate MPSI as a distinct and recognized infantile epilepsy syndrome. **Methods:** Six patients who fulfill the diagnostic criteria for MPSI, as defined by Coppola et al., were identified through retrospective chart review of the patients evaluated at three tertiary care epilepsy centers between 1993 and 2001. The CCTV/EEG data of the six patients were also analyzed. The clinical and EEG features of these patients were described in detail, and representative segments of the EEG were shown. **Results:** Our six patients resembled the previously described cases of MPSI via the diagnostic criteria: (a) seizure onset at younger than 6 months, (b) nearly continuous multifocal partial seizures, (c) seizures intractable to standard anticonvulsants, (d) absence of identifiable etiology, (e) rhythmic alpha or theta ictal EEG pattern, and (f) psychomotor arrest or regression after the seizure onset. Our six patients also served to highlight the variable features of this condition. Two of our six patients developed infantile



spasms, thereby showing definitively that MPSI can occur with or without comorbid spasms. Two of our patients were siblings, representing the first described familial cases of MPSI. The familial cases imply that both hereditary and nonhereditary etiologies probably underlie MPSI. **Conclusions:** MPSI is a globally occurring epilepsy syndrome. To account for the variations in prognosis, comorbidity, and familial predisposition, we hypothesize that MPSI represents an uncommon expression of an age-dependent epileptic encephalopathy. As with other age-dependent epileptic encephalopathies, MPSI's variable features are ascribed to the multiplicity of underlying etiologies. The common features of MPSI are ascribed to the nonspecific effects of seizures on a specific neurophysiologic substrate at a specific stage of CNS development (Fig. 1).

2.120
AGE-RELATED SECONDARILY GENERALIZED EPILEPSY IN CHILDREN WITH MALFORMATIONS OF CORTICAL DEVELOPMENT

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Rationale: The type of epileptic syndrome associated with malformations of cortical development (MCDs) can be variable, and the patient's age is one of the most important aspects for its determination. The objective of this study was to evaluate the occurrence of age-related secondarily generalized epilepsy (West and Lennox–Gastaut syndromes) in children with MCDs. **Methods:** From a group of 100 consecutive patients with the diagnosis of MCDs confirmed by high-resolution magnetic resonance imaging, we selected those with the first epileptic seizure before age 6 years. First we analyzed the occurrence of secondarily generalized epilepsy according to the type of MCD. Second, we analyzed whether the extension of MCDs favored the development of age-related secondarily generalized epileptic syndrome. For this second analysis, patients were divided into groups according to the extension of dysplastic lesion: diffuse (lissencephaly, subcortical laminar heterotopia, hemimegalencephaly) or focal (schizencephaly, polymicrogyria, focal cortical dysplasia, focal subcortical heterotopias). **Results:** There were 54 female subjects, ages ranging from 5 months to 70 years (mean, 17.5 years). Fifty-four patients had their first seizure before 6 years old. Among them, 20 patients (37%) had a secondarily generalized epileptic syndrome: six of nine had lissencephaly (agyria-pachigyria), two of two had subcortical laminar heterotopia, three of four had hemimegalencephaly, two of 19 had focal cortical dysplasia, four of eight had schizencephaly, one of four had focal heterotopias, and two fo eight had polymicrogyria. According to the extension of the dysplastic lesion, the group with diffuse lesion had secondarily generalized epilepsy in 73% (11 of 15) patients, as opposed to only 23% (nine of 39) in the group with focal lesion. **Conclusions:** Our results showed that secondarily generalized epilepsy before 6 years old occurs in 37% of patients with MCDs, especially when the dysplastic lesion is diffuse. However, it is interesting to note that, in childhood, 23% of the patients with a focal dysplastic lesion may have secondarily generalized epilepsy. This information is important because some of these patients with generalized epileptic syndrome due to a focal lesion may be candidates to epilepsy surgery. (Supported by FAPESP.)

2.121
HEMISPHERECTOMY IN TWO CASES OF MEDICALLY REFRACTORY REFLEX EPILEPSY

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Rationale: To report two cases of medically refractory but surgically amenable reflex epilepsy improved by functional hemispherectomy. At the end of this activity the participants should be able to discuss surgical therapy for symptomatic localization-related reflex epilepsy **Methods:** Two adolescent patients with startle-induced seizures unresponsive to medical therapy underwent a standard workup with magnetic resonance imaging, routine EEG, video-EEG monitoring, Wada testing, and neuropsychological evaluation. **Results:** Both patients, boys aged 13 and 15 years at the time of surgery, had left-sided hemiplegic cerebral palsy and mild global developmental delay. One patient had a neonatal MCA stroke with early neonatal seizures, and the other had an antenatal MCA stroke with infantile spasms beginning at 6 months. Both had a several-year seizure-free interval and then developed left hemitonic and clonic seizures. In one patient, these episodes occurred in response to sudden auditory stimuli as well as spontaneously up to 10 times every night and would often secondarily generalize. No significant response was seen with carbamazepine (CBZ), lamotrigine (LTG), or the vagal nerve stimulator. In the other patient, they occurred almost exclusively with auditory startle and would not generalize. CBZ and oxcarbazepine (OCBZ) were used without success. Right hemispheric interictal epileptiform spikes as well as right frontocentral ictal discharges were seen in both cases. Both patients underwent a right-sided functional hemispherectomy. The first patient, who had his surgery performed in 1999, remains seizure free with only the vagal nerve stimulator. He had mild worsening of his preexistent left hemiparesis as well as a transient impairment of short-term memory. The second patient underwent surgery in April 2002 and remains seizure free with OCBZ with no significant change in his motor or cognitive function. **Conclusions:** Patients with symptomatic localization-related reflex epilepsy that is medically intractable may still be excellent candidates for epilepsy surgery. (Supported by Pediatric Division of the Baylor College of Medicine Department of Neurology.)

2.122
DISTINGUISHING NONEPILEPTIC FROM EPILEPTIC EVENTS IN PATIENTS WITH COGNITIVE IMPAIRMENT: A VIDEO-EEG STUDY

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Rationale: Distinguishing epileptic from nonepileptic events (NEEs) in patients with cognitive handicaps or mental retardation (MR) is often challenging. Patients with MR have an increased incidence of epilepsy and associated medical conditions that can be confused with epilepsy. In addition, they often have repetitive behaviors, and limited verbal skils to report symptoms. We investigated the proportion of NEEs confused as epilepsy in this population by use of video-EEG telemetry. **Methods:** We prospectively followed up patients admitted for video-EEG monitoring to our institution for suspected seizures for 1 year. Clinical history of the events was obtained by the referring physician, from family members or guardians, and reviewed on admission by the medical and EEG staff. Only events suggestive of potential seizures were documented and reviewed on digital video and EEG monitoring, which were then read by the authors. Additional information on the patients' history were obtained from the medical charts. **Results:** The 164 patients were admitted to Columbus Children's Hospital for video-EEG monitoring over a 1-year period to characterize new or existing seizure types, and of these, 75 (46%) had MR; 25 of 75 (33%) were diagnosed as having NEEs. Of these patients, 21 of 25 (84%) had abnormal interictal EEGs; 19 of 25 (76%) had concurrent epilepsy, of which 12 (48%) were medically intractable; 21 (84%) were being treated with antiepileptic drugs (AEDs; mean, 1.6; range, 0–5); 17 of 25 (68%) had more than one symptom or episode (mean, two; range, one to four). Fifty-one total symptoms/events were then analyzed. The majority (51%) consisted of abnormal movements such as eye and mouth movements and tonic posturing; 35% had behavorial events (staring, self-stimulation, stereotypies). The remainder had sleep disturbances (five) or other manifestations (oxygen desaturation and dizziness, two). After video-EEG diagnosis of NEEs, the majority of patients (56%) had no additional AEDs added; 28% had their AED therapy decreased or discontinued; four patients had not been treated with AEDs before the study, and remained off AED therapy. **Conclusions:** In the cognitively handicapped population, NEEs could not be predicted based on interictal EEG findings or the clinical characteristics

of the events. These results are similar to previous studies in this population (Donat et al., 1990; Holmes et al., 1983). In contrast to those earlier studies, however, a far greater proportion of patients with MR now referred for video-EEG monitoring have concurrent epilepsy (76% in this study compared with 40% in the previous studies), of which 50% were intractable. This finding demonstrates the importance of video-EEG monitoring in patients with MR, a population in which stereotypical behaviors, abnormal interictal EEGs, and underlying epilepsy are frequently present. (Supported by Children's Hospital, Columbus, Ohio.) (Disclosure: Grant: Glaxo-Wellcome, Elan Pharmaceuticals, UCB Pharmaceuticals; Consulting: Glaxo-Wellcome, Elan Pharmaceuticals, X-Cell Pharmaceuticals, Ortho-MacNeill, UCB Pharmaceuticals, Novartis; Honoraria: Glaxo-Wellcome, Elan Pharmaceuticals, X-Cell Pharmaceuticals, Ortho-MacNeill, UCB Pharmaceuticals, Novartis.)

2.123

EPILEPSY AND EEG CHARACTERISTICS IN SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY

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Rationale: Participants will learn about SSADH deficiency, a disorder of γ-aminobutyric acid (GABA) metabolism, and gain diagnostic skills in the epilepsy and EEG characteristics of the syndrome. Succinic semialdehyde dehydrogenase (SSADH) deficiency is a rare metabolic encephalopathy that does not show a typical intermittent course with episodic decompensation. SSADH deficiency is a disorder of GABA metabolism characterized by detection of 4-OH-butyric aciduria with elevated CSF levels of GABA and γ-hydroxybutyrate (GHB). Patients typically have mental retardation, predominant language impairment, nonprogressive ataxia, hypotonia, autistic features, and aggressive behaviors. Although patients have been reported to have seizures, the frequency of seizures in this disorder, as well as associated semiology and EEG findings, have not been previously reported. **Methods:** We are following up a group of seven SSADH deficiency patients at our institution and report their seizure characteristics and EEG findings. We also reviewed the world literature and report the epilepsy/EEG features in published cases. **Results:** Of our seven patients, three have had seizures: all with generalized tonic–clonic seizures (GTCSs), one with absence; convulsive status epilepticus has occurred in two. EEG findings include diffuse and frontal background slowing, generalized spike–wave discharges with significant activation during sleep, and focal spike discharges in central/temporal areas. Sleep-spindle asynchrony was noted in a 21-year-old. Of 50 reported cases, 24 (48%) have had seizures. Of 25 cases with reported EEG, six had multifocal spikes, two with significant background slowing; one overnight study demonstrated a lack of stage REM sleep. **Conclusions:** Patients with SSADH deficiency have an ~50% incidence of seizures, including absence and convulsive, and both generalized and focal epileptiform discharges on EEG. The pathophysiology of seizures in SSADH deficiency is unknown. These patients have high CSF levels of GABA and GHB. GHB, a GABA-B agonist, induces absence in animal models. Imaging studies have thus far revealed predominantly T_2-MR hyperintensities in the globus pallidi as well as other white-matter abnormalities and cerebellar vermian atrophy. PET and SPECT studies are under way to further elucidate neurometabolic abnormalities in this disorder. SSADH patients commonly have absence and convulsive seizures and generalized and focal EEG discharges. Urinary organic acid analysis for the specific detection of 4-OH-butyric acid should be investigated in symptomatic epilepsies of unknown etiology. [Supported by NINDS NS-40270 (Dr. Gibson).]

2.124

A STUDY OF SEIZURE TYPES AND EPILEPTIC SYNDROMES IN CHILDREN OF INDIAN RAILWAY EMPLOYEES WITH EMPHASIS ON HEREDITARY FACTORS

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Rationale: To classify seizures in children of railway employees presented at Northern Railway Central Hospital New Delhi, to record the history of febrile seizure and occurrence of seizures in family members of the proband. **Methods:** All the epilepsy children presented at NRCH a referral hospital of Indian Railways at New Delhi were first classified by seizure types and, after investigations, reclassified by syndromic classification of ILAE-89. All information regarding investigation results, history of febrile seizure, and family history of seizure in the probands up to second-degree relatives was recorded. Antiepileptic drug (AED) responses were recorded in the form of seizure control. All the information was recorded on a prestructured proforma. **Results:** Total epilepsy cases of children attended at NRCH-286 in a 1-year period. Female cases, 118; male cases, 168; classification: seizure type: Focal/Partial/Secondary generalization, 96; generalized tonic or clonic or tonic–clonic, 142; juvenile myoclonic, 10; absence epilepsy, 20; West syndrome, four; single Sz, five; febrile seizure, nine; AEDs used: sodium valproate, 34; clobazam, nine; phenytoin, 23; carbamezepine, 200; combination, 20; total CT done, 168; normal, 58; abnormal, 110; total MRI done, 10; normal, three; abnormal, seven; percentage of epilepsy cases in total pediatric patients at NRCH, 4.57%; age distribution of patients: 0–5 years, 72; 6–10 years, 131; 11–16 years, 83; syndromic classification after investigations: localisation-related epilepsies and syndromes, 107; generalized epilepsies and syndromes, 120; epilepsies and syndromes undetermined, 17; special syndromes (febrile seizures. single sz., situational seizures, etc., 12; small ring-enhancing lesion, 30; percentage of febrile seizures in total epilepsy cases, 5.24%; percentage of cases where family history was positive in the family of proband, 20%. **Conclusions:** The syndromic classification is useful for judicious use of AEDs (when to start, when to withhold, when to withdraw); to predict prognosis; to define the likelihood of underlying pathology. The febrile seizure was present in 5.24% of cases, so febrile seizure is not a major risk factor for epilepsy in subsequent years of life. The family history was positve in 20% of cases up to second-degree relatives. Family history is a significant risk for epilepsy in the children of epilepsy parents. In age-wise distribution, the percentage of epilepsy children is greater in the age group of 6–10 years in our study because in the railways, the railway population is inhabited in linear fashion on the sides of track, and younger age groups like neonates are fewer in the study, as mothers do not come for confinement from far-off places to this referral railway hospital .They prefer delivery in hospitals near their homes. So neonatal period and young infants are fewer in the study. This gives different age prevalence than other studies in which seizure is more common in 0–1 years of age. (No financial support from any organization. Indian Railways, where the study was done, provide total free healthcare to its empolyees and their family members through Indian Railway Health Service.)

2.125

DIAGNOSTIC VALUE OF OVERNIGHT EEG TO EVALUATE FOR ELECTRICAL STATUS EPILEPTICUS OF SLOW WAVE SLEEP OR LANDAU–KLEFFNER SYNDROME

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Rationale: To determine the diagnostic value of overnight video EEG in patients with suspected Landau–Kleffner syndrome (LKS) or electrical status epilepticus of slow wave sleep (ESES), and to identify features in the clinical history predictive of overnight EEG results.

Methods: Retrospective review of clinical database at Washington University Pediatric Epilepsy Center at St. Louis Children's Hospital from 1995 to 2001. Children referred by a neurologist for 12–48 h of video-EEG monitoring to evaluate for possible LKS or ESES were enrolled. All studies included an overnight sleep recording. Medical records were reviewed to identify diagnosis of seizures, autistic spectrum disorder (ASD), other cognitive or language disorder, and the presence or absence of regression in language or cognitive skills. **Results:** Of 70 children identified, 48 were boys. Age at first video-EEG was 14–213 months (mean, 85.7 months). Thrity-four had ASD, of whom 11 had a history of regression. Thirty-six had other language/cognitive disorder (L/CD), 19 with regression. Overall, 28 children had normal studies (40%), seven had nonepileptiform abnormalities (10%). Of the 35 children (50%) with epileptiform activity (EA), 18 showed significant sleep activation (SAEA) that could be compatible with the diagnosis of LKS, and six revealed ESES. EA was found in 63% of 27 children with known seizures, and 44% of those without; 47% of children with ASD had EA, including 52% of the 25 ASD cases without known seizures, and 43% of the 23 ASD cases without regression. Of 31 children with a history of regression (11 with ASD, 20 with L/CD), 58% had EA, and 45% had SAEA. Of 39 children without regression, 44% had EA, and 26% had SAEA. Children with regression after age 3 years were more likely to have SAEA compared with those who regressed at younger than age 3 (not significant in current sample size) and children who did not have a documented regression ($p < 0.05$). SAEA was present in nine of 15 older children with regression (60%) versus five of 16 younger children (31%). Six children were diagnosed with ESES. All had L/CD with regression after age 3 years, a history of seizures and a prior epileptiform EEG. Fifty-three children had a routine EEG before the first video-EEG. Of 15 with a normal routine EEG, five had EA in the video study, and two of these were SAEA. Of the 35 children with epileptiform video-EEGs, 30 had prior routine EEGs, of which 25 were epileptiform. **Conclusions:** In a highly selected group of children referred by pediatric neurologists for possible LKS or ESES, overnight EEG revealed epileptiform activity in 50%. In 34% this was significantly activated by sleep, supporting the suspected diagnosis. In five children, the abnormality was not evident on routine EEG, and in six others, a diagnosis of ESES was made based on the overnight study. Therefore, ≥15% of studies yielded new information not evident on routine EEG, with potential to change clinical management. A history of regression in language or cognitive skills, older age at regression, and the presence of clinical seizures tended to increase the likelihood of epileptiform abnormalities on overnight EEG.

2.126
CORTICOSTEROID TREATMENT IN LANDAU–KLEFFNER SYNDROME

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Rationale: Landau–Kleffner syndrome (LKS) and its variants such as continuous spike–wave discharge of sleep (CSWS) are progressive epileptic encephalopathies of childhood. They consist of language (LKS) and/or cognitive/behavioral deterioration (CSWS) in a previously well child with continuous epileptic discharge on EEG (with or without clinical seizures). The treatment of this unusual group of patients is controversial. We report our experience in treating patients with LKS and its variants with corticosteroids. **Methods:** Patients were diagnosed with LKS or one of its variants after language regression or cognitive/behavioral deterioration with an epileptic EEG. Patients were then admitted to our Pediatric Epilepsy Monitoring Unit (PEMU) for 24-h continuous video-EEG monitoring, magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) scan, speech/language assessments, and neuropsychological testing. After confirmation of the diagnosis, the patients received prednisone, 1 mg/kg/day, for 6 months. The patients were then reassessed at 6 months, 1 year, and then yearly. Follow-up was for 1–10 years (mean, 4 years). **Results:** Eleven patients, three girls and eight boys, were studied. Age at onset ranged from 2 to 11 years (mean, 7.5 years). Eight patients had LKS, two had CSWS, and one patient had pervasive developmental delay (PDD) with language regression. Most patients had seizures (eight of 11); however, three patients did not have clinical seizures. The EEG was abnormal in 10 patients and included focal epileptic abnormalities in two, CSWS in seven, one patient with both focal epileptic changes and CSWS, and one patient (with PDD) was normal. MRI was normal in all patients. SPECT scan was abnormal in five patients, normal in three, and not available in three. All but one patient had significant improvement in language, cognition, and behavior, which continued after the corticosteroids. Side effects were few (four of 11) and transient and consisted of weight gain (two), behavioral change (one), and hypertension (one). **Conclusions:** Corticosteroids are a safe and effective treatment for patients with LKS. Most patients have significant improvement in language, cognition, and behavior after treatment. Side effects are few and reversible, and benefits, long lasting. Corticosteroids should be considered as a treatment option in children with LKS and its variants.

2.127
ONSET OF EPILEPTIC SPASMS AFTER AGE 2 YEARS: A REPORT OF FOUR CASES

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Rationale: Epileptic spasms are generally regarded as an age-dependent epileptic syndrome with onset during the first year of life. The objective of the present study is to demonstrate that epileptic spasms can infrequently present after age 2 years. **Methods:** Four patients in our database did not develop epileptic spasms until after age 2 years. Semiology of spasms and their electrographic presentation were analyzed by video-EEG telemetry review. Spasms were characterized by brief muscle contraction lasting between 200 and 500 ms, having a myographic crescendo–decrescendo pattern. The muscle contraction temporally corresponded to an EEG finding of a large-amplitude transient slow wave and/or attenuation of the background. Cognitive testing was done by the Weschler Intelligence Scales for Children III and Vineland Adaptive Behavior Scales. **Results:** The four patients identified had onset of spasms between 2.5 and 6 years (average, 3.8 years). Epileptic spasms persisted until ages 9–10.5 years, as documented by video-EEG monitoring. When compared with the patients who were younger than 2 at spasm onset, the frequency of spasms was relatively low, averaging 14 per day. Clinically, spasm semiology was flexor in two cases and mixed (flexor–extensor) in the remaining two patients. During the spasm, the EEG showed a slow transient wave form, followed by an attenuation of the background intermixed with low-amplitude fast activity. Episodically, patients 1 and 3 had a polyphasic blunted sharp wave seen at the onset of the spasm, instead of a slow-wave transient. Each patient had other seizure types, including complex partial, tonic, myoclonic, and secondarily generalized tonic–clonic seizures. Spasms were partially controlled, >50% reduction, by valproic acid and the ketogenic diet in one patient each, with the remaining two patients controlled by intravenous immunoglobulin. However, reduction in spasm activity only showed a transitory benefit for 3–12 months, with return of spasm frequency in all four patients. Mental retardation was present in all cases. The range of severity varied between patients. Two patients were severely retarded, while one was profoundly affected, with the remaining patient only moderately retarded. Cognitive decline was documented in two cases. **Conclusions:** Epileptic spasms can occasionally present de novo after the second year of life. The EEG and clinical features in these late-onset cases is similar to patients with "infantile-onset" spasms. Cases of late-onset spasms tend to have significant cognitive deficits. Furthermore, cognitive decline can be progressive.

2.128

LAMOTRIGINE ADJUNCTIVE THERAPY IN ADOLESCENTS WITH MENTAL RETARDATION AND REFRACTORY EPILEPSY: EFFECTS ON SEIZURE REDUCTION

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Rationale: Management of antiepileptic drugs (AEDs) in adolescents with mental retardation (MR) and epilepsy is difficult. These patients often have multiple seizure types and comorbid behavioral disorders. A focused analysis with adolescents was conducted from a larger study with lamotrigine (LTG) in patients with MR and epilepsy (*Neurology* 2000;54(suppl 3):A192). **Methods:** Patients were ≥12 years, had epilepsy with MR, and were treated with one to three AEDs. Patients entered an 8-week baseline with doses of concurrent AEDs kept constant. LTG (Lamictal) was titrated over the next 8 weeks, then during an 8-week maintenance phase, doses of all AEDs were held constant. During the final 12 weeks, the optimization phase, the number and doses of AEDs were adjusted as needed for optimal therapeutic response. **Results:** For the adolescent subgroup (≥12 and ≤20 years), n = 22, 50% girls, with mean age of 17 years ±2. Level of MR was 18% mild, 18% moderate, 23% severe, 41% profound. Patients' location was private families (68%), institutions (27%), group homes (5%). The most common seizures were complex partial (36%), partial with secondary generalization (23%), primary generalized seizures (45% tonic–clonic, 23% myoclonic, 18% absence). The mean LTG dose during maintenance was 154 mg/day ± 103 with valproate (VPA) and 323 mg/day ± 51 without VPA. Of all adolescent patients, 25% became seizure free, 45% experienced a 75% decrease in seizures; 63% of investigators rated patients as having moderate or marked improvement in seizure frequency, duration, and intensity. During optimization, seizure reduction and investigators' assessment were similar to the maintenance phase. **Conclusions:** Therapy with LTG improved seizure frequency and overall status in adolescents with epilepsy and MR. (Supported by GlaxoSmithKline.)

Neuropsychology/Language/Aphasia/Behavior

2.129

USE OF THE BRIEF VISUOSPATIAL MEMORY TEST–REVISED (BVMT-R) IN NEUROPSYCHOLOGICAL EVALUATION OF EPILEPSY SURGERY CANDIDATES

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Rationale: There have been numerous attempts to establish a valid neuropsychological measure of nonverbal memory that is sensitive to the effects of right temporal lobe dysfunction in presurgical subjects. Figural reproduction measures, including the Rey Complex Figure and the Wechsler Memory Scale designs, have been found to be relatively insensitive in this regard. More positive findings have been reported in studies using measures of figural learning over repeated trials. The purpose of this study was to examine the use of a commercial measure of visuospatial learning in a sample of epilepsy patients undergoing neuropsychological testing as part of a comprehensive presurgical workup. **Methods:** The Brief Visuospatial Memory Test–Revised (BVMT-R) was administered to 47 subjects (22 male, 25 female) undergoing VEEG monitoring. All subjects were found to have electrophysiologic evidence of "probable" unilateral temporal lobe onset, as determined by video-EEG recordings of ictal and interictal epileptiform abnormalities. Primarily left-side abnormalities (LTL) were detected in 25 subjects. Right-side abnormalities (RTL) were identified in 22 subjects. The mean age of the sample was 35.1 years (SD, 13.5). The mean age at onset of epilepsy was 22.4 years (SD, 12.7). Mean years of education was 13.9 years. Full-Scale IQ for the sample was 94.1. The LTL and RTL groups did not differ on any of these variables. The BVMT-R consists of six geometric designs represented on an 8" × 11" page. The designs are shown for a 10-s period, followed by an immediate reproduction of the designs in their correct location on the page. This procedure is repeated over three learning trials. Subjects are asked to reproduce the designs for a fourth time, ~30 min after the learning trials. This is followed by yes/no recognition testing, with six distractor foils. All reproductions are scored according to standardized criteria. The test includes six repeatable forms. The same form (Form 1) was used for all subjects in this study. **Results:** Differences between mean BVMT-R scores from the LTL and RTL groups were assessed with a series of independent *t* tests. No group differences were found in analyses of any of the learning, recall, or recognition measures. Receiver-operating-characteristic (ROC) curve analyses were used to determine empirical cutoff scores for maximal separation of the LTL and RTL groups. Cutoff scores below 16.5 (of a possible 36) over the three learning trials identified RTL subjects with 32% sensitivity and 68% specificity. Delayed-recall scores lower than 6 (of 12) were associated with 23% sensitivity and 68% specificity. **Conclusions:** The results of this study indicate that LTL and RTL subjects exhibit similar patterns of performance on the learning, delayed recall, and recognition trials of the BVMT-R. No differences in scores were obtained in comparison of group means or in examination of rates of impairment using empirically derived cutoffs. The findings suggest that the BVMT-R, like many other tests, lacks sensitivity to detecting the nonverbal memory deficits reported in patients with RTL epilepsy.

2.130

PRESERVED MEMORY ABILITIES IN SUBCORTICAL BAND HETEROTOPIA

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Rationale: Subcortical band heterotopia (SBH) is a disorder of neuronal migration that is associated with epilepsy and cognitive impairment. This condition is genetically related to lissencephaly and results from mutations of the doublecortin gene. Although it is known that patients with SBH display varying degrees of intellectual impairment, little is known about the pattern of spared and affected cognitive functions associated with this condition. We present a series of four patients with SBH who display intellectual deficits, but relatively intact memory abilities. This pattern of cognitive abilities has not been previously reported in individuals with SBH and is highly unique among individuals with focal epilepsy who characteristically display memory deficits. At the end of this activity the participants should be able to discuss the cognitive profile associated with subcortical band heterotopia. **Methods:** Clinical interviews and neuropsychological assessments of four patients (age 10–32 years) with SBH were conducted. Each patient was classified with SBH based on magnetic resonance imaging (MRI) evidence. **Results:** All four patients displayed deficits in overall intelligence, ranging from moderate mental retardation to the borderline level (IQ range, 44–77). Analysis of the pattern of performance of each patient across cognitive domains indicated a highly consistent pattern of impairment in processing speed, attention, language, and visuomotor abilities. By contrast, memory performance was a relative strength and clearly exceeded expectations based on intelligence and adaptive functioning. Table 1 presents a summary of the neuropsychological test findings. **Conclusions:** The most notable neuropsychological finding in these four patients with SBH was of relatively preserved memory abilities in the context of intellectual impairment. This cognitive profile is highly unique among individuals with focal epilepsy and is suggestive of intact functioning of the mesial temporal areas in this condition. These findings are supported by radiologic and pathological evidence in the literature of spared mesial

temporal structures in SBH. Understanding the cognitive strengths and weaknesses of patients with SBH is necessary to assist them in obtaining optimal educational services and achieving maximal independence. Future research with larger groups of patients is required to determine whether this pattern of spared and impaired cognitive functions is related to features of the heterotopic band or the degree of cortical abnormality.

TABLE 1. *Percentile scores on tests representative of each cognitive domain*

	Case 1	Case 2	Case 3	Case 4
Full-scale IQ	1	1	1	6
Processing speed	1	1	2	37
Language	1	—	1	1
Visuomotor	1	1	1	37
Memory	66	16	50	50

2.131

MAGNETIC RESONANCE IMAGING VOLUMETRY OF THE MEDIAL TEMPORAL CORTEX AND MEMORY PERFORMANCE IN DRUG-RESISTANT TEMPORAL LOBE EPILEPSY

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Rationale: Quantitative magnetic resonance imaging (MRI) displays volume reduction in the entorhinal and temporopolar cortices ipsilateral to the seizure onset in subpopulations of patients with drug-resistant temporal lobe epilepsy (TLE). This study investigates whether damage to these extrahippocampal medial temporal lobe cortical areas contributes to memory dysfunction in TLE. **Methods:** The control group consisted of 20 healthy individuals (10 female, 10 male subjects) with a mean age of 32 ± 9 years. Altogether 45 patients (22 female, 23 male; mean age, 33 ± 10 years) with unilateral TLE were scanned with 1.5-T Magnetom. Quantitative volumes of the hippocampus, as well as entorhinal, perirhinal, and temporopolar cortices were assessed. Neuropsychologic evaluation of verbal memory included delayed story recall (DSR) and delayed recall of paired associates. Assessment of visual memory included WMS delayed recall of figures (DRF) and delayed recall of the Rey-Osterrieth complex figure. All patients were subsequently operated on. **Results:** In left TLE ($n = 22$), the mean volume of the left hippocampus was reduced by 32% ($p < 0.01$), the mean volume of the left entorhinal cortex by 19% ($p < 0.01$), and the mean volume of the left temporopolar cortex by 20% ($p < 0.01$) when compared to that in controls. In right TLE ($n = 23$), the mean volume of the right hippocampus was reduced by 26% ($p < 0.01$) and the right entorhinal cortex by 10% ($p \leq 0.01$) when compared to controls. All contralateral cortical volumes were unaffected. There was a correlation between the performance in delayed recall of paired associates and left hippocampal ($r = 0.335$, $p < 0.05$), left entorhinal ($r = 0.348$, $p < 0.05$), or left temporopolar ($r = 0.340$, $p < 0.05$) volume. Respectively, performance in the delayed recall of the Rey-Osterrieth complex figure correlated with the right entorhinal volume ($r = 0.401$, $p < 0.05$), but not with right hippocampal volume. **Conclusions:** This study suggests that in human TLE, a decrease in the volume of left entorhinal and temporopolar cortices is associated with verbal memory impairment. Reduction in the volume of the right entorhinal cortex associates with visual memory impairment. Patients with TLE are, however, a heterogeneous group in terms of etiology, seizure frequency, medication, and other demographic parameters. The correlation analyses do not take into account other possible contributing and confounding factors. Therefore, further assessment with multivariate analyses is needed to specify the contribution of each of the medial temporal lobe structures to cognitive decline in TLE. (Supported by The Academy of Finland, the Kuopio University Hospital Research Fund, the North-Savo Regional Fund of the Finnish Cultural Foundation, the University of Kuopio, and the Vaajasalo Foundation.)

2.132

AN EXAMINATION OF THE ROLE OF UNDERLYING PATHOLOGY ON MEMORY PERFORMANCE IN PATIENTS AFTER TEMPORAL LOBECTOMY

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Rationale: Mesial temporal sclerosis (MTS) is frequently associated with intractable temporal lobe epilepsy (TLE). The literature documents a strong relation between MTS and memory impairment. In contrast, relatively little is known regarding the memory performance in patients with intractable TLE related to other kinds of pathology. The goal of the current study was to compare preoperative and postOperative performance on memory tests in patients who underwent a standard anterior temporal lobectomy (ATL) with different underlying pathologies. **Methods:** The current study employed a retrospective analysis of 99 patients with TLE (left TLE, 49; right TLE, 50) who underwent standard ATL from January 1998 to December 2001. The study relied on an IRB-approved archival database consisting of relevant demographic, medical, and neuropsychological data collected as part of the patients' routine medical care. The patients were divided into different pathology groups based on the surgical pathology report. The vast majority of patients were diagnosed with MTS (left, 34; right, 31). The other patients were divided among those with other pathology (e.g., Tumor/DNET, vascular, cortical dysplasia; left, six; right, eight), MTS + other pathology (left, seven; right, eight), and Normal or nonspecific changes such as mild gliosis (left, three; right, four). The primary variables of interest included the patients' index and individual subtest scale scores on the Wechsler Memory Scale–III. The data were analyzed at the group level and at the individual patient level. **Results:** The patient groups did not differ with respect to age, education, or Full-Scale IQ. The analyses for the left ATL patients indicated that patients with Other pathology (e.g., tumor, DNET, cortical dysplasia, vascular) generally performed better on most memory measures than those with MTS before surgery. After surgery, the left ATL patient groups without histopathologic evidence of MTS tended to show greater declines on memory tests using standardized regression-based change scores. The data for the right ATL pathology groups revealed better performance on the Family Pictures visual memory subtest in patients with Other pathology versus those with MTS before surgery. After surgery, right ATL patients with evidence of Other pathology (either Other or Other + MTS) were more likely to show declines on both the immediate and delayed Family Pictures subtests than those with only MTS or Normal/mild gliosis. **Conclusions:** The results of these preliminary data suggest that the underlying neuropathologic substrate is related to memory performance before and after ATL in patients with TLE. It is important to note that many patients in the Other pathology group had lesions involving mesial structures as well as neocortical regions. Thus, our findings do not appear to simply reflect the extent of mesial temporal involvement. These preliminary data suggest that the underlying neuropathologic status, to the extent that it is known before surgery, might assist in improving predictions of postoperative memory decline after ATL.

2.133

MEMORY ASSESSMENT IN SPANISH-SPEAKING PATIENTS WITH LATERALIZED TEMPORAL LOBE EPILEPSY: CAN DIFFERENCES BE DETECTED?

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Rationale: Assessment of memory function is an important part of comprehensive evaluation of patients with temporal lobe epilepsy

(TLE) who are surgical candidates. While there are many memory tests available for English speakers, the resources are much more limited when assessing Spanish speakers, both in terms of appropriate tests and research to support the utility of such measures. Common neuropsychological measures have been translated into Spanish, and a few tests have been specifically developed for use with Spanish speakers, although there is little, if any, literature to guide memory assessment in epilepsy in this population. The current study examined the utility of two different verbal memory measures in Spanish-speaking right and left TLE patients. **Methods:** Eighteen Spanish-speaking surgical candidates with Right ($n = 7$) or Left ($n = 11$) TLE underwent neuropsychological assessment as part of a neurodiagnostic workup of their seizure disorder. All were administered a Spanish translation of the Logical Memory (LM) subtest from the Wechsler Memory Scale–Revised/3rd edition (story memory test translated into Spanish), and the Spanish Verbal Learning Test (SVLT, Harris et al., 1995), a 16-item list-learning task developed for use with Spanish speakers. Right and Left TLE patients were of similar age (34 vs. 36 years) and education (7.8 vs. 7 years), and all patients reported Spanish as their primary or only language. Duration of epilepsy was also similar between groups (23.5 vs. 22.8 years). **Results:** Significant differences were observed between the Right and Left TLE groups on several SVLT scores, including Total Learning ($F = 6.22$, $p = 0.022$), Delayed Recall ($F = 4.72$, $p = 0.045$), and Words Learned on the fifth learning trial ($F = 11.01$, $p = 0.004$), with the Left TLE group performing more poorly. In contrast, no significant differences were seen for SVLT percentage retention of learned information or on any of the LM variables (immediate and delayed recall, percentage retention). In comparison with normative data, SVLT Total Recall for Right TLE patients was in the average range (T score, 47), whereas Left TLE subjects demonstrated mild to moderate impairment (T score, 34), indicating a more than one standard deviation discrepancy in overall learning between the groups. Performance on LM was equally poor across groups, with both groups performing more than one standard deviation below the mean using English norms. **Conclusions:** Despite the difficulties in assessing Spanish-speaking individuals given the paucity of standardized measures and appropriate norms, this study supports the utility of memory assessment in evaluation of lateralized TLE. The greater sensitivity of the SVLT compared to LM in identifying lateralized memory deficits in this sample suggests that using tests specifically developed for use with Spanish speakers may be of greater utility than conventional measures that have been translated. Therefore, neuropsychological assessment of Spanish-speaking TLE patients will be enhanced by the use of tests developed and normed for use with Spanish speakers, and inclusion of the SVLT as a measure of verbal memory in such evaluations is recommended.

2.134
THE NEUROPSYCHOLOGICAL EVALUATION OF ADULTS WITH HYPOTHALAMIC HAMARTOMA AND MILD EPILEPSY

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Rationale: Hamartomas of the hypothalamus (HH) are well known to produce a refractory epilepsy syndrome which may be associated with precocious puberty, cognitive difficulties, and behaviour problems. The pathogenesis of the latter two is not clearly understood. Fratelli et al. [Cognitive deficits in children with gelastic seizures and hypothalamic hamartoma. *Neurology* 2001;57:43–6] reported on eight children with HH and gelastic seizures and noted the severity of cognitive impairment was related to the severity of complex partial and gelastic seizures. However, the neuropsychological profile in adult patients with HH, whose epilepsy is only of mild or moderate severity, and who are functioning well in activities of daily living, is not understood. **Methods:** Six adult patients with HH underwent comprehensive neuropsychological assessment with the WAIS III, the Doors and People Memory test battery, and tests of executive functioning including verbal fluency, Trail making, and the Hayling and Brixton tests. Two patients were tested before and after stereotactic thermocoagulation of the HH. **Results:** Three patients were in the average or low-average range of IQ. These three patients showed impairment of memory function relative to intellectual function, and these ranged across verbal and visuospatial memory. In contrast, there were no impairments in executive functioning. These patients all had mild simple and complex partial seizures. Three other patients were in the borderline range of IQ, or slightly below this. They were overall lower functioning and showed relative impairments in working memory and mild executive impairment. However, relative to intellectual abilities, they did not show memory impairment. These three patients had more frequent and more severe seizures. Two patients underwent sterotactic thermocoagulation of the hamartoma with reduction in seizures . They reported improvement in memory postoperatively, although this was still abnormal. **Conclusions:** Memory impairment is an important finding in patients with HH, epilepsy, and average or low-average IQ. Cognitive impairment is greater in patients with more frequent and more severe seizures. Improvement in memory after treatment directed at the hamartoma suggests a causative relation between the epileptiform activity produced by the hamartoma and the cognitive difficulties.

2.135
VERBAL SEMANTIC MEMORY BEFORE AND AFTER SURGERY IN TEMPORAL LOBE EPILEPSY PATIENTS

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Rationale: At the end of this activity the participants should be able to discuss stages-of-processing memory theories versus distributed-memory theories and epilepsy surgery prognosis in regards to verbal semantic memory. **Methods:** Our sample included 17 patients (p) with temporal lobe refractory epilepsy and mesial lesion diagnosed by magnetic resonance images. All p. underwent temporal lobe resections. Patients were evaluated with a neuropsychological protocol before and 6 months after surgery, visual confrontation naming test (VCNT) results were selected for analysis. The exclusion criteria were IQ <70 and the presence of aphasic symptoms. Data were compared with normal population according to age and education. A $\chi 2$ test was used to compare both samples (before and after surgery). Results were correlated with age at epilepsy onset and education using Pearson test. **Results:** From the 17 p. analyzed, nine p. showed deficits on the VCNT compared with the normal population. When we compared results in the same p. before and after surgery, we found that 11 p. had a right anterior temporal lobectomy (RATL), and after surgery, in six p., there were nonsignificant improvement, and three p. had no significant decline. Six p. had a left anterior temporal lobectomy (LATL). After surgery, in three p. there was nonsignificant improvement, and two p. had impaired. One of these two p. showed a significant impairment 6 months after surgery ($p = 0.03$). No correlation was seen between age at epilepsy onset and education. **Conclusions:** In our sample we found, after surgery, one p with significant impairment. On the remaining p., it was not possible to define prognosis factors. Temporal lobe epilepsy surgery may determine significant verbal semantic memory decline. In nonaphasic p., this phenomenon may be due to impaired access to the semantic–lexical storage according to the stages-of-processing theories. We also discuss the hippocampal role in the verbal semantic memory processing on the distributed-memory theories framework. (Supported by CONICET–UBA.)

2.136
INVESTIGATING THE NEURAL BASIS OF HUMAN MEMORY DURING EPILEPSY SURGERY: DIFFERENTIAL LOCATION OF TEMPORAL LOBE NEURONS THAT DISTINGUISH CORRECT FROM INCORRECT IDENTIFICATION OR MEMORY

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Rationale: Surgery for epilepsy with a technique where the patient is awake for a portion of the operation under local anesthesia provides a unique opportunity to investigate the neurobiology of human cognition. With microelectrode recording during those operations, we have previously shown that 50–70% of neurons in lateral temporal cortex change activity with recent explicit memory, with regional differences in neurons changing activity with different aspects of memory (*Brain* 1988;111:1383; *J Neurosci* 1999;19:5674; *Nat Neurosci* 2002;5:64). The objective of this study is to further understand the temporal lobe organization of verbal memory by investigating the location of neurons with activity differentiating correct from incorrect identification or memory performance. **Methods:** Activity significantly differentiating correct from incorrect responses was identified in extracellular microelectrode recordings from 114 neurons at 62 sites in lateral or medial temporal lobe of 26 patients undergoing awake neurosurgery for epilepsy, during a measure that assessed identification and recent explicit memory for object names, text, or auditory words. Timing of the appearance of this significant differentiation was determined in 50-ms bins. **Results:** Different neurons in different regions differentiate identification or memory performance. The 13 neurons differentiating identification performance were overrepresented in medial-basal recordings. The nine neurons differentiating memory performance were overrrepresented in superior temporal gyrus recordings. All neurons showed these effects for only one modality. No neuron differentiated both identification and memory. No lateralization of these effects was observed. Within each group there was separation of neurons, showing differentiation early during perception and processing from those showing differentiation late, during output, with early differentiating neurons located more superiolaterally. For identification, this effect was significant, with lateral temporal neurons showing early differentiation, and medial-basal, late. For memory, all neurons showed differentiation during encoding, which continued throughout storage and retrieval in most neurons. Early differentiating neurons were in superior temporal gyrus; late, in middle temporal recordings. **Conclusions:** These recordings provide further definition of the role of different regions of temporal lobe in recent verbal memory. Superiolateral temporal cortex neurons have a role in retention of perceptual features (early differentiating neurons) and in monitoring of response (late differentiating neurons) for recent explicit verbal memory, further evidence for role of lateral temporal cortex in recent memory. Inferior lateral-basal-medial temporal neurons are more closely related to general semantic memory, also with separation of neurons retaining perceptual features of the specific stimuli from those related to retrieval of response motor programs or response monitoring. (Supported by NIH grant NS 36527 and a McDonnell Pew Cognitive Neuroscience grant.)

2.137

PREOPERATIVE NEUROPSYCHOLOGICAL PROFILE AND SURGICAL OUTCOME IN TEMPORAL LOBE EPILEPSY DUE TO UNILATERAL HIPPOCAMPAL SCLEROSIS

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Rationale: There is the possibility that specific sets of preoperative neuropsychological findings might predict surgical outcome. The objective of this work was to correlate specific preoperative neuropsychological findings with long-term surgical outcome in patients with temporal lobe epilepsy (TLE)/hippocampal sclerosis (HS). **Methods:** We tentatively considered verbal memory (Vmem) standardized test batteries as probes of function of the language dominant (usually left) TL, and non-verbal memory tests (NVmem) as probes of function of the nondominant (usually right) TL. Vmem and NVmem tests were thus applied to 91 consecutively operated-on patients with TLE/HS, followed up for a mean of 45 months, which conformed to one of the following four groups: (a) both Vmem/NVmem results within the normal range (WNR) (n = 30); (b) both Vmem/NVmem in the abnormal range (n = 20); (c) Memory tests WNR in the side operated on while abnormal on the contralateral side (n = 18); (d) Memory tests abnormal in the operated-on side, while normal on the nonoperated-on TL (n = 23). The proportion of patients in each group achieving class I outcome, according to Engel's classification, was noted. **Results:** Class I outcome was respectively achieved by 28 of 30 (93%) patients in group (a), 18 of 20 (90%) in group (b), 15 of 18 (83%) in group (c), and in 17 of 23 (73%) of those in group (d). Thus, a pattern of neuropsychological findings pointing to dysfunction of the contralateral TL did not predict poor surgical results when bona fide HS was unilaterally present in the operated-on side. Strinkingly, the least favorable outcome was observed in those patients in which both the HS and the memory neuropsychological dysfunction coincided in the same operated-on TL **Conclusions:** Preoperative neuropsychological findings pointing to dysfunction of the mesial temporal structures contralateral to a well-localized mesial temporal epileptogenic zone associated with clearcut HS does not predict unfavorable postoperative seizure outcome. (Supported by FAPERGS.)

2.138

VERBAL MEMORY IN TEMPORAL LOBECTOMY PATIENTS WITH BILATERAL LANGUAGE: IMPLICATIONS FOR POSTOPERATIVE COGNITIVE OUTCOME

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Rationale: Little is known about the lateralization of verbal memory in patients found to have some degree of bilateral language representation based on the intracarotid amobarbital procedure (IAP). The presence of some verbal memory capacity in the right hemisphere may be a positive prognostic indicator for verbal memory outcome after left temporal lobectomy. The objective of the present study was to review the evidence for right hemisphere verbal memory in bilateral language patients undergoing left temporal resection. **Methods:** The subjects were 22 adult chronic seizure patients who underwent left temporal lobectomy including resection of the hippocampus. All patients had definitive language lateralization per IAP. Fifteen (seven male, eight female) were exclusively left hemisphere dominant for language, while seven (three male, four female) demonstrated some language capacity in the right hemisphere. Mean age at surgery and baseline IQ did not differ for the two groups. Verbal recall performance during IAP and pre- and postoperative delayed retention and recognition on a verbal selective reminding test were compared for the two groups using *t* tests for independent samples. **Results:** Verbal recall during IAP left injection was higher for patients with bilateral language (B) compared to left-dominant patients (L) (B = 74% correct; L = 25% correct). Verbal recall after right injection showed a trend favoring the left-dominant group (B = 44%; L = 61%). These differences did not reach statistical significance. Pre- to postoperative difference scores in delayed retention showed a greater decline for left-dominant patients (–27%) compared to bilateral language cases (–15%). Pre- to postoperative recognition difference scores (adjusted for intrusion errors) demonstarted a significantly greater loss for the left-dominant group (–13%) compared to the bilateal patients (–2%; $p < 0.01$). **Conclusions:** These results suggest that patients with some duplication of language functions in the right hemisphere may have developed some verbal memory capacity on the right side as well. These patients may be at lower risk for significant verbal memory decline after left temporal lobectomy with hippocampal resection. Suggested criteria for establishing bilateral language in the IAP will be discussed.

2.139

VERBAL MEMORY IMPAIRMENT AFTER HIPPOCAMPUS-SPARING TEMPORAL RESECTIONS

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Rationale: In some patients with left temporal lobe epilepsy (TLE), resection of the left hippocampus poses a significant threat to verbal memory. In these cases, a resection that preserves as much hippocampal tissue as possible has been suggested as a way of avoiding or minimizing postoperative verbal memory impairment. Our previous observations, however, suggest that the left perirhinal region plays a role in verbal memory function[1]. We examined verbal memory outcome in three patients with hippocampus-sparing left temporal lobe resections to test the hypothesis that left anterior temporal lobectomy involving the perirhinal/entorhinal cortices, but preserving normal hippocampus, causes verbal memory impairment. **Methods:** Pre- and postoperative performance on a range of verbal memory tests including arbitrarily and semantically related verbal paired associate learning was studied in three patients who underwent resection of epileptogenic lesions in the anterior temporal lobe. Postoperative T1-weighted magnetic resonance imaging (MRI) scans were placed in stereotaxic coordinate space and residual mesial temporal structures identified using previously described anatomic landmarks[2,3]. **Results:** In two patients, the resection spared the amygdala and hippocampus, but adjacent perirhinal/entorhinal cortices were resected. In the remaining case, the perirhinal/entorhinal cortices, amygdala, and hippocampus were spared. Both cases with perirhinal/entorhinal damage had postoperative impairments in the acquisition of unrelated paired associates, which persisted over a 12-month follow-up period. Learning of semantically related paired associates showed an early postoperative decrement, but returned to normal levels within 12 months. The case with sparing of the perirhinal region did not show a postoperative change in associative learning. **Conclusions:** Hippocampus-sparing resections may result in verbal memory deficits when perirhinal/entorhinal tissue is resected. In these cases, the verbal memory deficit is task specific and is similar to the dissociation observed preoperatively in patients with left hippocampal sclerosis[4]. Whether this effect results from hippocampal deafferentation or is the result of perirhinal or entorhinal damage per se remains to be determined. (Supported by NHMRC, Australia.)

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2.140

RELATIONS AMONG AUTOBIOGRAPHICAL MEMORY, CONVENTIONAL MEMORY, AND SUBJECTIVE MEMORY IN TEMPORAL LOBE EPILEPSY

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Rationale: Memory difficulty is a common complaint among individuals with temporal lobe epilepsy (TLE). However, investigators have found no reliable relation between subjective memory reports and performance on traditional memory measures. We hypothesized that conventional memory measures, which assess memory for "impersonal" information (e.g., word lists, designs), might not adequately assess the type of memory difficulty patients typically describe, which often involves poor memory for personal events (e.g., vacations). We attempted to determine whether performance on an autobiographical memory measure would better correlate with patients' memory complaints. **Methods:** Subjects were 22 TLE patients (10 left, 10 right, TWO bilateral) who were administered the Autobiographical Memory Interview (AMI), Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale (Revised or III), and the Wechsler Adult Intelligence Scale (Revised or III). Subjective memory ratings and overall quality of life ratings were obtained from the Epilepsy Surgery Inventory-55 (ESI-55). Pearson correlations and regression analysis were performed to assess the relation among memory performances, subjective ratings, and Full-Scale IQ (FSIQ). **Results:** Performances on both the AMI ($r = -0.51$, $p < 0.02$) and Logical Memory subtest ($r = -0.58$, $p < 0.01$) correlated significantly with subject memory ratings; however, these correlations were not in the predicted direction. Regression analysis revealed that FSIQ correlated significantly with subjective memory ratings. Thus, individuals with higher FSIQ scores performed better on both autobiographic and Logical Memory measures and reported greater memory problems compared to patients with lower FSIQ scores. There was no significant relation between quality of life and subjective memory ratings. **Conclusions:** Contrary to our hypothesis, subjective memory ratings did not correlate better with autobiographical memory performance compared to performance on conventional memory measures. Rather, lower subjective memory ratings were associated with higher scores on both conventional and autobiographical memory measures, and vice versa. Interestingly, FSIQ also showed a significant inverse correlation with subjective memory ratings. These results suggest that patients with higher levels of intelligence are more sensitive to small decrements in memory functioning, despite relatively strong performances on both conventional and autobiographical memory measures. (Supported by the Epilepsy Foundation through the generous support of the American Epilepsy Society.)

2.141

DEFICITS OF VISUAL OBJECT PROCESSING IN TEMPORAL LOBE EPILEPSY: EVIDENCE FROM INTRACRANIAL EVENT-RELATED POTENTIALS

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Rationale: Temporal lobe epilepsies (TLES) are associated with material-specific memory deficits depending on the side of seizure origin. However, while verbal memory deficits in patients with left-sided TLE usually concern long-term storing and delayed recall, visual memory deficits in right-sided TLE involve earlier learning processes instead. Converging evidence from recent neuroimaging and electrophysiologic studies now indicates that the medial temporal lobes (MTLS) participate in visual object processing. We asked whether the hippocampus proper subserves this function and whether visual memory deficits are associated with deficits of visual object processing in TLE patients. **Methods:** Ninenteen TLE patients (nine left and 10 right) *with* ($n = 9$) or *without* ($n = 10$) visual memory deficits participated in the study. We recorded intracranial event-related potentials from within the hippocampus proper on the focal and on the nonfocal side using a visual object decision task. Patients were asked to discriminate between pictures of real objects and nonsense figures and to name the real objects. **Results:** Only in patients *without* visual memory deficits, neuronal activity of the nonepileptic hippocampus differentiated between both kinds of stimuli: While real objects elicited a pronounced positive component peaking between 500 and 900 ms, nonsense figures elicited a marked negative potential in the same time window. By contrast, in patients *with* visual memory deficits, similar and less pronounced positive components were elicited by both kinds of stimuli. In all patients, neuronal responses were reduced in the epileptic hippocampus whose activity did not differentiate between real objects and nonsense figures. **Conclusions:** Our findings confirm and extend results of earlier studies by demonstrating that the hippocampus proper participates in the semantic processing of visual stimuli. Moreover, our data indicate that this function can be impaired in TLE patients and thus suggest a specific neuropsychological mechanism that may contribute decisively to visual memory deficits in TLE.

2.142

MEMORY IMPAIRMENT DETERMINED BY IQ–MEMORY DIFFERENCE SCORE IN TEMPORAL LOBE EPILEPSY

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Rationale: Memory impairment is relatively common in temporal lobe epilepsy (TLE) even after taking into account IQ. One method of characterizing an individual's memory is to calculate the discrepancy between IQ and a memory index (IQ minus memory). In the past, a single discrepancy cut-off score has been used in making the judgment of impaired versus unimpaired memory. A recent publication (Hawkins and Tulsky, 2001) that analyzed data from a large sample of healthy controls, who were administered the latest editions of the Wechsler adult intelligence and memory scales (WAIS-III & WMS-III; Psychological Corporation, 1997), demonstrated that the discrepancy score method requires consideration of IQ level. A patient's IQ must be taken into account because the General Memory Index (GMI) among controls tends to be higher than full-scale IQ (FSIQ) at lower IQ levels, whereas the converse is true at higher IQ levels. Thus, a particular FSIQ-GMI discrepancy score may be clinically significant at one IQ level, but not at another. It is well known that TLE is associated with high risk of memory impairment when the memory score is considered in isolation. We assessed frequency of memory impairment in TLE using the FSIQ minus GMI discrepancy method, while taking into account FSIQ level. **Methods:** This study analyzed Bozeman Epilepsy Consortium data for 77 adult TLE patients (38 right, 39 left TLE). The WAIS/WMS III standardization sample (n = 1,250) served as the control group (Hawkins and Tulsky, 2001). For patients, means were age 35 (±11 years), age at epilepsy onset 16 (±12), FSIQ 88 (±11), and GMI 85 (±15). Thus, there was a mild deficit in both IQ and memory at the group level. The TLE sample was divided into four subgroups based on IQ (70–79; 80–89; 90–99; 100–109). Individuals whose FSIQ-GMI discrepancy score was ≥84th percentile of the standardization sample were considered to have memory impairment relative to IQ level. The FSIQ-GMI discrepancy score cut-off corresponding to the 84th percentile is as follows for each of the four FSIQ subgroups: 0, 6, 9, 12. **Results:** By the FSIQ-GMI discrepancy criteria, 16% of the WAIS/WMS III standardization sample had abnormal memory (i.e., an atypical GMI-FSIQ score) at each IQ level. In contrast, the frequency of discrepancy score–based memory dysfunction among the TLE patients ranged from 36 to 50% across the IQ subgroups, with 47% impaired overall. Frequency of memory impairment did not differ by laterality of seizure focus or age at epilepsy onset. Considering the GMI in isolation, 51% of the patients had impaired memory (GMI ≤–1 SD from the control mean). **Conclusions:** Classification of memory functioning can be based on a memory score alone. Alternatively, memory functioning can be judged in the context of IQ. However, it is not appropriate to use a single FSIQ-GMI discrepancy score cut-off for all patients. In this study, TLE patients were 3 times more likely than controls to demonstrate memory impairment when IQ-stratified base rates of the FSIQ-GMI discrepancy score were considered. Thus, memory impairment is common, although not pervasive, in TLE even after accounting for the fact that intelligence is often lower than average in this patient population. (Supported by the NIH.)

2.143

DEPRESSION IN INTRACTABLE PARTIAL EPILEPSY VARIES BY LATERALITY OF FOCUS AND SURGERY

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Rationale: Depression has been reported to occur after surgical treatment for medically intractable partial epilepsy. The risk of pre- and postsurgical depression may vary by laterality of seizure focus and surgery. We reviewed the pre- and postsurgical psychological assessments and clinical courses of patients to identify those at highest risk for postsurgical mood disorders. **Methods:** Psychiatric status was assessed in a consecutive series of epilepsy patients before and 1 year after epilepsy surgery using Scale 2 of the Minnesota Multiphasic Personality Inventory (MMPI-2) and a clinical depression index (CDI) that scored the occurrence of depressive symptoms, psychiatric referral, or attempted/completed suicide. **Results:** Scale 2 MMPI-2 and the CDI correlated significantly ($r = 0.297$, $p = 0.0005$). Left (n = 43 subjects) and right (n = 50) surgery groups did not differ by sex, seizure outcome, age, education, age at first seizure, duration of epilepsy, or intellect. Patients with left-sided foci had a significant improvement in Scale 2 MMPI-2 scores after surgery despite a tendency for worse presurgical scores than right-sided patients, who in turn tended to show worsening in postsurgical Scale 2 scores. CDI scores diverged significantly postsurgically, with right hemisphere subjects experiencing more morbidity than left-sided subjects. Findings for the anterior temporal lobectomy subgroup (n = 79) were similar to the overall sample. **Conclusions:** Patients undergoing right hemispheric epilepsy surgery are particularly susceptible to clinical depression despite more favorable presurgical personality assessments. Our findings support studies that show an interhemispheric modulation of depressive traits and symptoms. (Supported by Department of Neurology.)

2.144

IMPAIRED RECOGNITION OF EMOTIONS FROM FACIAL EXPRESSIONS IN SUBJECTS WITH RIGHT MESIAL TEMPORAL SCLEROSIS AND EPILEPSY

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Rationale: The contribution of the amygdala to human emotion recognition has been broadly investigated. Bilateral amygdala damage results in impaired recognition of facial expressions of emotion (FEEs), with a disproportionate deficit in fear recognition (Adolphs, 1994). Temporal lobe epilepsy (TLE) is the most frequent form of partial epilepsy in adults, and hippocampal–amygdalar sclerosis (HAS) the most common radiologic and neuropathologic finding. This form of human TLE is frequently associated with an history of febrile convulsion in early childhood and with the appearance of drug-resistance seizures durig adolescence. Recent studies raise concerns that it may be associated with a progressive seizure-induced damage to the medial temporal lobe structures beginning during childhood. The aim of this study was to investigate the recognition of FEEs in subjects with epilepsy and neuroradiologic evidence of HAS. **Methods:** Three patient groups and one normal subject group were studied: (a) 25 TLE patients with unilateral HAS: 15 subjects with a history of febrile convulsions; (b) 23 TLE subjects with MR evidence of anteromedial temporal lobe lesion other than HAS; (c) 33 extra-TLE subjects; and (d) 50 age-matched normal subjects. All epilepsy subjects were right-handed. None of the subjects in the study had a history of major psychiatric illness. All patients were taking antiepileptic medication (AED). Emotion Recognition was examined with a task that required subjects to match a facial expression with the name of the following basic emotions: happiness, sadness, fear, disgust, and anger. Pictures from the Ekman & Friesen series were used as stimuli. Tenface stimuli for each emotion were used, giving a total of 50 stimuli. A Face Identification task, which required subjects to match a target face with five alternatives, was used as a control task. **Results:** All subjects showed no deficit in the face-identification task. FEE recognition was impaired in patients with right HAS; recognition performances in epilepsy patients with left HAS, TLE, and extra-TLE with lesions other than HAS showed no differences with respect to normal control subjects. The deficit in FEE recognition was maximal for fearful faces. The degree of emotion recognition impairment was related to the age of the first seizure, and subjects with complicated febrile convulsions (before age 2 years) showed the strongest deficit. **Conclusions:** We observed that patients with TLE and right amygdalar damage were impaired in FEE recognition, expecially for fear, at variance with patients with other

localization-related seizures. The severe and selective impairment of fear recognition in epilepsy patients with a history of febrile seizures before age 2 years suggests that early right amygdala damage can affect the developement of facial expression–processing abilities. These data are further supported by preliminary fMRI findings showing that, in patients with right hippocampal–amygdalar sclerosis, the deficit in fear recognition is associated with the absence of a pattern of brain activation specific for the processing of fearful facial expression (Benuzzi et al. *N Y Acad Sci* 2002). (Supported by grant MURST 2000.) (Disclosure: Grant: MURST2000.)

2.145

VISUOSPATIAL AND VISUOMOTOR PERFORMANCE AFTER RIGHT TEMPORAL LOBECTOMY

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Rationale: Neuropsychological changes may follow temporal lobectomy. Information on visuospatial and visuomotor changes after nondominant temporal lobectomy is limited. **Methods:** Twenty-three consecutive patients undergoing right temporal lobectomy underwent neuropsychological testing before surgery (11 male,12 female subjects; mean age at surgery, 37.7 years). Postoperative testing was done in 19 patients 6 months after surgery. Surgery consisted of 4- to 7-cm anteroposterior as well as amygdala/anterior hippocampal resection.The following were tested: Wechsler Adult Intelligence Scale–Revised or Wechsler Abbreviated Scale of Intelligence, Visual Form Discrimination, Judgement of Line Orientation, Trailmaking Tests, Grooved Pegboard Test, Finger Tapping, and Hand dynamometer. **Results:** No changes were seen postoperatively in perceptual–organizational and motor components of general intelligence tests and in other visuomotor tests. However,a significant improvement in handgrip strength was seen for nondominant hand postsurgery ($t = -3.876$; $p < 0.006$) **Conclusions:** There is no evidence of visuospatial/visuomotor deterioration after right temporal lobectomy.Findings suggest an improvement in left hand grip strength during follow-up.

2.146

WADA MEMORY PERFORMANCE PREDICTS DEGREE OF SEIZURE RELIEF AFTER EPILEPSY SURGERY IN CHILDREN

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Rationale: Several studies have suggested Wada memory performance is related to seizure outcome in adult epilepsy surgery patients, but this relation has not been thoroughly investigated in children. To address this deficiency, we examined Wada memory asymmetries in youngsters from three comprehensive epilepsy surgery centers who subsequently underwent resective epilepsy surgery to determine if Wada memory performance could predict seizure outcome. **Methods:** One hundred twelve children (mean age, 12.8 years; range, 7–16 years.) with intractable epilepsy underwent Wada testing as part of their preoperative evaluation for surgery. Seizure onset was determined by simultaneous video/EEG monitoring of multiple seizures. All patients underwent resective epilepsy surgery (69, left hemisphere; 43, right hemisphere). Seventy-seven underwent unilateral temporal lobe resection, and 35 had extratemporal lobe resections. Seventy-six (68%) were seizure free (Engel class I), and 36 (32%) were not seizure free (Engel classes II–IV) at follow-up. Mean follow-up interval was 3.7 years (range, 6 months–10.2 years). Memory stimuli were presented soon after intracarotid amobarbital injection, and recognition memory for the items was assessed after return to neurologic baseline. Although minor institutional differences existed in procedures for amobarbital administration, there were no statistically significant difference between left (mean = 102.0 mg) and right (mean = 102.1 mg) hemisphere amobarbital doses. **Results:** Mean ipsilateral minus contralateral Wada memory difference scores were 22.9% for all seizure-free, and 1.2% for all non–seizure-free children ($p = 0.02$). When restricting the analysis to youngsters with temporal lobectomies (TLs), ipsilateral minus contralateral difference scores increased to 27.4% for seizure-free TLs, and 5.1% for non–seizure-free TL children ($p = 0.01$). With regard to individual patient prediction, 47 of 63 (75%) children who had memory score asymmetries in the correct direction were seizure free. In contrast, only 29 of 49 (59%) children whose memory score asymmetries were not in the correct direction were seizure free. **Conclusions:** These results suggest Wada memory performance asymmetries are related to degree of seizure relief after epilepsy surgery in children and adolescents. Moreover, the association between Wada memory asymmetries and postsurgical seizure relief seen in the present study is similar to results obtained in adult epilepsy surgery patients.

2.147

BASELINE NEUROPSYCHOLOGICAL MEMORY PERFORMANCE AND WADA MEMORY ARE INDEPENDENT PREDICTORS OF MEMORY CHANGE AFTER LEFT ANTERIOR TEMPORAL LOBECTOMY

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Rationale: Decline in recent memory function is a risk after left anterior temporal lobectomy (ATL). A variety of approaches have been used to predict risk to memory function after surgery, although most studies have not simultaneously included multiple behavioral measures to determine the relative contribution of each in assessing risk. In the present study, we report both baseline memory performance and Wada memory scores and assess their ability to forecast memory change after left ATL. **Methods:** Forty-four patients who had undergone left ATL were retrospectively identified after meeting the criteria of having undergone successful bilateral Wada memory testing preoperatively and having completed the WMS-R Logical Memory paragraph recall preoperatively and again during follow-up neuropsychological assessment. Wada memory was tested by presenting eight real objects beginning ~45 s after injection of 100–125 amobarbital and assessing object recognition after return to baseline. The predictor variables for Logical Memory II change included the interhemispheric Wada memory asymmetry and baseline Logical Memory II performance. **Results:** The average Wada memory asymmetry was 2.45 objects (SD, 3.2). Baseline Logical Memory II was 14.4 (SD, 8.5) and the average Logical Memory II decline was 4.2 (SD, 9.1). Data were analyzed using a simple linear regression model using baseline Logical Memory II and Wada memory asymmetris as predictors of pre- to postoperative LM II change. Baseline Logical Memory II was highly related to LM II decline following ATL ($p = 0.000002$; R-squared = 0.418). The inclusion of the Wada asymmetry score produced a significant increase in postoperative memory change prediction (incremental R-squared = 0.110; $p = 0.002$), resulting in a total R-squared with both variables in the model of 0.537. **Conclusions:** These results confirm previous reports that patients with higher baseline memory performance are more likely to display a greater memory decline following left ATL and that Wada memory scores are also related to postoperative memory decline. By itself, baseline Logical Memory II accounted for ~40% of the postoperative memory change. Including Wada memory in the prediction model, however, increased the predictive ability of the model by >10%. Thus, both measures are not completely redundant in their predictive ability, and each provides some independent measure of outcome prediction of memory change.

2.148

A COMPARISON OF SODIUM METHOHEXITAL (BREVITAL) AND AMOBARBITAL (AMYTAL) IN WADA TESTING

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Rationale: The Wada test, used to assess unilateral memory and language functioning and predict postsurgical outcome, has traditionally used the drug amobarbital (Amytal). Due to reduced availability of Amytal, we initiated the use of sodium methohexital (Brevital). Brevital, being shorter acting, limits the time to test language and memory, but patients clear more quickly and, if there are questions about the validity of the procedure, it can be repeated without significant concern about oversedation. Using these two anesthetics necessitates procedural differences, and it is possible that this could result in different findings. **Methods:** Fifteen Amytal patients and five Brevital patients, referred for Wada testing as part of a presurgical evaluation, were compared. Our Amytal procedure (AP) involved assessing language by having patients verbally identify and then remember a colored geometric shape, a phrase, two pictures, two words, a math problem, and a nursery rhyme. Our Brevital procedure (BP) is modeled after the procedure described by Buchtel et al. (2002). Language is assessed by naming objects during the first injection. To be remembered stimuli are presented after a second injection and include two objects, two words, a math problem, and a nursery rhyme. Memory testing includes recall and recognition testing and does not proceed until the patient's EEG is back to baseline and the patient reliably performs effortful cognitive tasks. The two procedures are compared in time from injection until patients can be tested for memory and time from injection until memory testing is completed. Results from both procedures were included when both hemispheres were tested in the patient. The results from two patients who had repeated Wadas are also compared. **Results:** Time from initial injection until patients could be tested for memory was significantly different (mean minutes for AP vs. BP of 9.4 vs. 5.4; $p < 0.01$) as was total time for testing (mean minutes for AP vs. BP of 14.1 vs. 9.5; $p < 0.01$). For both patients who had both AP and BP, the results were equivalent. In one case the Wada was repeated because of concerns about the validity of the AP. This patient remembered 60% with the left hemisphere injection and 80% with the right during the AP and 80% and 100% with the BP. In the case of a BP after a left temporal lobectomy and before additional surgery, the patient remembered 80% with the AP and 83% with the BP after a left hemisphere injection. All patients showed significant language impairment with left hemisphere injections and little to no language impairment with right hemisphere injections with both AP and BP. The total time necessary to complete the procedures was dramatically different because with the AP, we waited a minimum of an additional 30 min before testing the alternate hemisphere. **Conclusions:** Our preliminary experience with the BP suggests that this offers significant advantages over the use of the AP. The BP procedure can be completely much more quickly with an average savings of >35 min, could be more easily repeated if there are questions regarding validity, and yielded equivalent results to the AP.

2.149

CORRELATION OF WADA TEST PERFORMANCE WITH MAGNETIC RESONANCE IMAGING HIPPOCAMPAL VOLUMES AND T2 RELAXOMETRY

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Rationale: To determine the relation between magnetic resonance imaging (MRI) hippocampal volumetric and T2 relaxometry data, and Wada test performances in temporal lobectomy candidates. **Methods:** Left hemisphere language dominant temporal lobectomy candidates underwent Wada testing and MRI examinations including volumetric and quantitative T2 pulse sequences. Patients underwent a comprehensive presurgical evaluation including neurologic and neuropsychological examinations, and prolonged EEG-video monitoring. Follow-up neuropsychological testing was completed ~4 months after surgery. Wada testing utilized 100 mg of amobarbital diluted in 10 ml of sterile water introduced into the internal carotid artery via transcutaneous femoral catheterization. Eight objects were presented after confirmation of hemiparesis, and a recognition trial with 16 foils was conducted 10 min after the last object presentation. Incorrect recognitions were multiplied by 0.5 and subtracted from correct Wada recognitions. The side ipsilateral to the ictal focus was usually injected first, followed by the contralateral injection ≥25 min later. **Results:** In right TLE patients, the right hippocampal body ($r = 0.43$, $n = 26$) and tail ($r = 0.41$, $n = 26$) segments were correlated with the left injection memory. Correlations with hippocampal T2 values and the difference between hippocampal volumes were not significant. In left TLE patients, the right injection memory was correlated with the left hippocampal body T2 signal ($r = –0.36$, $n = 39$) and difference between hippocampal volumes ($r = –0.34$, $n = 39$). Backward stepping multiple regression analyses identified preoperative AVLT delayed memory (partial $r = 0.36$) and right Wada memory (partial $r = 0.54$) as the two predictors of postoperative AVLT delayed verbal recall in left TLE patients. In right TLE patients, preoperative delayed verbal memory from WMS-R Logical Memory ($r = .67$) and the right injection Wada memory ($r = .46$) were the best predictors for postoperative Logical Memory delayed recall. **Conclusions:** Wada memory testing including left and right internal carotid amobarbital injections accomplished on the same day is significantly associated with quantitative MRI hippocampal volume and T2 measurements. Individual (i.e., left or right) internal carotid amobarbital injections for Wada memory testing are correlated with verbal memory outcomes in both right and left temporal lobectomy patients. In left TLE patients, these results suggest that injection of amobarbital into the right internal carotid artery to measure functional adequacy of structures ipsilateral to ictal onset predicts verbal memory outcome. The data do not support right hippocampal functional reserve as a direct predictor of postoperative verbal memory change. Wada testing provides information concerning risk for verbal memory decline after temporal lobectomy in addition to information that is provided by MRI data. (Supported by R55 NS28374 from the National Institutes of Health Awarded to C.R. Jack, Jr., M.D.)

2.150

ANOSOGNOSIA DURING THE INTRACAROTID AMOBARBITAL (WADA) TEST IS UNRELATED TO MEMORY SCORE OR SIDE OF INJECTION

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Rationale: The Wada test is often accompanied by neglect for contralateral neurologic deficits, and aphasia but conflicting reports exist on the conditions that predispose to this phenomenon. Gillmore et al. (*Neurology* 1992;42:925) reported in eight patients that neglect was seen with right-sided methohexital injections. In another report by Adair et al. (*Neurology* 1992;45:241) with 52 left hemisphere dominant patients, 52% of left-sided methohexital injected (Linj) cases recalled the hemiparesis versus 3% after right injection (Rinj). Durkin et al. reported a much higher prevalence of anosognosia with the intracarotid amobarbital test in 150 patients with mixed dominance (*Neurology* 1994;44:978). **Methods:** This is a prospective study of anosognosia during the Wada test from 1997 to 2002. Patients evaluated by one examiner (P.C.V.N.) were included in the study. There were 182 intracarotid amobarbital injections (ICA) of which 152 were in 75 right-handed localization-related epilepsy patients. From 90 to 120 mg amobarbital was used for each study. After recovery from amobarbital and after memory testing was completed, patients were asked if they recalled having any problems with vision, weakness, language, or speech to assess awareness of the neurologic deficits. Memory recall was reviewed to see if poor memory performance correlated with anosognosia. Lateralization of the epileptogenic zone was examined for effect on anosognosia. **Results:** Aphasia occurred in 76 ICA tests; 62 patients were amnestic for the deficits, one was not asked, 13 recalled the aphasia. The 13 cases were all left dominant, and eight failed the memory portion of the test. Hemianopia occurred during 91 ICA tests. In 77, there was amnesia for the visual deficit (37 Linj and 40 Rinj), 12 were not asked, two recalled the hemianopia, and both of these were

dominant hemisphere Linj studies with failing scores on memory testing. Hemiplegia occurred in all 152 ICA tests; 133 were associated with amnesia for the deficit, 12 were not asked, and seven, all left dominant for language, recalled the hemiplegia including five with the left ICA test. Of the seven cases that recalled the hemiplegia, four failed the memory portion of the Wada test. The presence of anosognosia for aphasia, hemianopia, or hemiplegia was unrelated to whether the patient passed the memory portion of the Wada test, the side of injection, or lateralization of the epileptogenic zone (Fisher's Exact test). **Conclusions:** The amobarbital Wada test is usually associated with anosognosia for amobarbital-associated neurologic deficits. Anosognosia for hemianopia or hemiplegia was not significantly more likely with Rinj ICA than Linj ICA (Fisher's Exact test) and is not dependent on the localization of the epileptogenic zone. Additionally, anosognosia is independent of the memory score on the Wada test. It is possible that methohexital and amobarbital are not equivalent in their effect on cognition during the Wada test. These data emphasize the importance of developing a standardized Wada test and raise concerns about drug substitution when amobarbital is unavailable, as has occurred in recent years.

2.151

WADA WE DOING WITH WADA? A SURVEY OF CURRENT PRACTICE PATTERNS

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Rationale: Cross-center variation exists in the manner in which Wada procedures are performed, and this variation may well have increased over the past decade with the increasing numbers of epilepsy surgery centers. However, few data are available that characterize the extent and nature of such variation. This poster is meant to (a) provide the reader with a current understanding of the variations in this component of neurologic practice, and (b) highlight areas of discrepancy that empirical efforts may need to address. **Methods:** A 10-question survey on current Wada procedures was distributed via neurology and neuropsychology listservs, and responses were clarified via e-mail when they were unclear. To date, 21 North American (20 US, one Canadian) centers have responded. **Results:** Fourteen of the 21 respondents perform more than one Wada per month. Nearly every center uses amytal rather than brevital, and all but one center test only the anterior circulation. Every center injects both hemispheres on the same day, but the time between injections remains quite variable (mean = 34.5, SD = 15.12). Dosages have become relatively consistent between centers (dose1: mean = 111.87, SD = 12.89; dose 2: mean = 111.77, SD = 12.89), although some variability remains in whether centers use the same dosage in each hemisphere (69%), dose each differently (6%), titrate each individually (10%), or link second dosage to response to first dosage (15%). Likewise, the end points used to determine when to begin testing (hemiplegia, focal slowing on EEG, both, or some other criterion) remain variable (10, 10, 62, and 18%, respectively). Finally, substantial variability remains between centers in terms of when they perform baseline neuropsychological testing (same day, 43%; different day, 48%; both, 4%; none, 4%). **Conclusions:** There continues to be substantial heterogeneity in specific protocols used, although some changes are evident relative to earlier surveys. The range of dosing appears smaller, and the use of superselective procedures has decreased from ~20% in the early 1990s. The clinical impact of the remaining differences remains largely unknown. It is hoped that this survey can help to guide empirical examinations of the potential clinical implications of such variations by highlighting the practices that remain most discrepant between centers.

2.152

NAMING TO DESCRIPTION VERSUS VISUAL NAMING IN TEMPORAL LOBE EPILEPSY

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Rationale: The objective of this abstract is to highlight the potential importance of auditory-naming assessment in temporal lobe epilepsy (TLE). Object-naming ability usually is assessed with visual naming (VN) tests that present drawings. Although a significant minority of TLE patients demonstrates VN impairment, recent studies suggest that naming to description (NTD) is a more sensitive and perhaps more ecologically valid approach to the measurement of naming problems in TLE. In addition, dominant temporal lobe sites specifically associated with the ability to name objects based on their definitions have been identified presurgically. In one TLE study, when stimulation of the posterior temporal lobe disturbed naming, both VN and NTD were usually affected, but anterior temporal lobe stimulation disturbed NTD almost exclusively (Hamberger et al., 1999, 2001). These data indicate that NTD merits further analysis in patients with epilepsy. **Methods:** To further explore the nature of dysnomia in TLE, the current study assessed a group of patients with either left or bilateral TLE and a group of healthy controls on computerized, timed (E-Prime software) measures of VN and NTD. Two lists of 63 objects from the Snodgrass and Vanderwart (1980) corpus were compiled. The stimuli in each list were matched on age of word acquisition, familiarity, imageability, word frequency, and other variables. There was a VN and a NTD test for each list, and administration was counterbalanced across test type and list. Line drawings were used as the stimuli for VN. For NTD, a definition was created and audiotaped for each object. The vocabulary in the definitions was kept as basic as possible and each definition included a brief physical description of the object and either a functional attribute or an encyclopedic fact about it. Speed of naming responses was recorded by a voice-activated timer. Accuracy was recorded by the examiner. **Results:** Both NTD speed and accuracy scores distinguished patients from controls better than VN scores. NTD speed was the only naming test variable significantly associated with self-reported language problems on the QOLIE-89. It is notable that (a) NTD speed and accuracy correlated more strongly, compared to VN, with numerous neuropsychological test scores, (b) NTD speed correlated significantly with language complaints in general, not with word-finding problems specifically, and (c) language complaints showed strong correlations with multiple cognitive and demographic variables. **Conclusions:** It is well established that many individuals with left hemisphere TLE show VN impairment. NTD ability has received little attention in this group, although Hamberger et al. reported important differences between NTD and VN performance in both traditional clinical and electrical stimulation studies. Our investigation supports the usefulness of NTD in neuropsychological studies of TLE. NTD classified TLE and controls more accurately than VN. Although NTD has a broad range of verbal demands, this quality might actually make it a good analogue of conversational speech and an appropriate measure of word-finding problems. (Supported by The Epilepsy Foundation and NIH K23 NS42251 & RO1 NS37738.)

2.153

NAMING ABILITY AFTER TAILORED RESECTION WITH LANGUAGE MAPPING IN PATIENTS WITH LEFT HEMISPHERE TUMORS WITH EPILEPSY

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Rationale: Temporal resection for nonlesional epilepsy in the left, language-dominant, hemisphere carries the risk of decline in postoperative naming ability, and the risk is associated with later epilepsy onset age and absence of hippocampal sclerosis. The objective of the present study was to examine naming outcome after resection with language mapping in patients with epilepsy and left hemisphere tumors. **Methods:** The sample consisted of patients undergoing left hemisphere tailored resection of tumor and epileptogenic cortex after extraoperative language mapping and who had Boston Naming Test (BNT) evaluation before and 6–8 months postoperatively, and who had left hemisphere dominance for language by amobarbital testing. Reliable change index (RCI; 5 for BNT) was used as an indication of meaningful change. **Results:** Thirteen patients (five male/eight female) met the

criteria. Four had frontal and nine had temporal resection. Mean age was 34 years, and mean epilepsy-onset age was 25years. Mean BNT change for the frontal group was –1.25, and for the temporal group, –11.67. For the frontal group, one patient had a >RCI decline in BNT, but for the temporal group, six (67%) had a >RCI decline on the BNT. For the temporal group, there was correlation between BNT decline and onset age ($r = -0.8$, $p < 0.05$). **Conclusions:** Patients with temporal lesional epilepsy undergoing tailored resection were at risk for a decline in naming ability. Frontal resection patients do not show this risk. Late onset of seizures may be associated with greater decline.

2.154

PLASTICITY OF CORTICAL LANGUAGE REPRESENTATION IN TEMPORAL LOBE EPILEPSY

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Rationale: Electrical stimulation studies show large individual patient variability in the number and location of language nodes in the temporal lobe. This study sought to identify determinants of the variability in number of language nodes, and determine if an ipsilateral temporal seizure focus contributes to this variability. **Methods:** We retrospectively reviewed language maps obtained over the past 2 years at our center by direct electrical stimulation of subdural grid electrodes. We identified 14 language maps from patients with left temporal lobe epilepsy, left hemispheric language dominance on the IAP, and adequate sampling of the temporal neocortex during mapping. There were seven patients whose seizures began before the age of 13 years, and seven whose seizures began later. Temporal language nodes were classified as those associated with receptive errors, dysnomia, or mixed dysfunction. The number of nodes of each kind, and their combinations, were the primary dependent variables examined. Variables examined for predictive value included age, gender, education, age at onset of seizures, duration of epilepsy, type of temporal lobe epilepsy (mesial vs. neocortical), and number of temporal contacts tested. **Results:** For patients whose seizures began before 13 years (mean age, 28 years; SD, 18; range, 12–47: mean duration of epilepsy, 22 years; SD, 17; range, 2–45), the number of mixed and receptive language nodes combined was strongly correlated to the age at onset of epilepsy (correlation coefficient $r = 0.78$). By contrast to this group, for patients whose seizures began after the age of 13 years (mean age, 42 years; SD, 11; range, 25–55: mean duration of epilepsy, 18 years; SD, 10; range, 4–34), the number of language nodes was negatively correlated to age of seizure onset ($r = -0.51$), but positively correlated to duration of epilepsy, especially for dysnomia and mixed language deficits combined ($r = 0.67$). The mean number of language nodes for this group was 7.3 (SD, 3.0), significantly higher ($p < 0.01$) than that for the previous group (mean, 3.0; SD, 1.73). None of the other variables were significantly related to the number of language nodes for either group. **Conclusions:** Our data suggest that before maturation of language cortex, the earlier the age at seizure onset, the more likely it is for receptive and mixed-language representations to be located outside their usual temporal locations. In patients whose seizures began after the age of 13 years, the number of language nodes correlates negatively to age at seizure onset, but positively with duration of epilepsy. This finding, together with the significantly greater abundance of language nodes in this group, suggests that after maturation of the language cortex, the presence of a chronic ipsilateral epileptic focus may lead to an expansion of language representation in the temporal lobe. It is unclear whether this represents compensatory cortical plasticity, or an artifact of the electrical stimulation near an epileptic focus.

2.155

MMPI-2 STATISTICAL SUBTYPES IN TEMPORAL LOBE EPILEPSY

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Rationale: The MMPI-2 is commonly given to patients with temporal lobe epilepsy (TLE), but there is little agreement on the typical profiles or significance of MMPI-2 profiles in TLE. The MMPI-2 profiles of TLE patients are heterogeneous, with no single profile characteristic of TLE. In learning disabilities research, statistical subtyping by cluster analysis has been useful for identifying subtypes of personality and psychopathology, and the relation of these subtypes to cognitive dysfunction and neuropathology. Clustering of MMPI-2 profiles of TLE patients may be similarly informative. Subtypes derived by cluster analysis must demonstrate internal and external validity. Internal validity is demonstrated by replication of subtypes across clustering methods and samples. External validity is demonstrated by meaningful subtype differences on variables not used to develop the typology. The purpose of this study was to determine if internally valid MMPI-2 subtypes could be derived from TLE patients with cluster analysis. **Methods:** Sixty consecutive cases with TLE were reviewed. Forty-three cases had completed neuropsychological testing, including the MMPI-2. A multivariate (density) outlier detection algorithm resulted in deletion of seven patients, leaving 36 for clustering (18 female, 18 male subjects). Clustering was performed with MMPI-2 scales 1, 2, 3, 7, 8, 9, and 0. As clustering based on profile shape was desired, before clustering variables were transformed by removing profile elevation and dispersion. An initial cluster solution was developed using Ward's method followed by a k-means relocation pass. Replication was attempted using equal-variance maximum likelihood (EML), unweighted group average linkage (UPGMA), and complete linkage (COM) clustering methods with a k-means relocation pass. Agreement between solutions was evaluated using Rand's statistic. **Results:** Internal criteria (pseudo-F and t^2) suggested four clusters in the initial Ward′s solution. These clusters were replicated perfectly (Rand, 1.0) by EML and UPGMA methods. The COM solution was also very similar, with Rand, 0.98, and only one misclassification. The clusters and their code-types based on mean MMPI-2 profile were 13 ($n = 14$); Exaggerated (scale $F > 80$, $n = 8$); 278 ($n = 7$); and 21 ($n = 7$). The subtypes did not differ on duration of seizure disorder, age at onset of seizures, or WAIS-R IQ measures. The subtypes did differ on age at assessment ($p < .05$), with the Exaggerated subtype tending to be younger than the 278 subtype (29.4 vs. 45.9 years, respectively). The Exaggerated subtype tended to contain more males than females (75% of the cluster); the 21 subtype contained more females than males (71% of the cluster). **Conclusions:** This preliminary study suggests that in patients with TLE, reliable MMPI-2 subtypes can be derived using cluster analysis. The 13 code-type was the most frequent (~40%), with 278, 21, and Exaggerated types being about equally frequent (~20%). The age and sex differences between subtypes provide limited support for the external validity of the typology; however, the reliability and external validity of this cluster solution must be assessed in a larger sample of patients.

2.156

USE OF THE MINI-INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (VERSION 5.0) IN CHARACTERIZING PSYCHIATRIC COMORBIDITY IN PATIENTS WITH CHRONIC EPILEPSY

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Rationale: Interictal psychiatric comorbidity is a recognized complication of chronic epilepsy. Interest in the use of formal standardized psychiatric interview techniques to characterize lifetime-to-date and current psychiatric status is increasing; however, these procedures can be quite time consuming and are not designed for the typical clinical setting. Attempts have been made to develop brief and more efficient standardized clinical interview procedures, and the Mini International Neuropsychiatric Interview (v 5.0), or MINI, was developed to be utilized in medical settings. The purpose of this multicenter investigation was to examine the utility of the MINI in characterizing psychiatric

comorbidity in epilepsy, compare the validity of MINI diagnoses of current major depressive episodes to the current gold standard [Structured Clinical Interview for DSM-IV Disorders (SCID)], and develop an efficient and valid self-report screening instrument to detect depressive symptoms in patients with epilepsy. **Methods:** Patients with chronic epilepsy underwent standardized clinical interview with the MINI as well as the Mood Disorders module of the SCID before completing several self-report mood questionnaires. Rates of DSM-IV mood disorders were identified with the MINI and SCID, and the validity of the MINI determined. Selection criteria were age older than 17 years, on stable antiepileptic drug (AED) treatment for the past 30 days, intact reading ability, and no prior epilepsy surgery or current vagal nerve stimulator. **Results:** The majority of the inital 26 patients enrolled were women (61.5%) on monotherapy (61.5%) with complex partial seizures (70%). The mean age of the sample was 37.4 years with a mean onset age of 18 years. MINI revealed that current Axis 1 disorders were common, with Anxiety (50%) and Mood (40%) disorders the most frequent. Among current Mood disorders, most common were suicidality (23.1%), major depressive episodes (19.2%), and dysthymia (3.8%). Among the Anxiety disorders, most common were agoraphobia (30.8%), generalized anxiety disorder (19.2%), PTSD (11.5%), panic disorder (11.5%), and social phobia (11.5%). Using the SCID Mood module, current and lifetime-to-date disorders were common, including current (23.1%) and past (42.3%) major depressive episodes, current (3.8%) and past (3.8%) minor depression, current dysthymia (3.8%), mood disorder secondary to a medical condition (3.8%), and past hypomania (7.7%). Correlation between the MINI and SCID for current major depressive episodes was 0.89. **Conclusions:** These preliminary results using the MINI indicate the following: (a) Axis I disorders are common among patients with chronic epilepsy, (b) anxiety and mood disorders are among the most frequent disorders, and (c) psychiatric comorbidity can be efficiently screened with concise standardized psychiatric interview procedures that appear to have acceptable validity compared with the gold standard (SCID). This project will continue to accrue up to 200 patients, leading to better estimates of the frequency and distribution of Axis 1 disorders in chronic epilepsy, the validity of the MINI, and the reliability and validity of a new self-report inventory to detect depressive symptoms in epilepsy. (Supported by grant from GlaxoSmithKline.) (Disclosure: Grant: Unrestricted Educational Grant from GlaxoSmithKline.)

2.157

BEHAVIORAL ADVERSE EVENTS IN PATIENTS RECEIVING ZONISAMIDE

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Rationale: Zonisamide (ZNS) is a new antiepileptic drug (AED) approved as add-on therapy for partial seizures. Although ZNS has been widely used in Japan over the past decade, it is fairly new in the U.S. market. Premarketing data indicate a 25% incidence of behavioral adverse events (AEs) in patients receiving ZNS. In this study we report the incidence and characteristics of behavioral AEs in the United States in a multicenter postmarketing cohort. **Methods:** We analyzed data from the PADS (Post-marketing Antiepileptic Drug Survey) on behavioral AEs in 100 consecutive patients initiated with ZNS $\geq$6 months before the study. PADS is a prospective registry provided by a consortium of 16 epilepsy centers to study the population treated with new AEDs. Patients at each center are prospectively and consecutively entered. Initiation forms include demographic data, as well as data on seizure type/frequency, past behavioral and psychiatric disturbances, and current/past AED use. Follow-up forms include seizure outcome, adverse events, reason for discontinuation, if applicable, dose, and titration rate. **Results:** We obtained follow-up on 67 patients, with a mean follow up of 203.5 ± 133.3 days. Males 24, females 43, with mean age of 38.0 ± 16.3 versus 32.4 ± 9.3 years for patients with behavioral AEs ($p > 0.29$). Total number of patients reporting behavioral problems while taking ZNS was eight (11.9%). Behavioral AEs led to discontinuation of ZNS in six (8.9%). The average ZNS dose in patients with behavioral AEs was 250 ± 192.7mg/day, versus 292.9 ± 178.5 mg/day in the total ZNS population ($p > 0.47$). Behavioral AEs (pts could report more than one) included irritability (three), aggression (one), depression (one), agitation (one), mood swings (three), suicide attempt (two), and psychosis (one). A history of psychiatric/behavioral problems/mental retardation was noted in 37% of patients with behavioral AEs versus 30.5% of those without behavioral AEs. **Conclusions:** Behavioral AEs in patients receiving ZNS led to discontinuation only in 8.9%. No demographic group appeared at increased risk. No dose differences were found between patients with behavioral AEs and total ZNS population. Behavioral AEs seen with ZNS appear in accord with other AEDs and with premarketing data. (Supported by The PADS survey has received contributions from: Ortho-McNeil, Cyberonics, Abbott, Glaxo-Wellcome, Novartis, Elan, and UCB Pharma.) (Disclosure: Other: The PADS survey has received contributions from: Ortho-McNeil, Cyberonics, Abbott, Glaxo-Wellcome, Novartis, Elan, and UCB Pharma.)

2.158

PSYCHOSOCIAL AND EMOTIONAL STATUS OF PATIENTS WITH COEXISTING EPILEPTIC AND NONEPILETIC SEIZURES: COMPARISONS WITH EPILEPSY AND WITH NONEPILEPTIC SEIZURE PATIENTS

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Rationale: Patients with coexisting epileptic and nonepilepic seizures have neurologic and psychological processes affecting their medical condition and their emotional and psychosocial adjustment. In previous studies, adjustment difficulties have been found in patients who have either epileptic seizures or nonepileptic seizures. In many of these studies, however, these groups differ, with nonepileptic seizure patients having poorer adjustment. On the basis of this research, it would be expected that patients having both epileptic and nonepileptic seizures would have poor emotional and psychosocial adjustment. However, the degree to which these patients resemble those with epileptic seizures or those with nonepileptic seizures is unknown. The objective of this study was to compare the emotional and psychosocial adjustment of patients who have both epileptic and nonepileptic seizures with those who have either epileptic seizures or nonepileptic seizures. **Methods:** Comparisons were made between three groups of 21 adults each: Patients diagnosed with both epileptic and nonepileptic seizures (COEX), patients with nonepileptic seizures only (NES), and patients with epileptic seizures only (SZ). All patients had undergone long-term EEG and video monitoring, with seizure diagnoses made on the basis of these studies. All patients had assessments of intelligence and completed the Minnesota Multiphasic Personality Inventory (MMPI) and the Washington Psychosocial Seizure Inventory (WPSI). **Results:** Groups were compared using a one-way analysis of variance, with post hoc follow-up tests to examine differences between means. There were no differences between groups in gender or handedness. A significant difference was found in intelligence between COEX (low average FSIQ) and NES (average FSIQ) . On the MMPI, COEX patients showed elevations on eight scales. However, the only significant difference for this group appeared on Scale 8 (Sc), with COEX patients ($Sc = 83$) significantly more elevated than SZ patients ($Sc = 70$). On the WPSI, the COEX group reported significantly more adjustment difficulties than SZ patients in most areas assessed, including emotional status and relationships with family and others. They also reported much greater distress pertaining to seizures than the other two groups. Finally, the COEX and NES groups reported greater dissatisfaction with the medical management of their seizure disorders, compared to SZ patients. **Conclusions:** Although patients with coexisting epileptic and nonepileptic seizures reported emotional turmoil, it was similar to that of patients with epilepsy and those with nonepileptic seizures. However, they had poorer psychosocial adjustment in many areas when compared to these two groups. The direction of causality is not clear. It may be that the two disorders, in combination, have a more adverse impact on an individual's life than either disorder in isolation. Alternatively, higher levels of psychosocial distress in seizure patients may precipitate nonepileptic seizures. Interestingly, nonepileptic seizures

were associated with dissatisfaction about medical care, independent of the presence of epileptic seizures. This may be a manifestation of psychological forces at work in somatic disorders. However, it also may reflect a lack of treatment approaches for nonepileptic seizures in the medical arena.

2.159

DIFFERING EMOTIONAL CHARACTERISTICS OF PATIENTS WITH UNILATERAL SEIZURE ONSET AS ASSESSED WITH THE MINNESOTA MULTIPHASIC PERSONALITY INVENTORY (MMPI)

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Rationale: The current study is intended to determine whether unilateral seizure onset is related to differing mood states. **Methods:** We analyzed the Minnesota Multiphasic Personality Inventories (MMPI) completed during the presurgical evaluation of 103 epilepsy patients whose ictal and interictal EEG scalp recordings were lateralized to either the left (n = 57) or right (n = 46) frontal or temporal lobes. These patients were selected from a larger sample of presurgical epilepsy patients by excluding individuals with a history of neurologic disease or trauma thought to affect both cerebral hemispheres (e.g., head trauma, encephalitis), and those who had experienced a stroke, as the latter condition has been shown to be related to depression and mania in some patients. **Results:** Nonparametric tests showed that left and right hemisphere groups did not differ significantly in regards to age, gender, race, age at onset of seizures, general intelligence, reading ability, or psychiatric history. Results of t statistics with appropriate corrections to guard against type I error occurring due to multiple comparisons revealed that patients with right unilateral onset had significantly higher hypomania scores (Scale 9: R = 68.0; SD, 11.5; L = 60.3, SD, 11.5) on the MMPI than did the left unilateral onset group (t = –3.30, $p < 0.001$). Both left and right seizure onset groups produced significantly elevated depression scores (Scale 2: R = 70.2; SD, 9.0; L = 71.7, SD, 14.4), but did not differ significantly from one another on this scale. After further dividing the original groups by regional cerebral onset (i.e., frontal vs. temporal), multiple analyses of variance were performed to look at regional differences. Results of these analyses revealed that these groups again differed on the hypomania scale (F = 4.10; $p < 0.009$). Post hoc analyses showed that the right temporal and right frontal groups both obtained significantly higher scores on this scale than did the left temporal group (Scale 9: RT = 66.5; SD, 0.4; RF = 70.7; SD, 13.5; LT = 60.1, SD, 11.7). In addition, the right frontal group scored significantly higher on this scale than did the right temporal group (F = –4.18, $p < 0.002$). The left frontal group was too small to draw significant conclusions about the performance of these patients. Depression scores did not significantly differ between regional seizure-onset groups. **Conclusions:** These results indicate that symptoms of depression are common in focal epilepsy patients with unilateral seizure onset regardless of side of focus, whereas hypomanic symptoms seem to be more prevalent among epilepsy patients with right unilateral onset, particularly when seizures arise from the right frontal region. Elevated symptoms of hypomania observed in patients with right unilateral onset is consistent with lesional studies involving other patient groups (e.g., stroke) that have observed the onset of mania after right-sided insults. These findings contribute to existing research suggesting that mood states may be associated with specific brain regions or neural networks, and that disruption of such regions may not require the presence of a frank lesion. Moreover, this study highlights the need to address mood-related symptoms in patients with focal epilepsy.

2.160

PSYCHOGENIC NONEPILEPTIC SEIZURE RISK FACTORS/PREDICTORS VARY BY GENDER

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Rationale: Up to 25% of intractable seizure patients are estimated to have psychogenic nonepileptic seizures (PNESs), paroxysmal behavior falsely attributed to epilepsy whose morbidity worsens with delayed diagnosis. No population-based estimate of gender distribution is available, but 75% female prevalence is widely reported. Referral patterns to monitoring units may be distorted by reliance on gender-related PNES "risk factors" (RFs; i.e., sex abuse and somatization). Identification of explicit gender-related RF differences might clarify etiology and promote early monitoring of males with PNESs. **Methods:** We prospectively studied 85 admissions to our monitoring unit diagnosed as female epilepsy (n = 21); female PNESs (n = 29); male epilepsy (n = 17); and male PNESs (n = 9). Patients with PNES + epilepsy or who could not be diagnosed were excluded. Twelve main historic and symptomatic PNES RFs were derived from a structured interview and compared by gender for frequency, predictive value, and rank order. These include treatment hx., arrest or medicolegal hx., physical abuse, self-injurious behavior, subjectively worse or no better with AEDs, drug abuse hx., sz lasting longer than 5 min, headache aura, other somatization hx, more than three sz types, ETOH abuse, sexual abuse. **Results:** The presence of four or more RFs correctly classified 89% of PNES females (5% false positive) and 93% (12% false positive) of males. With five or more RFs, there were no false positives; male or female. Ranking of RFs differed significantly by gender with cooccurrence of only two (hx and legal/litigation hx) of the eight most frequent. Most frequent PNES RFs: male, hx (89%), legal, physical abuse hx (both 78%), self-injurious (67%), poor AED response (55%). Female, hx (83%), somatization (76%), ≥5-min. sz duration (72%), sex abuse, legal (both 66%). Individual RF frequency differed by gender: sex abuse (11% male vs. 66% female; $p < 0.001$; somatization (33% male vs. 76% female; $p < 0.03$. **Conclusions:** Risk-factor analysis correctly classified a high percentage of PNES patients, but men's PNES risk factors are somewhat different from those of women. Psychiatric treatment hx is the most common RF in both genders, but high base rates in epilepsy-only patients makes it less useful by itself. Men with PNES are less likely to have histories of somatization and sex abuse, and tend to be more often self-injurious and to have been subjects of violence. PNES women's higher rates of somatization may be related to their higher rates of sexual abuse. PNES males tend to average a smaller number of RFs and require fewer for accurate classification than women. Testing of the standardized PNES RF analysis protocol at other sites and development of gender-specific norms is warranted.

2.161

ASSOCIATION OF NEUROPSYCHOLOGICAL FINDINGS WITH CLINICAL OUTCOME IN NEWLY DIAGNOSED PARTIAL EPILEPSY

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Rationale: Cognitive disorders in people with epilepsy, particularly in chronic drug-resistant partial epilepsy, have long been recognized and documented. The purpose of the present study is to evaluate the neuropsychological performance of the patients at the time of the diagnosis of epilepsy, to perform a long-term follow-up of cognitive function in epilepsy, and to identify surrogate markers for disease modification. **Methods:** Altogether 112 patients with newly diagnosed partial epilepsy were allocated to antiepileptic drug (AED) treatment with either a sodium channel–blocking agent (carbamazepine, CBZ; n = 54) or with a γ-aminobutyric acid (GABA)ergic drug [tiagabine(TGB)/vigabatrin (VBG); n = 40/18). Altogether 68 patients with only a single seizure and no AED treatment served as a control group. The patients and control were tested with comprehensive neuropsychological battery at baseline and after 1-year follow-up. **Results:** More patients were initially seizure free with CBZ than with a GABAergic drug. As a group, the patients with either monotherapy showed no significant deterioration in verbal ability, memory performance, attention, or reaction times as compared to baseline. However, practice effect at 1-year reassessment was clearly shown in test scores of controls, but practice effect was less evident and slightly different in the

two AED groups. Part of the patients have already been through two, three and five follow-up assessments. A trend toward deterioration of neuropsychological performance in a subgroup of patients not achieving seizure freedom was noticed, but no relation to the type of initial treatment was found. **Conclusions:** Present follow-up study of newly diagnosed epilepsy patients with either sodium channel blocker or GABAergic AED treatment showed no decline in cognitive functioning. Practice effect was less evident than in controls, which may be the first indicator of adverse AED effects. In the future, the most useful way for evaluating the course of epileptic process and effects of therapy might be combining several measures of outcome such as seizure control, imaging data, and neuropsychological data. (Supported by Kuopio University Hospital EVO-grant.) (Disclosure: Honoraria: Aventis, Novartis, Sanofi Synthelabo.)

2.162

SIGNIFICANCE OF WECHSLER INTELLIGENCE SCALE FOR CHILDREN FOR LATERALIZING EPILEPTIC FOCUS IN CHILDHOOD EPILEPSY

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Rationale: Lateralization of epileptic focus is important to evaluate epilepsy patients for determination of epileptic lesions, especially in presurgical evaluation. Many adults with epilepsy were studied for the significance of intelligence tests for localizing epileptic focus by using the discrepancies of subscale examinations, but data for pediatric epileptic patients have not been published. We studied to disclose the lateralizing value of intelligence test in childhood epilepsy patients. **Methods:** Korean Version of Wechsler Intelligence Scale for Children (KEDI-WISC) was applied for intelligence testing in 100 childhood epilepsy patients (mean age, 9.91 years; range, 5–18 years; M/F ratio, 1:1.04) diagnosed at the department of pediatrics and epilepsy center at Sang-gye Paik Hospital. The clinical characteristics of patients including age, sex, handedness, epileptic syndrome, EEG findings, and magnetic resonance imaging (MRI) results were reviewed in relation to verbal and performance IQ. The discrepancy between verbal and performance IQ scores were compared with the lateralization of epileptic lesions from EEG and MRI findings to reveal the significance of lateralizing value of intelligence test. **Results:** Full-scale IQ scores ranged from 43 to 133 (mean, 88.4 ± 22.8), verbal IQs were from 44 to 129 (mean, 91.0 ± 20.2), and performance IQs were from 38 to 138 (mean, 87.5 ± 24.2) in epilepsy children. Full-scale, verbal, and performance IQs were significantly lower in patients with various abnormal brain MRI findings ($p < 0.05$). Significant discrepancy between verbal and performance IQ scores was noticed in 49 patients. Lower verbal IQs were observed in 17 patients, and lower performance IQs in 32 cases. Patients with significantly low performance IQ scores were associated with abnormal MRI and/or EEG findings in the nondominant hemisphere, and those with significantly low verbal IQ scores showed abnormal MRI and/or EEG features in the dominant hemisphere ($p < 0.05$). Patients with right hemispheric brain lesions had significantly lower performance IQ than other patients ($p < 0.05$). EEG findings were more closely related to the lateralizing value of IQ-score discrepancies than MRI. **Conclusions:** WISC has an importnat role to provide lateralizing value of hemispheric pathology in childhood epilepsy with MRI and EEG findings.

2.163

EPILEPSY IN THE ELDERLY: NEUROPSYCHOLOGICAL COMPARISON WITH HEALTHY SENIORS

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Rationale: Our current understanding of the cognitive and emotional consequences in epilepsy has evolved in large part from studies of younger persons with epilepsy. The information generated from neuropsychological studies may have generalizability to senior adults; however, aging presents its own set of unique aspects to the study of cognitive function. This study aimed at generating a description of the neuropsychological profile of elderly persons with epilepsy and contrasting it with a sample of healthy seniors using quantitative techniques. **Methods:** Participants with epilepsy ($n = 19$) were recruited from area outpatient neurology clinics, and healthy seniors ($n = 29$) were recruited from regional area senior centers. All participants were at least 60 years old, independent community dwelling, 6th grade education or higher, no history of substance/alcohol abuse, and no history of progressive CNS disease. Epilepsy patients experienced at least one seizure within the previous 3 months of enrollment. Epilepsy seniors were not restricted from the study based on seizure type due to etiologies of stroke, brain cancer, traumatic brain injury. Most patients had idiopathic etiology. Standardized measures of cognitive, emotional, physical (Adverse Events Profile) functioning were administered in a single session. Specific tests were the Dementia Rating Scale (DRS), Logical Memory test (LM) of the WMS-III, Boston Naming Test, Wide Range Acheivement Test, Grooved Pegboard Test, Executive Interview Test, Geriatric Depression Scale and Profile of Mood State. A series of one-way analyses of variance were performed to establish between-group differences. **Results:** Seniors with epilepsy were younger than healthy controls (64 vs. 72 years; $p < 0.001$) and had slightly more years of education (13 vs. 12). Women were more prevalent in the epilepsy group (12 vs. seven men) compared to fewer women in the healthy senior group (17 vs. 12 men). Seniors with epilepsy had average age at onset at 33 years (range, 11–63), with majority having seizure onset before age 40. Healthy seniors were taking an average of two medications (primarily hypertensive and arthritis medications), whereas epilepsy seniors received an average of two antiepilepsy medications. Epilepsy seniors performed below healthy controls on a global measure of cognitive function (DRS, $p < 0.04$), verbal memory (LM immediate recall, $p < 0.05$), along with trends for BNT ($p < 0.08$), LM delay ($p < 0.09$). Age at seizure onset was not related to cognitive performance. Epilepsy seniors reported significantly more affective and physical distress than healthy seniors (Adverse Events, $p < 0.02$; GDS, $p < 0.01$; POMS, $p < 0.01$). Symptoms of restlessness, tension/anxiety, depression, and fatigue were more characteristic of epilepsy seniors. **Conclusions:** These results provide preliminary evidence that epilepsy in seniors may have mild detrimental effects upon cognitive, emotional, and physical functioning compared to healthy seniors. Cognitive dysfunction was most evident on measures of memory and global cognitive function. These results were especially interesting in light of the fact that epilepsy seniors were younger and had slightly more education than healthy seniors. (Supported by Centers for Disease Control and Prevention.)

2.164

MITOGEN IMMUNE RESPONSES AND CEREBRAL LATERALIZATION IN PATIENTS UNDERGOING EPILEPSY SURGERY

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Rationale: Cerebral lateralization is postulated to affect immune function. In two separate cohorts of epilepsy patients, we previously demonstrated that left and right cerebral resections differentially affect T-cells. Language-dominant hemisphere resections reduced T cells, but resections in the nondominant side increased T cells. The objective of the present study was to determine if a similar effect was present for other immunologic indices: mitogen responses. **Methods:** In vitro responses to the T-cell mitogens, phytohemagglutinin (PHA) and concanavalin A (ConA), as well as the T-cell and B-cell mitogen to poke weed (PWM) were tested at three dilutions. Evaluations were obtained at preop and two postop (first week and 2 months) times in 15 patients (seven women, eight men; mean age, 37 years; age range, 19–61).

Epileptic focus was as follows: three left temporal, two left frontal, seven right temporal, and three right frontal lobe. All of the patients in this report were left language dominant. **Results:** PWM response was decreased in the first week postop [$F(1, 10) = 5.14$, $p = 0.05$], but left/right resections produced differential effects [$F(1, 10) = 4.50$, $p = 0.05$]. Preop and 2 months postop, PWM responses were greater for patients with a right cerebral focus compared to those with a left focus. In the first week postop, this asymmetry was reversed with a greater response for patients undergoing left cerebral resection. A trend for a similar effect was seen for ConA. **Conclusions:** Consistent with our prior T-cell studies, the present results demonstrate differential immunologic responses in humans to focal cerebral lesions as a function of cerebral lateralization. These findings are consistent with similar differential hemispheric effects in animal lesion studies. In addition, the present study suggests that the side of epileptic focus affects mitogen response separate from the effects of surgery. Further research is needed to delineate the mechanisms underlying cerebral lateralization of immune modulation. (Supported by Dana Foundation.)

2.165

OLFACTORY ASSESSMENT IN EPILEPSY PATIENTS

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Rationale: Olfactory sense has previously been found to be impaired in epilepsy patients, and, in cases where unilateral olfactory impairment is identified, may be used to assist in seizure focus lateralization. Many available tests of olfaction can be costly and complicated to use. The Alberta Smell Test (AST; Green and Iverson, 1989) has been used in normal and head-injured populations, and is reportedly an inexpensive, brief, and easily administered test of olfactory function. The purpose of the present study was to test the ease of administration and discriminability of the AST in epilepsy patients when compared to normal controls. **Methods:** The AST involves unilateral presentation of eight different scents to subjects who are asked to identify the odors from a choice card. There are 10 counterbalanced trials per nostril. Sixteen epilepsy surgical candidates and 16 healthy controls were tested. The epilepsy sample was 75% female ($n = 12$) whereas the control group was 63% female ($n = 10$). There were no significant differences between groups for age (epilepsy M, 34.2 years; control M, 33.6 years). The controls had more years of education than did the epilepsy subjects (epilepsy M, 13.9 years; control M, 17.3 years; $p < 0.01$). The number of current smokers did not differ between groups (epilepsy, $n = 6$; control, $n = 4$). The epilepsy group had average intelligence [M WAIS-III FSIQ, 94.8 (12.3)], had a mean seizure onset of 19.0 (18.5) years old, and had had epilepsy for a mean of 15.2 (10.6) years. There were three epilepsy subjects with right hemisphere seizure focus, nine with left hemisphere focus, two with bilateral independent foci, and one with generalized onset as identified through video-EEG monitoring. In one subject, seizure semiology was consistent with complex partial seizures of temporal lobe origin; however, focus laterality was not clear, and the subject did not seize during the video-EEG study. No subject reported a history of nasal injury, surgery, or polyps. **Results:** Using two-tailed *t* tests, when the two groups were compared on the total score for the AST, the epilepsy subjects performed significantly worse than controls [epilepsy M, 11.5 (2.2); control M, 14.7 (2.4); $p < 0.01$]. Unilateral olfactory functioning in both the left and right nostrils was also significantly reduced in epilepsy patients as compared to controls [Right: epilepsy M, 6.0 (1.2); control M, 7.3 (1.4); $p < 0.01$; Left: epilepsy M, 5.5 (1.6); control M, 7.4 (1.4); $p < 0.01$]. The current sample was not large enough to perform analyses using seizure focus laterality. **Conclusions:** The AST was brief (5 min) and easy to administer. All subjects tolerated the test without adverse effects. This olfactory measure was also found to discriminate epilepsy patients from normal controls, both in terms of overall performance and when each nostril was evaluated individually. These preliminary findings suggest that the AST is an effective, convenient, and inexpensive tool that can be used to investigate olfactory functioning in the epilepsy population. Further research will help to clarify whether the AST is useful in providing information regarding seizure focus laterality.

2.166

THE UTILITY OF A NOVEL NEUROPSYCHOLOGICAL SCREENING BATTERY FOR HISPANICS (NESBHIS) WITH SPANISH-SPEAKING EPILEPSY PATIENTS

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Rationale: The Neuropsychological Screening Battery for Hispanics (NeSBHis) is one of the few neuropsychological batteries that provides normative data stratified by age and education in a Hispanic-American population. Ensuing factor analyses of the same battery have shown that it can effectively distinguish a series of distinct neuropsychological functions (executive, language, visuospatial skills, and visual and verbal memory). Existing neuropsychological assessments with non-Spanish speakers have demonstratedspecific cognitive deficits in epileptic patients, particularly in verbal/visual, memory, and language functions. We assessed a Spanish-speaking epilepsy sample with this battery to determine commensurate findings. **Methods:** All patients were administered the NeSBHis while undergoing continuous video-EEG monitoring on the NYU Comprehensive Epilepsy Center Adult Unit. This battery consists of the following measures: Controlled Oral Word Association Test (F-A-S), Ponton-Satz version of the Boston Naming Test, Rey-Osterreith Complex Figure, World Health Organization (WHO)- University of California in Los Angeles (UCLA) Auditory Verbal Learning Test, Color Trails Test-Parts A and B, Escala de Inteligencia Wechsler para Adultos (EIWA) Digit Span, Digit Symbol, and Block Design subtests, Raven's Standard Progressive Matrices. Based on the adequate Hispanic-American neuropsychological norms that this battery provided, the decision to implement this series of tests as part of the presurgical workup for our Spanish-speaking epilepsy patients was made. **Results:** A total of 22 Spanish-speaking patients were administered this battery. Their mean age was 38 years (SD, 11.11). Their mean education was 11 years (SD, 3.52). Their mean age of seizure onset was 17 years (SD, 12.45). The sample consisted of seven women (31.8%) and 15 men (68.2%). Their general cognitive functioning was estimated through a measure of nonverbal reasoning. Their mean cognitive functioning fell within the Low Average/Borderline range. The greatest frequencies of cognitive deficits (≥ 2 SDs below the mean) were noted in confrontation naming, verbal memory on a list-learning task, visual memory, and also on a task that required color-numeric shifting under timed conditions. **Conclusions:** Preliminary results indicate that the NeSBHis is a valid tool for the neuropsychological assessment of Spanish-speaking epilepsy patients. As such, it can prove useful for characterization purposes and for pre- and postsurgical assesments. Future research directions with this instrument should determine whether it has further discriminatory potential in terms of more specific localization depending on seizure focus.

2.167

NEUROPSYCHOLOGICAL FUNCTIONING AMONG 32 PATIENTS WITH TEMPORAL LOBE EPILEPSY AND THEIR DISCORDANT SIBLINGS

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Rationale: The syndrome of temporal lobe epilepsy (TLE) is associated with an impairment of localization-related neuropsychological functions, mainly dysfunctions of distinct memory performances. This study was conducted to test for the quality and quantity of cognitive dysfunctions in patients with TLE by using results obtained in their unaffected siblings as measures of reference. **Methods:** We obtained results on a broad range of cognitive measures such as intelligence, verbal and nonverbal memory performance, attention, etc., in 32 patients with medically intractable TLE. We also sought further important information such as that related to academic achievement and career.

Because classic case–control studies do not take into account the probands' individual normalized range of performance, we conducted a discordant sibling study in which patients were compared with one of their unaffected siblings, thereby minimizing confounding influences of genetic and environmental factors. **Results:** Our results showed that clinically unaffected individuals outperformed their affected siblings on almost all measures obtained on a high significance level. Patients differed from their siblings at least by 1–2 SDs, differences being pronounced with respect to full-scale IQ and verbal memory. Regression analysis indicated greater differences in IQ with earlier onset of epilepsy, whereas greater differences in memory were seen with later onset of epilepsy. The duration of chronic epilepsy, however, did not explain the observed group differences. **Conclusions:** Our results provide further evidence that the functional impairment associated with TLE exceeds a disturbance of normal temporal lobe function. Instead, dramatic differences between patients and their siblings on a broad range of cognitive functions suggest a profound disturbance of CNS functioning, probably manifest at early stages of brain maturation and development. Such point of view may open novel research directions to improve our understanding of the pathological mechanisms underlying TLE. [Supported by The German Volkswagen-Stiftung and the Deutsche Forschungsgemeinschaft (DFG).]

2.168
MEASURING ANTIEPILEPTIC DRUG NEUROTOXICITY IN INDIVIDUALS: EEG VERSUS COGNITIVE MEASURES

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Rationale: Antiepileptic drug (AED) neurotoxicity may not be apparent on physical examination, and objective methods for detecting neurotoxicity would be useful. Cognitive tests may reveal AED effects in groups of subjects beginning AEDs, but may not be sensitive to change in individuals. This study tested the hypothesis that EEG measures would be more sensitive to individual change than would cognitive measures. **Methods:** The study compared subjects beginning an AED (AON; n = 72) with nonmedicated healthy controls (NCO; n = 74). AON subjects included 52 healthy volunteers participating in blinded AED trials, and 20 patients beginning conventional AED therapy. All subjects underwent structured EEG recording and cognitive testing before initiation of an AED, and 12–16 weeks later. Cognitive measures included Digit Symbol (DSMT), Digit Cancellation, Stroop, tapping speed, visual reaction time (VRT), Selective Reminding, Wonderlic Personnel Test, and Story Recall. Subjective measures included the Profile of Mood States (POMS: Fatigue and Confusion scales), and the Portland Neurotoxicity Scale (PNS). Quantitative EEG measures (occipital) included peak frequency (by power), median frequency (by power), percentage theta power, and percentage delta power. Test–retest changes for all measures were scored against test–retest regression equations derived from NCO subjects, and reported as Z scores. Z scores from the two groups were compared using the Wilcoxon test. We also counted the number of individuals exceeding a Z score of 2.0 (~95th percentile). **Results:** Five of the eight target cognitive measures (DSMT, Stroop, finger tapping, VRT, Story Recall) and all EEG and subjective measures revealed significant differences between AON and NCO subjects. EEG peak frequency change correlated with a cognitive summary score change, POMS-Confusion, and the PNS. AON subjects exceeding a Z score of 2.0 ranged from 5% (tapping) to 17% (Stroop) for cognitive measures, and reached 31% for the PNS. In contrast, 62% exceeded a Z of 2.0 for the EEG peak frequency measure, with similar results for other EEG measures ($p < 0.01$ vs. Stroop; $\chi 2$). **Conclusions:** Amongst subjects beginning an AED, EEG measures were considerably more sensitive than cognitive measures in detecting statistically significant individual change. The findings indicate that EEG measures can detect AED-related neurophysiologic dysfunction not apparent on cognitive testing or physical examination. EEG measures may be useful in the longitudinal assessment of AED neurotoxicity in individuals. (Supported by U.S. Department of Veterans' Affairs, Pfizer Inc., and Novartis Inc.]

2.169
DECLINE IN COGNITIVE FUNCTIONING ASSOCIATED WITH ZONISAMIDE THERAPY

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Rationale: The introduction of a new antiepileptic drug (AED) necessitates careful evaluation of its effect on cognition. However, since its introduction, there have been few empirical studies published that investigate cognitive effects of zonisamide (ZNS) therapy, although cognitive complaints are not uncommon in clinical practice. Reported here are the preliminary findings from a group of 16 epilepsy patients who were administered neuropsychological measures before and during treatment with ZNS. The objective is to investigate the effects of ZNS on cognitive functioning. **Methods:** Sixteen epilepsy patients (mean age, 37.8 years; 31% male) were selected from clinic files who had been administered a battery of neuropsychological tests before and during ZNS therapy for partial-onset seizures. Patients were included in the study if they had a baseline Full-Scale IQ >70. Length of time from initiation of ZNS ranged from 3 to 429 days, with the majority of participants taking ZNS for a minimum of 58 days at the time of testing. ZNS dosage ranged from 100 to 800 mg (mean dosage at the time of testing, 406 mg). The majority of patients were receiving polytherapy, which may have fluctuated during the course of ZNS treatment. The cognitive battery included measures of sustained attention, working memory, verbal fluency, and psychomotor speed. Paired *t* tests were calculated to compare mean performances at baseline and during ZNS therapy. Spearman rho correlations were also calculated to investigate the relation between cognitive change and ZNS dose. **Results:** Mean scores on cognitive tests declined for all tests relative to baseline with the exception of one measure of motor speed and dexterity (Grooved Pegboard). Statistically significant decline was observed on measures of verbal fluency (Controlled Oral Word Association) and working memory (Digit Span). There was a trend toward lower scores on measures of visuomotor processing speed (Digit Symbol-Coding) and verbal fluency (Animal Naming), although these comparisons did not reach statistical significance. Individual change scores were calculated for each measure and correlated with ZNS dose. None of the comparisons reached statistical significance, with the exception of a negative correlation observed between dosage and reaction time on a computerized continuous performance test (Vigil CPT). **Conclusions:** These preliminary results suggest ZNS may be associated with cognitive decline in some patients. Performance may be more affected on tasks requiring cognitive processing as opposed to psychomotor speed. Additional research is needed to further investigate the possible effects of dose, titration, and duration of ZNS therapy on cognitive test performance and to determine the incidence of patients' subjective complaints of cognitive change.

AEDs

2.170
PREGABALIN ADJUNCTIVE THERAPY IN PATIENTS WITH PARTIAL SEIZURES: ADDITIONAL EFFICACY ANALYSES

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Rationale: Pregabalin (PGB) is an alpha$_2$-delta ($\alpha_2\delta$) ligand that exhibits analgesic, anxiolytic, and anticonvulsant activity. Three controlled studies have demonstrated the efficacy, safety, and tolerability of PGB as add-on treatment for patients with refractory partial seizures with or without secondary generalization. Additional efficacy analyses have been conducted, and are presented, which further demonstrate the robust efficacy results in these three studies. **Methods:** In three randomized double-blind placebo-controlled 12-week multicenter studies in adjunctive therapy using PGB, patients experienced at least six partial seizures with no 4-week seizure-free interval during an 8-week baseline period. Two studies used a 1-week titration (1008-009 and 1008-011), and one study had no titration (1008-034). Randomized doses included placebo and ≤600 mg/day PGB. Additional efficacy measures include percentage of patients with seizure freedom for a minimum of 28 days from their last seizure in treatment and several response variables from the cumulative distributions of percentage change in seizure rates from baseline including 50% reduction (traditional responder rate definition), 75% reduction, and 25% increase (worsening). Results will be presented by study and by randomized dose. **Results:** A total of 1,052 patients were randomized to treatment (758 PGB and 294 placebo). The mean patient age at study entry was 37.9 years (range, 12–75 years), and the mean duration of epilepsy was 25.0 years. Study patients had highly refractory epilepsy, as was evidenced by the fact that ~25% of the patients were taking three concurrent antiepileptic drugs (AEDs) at baseline, 50% were taking two AEDs, and 25% were taking one AED and the mean and median baseline seizure rates were 24.4 and 11.2 seizures/month, respectively. The percentage of seizure-free patients was ≤17% (15 of 89 patients) in one 600-mg/day group. From the cumulative distribution of percentage change from baseline seizure rate, ≥50% reductions from baseline (i.e., responder rate) were 43–51% for the 600-mg/day PGB dose groups compared to 6–14% for placebo groups ($p \leq 0.001$ compared to placebo). The ≥75% reductions in seizure rates were 21–33% in the 600-mg/day PGB groups and 2–3% in the placebo groups (all values of $p \leq 0.001$). The ≥25% increases from baseline seizure rates (worsening) ranged from 21 to 33% in the placebo groups compared to only 4–13% in the 600-mg/day PGB groups (p values ≤0.001–0.082). **Conclusions:** These additional efficacy analyses, which include seizure freedom and several other response criteria, demonstrate further evidence in support of the primary conclusions of the effectiveness of PGB in patients with refractory partial seizures with or without secondary generalization. (Supported by Pfizer Global Research and Development.) [Disclosure: Salary: Pfizer (Not M.J.B.); Grant: Pfizer; Consulting: Pfizer; Ownership: Pfizer; Materials: Pfizer; Stock: Pfizer; Royalties: Pfizer; Honoraria: Pfizer (M.J.B.); Other: Pfizer.]

2.171

THE SAFETY OF A PARENTERAL FORMULATION OF CARBAMAZEPINE IN PERSONS WITH EPILEPSY

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Rationale: Carbamazepine (CBZ) is a commonly prescribed antiepileptic drug (AED). We are studying CBZ pharmacokinetics (PK) in young and elderly patients using an intravenous, stable-labeled CBZ formulation. This is a preliminary report on the safety and tolerability of the formulation. **Methods:** Adult patients (older than 18 years) with epilepsy without significant cardiac problems were enrolled. Patients receiving steady-state maintenance CBZ therapy were given a single 100-mg replacement dose of a 5H-dibenz[b,f]azepine-5-,13C, 15N-carboxamide (SL-CBZ) formulation as part of their daily regimen. The remainder of their daily doses was given orally. Blood pressure (BP) and heart rate (HR) data were collected before infusion, every 2 min during infusion, and every 15 min for the first hour after the completion of the infusion. Each subject was monitored by ECG before and during the infusion. The percentage change in BP and HR was determined by subtracting the observation recorded at the end of infusion from the baseline observation. The mean and standard deviation were determined for all parameters. 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 during the infusion if they were experiencing discomfort at the infusion site. **Results:** Seven younger (mean age, 39 years: three female and four male) and one male elderly subject (70 years) have completed the study. CBZ daily doses ranged from 400 to 2,400 mg. All subjects had a change in BP at the end of infusion of ±10% from baseline. The minimum and maximum BP and HR values were determined for each subject. The average percentage change of the minimum recorded BP from baseline during infusion was –9.8% ± 8.1 for systolic and –16% ± 17 for diastolic. The average percentage change of the maximum recorded BP from baseline during infusion was +9.8 ± 6.6 for systolic and +13 ± 19 for diastolic. The percentage change of BP in all patients from end of infusion to baseline was –0.63% ± 6.5 for systolic and –1.9% ± 12 for diastolic. The average percentage change in HR from end of infusion to baseline was 5.2% ± 14. The minimum and maximum observed BP or HR did not occur at the same time in each individual. One person reported transient light-headedness; no change in BP or HR was noted at that time. No subject reported discomfort at the injection site. There was no evidence of inflamation at the site of infusion. **Conclusions:** Our preliminary data indicate that this parenteral CBZ formulation can be safely administered to relatively healthy adult epilepsy patients. (Supported by NINDS P-50 NS16308 and MO1-RR0040.)

2.172

BEHAVIORAL SIDE EFFECTS OF LEVETIRACETAM

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Rationale: Increasingly, anecdotal reports and small series have reported an inordinate incidence of adverse behavioral consequences (ABCs) in patients to whom levetiracetam (LEV) has been administered. The objective of this study was to evaluate the behavioral side-effect profile of the new antiepileptic drug (AED) LEV. **Methods:** We retrospectively reviewed patients from the Minnesota Epilepsy Group's database identified as having medically intractable epilepsy to whom LEV was introduced as add-on therapy. Sixty-one patients aged between 17 and 76 years (median, 41) with histories of medically resistant epilepsy were reviewed for evidence of ABCs. ABCs were defined as any significant behavioral or mood change requiring medical, psychological, or community services/intervention. **Results:** Of the 61 patients identified who were taking doses of LEV between 500 and 3,000 mg/day (mean, 2,000), only five patients developed any adverse behavioral consequence. One patient developed a behavior of stealing, inappropriate aggression, and destruction of property. A second patient developed depression and lability after temporal lobectomy. A third patient developed depression. A fourth patient became irritable, impulsive, and experienced increased obsessive and compulsive behaviors. A fifth patient developed aggression and paranoid depression. All of these patients had LEV discontinued with a resolution of symptoms. **Conclusions:** In this retrospective study, the evidence of clinically significant adverse behavioral consequences of LEV was only 8%, indicating that the frequency of ABCs appears to be no higher, in fact less frequent, than reported for the other new AEDs. (Disclosure: Honoraria: UCB Pharma. For speaking engagement for M.D. meetings.)

2.173

OPEN STUDY ON THE EFFICACY OF LEVETIRACETAM MONOTHERAPY IN IDIOPATHIC GENERALIZED EPILEPSIES

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Rationale: Levetiracetam (LEV) is a novel antiepileptic drug (AED) with proven efficacy against partial seizures. Controlled studies of patients with generalized seizures have not yet been conducted; subgroup analyses from multicenter studies demonstrate that LEV reduces seizure frequency in patients with refractory secondarily generalized seizures. There is limited information about its effectiveness against primarily generalized seizures. In animal models, LEV protects against seizures in audiogenic susceptible rodents, and it is effective in the genetic absence epilepsy rat from Strasbourg model of absence seizures. We report the results of an open study on the efficacy of LEV as monotherapy in six patients with idiopathic generalized epilepsies. **Methods:** Median age at treatment onset was 19.5 years (range, 14–37). All six patients demonstrated at baseline generalized spike–wave discharges and photoparoxysmal responses in three. Three patients were diagnosed with juvenile myoclonic epilepsy (JME), one eyelid myoclonia with absences (EMA), one juvenile absence epilepsy (JAE), and one pure photosensitive epilepsy (PPE). Two patients were treated with LEV as first monotherapy. Four were treated with LEV monotherapy after a failure or unacceptable side effect of sodium valproate (VPA). LEV efficacy was evaluated clinically and by EEG-video monitoring **Results:** Median follow-up was 6.5 months (6–8). Median dosage of LEV was 2 g (0.5–2). All patients with JME showed a complete seizure control either for myoclonic jerks and generalized tonic–clonic seizures. Patient with EMA and JAE had incomplete seizure control. Patient with pure photosensitive epilepsy was seizure free. During the follow-up period, awake and sleep EEG normalized in four; photoparoxysmal responses were reduced in three patients. **Conclusions:** This study suggests that LEV monotherapy could be effective in idiopathic generalized epilepsies (myoclonic, generalized tonic–clonic seizures). Prospective randomized clinical studies are required. Currently, a multicenter controlled clinical trial of LEV for tonic–clonic and myoclonic seizures is being conducted in patients with JME.

2.174

BASIC CLINICAL PHARMACOLOGIC INVESTIGATIONS OF THE NEW ANTIEPILEPTIC DRUG SPM 927

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Rationale: SPM 927 is a functionalized amino acid that is being developed by Schwarz Biosciences GmbH as an oral and intravenous formulation for the treatment of epilepsy and neuropathic pain. Pharmacologic potential has been shown in various preclinical in vitro and in vivo models. The clinical pharmacologic properties of SPM 927 have been assessed in a series of Phase 1 studies in healthy subjects. The aim of this presentation is to describe the pharmacokinetics as well as the safety and tolerability profile of oral SPM 927. **Methods:** To evaluate basic pharmacokinetics, safety, and tolerability of SPM 927, a dose-escalating single-dose trial, a multiple-dose trial, and a food-interaction trial were conducted. The investigations were performed in healthy male white subjects, aged between 18 and 45 years, with a normal body weight. Approval by an IRB had been obtained; subjects gave written informed consent. In the single-dose trial, 16 subjects received oral doses of 400, 600, and 800 mg SPM 927 in a randomized, double-blind, placebo-controlled design. The multiple-dose trial (randomized, double-blind, placebo-controlled, group comparison) was performed in 33 subjects who received 300 or 500 mg SPM 927 b.i.d. over 14 days. The food effect was investigated in a randomized cross-over design with 24 subjects who received single oral doses of 300 mg SPM 927 with and without intake of a high-fat meal. **Results:** After 400-, 600-, and 800-mg doses of SPM 927, maximum plasma concentration (Cmax) was 8.7 ± 1.8, 14.3 ± 2.3, and 19.0 ± 4.8μg/ml; area under the plasma concentration–time curve (AUC) was 143 ± 27, 231 ± 49, and 302 ± 79μg × h/ml; time to maximum concentration (tmax) ranged between 1 and 4 h; terminal half-life (t1/2) was ~13 h. The multiple-dose administration resulted in unchanged pharmacokinetic properties of SPM 927. In the food-effect trial, equivalent pharmacokinetic parameters were found with and without intake of food: the 90% confidence intervals of the ratio "fed/fasted" for Cmax and AUC were 91–103% (point estimate, 97%) and 97–100% (point estimate, 98%), respectively. SPM 927 was found to be safe in all three studies. There was no evidence for an influence on vital signs, ECG parameters, or clinical laboratory values during treatment. Most frequent adverse events were CNS-related symptoms like dizziness, paresthesia, and fatigue. These symptoms were most pronounced after single doses of 800 mg and multiple doses of 500 mg, b.i.d. All 12 subjects in the 300-mg b.i.d. group completed the trial according to protocol. Among 11 subjects randomized to 500 mg b.i.d., four completed the trial at this dose; the remaining seven experienced mild to moderate CNS-related adverse events that resulted in a dose reduction to 400 mg b.i.d. **Conclusions:** SPM 927 was rapidly absorbed, and plasma concentrations were dose proportional. The elimination half-life of ~13 h indicates that an o.d. or b.i.d. treatment regimen may be possible. Pharmacokinetics after multiple dosing was not different from single-dose administration. After b.i.d. treatment, steady state was reached within 2–3 days. There was no influence of concomitant food intake. The 90% confidence intervals for Cmax and AUC were within the bioequivalence acceptance range of 80–125%. SPM 927 was safe and generally well tolerated after single doses of 400–600mg and multiple doses of 300 and 400 mg, b.i.d. (Supported by Schwarz Biosciences GmbH, Alfred-Nobel-Str. 10 40789 Monheim am Rhein Germany.) (Disclosure: Salary: Schwarz Biosciences GmbH.)

2.175

ANTICONVULSANT ACTIVITY, TERATOGENICITY, AND PHARMACOKINETICS OF NOVEL VALPROYLTAURINE DERIVATIVES

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Rationale: The objective of this study was to evaluate the structure–pharmacokinetic pharmacodynamic relations in the anticonvulsant activity and teratogenicity of novel taurine derivatives of valproic acid (VPA). **Methods:** The following four new taurine derivatives of VPA were synthesized and their anticonvulsant activity was evaluated in the Frings audiogenic seizure (AGS)–susceptible mice; valproyltaurine (VTA), valproyltaurinamide (VTD), *N,N*-dimethyl-valproyltaurineamide (DM-VTD), and *N*-isopropyl valproyltaurinamide (I-VTD). The ability of VTD, VTA, DM-VTD, and I-VTD to induce gross malformations was assessed after i.p. administration (600 mg/kg) of test compounds in SWV/Fnn mice, an inbred strain that is highly susceptible to antiepileptic drug (AED)-induced teratogenicity. The pharmacokinetics of these compounds was also assessed in SWV/Fnn mice after i.p. administration (300 mg/kg). Plasma and brain concentrations were analyzed using a gas chromatographic assay. **Results:** In the Frings AGS-susceptible mouse, VTD was 2–3 times more potent than I-VTD and DM-VTD after i.p. administration (ED_{50} values, 51, 126, and 154 mg/kg, respectively). In contrast, VTA was inactive in this model. In SWV/Fnn mice, VTA and VTD did not induce any congenital malformations in liveborn fetuses; however, VTD treatment resulted in a significantly higher rate of resorptions (25%) compared to control animals (4%). DM-VTD was found to be highly embryotoxic, causing 35% resorptions, and excencephaly in 17% of liveborn fetuses. Treatment with I-VTD caused 22% resorptions and induced malformations in 7% of the exposed liveborn fetuses. In comparison, VPA induced exencephaly in 82% of exposed embryos and caused 20% resorptions under similar experimental conditions. After i.p. administration to SWV mice, DM-VTD was metabolized by *N*-demethylations to *N*-methyl valproyltaurinamide and subsequently to VTD. Similarly, I-VTD was *N*-dealkylated to VTD. The obtained pharmacokientic parameters are presented in the table. **Conclusions:** Of the valproyltaurine derivatives evaluated, VTD displayed the highest anticonvulsant

potency, a good protective index, lack of induction of neural tube defects, and favorable pharmacokinetics. The results presented here support the continued evaluation of VTD as a novel investigational AED. (Supported by the NIH grant NO1-NS-4-2311 and the Horowitz Fund, Jerusalem, Israel.)

TABLE 1. *Pharmacokinetic parameters of valproyltaurinamides*

	VTD	I-VTD	DM-VTD
CL (ml/min/kg)	5.4	25	37
Vβ (L/kg)	0.81	0.86	0.69
$T_{1/2}$ (min)	103	24	13
T_{max} (min)	40	20	40
C_{max} (mg/L)	302	226	128
MRT (min)	156	37	42

2.176

GINSENG TOTAL SAPONIN REDUCES EPILEPTIFORM ACTIVITY IN RAT HIPPOCAMPAL SLICES

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Rationale: Ginseng has been used as a folk medicine in far-eastern countries for thousands of years. One of its pharmacologic effects on the CNS is to modify the neurotransmitter–receptor systems. Recently it was demonstrated that saponin elicited the inhibitory effect on electrically evoked response of CA1 region of rat hippocampal slices, suggesting that it could attenuate hyperexcitation of the neural systems (Lee et al. *Biol Pharm Bull* 2000;23:411). Therefore, we tested the potential inhibitory effect of saponin on epileptiform activity induced in rat hippocampal slices. The goal of this study is to further discuss the future direction for saponin research in epilepsy. **Methods:** Epileptiform activities were recorded in CA1 region of hippocampal slices from Sprague–Dawley rats using extracellular field potential recording with grass micropipette. To induce epileptiform activity, hippocampal slices were perfused with Mg^{2+}-free oxygenated artificial cerebrospinal fluid (aCSF) at 30°C. **Results:** Within 20 min of incubation with Mg^{2+}-free aCSF, spontaneous interictal bursts and ictal discharges were observed in slices from rats of postnatal days 11–14. Once stabilized, the duration of individual ictal discharge ranged from 5 to 80 s, occurring every 1–5 min. A subsequent treatment with 10 μg/ml saponin for 10 min completely blocked interictal bursts and also reduced ictal discharges in amplitude, duration, and occurrence rate by 91.1 ± 7.4%, 87.6 ± 10.4%, and 85.5 ± 14.8% (n = 9), respectively. No differential effect of saponin was shown between tonic-type and clonic-type ictal discharges; 1 μg/ml saponin treatment for 10 min was less effective (66.3 ± 15.7%, 76.9 ± 7.5%, and 62.5 ± 12.5% reduction in amplitude, duration, and occurrence rate, respectively, n = 3). In slices from 5- to 6-week-old adult rats, epileptiform activities were mainly characterized by interictal bursts of 100- to 300-ms duration, which was also suppressed after perfusion of 10 μg/ml saponin (97.2 ± 9.7% reduction in amplitude, n = 5). **Conclusions:** These results demonstrated that ginseng total saponin, a major component of ginseng root, was very effective in controlling epileptiform activity induced by Mg^{2+}-free aCSF in a dose-dependent manner. (Supported by Inha University grant 1996.)

2.177

COMPARATIVE SURVIVAL RATES OF ADD-ON THERAPY OF NEW ANTIEPILEPTIC DRUGS

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Rationale: Controlled prospective antiepileptic drug (AED) trials predominantly analyze responder rates. Tolerability is rarely counted as an exit event. But in clinical practice, long-term drug therapy is determined by efficacy and tolerability. The survival rate (number of patients still taking the drug after a period of time) is discussed to be a good indicator of the clinical benefit of a drug, including both aspects. **Methods:** We studied retrospectively outcome, adverse events, and survival rates (Kaplan–Meier) after 6 and 12 months of 205 patients taking levetiracetam (LEV), 227 patients taking topiramate (TPM), and 168 patients taking Oxcarbazepine (OCBZ) add-on therapy. **Results:** With LEV, there were 49% responders (≥50% seizure reduction) with 24% seizure-free patients. The survival rate after 6 months was 72%. Discontinuation was predominantly related to inefficacy. With TPM, there were 55% responders with 20% seizure-free patients. The survival rate after 6 months was 65%; after 12 months, 45%. Discontinuation of the drug was more related to inefficacy than to side effects. There was a good inverse correlation between level of efficacy and rate of side effects. With OCBZ, there were 52.9% responders, with 9.8% seizure-free patients. Survival rate after 6 months was 90%; after 12 months, 79%. Discontinuation was predominantly related to inefficacy. **Conclusions:** Our figures indicate that survival rates are not simply related to efficacy and tolerability. The drug OCBZ, with the lowest rate of seizure-free patients, had the highest survival rate, although tolerability is not different. That indicates that further factors determine the survival rates. One factor could be the general drug policy and the definition of a first-line drug. These aspects have to be taken into account when survival rates are comparatively studied in clinical settings.

2.178

META-ANALYSIS OF WITHDRAWAL TO MONOTHERAPY STUDIES: BASIS FOR HISTORICAL CONTROL

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Rationale: Food and Drug Administration (FDA) regulatory requirements for approval of antiepileptic drugs (AEDs) for use in monotherapy include demonstration of superiority over a comparator. This has led to inclusion of either a placebo or "pseudo-placebo" arm in several monotherapy studies. The FDA recognizes historical control as a valid control group, if multiple rigorous studies demonstrate a stable and highly reproducible behavior under similar conditions. Nine studies have been performed in which patients were randomized to either a pseudo-placebo or active study drug, and then discontinued toward monotherapy. Similar methods were used for all studies. We performed a meta-analysis of all pseudo-placebo arms to determine whether they could serve as a historical control for future monotherapy trials. **Methods:** Review of the literature and direct communication with pharmaceutical companies revealed nine (seven published, two unpublished) randomized controlled trials in which patients with refractory partial seizures were randomized to either active compound or pseudo-placebo, before (eight trials) or after (one trial) being discontinued toward monotherapy. All trials used similar inclusion criteria. Study drugs were gabapentin (GBP), tiagabine (TGB), topiramate (TPM), felbamate (FBM), and oxcarbazepine (OCBZ). The pseudo-placebo arm consisted of either low dose of the study drug or 15 mg/kg of valproic acid (VPA). The outcome measure chosen for this analysis was percentage of patients exiting the trial, estimated from Kaplan–Meier curves. Patients exited the trial if they experienced seizure worsening as identified by predetermined exit criteria. Four nearly identical exit criteria were used in eight of nine trials. The ninth trial used only three exit criteria, and only one exactly matched a criterion used in the other studies. This trial was also an outlier in terms of results. **Results:** A total of 398 patients were enrolled in the pseudo-placebo cohorts for the eight trials using almost identical exit criteria (range, 22–94 patients/cohort). Exit rates ranged from 81 to 100%, and confidence interval lower limits for exit rates are all >68%. **Conclusions:** These results indicate that the behavior of patients randomized to pseudo-placebo, and subsequently discontinued toward monotherapy is predictable and reproducible when a standard set of exit criteria is used. More than 68% will worsen and meet exit criteria. Choice of pseudo-

placebo does not appear to influence exit rate. These results may enable the use of historical controls for future monotherapy studies, obviating the need for a placebo/pseudo-placebo arm. (Disclosure: Salary: Wang/Pledger Johnson and Johnson PRD, L.L.C.; Grant: French, Novartis; Consulting: French, Novartis, Glaxo-Wellcome, Ortho-Mcneil, Abbott; Stock: Wang, The Johnson & Johnson; Honoraria: French, Novartis, Glaxo-Wellcome, Ortho-McNeil, Abbott.)

2.179

ZONISAMIDE AS ADJUNCTIVE AND MONOTHERAPY IN ABSENCE EPILEPSY

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Rationale: Zonisamide (ZNS) is a broad-spectrum antiepileptic drug (AED) structurally classified as a sulfonamide. It was approved in the United States in early 2000 for the treatment of partial seizures with or without secondary generalization in adults. Safety and efficacy in pediatric patients younger than 16 years have not been established for Food and Drug Administration approval in the United States. There has been extensive clinical experience with Japanese children indicating safety, tolerability, and effectiveness in the treatment of both partial- and generalized-onset seizures. As reported by Wirrell et al., the initial AED is successful in only 60% of children with absence epilepsy (AE). In their study valproic acid (VPA) was the most successful initial drug (Wirrel et al. *Epilepsia* 2001;42:760–3). Children with AE refractory to VPA or ethosuximide (ESM) or with unacceptable side effects may benefit from ZNS. We assessed the response to ZNS as adjunctive and monotherapy in a small group of children with AE. **Methods:** A retrospective data-base analysis revealed four children who were sucessfully treated with ZNS for AE. All children carried the diagnosis of primary generalized epilepsy confirmed on routine EEG or video-EEG monitoring and had normal magnetic resonance imaging (MRIs). Ages ranged from 8 to 12 years. All four were incompletely controlled on VPA and/or ESM at therapeutic drug serum levels. Three were started on ZNS as an adjunctive AED. One child was off all AEDs because of unacceptable gastrointestinal side effects from VPA, ESM, and lamotrigine (LTG) and began ZNS as monontherapy. Weights ranged from 31 to 40 kg. All began ZNS dosing at 100 mg/day administered at bedtime. Parents reported on seizure frequency, seizure severity, adverse events, and any side effect at a 1-month follow-up visit and every 2–3 months thereafter. **Results:** Three children tolerated the medication well with 100% reduction in seizures reported at the 1-month follow-up evaluation. They remained on their 100 mg/day original dose and experienced complete seizure control thereafter. The only side effects were reported in the fourth child, a preadolescent, with a 5-lb weight loss (6%) and complaints of feeling tired after 2 months on ZNS. Her dosing was lowered by allowing her to skip every third day of 100-mg/day dosing. She also experienced a possible brief seizure related to hyperventilation while running for a school bus after 2 months on the drug. No other side effects or seizure-like sypmptoms have been reported in the three children who took ZNS for 6 months and one who for 18 months. High therapeutic dosing of VPA was reduced in two children while taking ZNS adjunctive therapy. One child has continued on ZNS monotherapy for 6 months. All parents report ease of ZNS administration with once-a-day dosing. **Conclusions:** ZNS provided seizure control without significant side effects in the study subjects. These findings suggest that ZNS is effective and well tolerated as an adjunctive and possible monotherapy for AE. Smaller dosing formulations as anticipated shortly will facilitate administration in the younger child. (Supported by Elan Pharmaceuticals.) (Disclosure: Honoraria: Dr. Andriola receives honoraria from Elan Pharmaceuticals for speaking.)

2.180

MULTICENTER, OPEN-LABEL ASSESSMENT OF THE EFFICACY AND SAFETY OF ZONISAMIDE AS ADJUNCTIVE THERAPY FOR PRIMARY GENERALIZED EPILEPSY

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Rationale: Zonisamide (ZNS, Zonegran) is a broad-spectrum antiepilepsy drug (AED) approved in the United States for adjunctive treatment of partial seizures in adults with epilepsy. This study was designed to assess the safety and efficacy of ZNS in adults and children with primary generalized epilepsy. **Methods:** This open-label study included boys and girls 5 years of age or older with a diagnosis of primary generalized epilepsy. Patients had to have seizures refractory to other AEDs and could not have a diagnosis of secondarily generalized epilepsy from complex partial seizures. Initial ZNS dosages were based on patient body weight (12.5 mg/day for patients $\leq$40 kg, 25 mg/day for patients >40 kg); dosages were then titrated over 8 weeks to a maximum of 600 mg/day. Patients then completed an 8-week treatment period. Efficacy was assessed via changes from baseline to week 16 in type, duration, and frequency of seizures; patient and investigator global assessments (GAs); and quality-of-life (QOL) questionnaires. Safety was assessed via analysis of adverse events (AEs). **Results:** Ten female and nine male subjects (mean age, 21 years; range, 4–50 years) entered the study and received at least one ZNS dose; seven patients completed the study. Two patients withdrew for inefficacy, and one withdrew due to AEs. Nine patients are still ongoing in the study. Mean ZNS dosage for the completers was 297 mg/day. Responder (i.e., patients with a $\geq$50% seizure frequency reduction) numbers for each seizure type were three of five for absence, two of four for tonic–clonic, two of three for myoclonic, one of one for tonic, and two of seven for all seizures. For patient GAs, four patients (57.1%) showed improvement in current AED therapy, and one patient (14.3%) showed improvement in overall well-being. Six (85.7%) patients showed improvement on the investigator GA of current AED therapy. Three patients (42.9%) showed improvement on general QOL. Fourteen patients (73.7%) experienced one or more ZNS-related AE; most common AEs included headache (21.1%), somnolence (15.8%), diarrhea (15.8%), CNS depression (15.8%), and fever (15.8%). Two serious AEs were reported: moderate tension headache ($n = 1$) and fever, abdominal pain, weight loss, and elevated alkaline phosphatase ($n = 1$). The latter AEs resulted in withdrawal of the patient from the study. Fever, weight loss, and abdominal pain improved with discontinuation of ZNS. Slightly elevated alkaline phosphatase levels existed in this patient before ZNS initiation and were not thought to be attributable to ZNS. **Conclusions:** These preliminary data suggest ZNS may be effective in some patients with primary generalized epilepsy and is safe and well tolerated. Further studies of ZNS in this patient population are warranted. (Supported by Elan Pharmaceuticals, Inc.) (Disclosure: Grant: Elan Pharmaceuticals; Honoraria: Elan Pharmaceuticals.)

2.181

EFFICACY AND TOLERABILITY OF LEVETIRACETAM DURING 1-YEAR FOLLOW-UP IN PATIENTS WITH REFRACTORY EPILEPSY

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Rationale: Levetiracetam (LEV) is a new antiepileptic drug (AED) shown to be effective for the treatment of partial seizures in pivotal clinical trials. We prospectively followed up a consecutive group of patients with refractory epilepsy to investigate the efficacy and tolerability of LEV, especially in those patients who would not be eligible for clinical trials because of factors such as mental retardation, psychiatric disorders, or progressive neurologic disease. **Methods:** Every patient with severe epilepsy irrespective of seizure type attending the investigators' epilepsy clinic was offered LEV as an add-on treatment. Ninety-eight patients accepted to participate and were followed up for 1 year. Demographic data, seizure frequency, and side effects were recorded at baseline and during the first year of follow-up. The first 35 patients were given LEV at a starting dose of 500 mg, b.i.d., with weekly increments of 1,000 mg (fast titration). The other patients were given LEV with a starting dose of 250 mg, b.i.d., with weekly increments of 250 mg (slow titration). **Results:** There were 47 female and 51 male subjects with an average age of 39 years (SD, 14 years). Seventy-nine had localization-related seizures. Twelve had symptomatic generalized seizures, and seven had primarily generalized seizures. The median number of seizures per month was seven, and the median number of AEDs was two. Twenty-two patients were mentally retarded

(22%). In the total population, 14 patients were completely seizure free for at least the 6 last months, most from the first dose given. A total of 55 of the 98 patients were responders with >50% seizure reduction by the end of the first year. In the group with generalized seizures, only one of 19 became seizure free, but eight patients had a reduction of seizure frequency >50%. The average dose at the end of 1 year was 1,900 mg (SD, 900 mg). Thirty-seven patients discontinued LEV (median 19 weeks of treatment). Seventeen discontinued because of adverse effects. In the group with fast titration, 15 of 35 (43%) experienced tiredness during the first 12 weeks, and in the group with slower titration, this was experienced by 20 of 63 (32%). The difference was not statistically significant. Behavioral adverse events, mainly irritability, were reported by five during the first 12 weeks of treatment and by seven after the first 12 weeks of treatment. This led to discontinuation of the drug in four of these patients. One patient discontinued the drug because of psychosis. Four of the patients who discontinued because of behavioral adverse events had previously had behavioral problems and/or mental retardation. **Conclusions:** LEV appears to be well tolerated in this group of patients with severe epilepsy and shows efficacy even in a long-term follow-up. Behavioral adverse events were noted in a minority of patients and occurred mainly in patients who had a history of behavioral disturbance or were mentally retarded. (Supported by the Department of Neuroscience, Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden.) (Disclosure: Grant: Elinor Ben-Menachem has a research grant from UCB; Consulting: Elinor Ben-Menachem has been a consultant for UCB.)

2.182

IMPLEMENTATION OF AN EXTERNAL RESPONSIVE NEUROSTIMULATOR SYSTEM IN PATIENTS WITH INTRACTABLE EPILEPSY UNDERGOING INTRACRANIAL SEIZURE MONITORING

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Rationale: There is growing interest in responsive neurostimulation to terminate epileptic seizures. An external responsive neurostimulator (eRNS) and programmer system (PS) were developed and tested as a prototype for a future implantable device. The eRNS is a battery-powered device capable of detection and storage of EEG activity, seizure detection that can be screened and customized by the clinician for the patient's unique seizure pattern with delivery of automated responsive stimulation programmed by the PS. **Methods:** Informed consents were obtained consistent with Food and Drug Administration and IRB regulations. Patients studied were selected from those determined to require intracranial electrode arrays. Patients were then connected in parallel to both the eRNS and the usual video-EEG monitoring equipment in their institution. Sensitive but nonspecific detection algorithms derived from the individual's baseline data were programmed to trigger the storage of potential epileptiform electrocorticograms (EcoGs). Clinicians then used the PS to review stored ECoGs for identification of seizures, along with baseline and EEG and false positives; the information was submitted to the *Proposer,* an expert system in the PS that perfoms a multidimensional parametric search to determine detection parameters tuned to the patient's unique EEG seizure-onset pattern. Up to three seizure-onset patterns using multiple detection tools on multiple EEG channels could be configured. Real-time processing was implemented in an energy-efficient manner. After sufficient seizures were recorded for presurgical evaluation, but before electrode explant, the eRNS was programmed to deliver responsive electrical stimulation on seizure detection to desynchronize developing epileptiform activity. **Results:** The eRNS study began in April 2002. The results from the application of this system to patients through late 2002 will be presented. **Conclusions:** Heretofore, stimulation therapy for epilepsy using open-loop, continuous paradigms, or closed-loop systems used high-power computing devices to implement detection and decision-making algorithms. The eRNS is a system that uses the same resources and algorithms that will be available in a fully implanted neurostimulator. The potential for the eRNS to modify and reduce seizure evolution and propagation represents a novel and targeted approach using neurostimulation in the treatment of epilepsy. (Supported by NeuroPace, Inc., Sunnyvale, California.) (Disclosure: Grant: Clinical Research Study with NeuroPace, Inc. Sunnyvale, CA, for the Automated Response to spontaneous Epileptiform Activity using the external Responsive Neurostimulator (eRNS); Consulting: received consulting fees from NeuroPace, Inc., Sunnyvale, CA.)

2.183

EVALUATION AND COMPARISON OF SEIZURE CONTROL DURING ESCALATION OF LAMOTRIGINE, VALPROIC ACID, CARBAMAZEPINE, AND PHENYTOIN AS INITIAL MONOTHERAPY IN PATIENTS WITH EPILEPSY

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Rationale: The use of lamotrigine (LTG) requires initiation of low doses and careful titration. While the favorable efficacy and tolerability of LTG at maintenance doses are well established, there is a need to assess them and compare with other AEDs during the titration period. **Methods:** Seizure data from the escalation phase of four blinded and well-controlled studies of AED initial monotherapy [including lamotrigine (LTG), valproic acid (VPA), carbamazepine (CBZ), and phenytoin (PHT)] were aggregated. AEDs were initiated over a 6- to 8-week period. Patients studied were experiencing partial or generalized seizures or both. **Results:** Analysis of variance showed no significant difference between LTG and other AEDs. **Conclusions:** LTG efficacy during initial monotherapy dose escalation is comparable to the efficacy during initial monotherapy dose escalation of VPA, CBZ, and PHT. (Supported by GlaxoSmithKline Research and Development.) (Disclosure: Salary: Coauthors are employees of GlaxoSmithKline; Grant: Dr. Biton received a research grant for conduct of this study from GlaxoSmithKline; Consulting: yes; Honoraria: yes.)

TABLE 1. *Change in seizure frequency from baseline to end of escalation*

	LTG	VPA	CBZ	PHT
Subjects	269	60	121	90
Mean baseline seizures/month (SD)	4.1 (13)	4.8 (14)	3.7 (15)	2.9 (6)
Patients with 50% seizure reduction	66%	70%	79%	72%
Patients seizure free	58%	63%	67%	64%
Mean percentage seizure reduction (SD)	0.05 (15)	1.87 (16)	1.16 (19)	+0.11 (12)[a]

[a] Patients taking PHT experienced a mean increase in seizure frequency.

2.184

UTILITY OF ADJUNCTIVE LAMOTRIGINE THERAPY FOR SEIZURE CONTROL IN A COMMUNITY NEUROLOGY SETTING

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Rationale: Lamotrigine (LTG) has been studied in clinical trials at tertiary settings enrolling highly selected patients. The utility of LTG in a broadly based neurology practice setting may be different. **Methods:** Patients with partial epilepsy aged 16 years and older entered the study either because of poor seizure control or unacceptable side effects with their current antiepileptic drug (AED) therapy. Open-label LTG (Lamictal) was titrated according to labeling to a target dose of 300–500 mg/day [100–400 mg/day for patients with an AED regimen containing valproate (VPA)], based on individualized adjustment. Seizure control was assessed using patient diaries during the last 8 weeks of the 16-week adjunctive phase. Investigators also assessed overall clinical status. **Results:** The 547 patients were enrolled (mean age, 42.7 years, 58% women, median baseline seizure frequency, two per month). Of these 547, 421 patients (77%) completed the adjunctive phase. Average daily maintenance dose of LTG was 300 mg in patients taking enzyme-inducing AEDs [e.g., phenytoin (PHT), carbamezepine (CBZ)] and 200 mg in patients taking an AED regimen containing VPA, an enzyme inhibitor. During the last eight weeks of adjunctive therapy, average seizure counts decreased 34% from baseline ($p < 0.01$). There was a 70% responder rate (≥50% reduction in seizures), and 43% were seizure free. Investigators' overall assessment noted improvement in 71% of patients. Two patients had worsening of seizures as serious adverse events leading to discontinuation. Sixty (11%) patients discontinued because of LTG adverse events, and two patients (0.4%) discontinued because of serious allergic reactions (hypersensitivity syndrome). **Conclusions:** In the community neurology setting, addition of LTG to other AEDs produces substantial reductions in seizures. (Supported by GlaxoSmithKline Research and Development.)

2.185

CLINICAL EXPERIENCE OF LEVETIRACETAM (LEV) IN REFRACTORY ADULT EPILEPSY PATIENTS

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Rationale: Levetiracetam (LEV) is a new antiepileptic drug (AED) available for treatment of epilepsy. The efficacy of LEV was assessed in a medically intractable adult epilepsy population. Specifically, we determined the percentage of responders, the magnitude of their improvement, and their optimal dose and blood-level range. We also determined the number of patients who showed no response to the drug, and the number who stopped the drug because of side effects. The reader should be able to evaluate the efficacy of LEV and understand a target dose range and blood-level range likely to be useful in treatment with LEV. **Methods:** We retrospectively reviewed 42 outpatient charts of adult patients with medically intractable epilepsy who began treatment with LEV between November 2000 and October 2001. Excluded from analysis were patients who had nonepileptic seizures or had surgery for epilepsy while taking LEV, or whose seizure counts were not reliable. Seizure type and frequency were tabulated using reports of the patient, family, or caregiver, as documented in the medical record. Seizure counts were determined for the 6 months before LEV use and compared with a minimum of 6 months after initiation. Demographics, seizure types and frequency, number of previous AEDs, number of concomitant AEDs, adverse events, dose at time of best response, and corresponding blood levels were recorded when available. Patients were identified who stopped LEV because of side effects, and the nature of their side effects was recorded. **Results:** Forty-two patients met inclusion criteria, including 23 men and 19 women (aged 18–67 years; mean, 40 years). Five (12%) discontinued LEV because of side effects: three because of behavior change; one because of gait disturbance; one because of depression. Eleven (26%) had no significant improvement and discontinued LEV. Nine (21%) had no improvement but remained with LEV. Seventeen (40%) responded to treatment: eight became seizure free; six had >75% reduction in seizures; two had >50% reduction; one had 25% reduction. Mean dose at the time of maximum efficacy in the 17 responders was 1,750 mg/day (range, 1,000–3,000 mg; median, 1,750 mg). Mean concurrent LEV blood levels (available for 12 responders) was 22 mg/ml (range, 13–42 mg/ml; median, 19 mg/ml). None to five (mean, 1.8) concomitant AEDs were used. Seizure types will be discussed. **Conclusions:** Of the 42 medically intractable adults, 38% responded to LEV with >50% reduction in seizure frequency, with eight becoming seizure free; 12% stopped LEV because of side effects. LEV appears to be a very useful drug in this intractable population.

2.186

LEVETIRACETAM REDUCES INTERICTAL SPIKE–WAVE COMPLEXES IN PATIENTS WITH IDIOPATHIC GENERALIZED EPILEPSY

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Rationale: Levetiracetam (LEV) reduces the frequency of seizures and interictal spike–wave complexes (SWCs) in patients with partial epilepsy. Although LEV has been shown to inhibit photomyoclonic responses in patients with generalized epilepsy, its effect on interictal generalized SWCs is unkown. This study reports the effect of LEV on interictal SWCs in four patients with idiopathic generalized epilepsy. At the end of this activity, the participants should be able to discuss the short-term effect of LEV on SWCs in patients with generalized epilepsy. **Methods:** Four patients with medically intractable epilepsy were admitted to Washington University's Adult Epilepsy Monitoring Unit for seizure characterization and were found to have idiopathic generalized epilepsy by ictal and interictal recordings. None of the patients had abnormalities on brain magnetic resonance imaging (MRI). Each of these patients underwent video-EEG monitoring before and after LEV administration. The incidence and duration of the SWCs, controlled for sleep stage, were analyzed qualitatively for patient 1 and quanitatively for patients 2–4. Serum levels of LEV were measured for patients 2–4. **Results:** Patient 1 had frequent SWCs before LEV and no SWCs after LEV. Patient 2 had 85 SWCs per hour before LEV and no SWCs per hour 24 h after receiving two doses of 1,500 mg LEV. Upon hospital admission, while taking LEV (1,000 mg, b.i.d.), patient 3 had zero SWCs per hour. After discontinuing LEV for seizure monitoring, patient 3 averaged 27 (range, six to 90) SWCs per hour for the 24 h before LEV administration. From 2 h after LEV (1,500 mg) administration to the end of the recording (15 h later), patient 3 had 0 SWCs per hour. In the absence of LEV, patient 4 averaged 10 SWCs per hour while awake and 35 SWCs per hour in stage II sleep. From 2 h after receiving LEV (2,000 mg) through the remainder of the recording (18 h later), patient 4 averaged 0.25 SWCs per hour in wakefulness (97% reduction, $p = 0.01$) and 12 SWCs per hour in sleep (64% reduction, $p < 0.001$). **Conclusions:** In the short term (within 24 h) after receiving LEV, LEV decreased the frequency of SWCs in four patients with idiopathic generalized epilepsy; the efficacy of LEV was dependent on sleep stage in patient 4. (Supported by an epilepsy fellowship training grant.) (Disclosure: Grant: F. Gilliam has a clinical research grant funded by UCB Pharma; Consulting: A. J. Fessler has served on the advisory board for UCB Pharma; Honoraria: H. Attarian and F. Gilliam have received honoraria from UCB Pharma.)

2.187

MULTICENTRIC RETROSPECTIVE ANALYSIS OF THE EFFICACY AND SAFETY OF TOPIRAMATE AS AN ADD-ON THERAPY ACCORDING TO THE TOPOGRAPHIC FORM OF FOCAL EPILEPSY

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Rationale: The objective of this study was to evaluate, in clinical practice, the effacy of topiramate (TPM) in partial epilepsy, considering its topographic form. Safety of TPM was also assessed (Biraben A, Genton P. *Rev Neurol (Paris)* 2000;156:993–9; Genton P, Biraben A.

Rev Neurol (Paris) 2000;156:1120–5). **Methods:** Data trom 361 patients were collected by 70 investigators in this retrospective, multicentric, open, pragmatic study. Tolerability was assessed in these 361 patients; 237 patients were treated during at least 3 months with TPM, and efficacy was evaluated in these patients considering the topographic form of the epilepsy. **Results:** TPM was titrated slowly (mean rate, 43 mg/week) and was given at a final dose of 346 mg/day. TPM was prescribed as an add-on therapy with one antiepileptic drug (AED) for 12% of patients, and 87%, with at least two other AEDs. Of patients, 52.7% were considered as responders (9.3% seizure free). Topographic form analysis showed there were responders in all topographic groups. A good response was observed in epilepsy originating from the central areas, which are ofen drug resistant (19% of seizure free, 66.6% of responders). On the safety-analysis population (n = 361), 64% of the patients reported at least one adverse event (AE), which led to treatment withdrawal in only 18.5% of the patients. AEs were mostly CNS related (somnolence, 16.1%; fatigue, 11.9%) and weight loss (14.7%; mean, 4.5 kg or 6.6% of body weight). Discontinuation of TPM was caused by AEs (13.6%), lack of efficacy (8.3%), seizure worsening (6.1%), or by a combination of these (5%). **Conclusions:** This analysis confirmed the efficacy of TPM as add-on therapy in focal epilepsy in clinical practice. TPM seems also to be efficient in all the topographic form assessed in this study, with good results in epilepsy originating from central areas. Considering a slower titration profile, we also observed a better safety profile for TPM compared to controlled studies. (Supported by Janssen-Cilag France.) (Disclosure: Salary: Philippe Bouhours, salary from Janssen-Cilag.)

2.188

CLINICAL EXPERIENCE WITH LAMOTRIGINE

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Rationale: Lamotrigine (LTG) is an antiepileptic drug (AED) approved as adjunctive treatment or monotherapy for generalized- and partial-onset seizures with or without secondary generalization. The purpose of this study was to review our clinical experience with LTG in the different epilepsies in an academic referral center. **Methods:** Patients with persistent seizures despite adequate trials of other AED(s) were started on LTG at a dose of 50 mg/day, titrating up every 2 weeks to a maximum dose of 800 mg/day, except for patients taking valproate (VPA), who were started on 25 mg/day once every other day for 2 weeks, titrated up every 2 weeks to 200–300 mg/day. These patients were retrospectively followed up for efficacy (>50% seizure reduction) and adverse effects. **Results:** Forty patients, who range in age from 18 to 78 years, were entered into the study. Seizures were classified as generalized (n = 16) and complex partial with secondary generalization (n = 24). Two patients had Lennox–Gastaut syndrome. Associated conditions included mental retardation, attention-deficit disorder, cerebral palsy, depression, history of hypoxic and traumatic brain injury, and a meningioma. Two patients had vagal nerve stimulators. All patients were taking one or two AED(s) when LTG was added. Mean duration of treatment at the last clinic visit was 7 months. Ultimately, seven patients (17.5%) remained on monotherapy. Five of these seven patients achieved 100% seizure control, one had >80% reduction in seizures, whereas one patient had to stop treatment because of a late-emerging rash . Efficacy of >50% seizure control was reported in 60% of the patients, including the two patients with Lennox–Gastaut syndrome. Rash led to discontinuation of the drug in one patient. Four patients had an increase in seizures after LTG was added, and the medication was discontinued. Two patients experienced insomnia; in one, this responded to dose reduction, and in the other to melatonin. Two patients experienced weight loss considered secondary to elimination of VPA. **Conclusions:** LTG is well tolerated in the majority of patients (87.5%) in this varied population of adults with generalized and partial-onset epilepsy. Approximately 60% had significant decrease in seizure severity and frequency. After previous exposure to multiple AED(s),17.5% of patients remain well controlled with LTG monotherapy. Improved quality of life secondary to weight loss, and elimination of tremor and menstrual irregularities were noted in those patients who could discontinue VPA.

2.189

ZONISAMIDE THERAPY IN PATIENTS WITH ABSENCE SEIZURES

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Rationale: Zonisamide (ZNS; Zonegran) is a unique antiepilepsy drug (AED) that is chemically classified as a sulfonamide. Its mechanism of action appears to be broad based and involves inhibition of voltage-sensitive sodium channels and T-type calcium channels. ZNS has been available in Japan for more than a decade and was approved in the United States in 2000 for adjunctive treatment of partial seizures in adults with epilepsy. To date, little information is available regarding the use of ZNS in patients with absence seizures. The objective of this case-review study was to assess the efficacy and safety of ZNS as adjunctive therapy in patients with absence seizures. **Methods:** Three female patients (aged 21, 11, and 51 years) with atypical or typical absence seizures had ZNS added to their current AED regimen after their current regimens failed to produce an adequate therapeutic response and/or produced adverse events. ZNS was delivered twice daily at a dosage of 600 mg/day in one patient and 400 mg/day in two patients. Efficacy was assessed by normalization of electroencephalogram (EEG) readings and/or reduction in seizure frequency. Safety was assessed by examination of adverse events. **Results:** After initiation of ZNS therapy, all patients exhibited improvement in seizure control. All patients have shown a decrease in seizure frequency, one of whom has been seizure free for 6 months. Additionally, ZNS normalized EEG readings in one patient who had abnormal readings before ZNS therapy. All three patients have been controlled with ZNS alone or in combination with other AED(s). ZNS has been well tolerated in all three patients, and no adverse events associated with ZNS have been reported. **Conclusions:** All patients in this case review demonstrated decreased seizure frequency when ZNS was added to their therapeutic regimen, and no adverse events associated with ZNS have been reported. These results suggest that adjunctive therapy with ZNS may be used to treat atypical and/or typical absence seizures that are inadequately controlled with other AEDs. It is hoped that these preliminary results will encourage further investigation of the use of ZNS in patients with absence seizures. (Disclosure: Honoraria: Elan Pharmaceuticals.)

2.190

UTILITY OF LEVETIRACETAM IN MONOTHERAPY IN PATIENTS WITH PARTIAL AND GENERALIZED EPILEPSIES

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Rationale: Levetiracetam (LEV) has been approved for use as add-on therapy for patients with partial seizures with or without secondary generalization. Preclinical studies have shown efficacy of LEV in monotherapy. We wanted to determine if LEV could be used in monotherapy in a variety of seizure types. At the end of this activity, participants should be able to appreciate off-label uses of LEV. **Methods:** Charts of all patients with epilepsy followed up at the Duke Epilepsy Center and the Neurodiagnostic Center, Durham Veterans Affairs Medical Center were reviewed, and patients taking LEV were identified. From these patients, only those using LEV as the sole antiepileptic drug (AED) were further evaluated. Patients taking other AEDs for reasons other than epilepsy were also excluded. The characteristics of the remaining patients were analyzed. **Results:** Of >300 patients taking LEV, 21 were taking it as monotherapy for epilepsy. The mean age of these 21 patients was 42.8 years (range, 16–66 years); there were 11 women and 10 men. The mean duration of follow-up was 8.7 months (range, 3–23 months). Eighteen (86%) had complex partial seizures with or without secondary generalization. Three (14%) had generalized

epilepsy, one with childhood absence epilepsy, one with juvenile myoclonic epilepsy, and one with epilepsy with grand mal seizures on awakening. The mean dose was 1,619 mg (range, 500–3,000 mg). All but three patients had been seizure free since LEV monotherapy was started. Only one patient complained of side effects of diffuse dysesthesias in the extremities and scalp. **Conclusions:** LEV is an effective AED in monotherapy in partial seizures. It may also be useful in various primary generalized epilepsies. (Supported in part by UCB Pharma.) (Disclosure: Consulting: Ortho McNeill Pharmaceuticals; Honoraria: UCB Pharma, GSK Pharmaceuticals.)

2.191

LEVETIRACETAM: RETROSPECTIVE EXPERIENCE IN PEDIATRIC PATIENTS WITH MULTIPLE SEIZURE TYPES

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Rationale: Limited published data is available regarding levetiracetam (LEV; Keppra) use in pediatric patients, and no published data are available in this population for seizure types other than partial onset, use as monotherapy, or at doses >20 mg/kg/day. The objective of the present evaluation was to examine retrospectively the outcome of LEV treatment in a group of pediatric patients, many of whom have failed one or more previous antiepileptic drug (AED) regimens. LEV has advantages for the pediatric population that include rapid onset, linear kinetics, lack of liver metabolism, lack of drug–drug interactions, lack of protein binding (<10% bound), and lack of reactive metabolites. LEV has not been shown to cause weight gain, alopecia, or increased incidence of rash. **Methods:** We reviewed data from 55 patients (age range, 7 months to 31 years; weight range, 9.5–77 kg). Most patients experienced multiple seizure types, which included generalized tonic–clonic, n = 22; complex partial, n = 23; absence, n = 12; myoclonic/juvenile myoclonic epilepsy, n = 5; tonic, n = 2; Lennox–Gastaut syndrome, n = 1; atonic, n = 1; frontal lobe, n = 1; and benign focal epilepsy of childhood, n = 1. Efficacy was evaluated on a scale of poor response to excellent response. Safety reports were collected. Descriptive statistics were performed. **Results:** The analysis included male and female children, who had a history of AED use (none, n = 5; one, n = 15; two or more, n = 35) and LEV exposure [dose: range, 375–6,000 mg/day (7.7–314.5 mg/kg/day)] either as monotherapy, n = 20 (36.4%) or adjunctive therapy [one, n = 17 (30.9%); two or more, n = 18 (32.7%)]. LEV therapy resulted in an excellent response, n = 11 (20.0%); good response, n = 7 (12.7%); some improvement, n = 7 (12.7%); poor response, n = 27 (49.1%); and uncertain effect, n = 3 (5.5%). Patient or caregiver reports regarding safety included no adverse effects, n = 32 (58.2%); aggression, n = 8; sedation, n = 3; irritability, n = 3; paresthesia, n = 1; ataxia, n = 1; depression, n = 1; rash, n = 1; diarrhea, n = 1; acne, n = 1; tremor, n = 1; nausea, n = 1; sexual self-stimulation, n = 1. **Conclusions:** We conclude that treatment with LEV was associated with outcome improvement in 45.5% of pediatric patients, most with multiple seizure types. Safety reporting was as predicted by well-controlled adult studies. LEV would appear to be a favorable treatment for pediatric patients.

2.192

EVALUATION OF LAMOTRIGINE AS ADJUNCTIVE AND MONOTHERAPY IN ELDERLY PATIENTS WITH EPILEPSY: A SUBANALYSIS OF A LARGE OBSERVATIONAL STUDY

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Rationale: With the increasing age of the general population, the number of elderly patients with epilepsy is also increasing. Management of epilepsy in this population presents unique pharmacodynamic and pharmacokinetic challenges. **Methods:** In an open-label trial, patients with epilepsy aged 16 years or older with partial-onset seizures who wanted to change their antiepileptic drug (AED) because of inadequate seizure control and/or unacceptable side effects were enrolled. Open-label lamotrigine (LTG; Lamictal) was titrated according to labeling to a target dose of 300–500 mg/day [100–400 mg/day for patients with an AED regimen containing valproate (VPA)], based on individualized adjustment. After completing a 16-week LTG adjunctive therapy phase, eligible patients who took a single enzyme-inducing AED (e.g., carbamazepine or phenytoin) began a 12-week monotherapy phase. Multiple assessments of tolerability and effectiveness were made (see Table). **Results:** Sixty-two of the 547 patients in the trial were older than 60 years (range, 60–93). Of these 62 patients, 46 (74%) and 21 (39%) completed the adjunctive and monotherapy phases, respectively. Improvements were seen in all of the following assessments. Efficacy and tolerability results from this elderly population were similar to the nonelderly patients in the overall study population. **Conclusions:** In this elderly population, LTG was well tolerated and effective as both adjunctive and monotherapy treatment and resulted in improved patient satisfaction and quality of life. (Supported by GlaxoSmithKline Research and Development.) (Disclosure: Salary: Employee of GlaxoSmithKline.)

TABLE 1. *Efficacy and tolerability results*

	Adjunctive phase	Monotherapy phase
Mean lamotrigine dose	306	413
Percentage seizure free	52	64
Liverpool AEP score[a]	–2.3	–5.7
QOLIE 31 score[b]	6.7	10.4
Investigators' overall assessment, percentage rated as improved	53	95
Percentage of patients satisfied with AED	80	86

[a] Mean change from baseline; lower score indicates improvement.
[b] Mean change from baseline; higher score indicates improvement.

2.193

RAPID DOSE ESCALATION OF LAMOTRIGINE IN PATIENTS WITH REFRACTORY SEIZURES

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Rationale: Lamotrigine (LTG) is a novel antiepileptic drug (AED) with proven efficacy against refractory complex partial seizures. A slow titration of LTG over 1 month is recommended to decrease the incidence of adverse events, notably rash. Of particular concern is the concomitant use of LTG with valproic acid (VPA), which has led to an increased incidence of rash. Unfortunately, this slow titration precludes its utility in critically ill patients requiring immediate intervention for cessation of refractory seizures. The intention of the use of this rapid dose escalation of LTG was to potentially spare the use of high-dose barbiturate therapy. The purpose of this report was to evaluate the tolerability of rapid LTG titration in patients with seizures refractory to traditional AEDs in a controlled intensive care unit setting. **Methods:** After human investigation committee approval, a search of our hospital database identified charts in which LTG was prescribed in the intensive care unit. **Results:** The median age was 60 (27–81) years with six female and three male subjects. Admission diagnosis included status epilepticus (three), ischemic stroke (two), aneurysmal subarachnoid hemorrhage (two), traumatic brain injury (one), and intracerebral hemorrhage (one). Only four of nine patients had history of seizures. All patients were receiving at least one other AED at the time LTG was prescribed (median, three; range, one to four), primarily phenytoin (PHT; eight of nine), carbamazepine (CBZ; five of nine), and VPA

(five). The initial LTG dose ranged from 25 to 100 mg/day with a median maintenance dose of 300 mg/day (range, 100–500 mg/day) per gastric tube, and this was achieved in 3 (1–4) days. All patients expressed clinical seizure activity, and four of nine displayed epileptiform activity on EEG before LTG initiation. Clinical seizure activity ceased in eight of nine patients within 1 (1–19) day of LTG initiation. Thirty-three percent of patients required supplemental doses of lorazepam (LZP; median, 2.5 mg; range, 1–4 mg) after LTG initiation. Only one patient required high-dose barbiturate therapy to gain control of the seizures. Two patients developed a rash. Of those, the rashes were thought to be due to other agents (risperidone and ampicillin/sulbactam) and not related to LTG. Both of the suspected agents were discontinued while LTG therapy was continued, with resolution of the rash. All patients were discharged to home, rehab, or nursing home taking LTG, with the exception of one patient who died. **Conclusions:** In this report, rapid escalation of LTG was well tolerated in these nine patients. LTG also appears to abate seizure activity quickly after initiation of this rapid dose titration. The use of LTG may indeed spare high-dose barbiturate therapy for refractory seizures. Further investigation of rapid dose escalation with LTG is needed in critically ill patients as an alternative for refractory seizures. The information presented should provide clinicians with the initial experience of rapidly administering LTG to critically ill patients. [Supported in part (W.M.C.) by NIH/NINDS NS 38905.]

2.194

EVALUATION OF SEIZURE CONTROL, ADVERSE EVENTS, AND QUALITY OF LIFE IN PATIENTS CONVERTING TO LAMOTRIGINE MONOTHERAPY

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Rationale: The goals of successful antiepileptic drug (AED) therapy are no seizures and no side effects. Therefore, patients with epilepsy who experience inadequate seizure control and/or intolerable side effects may want to change AED therapy. This study examined the changes in seizure control and quality of life after converting from enzyme-inducing AED [e.g., carbamazepine (CBZ), phenytoin (PHT)] to lamotrigine (LTG) monotherapy. **Methods:** In an open-label trial, epilepsy patients) aged 16 years or older with partial onset seizures who wanted to change their AED because of inadequate seizure control and/or unacceptable side effects were enrolled. Patients must have had partial seizures with or without additional seizure types. After completing a 16-week LTG (Lamictal) adjunctive therapy phase, eligible patients taking a single enzyme-inducing AED began a 12-week monotherapy phase. Patients' seizure rates and scores on the Liverpool Adverse Event Profile (AEP), POMS, and QOLIE-31 questionnaire at end of LTG monotherapy were compared to baseline (screening visit). **Results:** Of 178 patients who started the LTG monotherapy phase, a total of 143 patients (80%) completed the monotherapy phase. Median dose of LTG was 400 mg/day at the end of monotherapy phase. Compared to baseline, mean seizure frequency (3.9 vs. 1.8 per month) and seizure-free rates (24 vs. 51%) improved. After LTG monotherapy, improvement in patients' scores on the AEP were also noted (baseline score, 41.2; monotherapy score, 35.2). Total mood disturbance measured by the POMS improved during monotherapy (56.5 vs. 31.0). Patients also reported improvements in all seven QOLIE-31 subscales at the end of LTG monotherapy with the mean change from baseline in the Overall Score of 14.6. At the end of monotherapy, 85% reported moderate or high satisfaction with LTG monotherapy compared to 25% before switching to LTG. **Conclusions:** Patients converting to LTG monotherapy from a single enzyme-inducing AED for either seizure-control or tolerability issues experienced improvement in seizure control, adverse-event profile, and quality of life as measured by the QOLIE-31. (Supported by GlaxoSmithKline Research and Development.) (Disclosure: Salary: Coauthors are employees of GlaxoSmithKline; Grant: Leschek-Gelmen received a grant from GlaxoSmithKline for conduct of the study; Honoraria: Lescheek-Gelman received funding from GlaxoSmithKline and Pfizer.)

2.195

A RETROSPECTIVE STUDY EVALUATING THE EFFICACY AND SAFETY OF LONG-TERM USE OF LAMOTRIGINE

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Rationale: Since the introduction of lamotrigine (LTG) in the United States, there has not been a large retrospective study evaluating efficacy and safety after long-term use. At the end of this activity participants will be able to determine the potential role of LTG therapy in treatment of multiple epilepsy syndromes. **Methods:** We completed a retrospective analysis of 454 patients from two clinics starting from 1991, when LTG was first used in these clinics, to 2002. The 116 patients were from a community-based Epilepsy Foundation clinic, and the other 338 were from a university-based epilepsy referral clinic. The average age of the patient population was 36 years, and the range of ages was from 3 to 96 years; 24% were white, 13% were black, and 63% were Hispanic. Both primary and secondarily generalized epilepsies were included, as well as simple and complex partial seizures. The primary end points were being seizure free at 6 weeks and at 6 months. **Results:** LTG was helpful in the treatment of all types of seizures, regardless of age, sex, or race of patient, etiology of epilepsy, or length of time from diagnosis to initiation of LTG therapy; 80% of the Foundation clinic patients reported being seizure free at 6 weeks. Of the university referral clinic patients, 50% of those with complex partial seizures or secondarily generalized seizures, and 60% of those with primary generalized seizures reported being seizure free 6 weeks after initiating LTG. In all populations, the percentage that remained seizure free at 6 months was ~50% of the percentage that were seizure free at 6 weeks. The average dosage for the university referral clinic patients was 400 mg daily, and 18% were converted to monotherapy with LTG. Their average serum LTG level was 5 mg/ml; 23% of all patients discontinued LTG. Only 7% discontinued the drug because of a rash, but there were no reports of life-threatening rashes. The most common reason for discontinuing LTG was no reduction in seizure frequency. In addition, there were several pregnancies during the study period, but there were no reports of fetal malformations directly attributable to the LTG. **Conclusions:** LTG is an effective agent in the treatment of multiple epilepsy syndromes. This is true for both the economically selected patients seen in the community-based Epilepsy Foundation clinic and the refractory patients seen in the university referral clinic. LTG is, however, somewhat less effective in refractory patients that have already been receiving multiple drug therapy in the past. Its side-effect profile is equivalent to that of other AEDs currently available. (Supported by University of Miami International Center for Epilepsy.)

2.196

TOPIRAMATE: TREATMENT OF EPILEPSY IN CHILDREN YOUNGER THAN 12 YEARS

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Rationale: The objective of this trial was to evaluate the efficacy and safety of topiramate (TPM) as an add-on therapy in children younger than 12 years. **Methods:** Pooled data from 207 patients from this open, prospective, and pragmatic study have been analyzed. Effi-

cacy was assessed, according to epileptic syndromes, age, duration of epilepsy before TPM, and doses of TPM, as well as tolerability. **Results:** The mean TPM dose was 4.7 kg/mg/day, with an initial dose of 1 mg/kg/day, and slow titration at 1 mg/kg/day/2 weeks. After a median follow-up with TPM of 5.6 months (range, 0.2–30.7 months), the overall seizure frequency had significantly decreased ($p < 0.05$): seizure frequency was reduced by ≥50% in 48% (9% seizure free) of the patients without effect of the dose used, and 34% were non responders. TPM was effective in partial and generalized epilepsy, with, respectively, 50% responders among 128 patients and 44% among 79. For the last, responders were more frequent in generalized symptomatic epilepsy, severe myoclonic epilepsy, and myoclonoastatic epilepsy. For all patients, improvement was well maintained during the treatment period. Worsening of seizure frequency concerned 13% of patient with partial epilepsy and 17% with generalized. It led to withdrawal of treatment from 8% of them. The commonest reported adverse events were moderate neurobehavioral and gastrointestinal disorders. Adverse events led to withdrawal of treatment from 13.5% of patients. Children younger than 4 years had a good tolerability. **Conclusions:** These results confirm that TPM is effective and well tolerated for a broad range of childhood epilepsy before age 12 years, including refractory partial and symptomatic and myoclonic generalized epilepsy. It has to be considered for children younger than 4 years. Slow and progressive titration is important for its use. (Supported by Janssen-Cilag France.)

2.197

CONVERSION FROM IMMEDIATE- TO EXTENDED-RELEASE CARBAMAZEPINE MARKEDLY REDUCES CNS-RELATED SIDE EFFECTS IN PATIENTS WITH PARTIAL-ONSET EPILEPSY

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Rationale: The objective of this study was to determine whether extended-release carbamazepine (ER-CBZ) reduces side effects and seizures compared to therapy with immediate-release carbamazepine (IR-CBZ). Fluctuation in blood concentrations of short-acting anticonvulsants (AEDs) may increase risks for side effects during periods of peak concentrations and of seizure breakthroughs during concentration troughs. Extended-release AED formulations may potentially alleviate side effects and reduce seizures associated with daily medication fluctuations. **Methods:** We screened all patients who were treated for partial-onset seizures with IR-CBZ while under care at the Johns Hopkins adult epilepsy clinic. Patients were studied if they received IR-CBZ for a 1-year study period and then were converted to ER-CBZ. Patients were monitored for 1 year during ER-CBZ treatment or until treatment was discontinued or new AEDs were initiated. Patients were excluded if they had severe medical or psychiatric disorders, pregnancies, or received epilepsy surgery during study periods. We compared IR-CBZ and ER-CBZ treatment periods for changes in patient self-reporting of side effects and changes in seizure frequencies. **Results:** A total of 63 patients switched from IR-CBZ to ER-CBZ: 29 men and 34 women with a mean age of 39 years (range, 19–76). Daily CBZ doses for the two treatments were the same: IR-CBZ mean, 961 mg ± 397 SD; ER-CBZ mean, 989 mg ± 341 SD ($r = 0.7$, $p < 0.001$). Nineteen patients (30%) converted from IR-CBZ to ER-CBZ for dosing convenience and did not have seizures or side effects. Thirty-one patients (48%) had CNS toxicity during treatment with IR-CBZ (sedation, confusion, dizziness, ataxia, or diplopia); with ER-CBZ treatment, only 16 (25%) had these symptoms ($\chi 2 = 0.94$, $p < 0.01$). Monthly seizure frequency decreased slightly after conversion from IR-CBZ (median, 1.5 ± 0.8 SEM) to ER-CBZ (median, 1.0 ± 0.7 SEM); however, this difference was not significant (paired *t* test, $p = 0.2$). **Conclusions:** CNS-related side effects are common during treatment with IR-CBZ and are markedly reduced after conversion to ER-CBZ. Seizures are reduced only slightly in a referral epilepsy population (mean number of previous failed AEDs, 2.9) after conversion to ER-CBZ. Many patients switch from IR-CBZ to ER-CBZ for the convenient b.i.d. dosing schedule, but CNS side effects are a major source of morbidity for patients treated with AEDs and can potentially be reduced using slow-release preparations. (Supported by Shire US Inc.) (Disclosure: Grant: G. Krauss, Shire; Consulting: G. Krauss, Shire.)

2.198

SAFETY AND EFFICACY OF OXCARBAZEPINE AFTER 2 YEARS' TREATMENT IN PATIENTS WITH INADEQUATELY CONTROLLED PARTIAL-ONSET SEIZURES

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Rationale: To evaluate the 2-year long-term safety and efficacy of oxcarbazepine (OCBZ) in patients with inadequately controlled partial-onset seizures who had completed a double-blind, dose-controlled study. **Methods:** During the randomized, double-blind portion of the study, patients who experienced two to 40 partial-onset seizures during the Baseline Phase while taking one to two antiepileptic drugs (AEDs) were randomized to 300 or 2,400 mg/day OCBZ, and their background AEDs were discontinued. Patients completed the study by receiving 126 days of double-blind treatment or by meeting one or more predefined exit criteria. Eligible patients for the open-label extension entered an 8-day Blinded-Conversion Period in which patients randomized to 300 mg/day had their dose titrated to 2,400 mg/day, while patients randomized to 2,400 mg/day continued on this dose of OCBZ. Thereafter, the OCBZ dose was individualized to provide optimal seizure control with acceptable tolerability. The maximum allowable dose was 3,000 mg/day, except with monitor approval. Concomitant AEDs were allowed during the Open-label Extension Phase. We report the 2-year safety and efficacy results. The efficacy results were obtained by comparing the seizure frequency during the open-label extension to the prospective Baseline phase that preceded the core trial. **Results:** Of the 77 patients (42% men, 58% women) who were enrolled in the long-term Open-label Extension Phase, 35 completed 2 years of therapy. The reasons for exiting were unsatisfactory seizure control (26%), adverse events (18%), and other (10%). Overall, 47% of patients receiving OCBZ experienced a ≥50% reduction in seizure frequency, and 7% remained seizure free throughout the 104 weeks of open-label therapy. Compared to baseline, 58% of the patients receiving OCBZ as monotherapy were responders, and 11% were seizure free. In contrast, 37% of patients receiving OCBZ as adjunctive therapy were responders, and 3% were seizure free. The most common adverse events were dizziness (46%), headache (32%), fatigue (30%), diplopia (30%), nausea (26%), abnormal vision (21%), and somnolence (21%). Overall, the adverse events were mild and transient. **Conclusions:** The results indicate that OCBZ maintains its safety and efficacy as monotherapy and adjunctive therapy during long-term treatment of patients with partial seizures. (Supported by Novartis Pharmaceuticals.) (Disclosure: Salary: Dsouza, Novartis Pharmaceuticals; Grant: Beydoun, Sachdeo, Novartis Pharmaceuticals; Consulting: Beydoun, Sachdeo, Novartis Pharmaceuticals; Honoraria: Beydoun, Sachdeo, Novartis Pharmaceuticals.)

2.199

CLINICAL EXPERIENCE WITH LEVETIRACETAM: A PROSPECTIVE OBSERVATIONAL STUDY

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Rationale: Levetiracetam (LEV), the S-enantiomer of the ethyl analogue of piracetam, is a novel antiepileptic drug (AED) that has been licensed in the U.K. as add-on therapy in patients with partial and/or secondarily generalised seizures since January 2001. The objectives of this study were to explore its efficacy and tolerability as adjunctive treatment in everyday clinical practice. **Methods:** LEV was added to the existing regimen in patients with difficult-to-control epilepsy of any seizure type. The major efficacy end points were seizure freedom for 6

months on an unchanged dose of LEV, >50% reduction in seizure frequency compared to a 3-month prospective baseline period (responder) at optimal dosage, or discontinuation due to adverse effects, lack of efficacy, or both. **Results:** To date, 132 patients have been recruited with 77 having reached an end point. Of these, 23 were seizure free, and 16 could be classed as responders. Overall, 34 patients had LEV discontinued within the first few months of initiation of therapy (19 side effects, 12 lack of efficacy, three worsening of seizures). Of the 19 patients reporting intolerable side effects, 14 complained of sedation. Eighteen of 38 patients with learining disability reached an end point, six of whom were seizure free, and a further six had >50% seizure reduction. Analysis by seizure types and concomitant AEDs will be discussed, and the daily LEV doses and serum concentrations will be correlated with outcome. **Conclusions:** LEV is efficacious adjunctive treatment in clinical practice with a significant number of patients experiencing remission of ≥6 months. Sedation was the commonest reason for discontinuation. (Supported by an unrestricted grant from UCB Pharma.) (Disclosure: Grant: Unrestricted grant from UCB Pharma; Consulting: UCB Pharma; Honoraria: UCB Pharma.)

2.200

FINAL RESULTS FROM THE K.E.E.P.E.R. TRIAL: A PHASE IV COMMUNITY-BASED CLINICAL TRIAL INVESTIGATING LEVETIRACETAM AS ADD-ON THERAPY IN PARTIAL-ONSET SEIZURES

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Rationale: The Keppra (levetiracetam, LEV) K.E.E.P.E.R. Study is a Phase IV, prospective, open-label clinical trial designed to investigate the safety and efficacy of LEV as add-on therapy in adult patients with partial seizures treated in a community-based neurology practice setting. We now present the final results from this study. **Methods:** Patients enrolled in this 16-week, five-visit study were to have had between three and 42 partial seizures over the 3 months before study entry. Patients had to have been taking at least one, but no more than two concomitant AEDs at study entry, and these were to have been stable for ≥4 weeks before the first visit. Patients were to have completed seizure diaries throughout the course of the study. Patient demographics, responder rate (≥50% reduction from baseline seizure frequency), partial seizure freedom, incidence of adverse events, and Global Evaluation Scale (GES) assessment (an investigator-completed clinical impression rating) were calculated and reported. **Results:** For the 1,030 patients included in the intention-to-treat (ITT) analysis, the mean age at study entry was 42.2 years; race was predominantly white (77.8%), with more female (54.6%) than male subjects (44.7%). The mean monthly baseline seizure frequency was 5.0 (range, 0.0–46.4). There were 747 (72.5%) patients who completed the study; 12.9% of patients discontinued because of adverse events. Overall, there was a 57.9% responder rate, a 62.3% median percentage reduction in partial seizures, and 20% of patients achieved complete partial seizure freedom. During the final 6 weeks of treatment, the responder rate was 66.7%, and 42.1% of patients achieved complete partial seizure freedom. The overall profile of adverse events is similar to that seen in the LEV clinical development program. The most frequently reported adverse events were somnolence, dizziness, asthenia, and headache. Adverse events categorized as behavior related were reported at a rate lower than that seen in the LEV clinical development program. The investigator-reported GES data indicated that 74.3% of patients had an overall clinical improvement from their baseline status. Of these patients, 26.0% showed moderate improvement (second highest rating), and 37.0% showed marked improvement (highest rating). **Conclusions:** These results suggest that in a community setting, the safety profile of LEV is similar to that seen in the clinical development program, with no new adverse findings. These results also suggest a greater degree of efficacy when LEV is used in this setting, perhaps reflecting a more "typical" epilepsy patient than those enrolled in Phase III trials. (Supported by UCB Pharma, Inc.) (Disclosure: Salary: L. Magnus and A. Herbeuval are employed by UCB Pharma, Inc.; Honoraria: M. Morrell, J. Ferrendelli, J. French, and I. Leppik receive honoraria for speaking from UCB and other pharmaceutical companies.)

2.201

CLINICAL EXPERIENCE WITH LEVETIRACETAM (LAMICTAL) IN PEDIATRIC POPULATION

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Rationale: Epilepsy is a common neurologic disorder affecting almost 0.5–1% of the population. Nearly 30% of patients with epilepsy are refractory to currently available drugs. Lamotrigine (LTG) is one of the newer antiepileptic drugs (AEDs) that is extensively studied in Europe and United States. It has better tolerability and a wider spectrum than most. This study serves to establish the usefulness of LTG in the pediatric population of an academic referral center. **Methods:** An observational study was conducted with 35 children (23 girls, 12 boys) between the ages of 3 and 21, given LTG as either monotherapy or add-on therapy between the period of April 2000 to April 2002 with a mean duration of 8 months. Parameters followed were efficacy, length of treatment, side effects, and the type of seizure. Initial dosing was as low as 2 mg every other day in younger patients taking VPA with titaration ≤400 mg/day in older patients. **Results:** A total of 35 patients were observed, 10 (28.5%) were discontinued from the study, five (14.2%) for lack of efficacy, and five (14.2%) for side effects. Eight of the 35 patients developed side effects (22.8%): a rash in four, lethargy in three [all were also taking carbamazepine (CBZ)], and panic attacks in one patient. It was possible to restart the drug in three of the eight after adjusting the dose. One of the patients who had a rash was rechallenged at a slower titration and tolerated the medication well. In the 25 patients who tolerated LTG, seizures were classified as generalized (n = 15), partial with or without secondary generalization (n = 12), BECTS (n = 2), Lennox–Gastaut syndrome (n = 2), and absence epilepsy (AE; n = 4). Associated disorders were present in the majority and included mental retardation, cerebral palsy, autism, traumatic and anoxic brain injury, and brain tumors. LTG was used as monotherapy in four of 25 (16%). All had primary generalized seizures and experienced complete control. It was used as add-on therapy in 21 of 25 (84%); 14 of 25 (56%) showed >50% improvement in the seizure control, especially when combined with PHT for partial seizures. The remaining eight of 25 (22.8%) showed <50% improvement. In this study LTG was more effective in generalized onset epilepsy than in partial. Three of the four patients who has AE were seizure free for >1 year. Three of these patients were switched from valproate either because of side effects (weight gain, hair loss), or lack of efficacy. **Conclusions:** Our study adds to the positive clinical experience with LTG in terms of efficacy as a broad-spectrum AED with a very good side-effect profile. It indicates also that it is effective as monotherapy, especially when used in AE. However, the sample size was small, and further double-blinded, randomized studies needed especially in the primary generalized epilepsies.

2.202

LAMOTRIGINE AS ADJUNCTIVE THERAPY IMPROVES TOLERABILITY, PATIENT SATISFACTION, AND QUALITY OF LIFE IN A COMMUNITY NEUROLOGY SETTING

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Rationale: Lamotrigine (LTG) has been studied in clinical trials at tertiary settings enrolling highly selected patients. The utility of LTG in a broader-based neurology practice setting may be different. **Methods:** Patients with partial epilepsy aged 16 years and older entered the study

either because of poor seizure control or unacceptable side effects with their current antiepileptic drug (AED) therapy. Open-label LTG (Lamictal) was titrated according to labeling to an adjunctive therapy target dose of 300–500 mg/day [100–400 mg/day for patients on an AED regimen containing valproate (VPA)], based on individualized adjustment. Investigators completed subjective assessments in seven domains and a global assessment, and patients completed the QOLIE-31 (quality of life inventory); the POMS mood profile; a self-rated measure of satisfaction; and the Liverpool Adverse Event Profile (AEP), a measure of anticonvulsant tolerability. **Results:** 547 patients were enrolled (mean age, 42.7 years; 58% women, median baseline seizure frequency, two per month). Of these 547, 421 patients (77%) completed the adjunctive phase. Concomitant AEDs were primarily carbamazepine (CBZ; 38%), phenytoin (PHT; 35%), and VPA (25%). After 16 weeks of adjunctive therapy, investigator assessment improved in every tested category ($p < 0.01$); self-scored patient satisfaction improved ($p < 0.01$); the POMS mood instrument showed improvements on every subscale ($p < 0.01$); the AEP survey on showed improvement in every subscale ($p < 0.05$) except disturbed sleep; and quality of life improved on every subscale of the QOLIE-31and overall ($p < 0.01$). Sixty (11%) patients discontinued because of LTG-related adverse events, and there were two (0.4%) serious allergic reactions (hypersensitivity syndrome) reported. **Conclusions:** In the community neurology setting, the addition of LTG to other commonly used AEDs produces substantial improvement in global investigator assessments, mood, medication tolerability, and quality of life. (Supported by GlaxoSmithKline Research and Development.)

2.203
ZONISAMIDE MONOTHERAPY USE IN A MULTIGROUP CLINIC

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Rationale: Extended clinical experience with zonisamide (ZNS) monotherapy has been very limited and usually restricted to tertiary referral centers. We report our experience in patients, with follow-up to 1 year, who presented for consultation to the neurology department of a large multigroup clinic. **Methods:** We reviewed the charts of patients given ZNS as monotherapy at the Kelsey-Seybold Clinic, Houston, Texas, from April 2001 to April 2002. **Results:** Group 1 with patients naive to antiepileptic drugs (AEDs; seven with primary generalized seizures, seven with partial seizures) had treatment initiated with ZNS; 12 continue to take the agent (follow-up, 2–11months). Two patients required change of treatment because of untoward effects or seizures. Daily dosage ranged from 50 to 200 mg/day in the seven female and seven male patients, aged from 12 to 56 years. Twelve patients remain seizure free, three with follow-up of >6 months. Group 2, with 33 patients, had treatment changed to ZNS monotherapy from another agent; 15 had partial, and 18 had generalized seizures. Doses ranged from 50 to 300 mg/day; 22 patients remained on monotherapy (follow-up, 1–12 months). Six patients required a second agent for seizure control; three changed to a different AED because of an untoward effect (one), to lose weight (one), seizure recurrence (one). Two patients discontinued ZNS against medical advice. Eleven patients have remained seizure free for >6 months, and one has remained seizure free for >1 year. **Conclusions:** We conclude that ZNS is effective and tolerated in a large percentage of patients with multiple seizure types. The dosage range in patients with monotherapy appears lower than in reported doses required in add-on studies. (Supported by Bob and Vivian Smith Foundation.)

2.204
CLINICAL EXPERIENCE WITH TOPIRAMATE

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Rationale: Topiramate (TPM) is a broad-spectrum antiepileptic drug (AED) with a multiple mechanism of action. It is approved for use in the United States as adjunctive therapy in adults and children from age 2 years with partial-onset seizures or generalized-onset seizures. The purpose of this study was to review our recent clinical experience with TPM in an academic referral center. **Methods:** A retrospective review of the patients treated with TPM at Stony Brook University Epilepsy Management Program was carried out between April 2000 and April 2002. There were 45 patients, 28 children (16 and younger) and 17 adults. These patients were taking one or two AEDs when TPM was started. Information was obtained in regard to efficacy, tolerability, and duration of treatment. **Results:** There were 28 children (3 months to 15 years) with seizures classified as generalized onset ($n = 8$) and partial in onset with secondary generalization ($n = 20$). Associated disorders were present in the majority and included mental retardation, attention-deficit disorder, cerebral palsy, hydrocephalus, and tic disorder. Efficacy of >50% seizure reduction was found in 16 of 28 (57%) of these patients, three of whom are seizure free. Seventeen adults (aged 17–66 years) were treated. Efficacy of >50% seizure reduction was found in seven of 17 (41%) of these patients. An additional two patients had no further seizures, but only experienced auras after TPM was started. Two patients remained seizure free for the duration of the study. TPM was discontinued in six patients (13%) for lack of efficacy and in three for side effects. The most common reported side effect was lethargy ($n = 14$, 31%). Mean duration of treatment with and without discontinuation of TMP as of April 2002 was 6.5 months. An obese patient experienced a 35-lb weight loss after taking TMP for 4 months. She continues to be seizure free with monotherapy. No patients experienced problems with renal calculi or glaucoma. **Conclusions:** TPA provided improved seizure control in 41% of the adults and in a higher percentage of the children (57%). It was generally well tolerated, with few patients discontinuing because of side effects. Weight loss was a desirable side effect for a few obese patients.

2.205
A COMPARISON OF LAMOTRIGINE AND TOPIRAMATE IN JUVENILE MYOCLONIC EPILEPSY

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Rationale: Although lamotrigine (LTG) and topiramate (TPM) are Food and Drug Administration approved only for partial epilepsy, these two drugs are also used in juvenile myoclonic epilepsy (JME) patients. LTG results in 70– 80% seizure-free rate in JME, but little is known about its tolerability. The tolerability and efficacy of TPM in the treatment of JME is unknown. We compared the efficacy of LTG and TPM in different seizure types and evaluated their tolerability in the treatment of JME. At the end of this activity the participants should be able to understand advantages and disadvantages of LTG and TPM therapies in JME. **Methods:** Charts of JME patients treated with LTG and TPM were evaluated for control of different seizure types. Forty-eight patients received LTG and/or TPM. Age of patients ranged between 19 and 50 years. Fifteen patients were men, and 33 were women. The criteria for classification of seizure control were as follows: GTC: good (<1/year), moderate (1–4/year), poor (>4/year); myoclonic (Mcl): good (<5/month, rare or occasional), moderate (5–14/month or few), poor (>15/month or daily); absence: (<5/month, rare or occasional), moderate (5–14/month or few), poor (>15/month or daily). **Results:** Data are given in the Table; 62% of LTG- and 78% of TPM-treated patients received polytherapy. LTG and TPM did not differ significantly in GTC and Mcl seizure control; however, the control of Mcl seizure was suboptimal with both drugs. LTG was also effective in controlling absence seizures. The number of patients treated with TPM for absence seizures was inadequate. Seizure control did not differ when patients receiving LTG monotherapy were compared with patients receiving LTG polytherapy (data not included in Table 1). A similar comparison was not possible for TPM-treated patients because of inadequate numbers. The relative risk of discontinuation from the TPM therapy was twice compared with LTG therapy ($p = 0.035$). For both LTG and TPM, nearly two thirds of the patients were discontinued from the

therapies because of side effects and the remaining one third for inefficacy. **Conclusions:** LTG is effective in JME patients as monotherapy and polytherapy, whereas TPM is effective as polytherapy. Seizure control did not differ when patients receiving LTG monotherapy were compared with patients receiving LTG polytherapy. This finding suggests that LTG monotherapy may be as good as polytherapy; however, this conclusion may not be definitive because the patient selection was not randomized. The withdrawal rates for the drugs were 57 and 29%, respectively. More effective therapy is needed to improve the control of Mcl seizures. (Disclosure: Grant: Ortho McNeill and Glaxo Wellcome; Consulting: Ortho McNeill; Honoraria: Ortho McNeill and Glaxo Wellcome.)

TABLE 1. *Antiepileptic drugs, number of patients, number of patient-years, and seizure control*

Drugs	No. of pts. (pt yr)	GTC (%)	Myoclonic (%)	Absence (%)	Pt. withdrawal (%)
LTG	42 (103)				12 (29)
Good		15/19 (79)	17/29 (59)	6/10 (60)	
Moderate		2/19 (11)	3/29 (10)	3/10 (30)	
TPM	23 (38)				13 (57)
Good		8/10 (80)	7/14 (50)	0/2 (0)	
Moderate		0/10 (0)	3/14 (21)	½ (50)	

2.206
LONG-TERM EFFICACY AND TOLERABILITY OF LEVETIRACETAM IN 103 PATIENTS WITH PARTIAL AND GENERALIZED EPILEPSY
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Rationale: Levetiracetam (LEV) is approved as adjunctive therapy for partial seizures; however, animal studies suggest that LEV may also be effective in generalized seizures. Some human studies found that LEV may be effective in generalized epilepsy , but others were inconclusive. LEV is well tolerated; however, in some patients, somnolence in the first 4 weeks of treatment may lead to reduction or discontinuation of LEV. We report 103 patients with partial and generalized epilepsy treated with LEV using slow titration, and followed up closely for almost 2 years, to determine long-term efficacy and tolerability. **Methods:** One hundred three patients with refractory epilepsy were treated with LEV; the patients were not selected based on seizure type. The age at seizure onset ranged from 1 to 35 years, and the age at the time of treatment with LEV ranged from 9 to 53 years; 92 of 103 (89%) had partial seizures, and 11 of 103 (11%) had generalized seizures. All patients have tried at least two or three AEDs (antiepileptic drugs). In most patients, LEV was added starting with 250 mg b.i.d., and increased by 250 mg every 1 or 2 weeks. In two patients with epilepsia partialis continua, LEV was titrated faster in the epilepsy monitoring unit. The average dose was 2,000 mg/day, and the maximun dose was 4,000 mg/day. Seven patients were converted to monotherapy, and several others are currently being converted. Patients were followed up in the clinic at 3- and 6-month intervals (longest follow-up almost 2 years), and response and side effects were recorded. **Results:** The responder rate (>50% seizure reduction) for the 103 patients was 47%. As many as 17% (18 of 103) of these patients became seizure free (longest follow-up almost 2 years). 9.7% (10 of 103) of the patients discontinued LEV because of lack of efficacy or poor tolerability; however, only 3.8% (four of 103) of the patients discontinued LEV because of significant behavioral disturbances (aggression, depression, hostility). In the remaining patients, LEV was well tolerated including several patients who had continued to have seizures after epilepsy surgery and became seizure free when LEV was added; some patients remained seizure free even when converted to monotherapy. LEV was also particularly helpful in those patients with refractory epilepsy due to brain tumors because of the lack of pharmacokinetic interactions with chemotherapy agents. **Conclusions:** LEV demonstrated a broad spectrum of action in both children and adults with partial and generalized epilepsy. Our study showed that LEV can be effective as monotherapy, and that slow titration improves tolerability.

2.207
MYOCLONIC AND ATONIC SEIZURES: RESPONSE TO ZONISAMIDE IN PEDIATRIC PATIENTS
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Rationale: Zonisamide (ZNS; Zonegran) is a broad-spectrum antiepilepsy drug (AED) that has been available in Japan since 1989 and was approved in the United States in March 2000 for the adjunctive treatment of partial seizures in adults. The objective of this study was to evaluate the efficacy and safety of ZNS in children with atonic and/or myoclonic seizures. **Methods:** This retrospective chart review evaluated 11 pediatric patients with atonic and/or myoclonic seizures receiving ZNS. Efficacy of ZNS was assessed via reduction in the frequency of atonic and myoclonic seizures. Safety was evaluated by reports of adverse events. **Results:** Mean patient age was 5.5 years (range, 2–13 years). Mean age at seizure onset was 1.0 year (range, birth to 4 years). Six patients (54.5%) had myoclonic seizures, four patients (36.4%) had atonic seizures, and one patient (9.1%) experienced both atonic and myoclonic seizures. Eight patients (72.7%) had other seizure types in addition to atonic/myoclonic seizures. All patients had been previously treated with at least three AEDs, and the number of current AEDs (in addition to ZNS) ranged from one to two. Mean ZNS dosage was 372.7 mg/day (range, 200–600 mg/day) or 21.5 mg/kg per day (range, 12.5–35 mg/kg per day). Of those with myoclonic seizures, one patient was seizure free for a period of 10 months after having experienced daily seizures refractory to trials of at least five other AEDs; two patients had >50% improvement; and three patients had no change in seizure frequency after receiving ZNS. Of those with atonic seizures, one patient was seizure free for a period of 5 months. This patient with Lennox–Gastaut syndrome had previously experienced daily seizures and had failed trials of at least six AEDs. Two patients had slight improvement, and one patient had no change in seizure frequency after receiving ZNS. The patient with both myoclonic and atonic seizures had >50% improvement in seizure control while taking ZNS. Four patients experienced adverse events, which included drowsiness (n = 1), vomiting/diarrhea (n = 1), decreased appetite (n = 1), and increased phenytoin (PHT) levels (n = 1) in a patient who was concurrently receiving PHT. **Conclusions:** The majority of patients in this chart review experienced slight improvement or better seizure control while taking ZNS. ZNS was also safe and well tolerated in this group of pediatric patients. Further studies are warranted to investigate the use of ZNS for treating myoclonic and atonic seizures in pediatric patients.

2.208
TOLERABILITY OF RAPID ZONISAMIDE TITRATION IN HOSPITAL SETTING
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Rationale: It is sometimes better to introduce new antiepileptic drugs (AEDs), in a limited time frame utilizing rapid titration while patients are hospitalized, thereby obtaining better seizure control and limiting adverse events (AEs). Zonisamide (ZNS), a new AED, is used in this study. The objective is to better understand the rapid titration within a hospital setting for patients treated with ZNS. **Methods:** Fifty-five adult patients with medically intractable epilepsy, aged 20–91 years (average age, 43.5 years; 24 men, 31 women), were admitted to the hospital for the addition of ZNS to obtain better seizure control. The titration schedule was individualized for each patient based on his or her tolerability for the drug, Aes, and seizure control. ZNS was started at 100 mg/day on day 1 of the titration. Days to complete titration

ranged from 1 to 9 days, with the average being 5.8 days. Maximum ZNS doses ranged from 100 to 700 mg/day; average, 350 mg/day. Patients were taking from one to four other AEDs. Five patients were taking one (AED) (9%), 27 taking two (AEDs) (49%), 16 taking three (AEDs) (29%), and four were taking four (AEDs) (13%). Inpatient ZNS blood levels were available on 28 patients, with the average level being 11.7 μg/ml. **Results:** Of the 55 patients started on ZNS while in the hospital, only three (6%) were discontinued before discharge: one for a noticeable increase in seizure activity, one for confusion, and one for a decreased spontaneity and sleepiness. Nine patients (16%) discontinued ZNS before or at the first clinic visit. Normal time frame for first clinic visit after hospitalization was 6–8 weeks. Reasons for discontinuation were two patients with noticeable increase in seizure activity, two with tinnitus, two with no noticeable improvement in seizures, one with active EEG and incontinence, and one with incontinence, vomiting, mood swings, and appetite fluctuations. The last patient switched back to her previous AEDs 1 week after hospital discharge. Twenty-one of the 55 patients (38%) had a ≥50% reduction in seizures including six patients who were seizure free. Nine patients (16%) had improved seizure control, and six (11%) had no change. Seven (13%) had a decrease in seizure control including two patients who were noncompliant with their medications, and one who needed a replacement of the vagus nerve stimulator. Thirty-six patients had blood levels measured by their first clinic visit. The average level was 21.9 μg/ml, which reflects the average dose of 386 mg of ZNS. **Conclusions:** A rapid titration of ZNS in the hospital environment can be achieved safely with minimal adverse effects along with the expectation of significantly improved seizure control.

2.209

TWO-YEAR, LONG-TERM, OPEN-LABEL EXTENSION STUDY OF EFFICACY AND SAFETY OF OXCARBAZEPINE IN PATIENTS WITH UNCONTROLLED PARTIAL-ONSET SEIZURES

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Rationale: To evaluate the 2-year long-term safety and efficacy of oxcarbazepine (OCBZ) in presurgical patients with uncontrolled partial-onset seizures who had completed a double-blind, placebo-controlled phase. **Methods:** In this randomized, double-blind, placebo-controlled, parallel-group trial, all antiepileptic drugs (AEDs) were discontinued ≥48 h before randomization, except lorazepam (LZP) ≤8 mg/day to maintain seizure frequency in a safe range. Patients (aged 11–62 years) were randomized to receive either OCBZ, 2,400 mg/day, or placebo for the 10-day double-blind phase. Patients exited the study by completing the 10-day double-blind phase or by experiencing four partial seizures, two new-onset secondarily generalized seizures, serial seizures, or status epilepticus. After exiting from the double-blind phase, patients were eligible to enter an open-label extension phase. During the open-label extension phase, patients received 1,500 mg/day for 1 day. Thereafter, the dose was adjusted for each patient to provide the lowest dose that provided seizure control with acceptable tolerability. The maximum allowable dose was 3,000 mg/day, except with monitor approval. Concomitant AEDs were allowed during the open-label extension Phase. We report the 2-year safety and efficacy results. **Results:** A total of 97 patients (54% male, 46% female subjects) with a mean age of 33 years entered the open-label extension phase; 43 completed 2 years of open-label therapy. The reasons for exiting were unsatisfactory seizure control (30%), adverse events (17%), and other (9%). Compared to baseline, 94% (n = 91) of the patients receiving OCBZ experienced a >50% reduction in seizure frequency, and 5% (n = 5) remained seizure free during the 2-year open-label extension phase. These were the same five patients that were seizure free at 1 year. Throughout the 2-year period, the most common adverse events (incidence, >20%) reported were headache (61%), dizziness (58%), diplopia (45%), fatigue (41%), nausea (36%), vomiting (27%), somnolence (24%), viral infection (22%), and abnormal vision (21%). Overall, the adverse events were mild and transient. **Conclusions:** The results indicate that OCBZ maintains its efficacy during long-term management of patients with partial seizures. (Supported by Novartis Pharmaceuticals.) (Disclosure: Salary: D'Souza, Novartis Pharmaceuticals; Grant: Schachter, Vazquez, Novartis Pharmaceuticals; Consulting: Schachter, Vazquez, Novartis Pharmaceuticals; Honoraria: Schachter, Vazquez, Novartis Pharmaceuticals.)

2.210

EFFICACY AND TOLERABILITY OF TOPIRAMATE ADD-ON ≤200 MG/DAY COMPARED WITH HIGHER DOSES

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Rationale: Initial double-blind placebo-controlled trials of topiramate (TPM) in adult patients with refractory epilepsy evaluated dosages of 400–1,000 mg/day. Recent data and postmarketing experience suggest that ≤200 mg/day add-on is an effective and well-tolerated dose. In this observational study, the efficacy and tolerability of TPM add-on was evaluated in patients with epilepsy, allowing flexible dosing. We report the results of patients receiving ≤200 mg TPM/day compared to those with higher doses. **Methods:** In this prospective multicenter observational study, patients aged 16 years or older were evaluated at baseline and 4, 8, 12, and 26 weeks thereafter. Seizure frequency and adverse events (AEs) were assessed at every visit. Dosages of TPM and concomitant antiepileptic drugs (AEDs) could be adjusted according to patient response. **Results:** The 574 patients (54% male, mean age 39 ± 13 years; median time since diagnosis, 13 years; >80% partial epilepsy) completed the 26-week observational period: 282 received ≤200 mg (mean dose, 160 ± 52 mg/day, group [A]), and 292, >200 mg TPM/day (mean dose, 380 ± 110 mg/day, group [B]). Both groups were comparable in demographics and epilepsy history. Baseline seizure frequency was four per month in [A] and six per month in [B] ($p < 0.001$). At end point, median seizure reduction was 80% [A] and 67% [B] ($p < 0.0001$ vs. baseline each, $p = 0.005$ between groups). Responder rates (≥50% reduction in seizure frequency) were 71.3 and 68.9%, with 25.6% of the patients in [A] and 9.8% in [B] remaining seizure free for ≥3 months ($p < 0.001$). Interestingly, there was no significant difference in total AEs (27.0% [A] and 27.1% [B]). AEs reported by ≥5% of the patients were somnolence (8.2 and 5.8%), dizziness (5.1 and 5.0%), and weight loss (6.4 and 4.8%) for groups A and B, respectively. Mean weight reduction at 6 months was similar in both groups (2.0 ± 4.4 kg [A] and 1.6 ± 4.6 kg [B], NS). **Conclusions:** In this large patient population, TPM add-on showed significant efficacy in dosages both ≤200 and >200 mg/day. Individual dosing of TPM and adjustment of concomitant AEDs in this study seems to contribute to the good tolerability and to the fact that we did not observe significant differences in tolerability with higher doses of TPM as add-on therapy. (Supported by Janssen-Cilag Germany.) (Disclosure: Salary: Andreas Schreiner is a full-time employee of Janssen-Cilag Germany.)

2.211

ZONISAMIDE THERAPY IN FRONTAL LOBE OR PROGRESSIVE MYOCLONIC EPILEPSY

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Rationale: Zonisamide (ZNS; Zonegran) is a novel antiepilepsy drug (AED) approved for use in the United States as adjunctive treatment of partial seizures in adults with epilepsy. ZNS antiseizure properties appear to stem from its ability to block both sodium and T-type calcium channels. ZNS broad spectrum suggests that it may be effective against multiple seizure types. However, little information exists to date regarding the use of ZNS in patients with frontal lobe or progressive myoclonic epilepsy. The objective of this study was to assess the efficacy of ZNS in patients with frontal lobe or progressive myoclonic epilepsy. **Methods:** In this case review, nine patients (four male and

five female subjects) with frontal lobe or progressive myoclonic epilepsy were placed given ZNS therapy after failing to adequately respond to other AEDs. The patients ranged in age from 5 to 50 years (mean, 26 years). ZNS was used as adjunctive therapy and administered either once (n = 1) or twice (n = 8) daily in dosages ranging from 300 to 500 mg/day (mean, 422 mg/day). Efficacy was assessed via reduction in seizure frequency, type, and duration after initiation of ZNS treatment. **Results:** Multiple seizure types were observed in this small group of patients, and none of the patients experienced adequate seizure control with previously administered AEDs. Several patients had failed treatment with newer AEDs; one child failed treatment with a ketogenic diet, and a vagus nerve stimulator was tried without success in another pediatric patient. All patients experienced a decrease in seizure frequency after initiation of ZNS treatment. One 50-year-old man with a brain tumor and focal seizures with rapid secondary generalization experienced no further seizures after beginning ZNS treatment. Improvements in alertness, social interaction, cognition, and behavior were noted in some pediatric patients after beginning ZNS treatment. **Conclusions:** All nine patients in this study demonstrated improvement in seizure frequency when ZNS was added to their therapeutic regimen. These results suggest that ZNS may be effective against a variety of seizure types experienced in patients with frontal lobe or progressive myoclonic epilepsy. These preliminary findings warrant further investigation of ZNS in these patient populations. (Disclosure: Consulting: Elan Pharmaceuticals, UCB, Abbott Laboratories, Ortho-McNeil, GlaxoSmithKline; Honoraria: Elan Pharmaceuticals, UCB, Abbott Laboratories, Ortho-McNeil, GlaxoSmithKline.)

2.212

CLINICAL AND ELECTROENCEPHALOGRAM IMPROVEMENTS IN PEDIATRIC PATIENTS TREATED WITH ZONISAMIDE

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Rationale: Zonisamide (ZNS; Zonegran) is a novel antiepilepsy drug (AED) approved in the United States for adjunctive treatment of partial seizures in adults with epilepsy. The objective of this report is to present information regarding clinical and electroencephalogram (EEG) improvements in two pediatric patients treated with ZNS. **Methods:** Patient 1 (9-year-old boy) displayed intractable partial and secondarily generalized tonic–clonic seizures of left frontal lobe origin secondary to a low-grade astrocytoma. EEG showed bifrontal spikes (left>right) and secondarily generalized spike and polyspike and wave discharges. A partial left frontal lobectomy was performed (October 2000) with removal of the astrocytoma. Despite initial improvement, 4 weeks after surgery, he had multiple seizures per hour, characterized by staring, automatisms, and head and body drops. EEG confirmed numerous seizures of left frontal lobe origin, as well as interictal bifrontal spikes and secondarily generalized spike–wave bursts. His AEDs included divalproex sodium (DVPX), topiramate (TPM), levetiracetam (LEV), and phenytoin (PHT). ZNS was added (100 mg/day). All other AEDs were discontinued, except DVPX (1,500 mg/day). Patient 2 (10-year-old boy) was followed up for Landau–Kleffner syndrome (onset at age 2 years). He had previously been treated with steroids and DVPX, with good clinical and EEG response. At age 8.5 years when taking DVPX alone, he developed relatively rapid language and behavioral regression. A 24-h EEG showed a recurrence of epileptiform abnormalities characterized by almost continuous left temporal and central spikes. Magnetoencephalography (MEG) showed additional right-sided epileptiform discharges, ruling out surgical treatment with subpial transection. He also developed episodes of staring and confusion suggestive of complex partial seizures. ZNS was initiated at 100 mg/day and titrated to 300 mg/day. TPM was rapidly weaned, and DVPX therapy continued (375 mg/day). **Results:** Patient 1 had complete cessation of seizures 2 days after starting ZNS and has remained seizure free with the combination of ZNS (100 mg/day) and DVPX (500 mg, b.i.d.). Repeated EEG after 8 months showed mid bifrontal slowing (left>right), with no epileptiform activity. Patient 2 had marked improvement in speech and language within 1 month of beginning ZNS and DVPX. Episodes suggestive of complex partial seizures subsided. EEG after 4 months of ZNS and DVPX therapy was normal, with no epileptiform activity. No adverse events associated with ZNS were reported by either patient. **Conclusions:** Experience in these patients suggests that ZNS may be useful in some difficult-to-treat pediatric patients. The patients demonstrated marked improvement, both clinically and electroencephalographically, with the addition of ZNS to their therapeutic regimen, and no adverse events were reported. (Disclosure: Consulting: Elan Pharmaceuticals; Honoraria: Elan Pharmaceuticals.)

2.213

LONG-TERM SAFETY OF CARBAMAZEPINE EXTENDED-RELEASE CAPSULES TWICE DAILY IN THE TREATMENT OF SEIZURE DISORDERS

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Rationale: The objective of this study was to evaluate the long-term safety of carbamazepine (CBZ) extended-release capsules (CBZ-ERC; Carbatrol) in patients with seizure disorders. CBZ is established as effective first-line therapy for patients with seizure disorders. Extended-release formulations allow twice-daily dosing, which improves adherence. CBZ-ERC consist of three types of beads: uncoated immediate-release, polymer-coated extended-release, and pH-sensitive coated enteric-release to provide decreased fluctuations of CBZ throughout the 12-h dosing interval. A previous, 6-month study demonstrated that switching patients from multiple daily-dose CBZ to twice-daily CBZ-ERC was safe and effective (*Neurology* 1998;1:1727–9). **Methods:** The 118 pts with seizure disorders enrolled in a 36-month, open-label evaluation of twice-daily CBZ-ERC at an initial daily dose equivalent to the daily dose before entry. CBZ-ERC dose could be changed if clinically necessary ≤1,600 mg/day. Up to two other AEDs could be maintained at a stable dose. Patients kept a seizure diary, reported adverse events (AEs) and returned to the clinic every 6 months for evaluations. **Results:** Of 118 patients enrolled, 81 (68.6%) either completed 36 months of participation or were still participating when the study was phased out after commercial availability of CBZ-ERC. Of the 37 patients discontinued from the study, nine met seizure-escape criteria, but seizures were well controlled in the remainder. Overall seizure frequency was stable throughout. At baseline, 6-month, and 12-month time points, mean highest 2-day generalized tonic–clonic (GTC) seizure frequencies were 0.2, 0.1, and 0.1, respectively, whereas mean highest 2-day non-GTC seizure frequencies were 1.2, 1.3, and 1.4, respectively. Drug-related AEs, reported by >1% of patients, were typical of CBZ and are listed. Only three patients discontinued because of AEs, and all were deemed unrelated to study drug by the investigator. Quality-of-life measures showed no improvement beyond that attained in the previous 6-month study. **Conclusions:** CBZ-ERC is well tolerated and can be used safely and effectively for long-term treatment of seizure disorders. (Supported by Shire US Inc.) (Disclosure: Grant: W.R. Garnett, Shire; Consulting: V.M. Thadani, Shire; Honoraria: V.M. Thadani, Shire, R.E. Hogan, Shire; W.R. Garnett, Shire.)

TABLE 1. *Treatment-related adverse events*[a]

Event	No. patients (%)
Any	23 (19.5)
Dizziness	8 (6.8)
Asthenia	4 (3.4)
Amnesia	3 (2.5)
Diplopia	3 (2.5)
Nausea	2 (1.7)
Vomiting	2 (1.7)
Ataxia	2 (1.7)
Abnormal thinking	2 (1.7)

[a] Reported by ≥1% of patients.

2.214

SEIZURE CONTROL AND EEG RESPONSE IN PRIMARY GENERALIZED EPILEPSY PATIENTS TREATED WITH TOPIRAMATE

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Rationale: Interictal epileptiform spike–wave activity indicates hyperexcitability and increased risk for clinical seizures. Although reduced spike–wave activity is a putative marker of seizure control, studies with broad-spectrum antiepileptic drugs (AEDs) show no consistent correlation between spike–wave activity and seizure control in primary generalized epilepsy. This study evaluated the effect of the broad-spectrum AED topiramate (TPM) on interictal epileptiform discharges in patients with primary generalized epilepsy. **Methods:** Patients in this open-label, multicenter study had primary generalized epilepsy (newly diagnosed or on a stable AED regimen; typical absence, progressive myoclonic epilepsy excluded) and epileptiform activity on a 30-min EEG. TPM effect on spike–wave activity was evaluated by comparing 24-h ambulatory outpatient EEGs at baseline and after 1 week at optimum/maximally tolerated dose. EEG studies, staged by state (awake; sleep stages 1, 2, 3, 4; REM sleep), were analyzed by a blinded independent reader. **Results:** Evaluable EEG data were available for 11 patients (all female, 8–48 years). Seizure control was improved in seven (64%) patients; four (36%) had no seizures. Absence seizures were reduced in five of seven patients. Mean spike frequency decreased in seven patients (pretreatment, 2.42 spikes/h; posttreatment: 1.65 spikes/h). Two EEG responders were seizure free; three had improved seizure control; two had mixed responses. Two EEG nonresponders were seizure free; two had mixed responses. EEG nonresponders had fivefold higher baseline spike–wave discharge frequency (11.12 spikes/h), which was increased at posttreatment EEG (24.62 spikes/h). Neither clinical nor EEG response correlated with TPM blood levels. **Conclusions:** Seizures in primary generalized epilepsy, including absence seizures, were reduced with TPM treatment; epileptiform spike–wave activity was reduced in >50% of patients. Epileptiform activity was less likely to be suppressed in patients with high baseline discharge frequencies. Consistent with findings in other studies of broad-spectrum AEDs, EEG response was not predictive of clinical response. (Supported by Ortho-McNeil Pharmaceutical.) (Disclosure: Grant: Ortho-McNeil/Johnson & Johnson, UCB Pharma; Consulting: GlaxoSmithKline, Novartis; Honoraria: Pfizer/Parke-Davis.)

2.215

ONE-YEAR POSTMARKETING EXPERIENCE WITH LEVETIRACETAM FOR TREATMENT OF DRUG-RESISTANT EPILEPSY: A CROSS-SECTIONAL STUDY

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Rationale: Levetiracetam (LEV) is a newly approved drug for add-on therapy of focal epilepsies. There are limited experiences in generalized epilepsies. We aimed to assess the safety, efficacy, and tolerability of LEV in treatment of drug-resistant focal and generalized epilepsies. **Methods:** All adults treated with LEV at the Universitätsklinik für Neurologie, Innsbruck (n = 71) were evaluated retrospectively. We analyzed seizure type, etiology, epilepsy syndrome, and seizure frequency. The treatment response to LEV, side effects, and tolerability were assessed. **Results:** Total number of patients were 71 (42 women) with an age range of 18–69 years. Of the patients, 50.7% had temporal lobe epilepsy (TLE), 29.6%, extratemporal epilepsy (ETE), and 19.7% generalized epilepsy (GE). The etiology was symptomatic in 69%, cryptogenic in 21.1%, and idiopathic in 9.9%. Mean age at epilepsy onset was 15 years (SD, 10.6); mean number of seizure days per month was 10.2 (SD. 10). At follow-up (mean, 28 weeks; SD, 17.6), 21.1% of all pts were seizure free, 12.7% had a seizure reduction of >75%, and 11.3% had a seizure reduction of >50%. Retention rate was 69.6%. The reason for withdrawal was lack of efficacy in 13 patients, side effects in two, and a combination of both in five patients. Responder and nonresponder did not differ in age, epilepsy and seizure type, etiology, number of concomitant medications, mean LEV doses (2,687.5 mg ± 578.5 vs. 2,675.7 ± 792.4), blood level (28.4 mg/L ± 16 vs. 30.6 mg/L ± 11.3), duration of treatment with LEV (32 ± 17.6 vs. 28 ± 17.2 weeks). There was a linear relation between LEV dose and blood level ($r = 0.419$; $p < 0.05$) None of the analyzed factors was predictive for respondership or withdrawal of LEV for any reason in a cross-validated discriminant analysis. **Conclusions:** Our observational study confirms the initial studies of LEV in terms of high efficacy and tolerability. It also indicates an efficacy in generalized epilepsies combined with a low incidence of side effects. LEV appears to be a promising broad-spectrum treatment for focal and generalized epilepsies.

2.216

USE OF LEVITIRACETAM IN PATIENTS WITH BRAIN TUMORS AND INTRACTABLE PARTIAL EPILEPSY

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Rationale: To evaluate the efficacy of levitiracetam (LEV) in adults with brain tumors and intractable partial seizures. From this study, the participants should be aware of the treatment options in patients with brain tumors and uncontrolled partial seizures. **Methods:** All patients with brain tumors and uncontrolled partial seizures who were seen by the authors between March 2000 and March 2002 were offerred all antiepileptic drug (AED) therapy alternatives. Patients with either primary brain tumors and metastatic tumors were included. Benefits and risks of each AED were detailed. Each patient was followed up by the same epileptologist, and seizure frequency as well as side effects were assessed at each follow-up visit. Initial target dose of LEV was 500 mg, b.i.d., over 1 week. Additional increases or decreases in the LEV dose was based on clinical response to drug and side effects. **Results:** Of 38 patients identified (14 astrocytomas, eight glioblastoma multiforme, 10 oligodendrogliomas, one each hemangiopericytoma, meningioma, and primary CNS lymphoma, and three metastatic tumors), 30 elected to initiate LEV therapy. Adjunctive AED therapy consisted of one to four AEDs in all but two patients, who had acute allergic reations to recent AED therapy, which was subsequently discontinued. LEV dosages ranged from 250 to 3,500 mg/day (median, 1,750 mg; mean, 1,826 mg). With 2- to 18-month follow-up, eight patients have become seizure free, and seven patients have had >90% reduction in seizures. In six patients, there was no significant improvement, with one patient having worsening of seizures. Three patients (one seizure free) are taking LEV monotherapy, two of whom entered with no AED because of recent AED allergic reaction. Excessive sedation was noted in three patients, requiring dose reduction or discontinuation. In 14 of 30 patients, phenytoin (PHT; 200–400 mg per day) was the adjunctive AED. **Conclusions:** LEV is effective and can be successfully introduced quickly in patients with brain tumors and intractable partial seizures. Many patients can be adequately contolled with dual therapy using LEV, and monotherapy can be achieved in some cases. Rapid transition to LEV is possible in patients with AED allergic reactions with good outcome. (Disclosure: Consulting: Elan, Excel, UCB Pharma, GlaxoSmithKline; Honoraria: Elan, Excel, UCB Pharma, GlaxoSmith Kline.)

2.217

THE EFFECTS OF OXCARBAZEPINE VERSUS CARBAMAZEPINE THERAPY ON HEALTHCARE UTILIZATION AND COSTS AMONG EPILEPSY PATIENTS IN A MANAGED-CARE SETTING

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TABLE 1. *Changes in the mean costs of health-care services in 6 months, by therapy*

Measure	Carbamazepine (1) (n = 414)			Oxcarbazepine (2) (n = 39)			
	Preindex	Postindex	Change	Preindex	Postindex	Change	Difference (2) – (1)
Serum AED level tests	$14	$30	$15	$0	$4	$4	–$12
Kidney/liver-function tests	$49	$61	$12	$17	$54	$36	$24
Emergency room visits	$116	$78	–$38	$248	$56	–$191	–$153
Physician visits	$60	$68	$8	$96	$54	–$42	–$51
Hospitalizations	$446	$554	$108	$403	$219	–$184	–$292
AED medications	$0	$144	$144	$0	$404	$404	$261
TOTAL	$685	$935	$249	$764	$791	$27	–$222

Rationale: Oxcarbazepine (OCBZ) is an antiepileptic drug (AED) indicated for partial seizures as monotherapy or adjunctive therapy for adults and as adjunctive therapy for children ages 4–16 years. There are limited data on the economic implications of this therapy relative to older medications for partial seizures. The objective of this study was to explore resource use and costs among patients who were newly started on OCBZ or carbamazepine (CBZ) therapy in a managed-care setting. **Methods:** We used a retrospective cohort design and administrative claims data to examine healthcare resource use and costs among patients prescribed OCBZ versus CBZ. The study population included outpatients diagnosed with a seizure disorder who were newly started on OCBZ or CBZ between February 2000 (date of first availability of OCBZ) and December 31, 2000. The proportions of patients using seizure-related healthcare resource utilization and costs were assessed on a descriptive basis, in terms of the net change between the study cohorts from 6 months before index to 6 months after index. **Results:** In total, 453 patients were eligible for inclusion; 414 in the CBZ cohort and 39 in the OCBZ group. Patients averaged 36 years of age, and 46% were male. Over 6 months, serum AED drug level assays increased 10.3% in the OCBZ group versus 20.5% in the CBZ group, but the opposite was found for liver-function tests (12.8 vs. 7.5%, respectively). The increase in physician visits was smaller in the OCBZ group (2.5 vs. 6.7% for CBZ). Moreover, although a decline was noted for ER visits and hospitalizations in both treatment cohorts, this decrease was greater in the OCBZ group (15.4 vs. 7.3%, and 7.7 vs. 0.2%, respectively). Correspondingly, mean medical costs per patient were $484 lower in the OCBZ cohort. This more than offset higher costs of therapy among OCBZ patients (mean, $261), resulting in an overall per-patient cost savings of $222. **Conclusions:** This descriptive study suggests that in a managed-care setting, relative to CBZ, the use of OCBZ may be associated with lower healthcare utilization and costs among patients newly starting therapy. Whether the reduction in costs is due to better tolerability and/or improved seizure control cannot be directly assessed in a database study. However, the findings from this study suggest avenues for further outcomes research. (Supported by Novartis Pharmaceuticals Corp.) (Disclosure: Salary: Sobin Chang is an employee of Novartis Pharmaceutics Corp.; Grant: Luke Boulanger, Mark Friedman, Mellissa Yong, Peter Neumann, and Joseph Menzin received a research grant from Novartis Pharmaceuticals, Corp.)

2.218

COMPARISON OF COSTS AND COST-EFFECTIVENESS OF OXCARBAZEPINE AND SODIUM VALPROATE FOR NEW/ RECENT-ONSET PARTIAL SEIZURES

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Rationale: The objective of this study was to determine the comparative costs and cost-effectiveness of oxcarbazepine (OCBZ) and sodium valproate (VPA) in the treatment of new and recent-onset partial epileptic seizures. **Methods:** Low-, moderate-, and high-dose maintenance regimens were determined for each drug based on prescription audit information captured in the prescribing physician's office. Unit drug costs based on wholesale acquisition costs were then used to compute a daily drug cost for each dosage level. A decision-analysis model using a Monte Carlo simulation was developed to evaluate the cost-effectiveness of OCBZ and VPA. The model contained the computed daily drug costs along with direct payer costs associated with initiation and maintenance of therapy, treatment of adverse events, and switching from one drug to another because of poor seizure control or adverse events. The probabilities of maintaining seizure control and of experiencing adverse events were obtained from double-blind clinical trials comparing OCBZ and VPA. **Results:** The average daily drug costs weighted over the three dosage levels were $4.72 ($1.49–7.66) for OCBZ and $3.17 ($2.45–3.87) for VPA. Total 1-year costs for OCBZ, including costs of adverse events and costs of switching drugs because of poor seizure control or adverse events were $3,511 for OCBZ and $5,931 for VPA. The computed number of months on initial therapy was 9.95 for OCBZ and 9.66 for VPA. The analysis was carried out to 4 years using the same probabilities for adverse events and seizure control. The 4-year costs were $20,426 and $23,790 with 25.2 and 24.6 months of therapy for OCBZ and VPA, respectively. **Conclusions:** These findings suggest that OCBZ results in lower expected total costs compared to VPA when drug costs, evaluation and management, adverse events, and costs of switching therapies are taken into account. (Supported by Novartis Pharmaceuticals Corporation.) (Disclosure: Salary: Novartis Pharmaceuticals Corporation; Consulting, Novartis Pharmaceuticals Corporation; Honoraria: Novartis Pharmaceuticals Corporation.)

2.219

PHYSICIANS UNDERESTIMATE THE FREQUENCY OF GENERIC CARBAMAZEPINE SUBSTITUTION: RESULTS OF A SURVEY AND REVIEW OF THE PROBLEM

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Rationale: Generic substitution of antiepileptic drugs (AEDs) may lead to breakthrough seizures and adverse events, but prescribers of AEDs may be unaware how frequently generic substitution actually occurs. **Methods:** Surveys were administered to 845 physicians at the 2001 American Epilepsy Society (AES) meeting and the 2001 American Academy of Neurology meeting. Two hundred fifty-eight physicians responded to the AES survey, and 587 physicians, to the AAN survey. Questions were multiple choice and displayed on a computer screen. Among other questions, physicians were asked: What percentage of patients are substituted for a generic short-acting carbamazepine (CBZ) in the United States annually? and Are you comfortable with patients receiving multiple formulations of generic CBZ? Responses to the first question were compared to the actual rate of generic substitution determined by an independent audit of 1,036,000 Tegretol prescriptions. **Results:** In the AES survey, 10.9% of respondents estimated that 10% of patients had CBZ generic substitutions; 41.9%, a 30% substitution rate; 30.2%, a 50% rate; and 17.1%, a 70% rate. The AAN respondents had similar estimates: 17.5% guessed a 10% rate; 40.0%, a 30% rate; 30.2%, a 50% rate; and 12.3%, a 70% rate. In the AES survey, 86.4% of respondents were not "comfortable with patients receiving multiple formulations of generic CBZ." Similarly, in the AAN survey, 80.3% of respondents did not endorse generic substitution of CBZ. An independent audit of generic substitutions revealed that of 766,000 prescriptions for 200 mg Tegretol, pharmacists substituted

551,000 (72%) with generic CBZ. Of 199,000 prescriptions for 100 mg Tegretol, 140,000 (70%) were filled with a generic. Of 71,000 prescriptions for Tegretol, 100 mg/5 ml suspension, 10,000 (14%) were filled with a generic. The overall substitution rate was 701,000/1,036,000 (68%), much higher than estimated by the majority of surveyed attendees. **Conclusions:** Most surveyed physicians at the 2001 AES and AAN meetings significantly underestimated the number of generic substitutions that occur for brand-name short-acting CBZ. Given the potential for breakthrough seizures and adverse events related to generic substitution, physicians need to be more vigilant in their prescription-writing practices to prevent unwarranted generic substitution. (Supported by Shire, US.) (Disclosure: Grant: Shire US, Inc.; Honoraria: Novartis.)

2.220

OXCARBAZEPINE-INDUCED HYPONATREMIA IN CHILDREN AGED 0–10 MONTHS

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Rationale: Oxcarbazepine (OCBZ) use in a clinical setting has been noted to contribute to development of hyponatremia in a manner similar to carbamazepine (CBZ). Children with severe developmental disabililties are more susceptible to hyponatremia due to OCBZ than developmentally normal children. The objective of this study was to define the actual clinical incidence of hyponatremia in children taking OCBZ. **Methods:** A total of 96 children (47 girls/49 boys; mean age, 8.5 years; range, 6 months to 18.6 years; average age at seizure onset, 3.1 years) were identified as being treated with OCBZ. Fifty-five patients were identified from Minnesota Epilepsy Group's pathology database. Forty-one children were identified from the authors' database at Riley Hospital for Children. **Results:** In 77 of 96 (80.2%) patients, posttreatment serum sodium levels were available. Fifty-nine of these also had OCBZ levels. Two of the patients had symptomatic hyponatremia (Na <125). Both of these patients were G-tube fed all nutrition and medication. One patient was also taking Topamax; the other patient was on a weaning dose of phenobarbital (PB). Five patients had asymptomatic hyponatremia (Na <135). Average dose of OCBZ was 34.8 mg/kg/day, with an average level of 24.37 μg/ml. The patients were taking an average of 2.1 antiepileptic medications (AEDs). Twenty of 96 (20.8%) patients were receiving OCBZ monotherapy. Seven of 96 (7.3%) patients had a vagal nerve stimulator; 66/96 (68.8%) patients were developmentally delayed (documented or clinical judgment IQ <70). No correlation between development, dose, age, or number of concurrent AEDs and asymptomatic hyponatremia was found. Twenty of 96 (20.8%) patients did not have follow-up sodium levels. None of these patients had clinical indication to obtain sodium levels. **Conclusions:** Sodium measurement is not indicated for children with refractory epiilepsy taking OCBZ unless the patient is receiving G-tube feedings where normal homeostatic behaviors are not possible. (Disclosure: Consulting: Yes; Honoraria: Yes.)

2.221

RISK OF OSTEOPOROSIS IN MEN WITH EPILEPSY

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Rationale: Osteoporosis and the associated morbidity is a major burden on the economy (1). It has been recognized that especially postmenopausal white women are at risk for developing osteoporosis (1). Recently, women with epilepsy have been identified as being at even greater risk for this disease. This is partially due to antiepileptic drugs' (AEDs) having a negative effect on the bone density (2). The risk for men in general and especially for men with epilepsy is not well recognized. We are trying to demonstrate that men with epilepsy would benefit from early screening for osteoporosis and potentially from calcium and vitamin D supplementation. At the end of this activity the participants should be able to recognize the risk for men with epilepsy to develop osteoporosis and apply treatment modalities. **Methods:** Retrospectively we analyzed the charts of 50 epileptic men (age range, 18–71 years; mean age, 41 years) that were seen in our epilepsy clinic. We also interviewed these patients regarding their calcium intake, exercise habits, and whether they supplemented calcium and/or vitamin D. Overall, 15 primary and secondary risk factors that have been associated with an increased risk for developing osteoporosis were evaluated (1). **Results:** Of these 50 men, all had taken at least one of the AEDs associated with reducing bone mass at one point of their disease. Onset of epilepsy was before the age of 25, which is the age of highest bone mass, in 74% of patients. Only 18% of patients performed adequate exercise, and only 12% ingested the daily recommended calcium amount of 800–1,200 mg. An additional handicap prevented 34% from getting adequate exercise. A total of two patients were taking long-term steroids one for Rasmussen encephalitis and one for CNS sarcoid. Of the 50 patients, 10% had a dexascan performed, which showed signs of osteopenia/osteoporosis in three patients, one had normal bone mass for age, and one had increased bone density. The patients with decreased bone mass were 32 years, 47 years, and 52 years, and all had their epilepsy since early childhood. Calcium supplementation was taken by 14% of all patients; 4% took vitamin D, and 4% took alendronate. The only patients that took supplementations were taking long-term steroids or had proven loss of bone mass. **Conclusions:** Men with epilepsy appear to be at risk for developing osteoporosis even at an early age. All of them have taken at least one of the older AEDs, that have been associated with decreased bone density (2), at some point of their illness. A lot of them have had epilepsy since early childhood, taking AEDs before they had accumulated their peak bone mass. Epilepsy seems often to be associated with other comorbidities, preventing the patient from exercising sufficiently to prevent osteoporosis. However, further studies on the effect of AEDs, especially the newer ones, on bone metabolism are needed. Men with epilepsy and especially those with epilepsy since childhood would benefit from early screening for osteoporosis, as well as supplementation of vitamin D and calcium to prevent osteoporosis. (Disclosure: Honoraria: GSK, Cyberonics, Ortho-McNeil, Novartis.)

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2.222

GABAPENTIN-INDUCED STATUS EPILEPTICUS

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Rationale: Gabapentin (GBP) is an antiepileptic drug (AED) now used for many conditions other than epilepsy. It has stable pharmacokinetics and relatively few side effects and drug interactions. We report a case of an elderly lady taking GBP, who had markedly elevated GBP levels, developed status epilepticus, and died subsequently. **Methods:** A 72-year-old lady was found unresponsive and comatose at home, last seen by relatives ~24 h before. At the local ER, she was found to have agonal breathing and facial twitching. She was intubated and given i.v. lorazepam (LZP; 2 ± 3 mg). An EEG done at that time reportedly showed evidence of status epilepticus, and she then was given i.v. phenobarbital (PB). She was transferred by helicopter to UW Hospital for further management. Her medical history was significant for congestive heart failure, polyneuropathy, polyradiculopathy, monoclonal gammopathy, chronic atrial fibrillation, and depression. She had undergone cholecystectomy, appendectomy, and hysterectomy in the past. Her medications included GBP, 900 mg t.i.d. (recently increased from 300 t.i.d.) for polyneuropathy, furosemide 80 mg qd, levothyroxine 125 μg qd, lisinopril 10 mg qd, fluoxetine 20 mg qd, and Premarin 300 μg qd. On examination, she was intubated and was on a ventilator.

She was comatose and unresponsive. Fundi were normal. Pupils were 3 mm and nonreactive. Corneal reflexes were absent. All four limbs were flaccid and areflexic. Plantars were mute. Laboratory findings: CBC was normal; sodium, 140 mEq/L; potassium, 5.2 mEq/L; chloride, 99 mEq/L; glucose, 139 mg%; BUN, 67; creatinine, 4.2 (4.8); CK 6252 GBP levels, 84 (day 1), 62.7 (day 2), 17.7 (day 3); EEG, phase-reversing sharp waves in R parasagital + diffuse slowing. The patient did not recover and died 1 week after admission. Autopsy of the brain was essentially unremarkable. **Results:** GBP was introduced as an adjunctive therapy for treatment of seizures. However, after gaining experience with its safety profile and lack of drug interactions, it was used extensively for conditions other than epilepsy, most commonly for chronic pain, depression, and headache. There have been anecdotal reports noting its lack of toxicity despite large doses and elevated levels. Our case report illustrates a patient who developed status epilepticus and had markedly elevated GBP levels. Her laboratory work also demonstrates signs of acute renal failure, which is probably due to the status, as indicated by elevated CK levels. Although there was no clinical improvement with lowered GBP levels seen serially, it is likely that elevated GBP levels led to the development of status, as she died of complications of status epilepticus. **Conclusions:** High doses of GBP or rapid increase in dosage can lead to elevated GBP levels and result in serious consequences such as status epilepticus. It should be used carefully in the elderly, especially with comorbid conditions. The prolific use of GBP in many neurologic and nonneurologic conditions should be tempered with caution, until we completely understand the mechanisms of action and toxicity. [Disclosure: Grant: UCB Pharma, GlaxoSmithKline (Gidal); Consulting: UCB Pharma, GlaxoSmithKline, Ivax (Gidal); Honoraria: UCB Pharma, Pfizer, GlaxoSmithKline, Elan Pharma (Gidal, Dixit).]

2.223
ORAL CONTRACEPTIVE-AED INTERACTIONS: NO EFFECT OF TOPIRAMATE AS MONOTHERAPY AT CLINICALLY EFFECTIVE DOSAGES OF 200 MG OR LESS

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Rationale: Topiramate (TPM) may be preferentially used in women because of its clinical profile, including effectiveness in disorders that are more common in women [e.g., juvenile myoclonic epilepsy (JME); migraine] and low risk of weight gain. In an early interaction study with TPM and oral contraceptives (OCs) in women with epilepsy, TPM added to valproate (VPA) was associated with no effect on the progestin (norethindrone, NE) pharmacokinetics and a modest dose-related decrease in estrogen (ethinyl estradiol, EE) exposure (mean total EE exposure reduction, 200 mg/day, 18%; 400 mg/day, 21%; 800 mg/day, 30%). The study reported here evaluated the TPM–OC interaction at TPM dosages most likely to be useful as monotherapy in, for example, newly diagnosed epilepsy and migraine prophylaxis: 50, 100, and 200 mg/day. Carbamazepine (CBZ) was used as a positive control for clinically significant effects on OC pharmacokinetics. **Methods:** In this open-label, randomized study, 48 healthy, nonobese women (BMI, $\leq$27 kg/m^2; aged 18–40 years) received TPM, 50 mg/day; TPM, 100 mg/day; TPM, 200 mg/day; or CBZ, 600 mg/day added to an OC (1.0 mg NE; 0.035 mg EE). A second TPM, 200 mg/day group was composed of 12 obese women (BMI, 30–35). Two menstrual cycles were evaluated: Cycle 1, OC alone; Cycle 2, OC + TPM or CBZ. During Cycle 2, TPM and CBZ were titrated to assigned dosages by day 12 and maintained until day 21. Pharmacokinetic parameters determined from blood samples drawn on day 21–22 included peak plasma concentration (C_{max}), time to peak concentration (t_{max}), area under the plasma time–concentration curve during the dose interval (AUC), and oral clearance (CL/F) for NE and EE. Pharmacokinetic parameters with and without study drug were compared by analysis of variance. **Results:** TPM did not affect NE pharmacokinetics. In CBZ-treated subjects, NE C_{max} and systemic exposure (AUC) were reduced 37 and 58%, respectively ($p < 0.05$). Compared with the OC alone, EE C_{max} with TPM coadministration changed –7% (50 mg); +5% (100 mg), –15% (200 mg nonobese), and –11% (200 mg obese); EE AUC changed –11%, +6%, –11%, and –9%, respectively. The treatment effect with TPM was not significant for C_{max} or AUC in any treatment group. In contrast, EE C_{max} was reduced 19% with CBZ coadministration ($p < 0.05$); AUC was reduced 42% ($p = 0.0001$). **Conclusions:** With TPM 50–200 mg/day as monotherapy, dose-related effects on EE pharmacokinetics were not observed, although high-dose TPM (e.g., 800 mg/day) may reduce EE exposure, as demonstrated in an earlier study in women with epilepsy. As monotherapy, TPM, 50–200 mg/day, does not have a significant pharmacokinetic interaction with OCs. (Supported by Johnson & Johnson Pharmaceutical Research & Development.) (Disclosure: Salary: Johnson & Johnson Pharmaceutical Research & Development.)

2.224
SODIUM VALPROATE, PARKINSONISM, AND COGNITIVE IMPAIRMENT

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Rationale: After reports of a reversible valproate (VPA)-induced extrapyramidal syndrome with cognitive impairment, we wanted to ascertain the incidence of such a syndrome among patients receiving sodium VPA in the Greater Manchester area. VPA is a widely used antiepileptic drug (AED), efficacious in both primary generalised and localisation-related epilepsies. In recent years, there have been case reports suggesting the existence of a reversible extrapyramidal syndrome induced by exposure to VPA. These studies recruited patients attending University hospital–based epilepsy clinics and did not exclude patients with previous exposure to neuroleptic, antidepressant, or antiemetic drugs. In the present study, patients attending their family practitioner, a community-based epilepsy clinic attended by individuals with well-controlled epilepsy, and a University hospital epilepsy clinic were assessed for the presence of extrapyramidal signs and symptoms. **Methods:** Forty consecutive patients receiving VPA monotherapy, none of whom had been exposed to neuroleptic, antidepressant, or antiemetic drugs, were recruited. All patients had received VPA monotherapy for a minimum of 12 months before recruitment. A control group of 16 patients taking carbamazepine (CBZ), subject to the same inclusion and exclusion criteria as the VPA monotherapy group, were recruited. All patients underwent a full neurologic examination, completed the mini-mental state (MMS), and had their posture, gait, fine-finger movements, and tremor, if present, videoed. Those considered to have extrapyramidal signs underwent the Unified Parkinson Disease Rating Scale (UPDRS) parts 1–3. The videos were reviewed "blind" to patient therapy by M.K., and those considered to exhibit extrapyramidal features were invited to clinic for further examination by him. **Results:** Fifty-six patients were examined, 40 taking VPA (24 male, 16 female), and 16 taking CBZ (four male, 12 female). No significant differences existed in mean age, duration of therapy, or duration of epilepsy, between control and study groups. Three (7.5%) of the VPA monotherapy patients were found to have extrapyramidal signs (rigidity, tremor, gait disturbance, bradykinesia). Mean UPDRS score was 2.95. None of the CBZ group exhibited extrapyramidal signs. There were no significant differences in MMS scores between the two groups. There was no correlation between UPDRS score and dose of VPA or duration of therapy. There was a correlation between UPDRS score and age ($p = 0.01$; $r = 0.405$). **Conclusions:** In conclusion, there was a higher incidence of extrapyramidal signs in patients receiving VPA monotherapy in this study (7.5%) than would be expected in the general population (0.5%), although the presence and severity of these signs were not correlated with either the dose or duration of therapy with VPA. This suggests that certain patients may be more susceptible to such a syndrome. It should be noted that the method of recruitment may also confound results, and so further large-scale studies are needed to elucidate the extent of this phenomenon in people exposed to VPA. [Supported by (K.R.E.) educational grants from Sanofi-Synthelabo Pharmaceuticals and the Wigan and Leigh Epilepsy Fund. Drs Kellett, Clough, and Duncan are National Health Service employees and received no grants or honoraria during their envolvement with this study.] (Disclosure: Honoraria: Dr. Duncan has received honoraria from Novartis, Janssen, and Sanofi Pharmaceuticals.)

2.225

POSSIBLE RELATION OF LEVETIRACETAM THERAPY TO HEMORRHAGIC COMPLICATIONS IN EPILEPSY SURGERY

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Rationale: Much attention has been paid to the possibility of a bleeding diathesis due to valproate (VPA; e.g., Zeller et al. *Epilepsia* 1999;40:186–9; Anderson et al. *J Neurosurg* 1997;87:252–6). To our knowledge, no reports have surfaced of possible bleeding complications due to any of the newer anticonvulsants (AEDs). A dramatic case at our center of hemorrhagic complication (index case) of epilepsy surgery in a patient taking levetiracetam (LEV) prompted a review of our surgical cases for any other possible LEV-associated hemorrhages. **Methods:** A retrospective chart review of all epilepsy surgeries performed at our institution in the past 3 years was initiated. Hemorrhagic complication was defined as hematoma, bleeding requiring transfusion, bleeding requiring premature termination of the initial surgical procedure, or a repeated procedure to address bleeding. Cases were considered to be associated with LEV if it was being received at the time of surgery or had been discontinued the day before surgery. Each chart was also reviewed for other possible causes of bleeding [disseminated intravascular coagulation (DIC), underlying coagulation disorder, etc.]. **Results:** Three cases were uncovered, all unexplained. Two were in the context of LEV therapy. The first case (index case) had had previous surgeries (off LVT) without complications. He was noted to have significant oozing at the time of subdural electrode implantation, although preop screen was normal. LEV was stopped to provoke seizures, and he went for resection 7 days later without excess bleeding. Preop medications, LEV and oxcarbazepine (OCBZ), were resumed that evening. The next day he developed subural, epidural, and subgaleal hemorrhage, requiring reoperation. LEV has not been resumed; extensive w/u for known coagulopathies was negative. The second case had a subdural hematoma requiring multiple procedures to control. The third patient was in status on pentobarbital (PTB) and propofol; subdural strips could not be placed due to bleeding. Two more cases of bleeding abnormalities without surgical complications were detected: a patient taking LEV, lamotrigine (LTG), and topiramate (TPM) had persistently abnormal coagulation studies with negative hematologic evaluation; the second, taking LTG and TPM, had significant oozing at surgery insufficient to meet these criteria. **Conclusions:** In clinical trials, LEV altered leukocyte levels, produced a significant increase in frequency of upper respiratory tract infections, and produced statistically significant but clinically trivial decreases in erythrocyte count [Harden. *Epilepsia* 2001;42(suppl 4):36–9]. The possibility may exist that LEV has a subtle effect on megakaryocytes, producing a previously unappreciated bleeding diathesis. Our findings suggest a higher than expected association between LEV treatment and hemorrhagic complications of epilepsy surgery in our center's series of patients. We are continuing our analysis to permit calculation of relative risk versus other AEDs. We urge other surgical centers to review their own experience for any evidence of LEV-associated hemorrhagic complications. (Disclosure: Grant: Werz MA, GlaxoSmithKline; Consulting: Werz MA, GlaxoSmithKline; Honoraria: Werz MA, GlaxoSmithKline; Swartz B, GlaxoSmithKline, UCB-Pharma, Ortho-McNeil, Novartis.)

2.226

SAFETY PROFILE OF LEVETIRACETAM

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Rationale: The most rigorous method of adverse-event (AE) assessment for new compounds is via randomized controlled regulatory trials (RCT). However, populations enrolled in such trials are highly selected; postapproval trials are less rigorous, but include broader population who may have different risks for AEs. In this study we compared AE data from these two methods of AE ascertainment. **Methods:** We analyzed data on AEs from patients initiating levetiracetam (LEV) in the PADS (Postmarketing Antiepileptic Drug Survey) database. PADS is a prospective registry provided by a consortium of 16 epilepsy centers to study the population treated with new AEDs. Patients at each center are prospectively and consecutively entered. Initiation forms include demographic data, as well as data on seizure type/frequency, past behavioral and psychiatric disturbances, and current/past AED use. Follow-up forms include seizure outcome, adverse events, reason for discontinuation, if applicable, dose and titration rate. We compared results to a pooled safety analysis of patients enrolled in RCTs. **Results:** We studied 288 patients; with a mean follow up of 240 ± 135.6 days. Males, 135, females, 153. Age range was 8 months to 83 years (mean, 38.2 ± 15.7 years). The average dose of LEV was 1,767 ± 1,013 mg, and the average highest dose was 1,919 ± 1,045 mg. Increased seizure frequency was reported in 2.4 versus 14% in premarketing studies, insomnia in 3.8 versus 5.5% in premarketing, and weight change in 5.6 versus 8.5 in the premarketing phase. There was no report of infection in our group versus (13.4%) in premarketing phase. Most of the AEs reported in this study were mild to moderate; however, 16.9% of patients described their symptoms as severe versus 14.7% in the premarketing group. Only 14.2% discontinued LEV because of AEs versus 15% in premarketing studies. AEs that lead to discontinuation include dizziness, 0.3%; ataxia, 0.7%; diplopia, 0.3%; nausea, 1%; insomnia, 0.7%; rash, 0.3%; psychomotor slowing, 0.7%; weight change, 0.3%; increase in seizure frequency, 2.4%; and behavioral changes, 4.9%. **Conclusions:** LEV is well-tolerated AED. Postmarketing data are consistent with pooled premarketing safety data of LEV. The main AEs noted are fatigue, somnolence, headache, and dizziness, as well as behavioral AEs. Most of the AEs reported were relatively mild to moderate, and discontinuation was noted only in few patients. (Supported by contributions from Ortho-McNeil, Cyberonics, Abbott, Glaxo-Wellcome, Novartis, Elan, and UCB Pharma.) (Disclosure: Other: The PADS survey has received contributions from Ortho-McNeil, Cyberonics,Abbott, Glaxo-Wellcome, Novartis, Elan, and UCB Pharma.)

2.227

LACK OF EFFECT OF LAMOTRIGINE MONOTHERAPY ON HOMOCYSTEINE, FOLATE, OR VITAMIN B_{12} CONCENTRATIONS IN PATIENTS WITH EPILEPSY

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Rationale: At the end of this activity, the participant should be able to discuss the relation between lamotrigine (LTG) treatment and changes in homocysteine, folate, and vitamin B_{12} concentrations. Homocysteine is a thiol-containing amino acid that is formed by demethylation of methionine. Modest elevations in total plasma concentrations of homocysteine (tHcy) (15–30 μM) appears to be an important, independent risk factor for both cardiac and cerebrovascular disease. Elevated tHcy concentrations may be associated with cognitive declines in neurodegenerative disorders. A role for elevated tHcy in teratogenicity has also been suggested. Data suggest that a deficiency in vitamin cofactors needed for Hcy metabolism (e.g., folate, vitamin B_{12}) is

TABLE 1. *Most-reported adverse events*

	Fatigue/somnolence	Dizziness	Headache	Ataxia	Nausea	Rash	Depression/behavioral
Premarketing (n = 769)	29.5%	8.8%	13.7%	3.4%	4.4%	3.1%	13.3%
Postmarketing (n = 288)	22.9%	6.6%	3.8%	4.5%	3.8%	1.0%	13.5%

associated with increased tHcy concentrations. Older, enzyme-inducing antiepileptic drugs [AEDS; phenytoin (PHT), phenobarbital (PB), carbamezapine (CBZ)]) are associated with reduced folate and increased tHcy concentrations, with data derived mainly from cross-sectional studies. Little is known regarding the newer AEDs and changes in tHcy. We therefore investigated whether a non-inducing AED such as LTG is associated with changes in tHcy plasma concentrations. **Methods:** Plasma tHcy, erythrocyte and plasma folate, and serum vitamin B_{12} were analyzed as part of a multicenter evaluation of LTG monotherapy in epilepsy. Blood samples were obtained before (baseline) and after 32 weeks of monotherapy treatment with LTG. Patients receiving other AEDs at baseline were excluded from analysis. Data are analyzed using Wilcoxon rank test with significance assigned at $p < 0.05$. All data are presented as mean (SD). No attempt was made to control for, or intervene with, patients' dietary habits. **Results:** Eleven patients (eight women) with newly diagnosed epilepsy were evaluated. Patients were not pregnant, nor had gastrointestinal, hepatic, or renal disease. Mean age and weight were 37.8 (13.8) years, 74.9 (19.9) kg. Mean LTG dose during the maintenance period was 249.6 (73.7) mg/day. Mean tHcy, erythrocyte and plasma folate, as well as vitamin B_{12} concentrations did not significantly differ from pretreatment values. No tHcy values exceeded 15 μM. Data for all indices are presented in Table 1. **Conclusions:** In contrast to previous reports with older enzyme-inducing AEDs, these preliminary observations in a group of patients receiving initial monotherapy with LTG for 32 weeks suggest that this agent is not associated with significant alterations in either folate, vitamin B_{12} or tHcy concentrations. Future studies directed toward confirming these observations as well as identifying the significance of elevations in tHcy in this population would be useful. (Supported by GlaxoSmithKline.) (Disclosure: Salary: Alain Vuong, Anne Hammer, Pamela Barrett: GSK; Grant: Barry E. Gidal, GSK, UCB-Pharma, Pfizer; Raj Sheth: GSK, IVAX; Consulting: Barry E. Gidal, GSK, UCB-Pharma, IVAX; Raj Sheth, GSK; Honoraria: Barry E. Gidal, GSK, UCB-Pharma, Pfizer; Raj Sheth, GSK, Ortho-McNeil.)

TABLE 1. *Data for all indices*

Indices	Baseline	Week 32
Erythrocyte folate (n*M*)	2,199 (1,088.7)	2441.4 (1,789) (p = 8)
Plasma folate (n*M*)	66.6 (33)	87.2 (93.3) (p = 0.5)
Vitamin B_{12} (p*M*)	393.7 (179.7)	450.2 (245.9) (p = 0.1)
Plasma homocysteine (μM)	6.9 (1.2)	7.5 (2.6) (p = 0.9)

2.228

EVIDENCE FOR FRONTAL LOBE–ASSOCIATED COGNITIVE IMPAIRMENT IN PATIENTS WITH EPILEPSY TAKING TOPIRAMATE: EFFECTS BEYOND TITRATION PERIODS AND DOSAGE

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Rationale: Adverse effects of topiramate (TPM) are described as predominantly related to frontal lobe function; development of side effects appears to be based on an idiosyncratic susceptibility for the agent rather than to be dose dependent. TPM is a highly effective drug used in the treatment of partial-onset epilepsy with or without secondary generalization. TPM can produce considerable cognitive side effects such as psychomotor slowing, impaired memory function, speech-related problems, and further cognitive complaints. It has been argued that most of these effects develop during titration periods (generally within the first 2 months of treatment) as a result of high initial doses or rapid dose escalation, and that problems resolve when patients become habituated to the agent or dosage is adjusted. In this study we investigated the effects of TPM on cognitive performance in patients with epilepsy who had been receiving TPM for >2 months in relation to current blood serum levels and daily dosages of TPM. **Methods:** This was a retrospective study. The neuropsychological test scores of a sample of 64 patients taking TPM were compared to those of a group of 86 patients taking lamotrigine (LTG) as corresponding agent (control). Groups did not differ with regard to gender, age, IQ, number of adjunctive antiepileptic drugs (AEDs), onset and duration of epilepsy, or localization and lateralization of epileptic focus. All patients had undergone neuropsychological assessment of language abilities, motor function, attention, and verbal and nonverbal memory. **Results:** The TPM group performed significantly poorer on verbal fluency ($p < 0.001$), measures of working memory ($p = 0.001$), and verbal and nonverbal recognition memory ($p < 0.01$), as compared to the LTG group (multivariate analyses of variance). Neither language function per se, nor general memory capacity nor attention turned out to be selectively affected by TPM. Within the TPM group, none of the tested parameters was correlated to current blood serum levels or daily dosages of TPM. **Conclusions:** According to present data, TPM appears to exert negative influence, particularly on measures of working memory indicating frontal lobe dysfunction. Because these results were obtained beyond titration periods, it can be assumed that cognitive side effects due to TPM tend to persist. Obviously many patients do not habituate to this agent and may develop adverse effects at low dosages. These findings are of special importance for test results of patients with epilepsy undergoing presurgical neuropsychological assessment for the purpose of evaluation of seizure focus lateralization or localization. The test results of patients taking TPM have to be considered with special care not to overestimate frontal lobe dysfunction.

2.229

CARBAMAZEPINE AND OXCARBAZEPINE DECREASE PHENYTOIN METABOLISM THROUGH INHIBITION OF CYP2C19

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Rationale: Unexplained reports of clinically relevant elevations of phenyoin (PHT) plasma levels after the addition of carbamazepine (CBZ) as well as decreases in the formation clearances of its major metabolite 5-(4-hydroxyphenyl)-5-phenyl hydantoin (HPPH) have been observed in several studies (Leppik et al. Metabolism of antiepileptic drugs. New York: Raven Press, 1984:217–22; Zielinski et al. *Ther Drug Monit* 1985;7:51–3; Zielinski et al. *Ther Drug Monit* 1987; 9:21–3; Browne et al. *Neurology* 1988;38:1146–50). However, CBZ is a well-known inducer of cytochromes P450 (CYP) such as CYP3A4 and CYP2C9. PHT is metabolized to HPPH by CYP2C9. The identification of CYP2C19 as a second enzyme contributing to HPPH formation has provided a rationale for a number of PHT interactions with inhibitors of that enzyme (ticlopidine, felbamate, and topiramate). These interactions exhibit a significant degree of intersubject variability associated with the variable contribution of CYP2C19 and its pharmacogenetic behavior. The present study was designed to test the hypothesis that CBZ (and/or carbamazepine 10,11 epoxide; CBZE) inhibit PHT metabolism through inhibition of CYP2C19. Parallel studies were also undertaken with oxcarbazepine (OCBZ), and its 10-monohydroxy metabolite (MHD). **Methods:** The inhibition potency of CBZ, CBZE, OCBZ, or MHD on PHT metabolism to HPPH was evaluated in incubations with cDNA-expressed CYP2C19 with 20 and 40 μM PHT. To further support and quantify the inhibitory effects of CBZ, CBZE, OCBZ, and MHD, the CYP2C19 probe (*S*)-mephenytoin was used (25–225 μM), and inhibition constants were determined in two systems: cDNA-expressed CYP2C19 and human liver microsomes. **Results:** Incubation of PHT with CBZ (both at therapeutic concentrations) showed that CBZ is a potent inhibitor of HPPH formation. The degree of inhibition was dependent on CBZ concentration (33–64% at 30–90 μM CBZ.) CBZE was a less potent inhibitor (7–33% at 15–60 μM). Relevant concentrations of OCBZ (4–12 μM) and of MHD (10–40 μM) also inhibited the metabolism of PHT, and the degree of inhibition was dependent on inhibitor concentrations. MHD was a more potent PHT inhibitor than OCBZ. The inhibitory effects of CBZ and OCBZ and their metabolites on CYP2C19 (*S*)-mephenytoin

metabolism were confirmed in cDNA-expressed CYP2C19 and human liver microsomal preparations. CBZ and MHD exhibited K_i values within their respective therapeutic ranges (8.3 ± 1.8 and 15 ± 10 μ*M,* respectively), indicating that they will behave as inhibitors under normal conditions of use. The K_i values obtained for CBZE (53.5 ± 22.2 μ*M*) and OCBZ (17.9 ± 2.7 μ*M*) were higher than their respective therapeutic concentrations, indicating that these species could only contribute to a small extent to the inhibition produced by CBZ and MHD, respectively. **Conclusions:** CBZ, OCBZ, and their metabolites have the potential to inhibit the metabolism of CYP2C19 substrates in vivo. These observations can explain the reported elevations in PHT concentration after the addition of CBZ or OCBZ and the associated intersubject variability. [Supported by grants from the National Institutes of Health (GM32165).] (Disclosure: Grant: The laboratory of Dr. Levy received a research grant from Warner Lambert-Parke Davis.)

2.230

APPARENT INDUCTION OR EXACERBATION OF PRIMARY GENERALIZED SEIZURES AFTER INITIATION OF OXCARBAZEPINE

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Rationale: In 1983 Shields and Saslow reported new onset of generalized seizures after initiating carbamazepine (CBZ) therapy (*Neurology* 1983;33:1487–9). We now report three cases in which treatment with oxcarbazepine (OCBZ) appears to have induced onset of, or exacerbated, generalized seizures. After review of these case reports, participants will be aware of this possible complication. **Methods:** Review of clinical history and EEGs in children with focal seizures treated with OCBZ who had onset of generalized seizures for the first time after OCBZ was started. **Results:** Patient 1 had a history of complex partial seizures since age 3 years refractory to phenytoin (PHT), primidone (PRM), valproate (VPA), lorazepam (LZP), felbatol, phenobarbital (PB), and CBZ. Her EEG revealed left frontal epileptiform activity. At age 13 years, while still taking PB and CBZ, treatment with OCBZ was initiated, and CBZ was discontinued. Approximately 3 months later, she was noted to have new onset of eye-fluttering episodes. An EEG revealed generalized 3.5-cps spike and slow-wave activity. After discontinuation of OCBZ, the eye fluttering ceased. Patient 2 had onset of left-sided focal seizures at age 3 months refractory to PB, CBZ, LTG, PHT, gabapentin (GBP), and VPA. Multiple EEGs revealed no epileptiform activity. At age 5 years, OCBZ was added to VPA with good seizure control. The VPA was discontinued, and within 2 months, she had onset of frequent generalized convulsive seizures. An EEG revealed frequent bursts of generalized spike and slow-wave activity. The OCBZ was discontinued, and treatment with zonisamide (ZNS) was initiated, with improvement of the seizures. Patient 3 had a history of eye-fluttering episodes with altered responsiveness since age 8 years, and onset of generalized convulsive seizures at age 10. An EEG at that time revealed epileptiform discharges in the left frontal region. The eye flutters persisted on PHT. Switching to OCBZ resulted in a marked increase in eye-fluttering episodes, as well as clumsiness and confusion. A repeated EEG done 6 weeks after the initial EEG revealed frequent, generalized 3-cps spike and slow-wave discharges. Discontinuation of OCBZ and treatment with VPA resulted in a marked improvement in overall level of functioning and decreased, although not complete resolution of, eye fluttering. Further improvement was achieved by addition of ethosuximide. **Conclusions:** It appears that OCBZ induced or exacerbated primary generalized epileptiform activity in these patients, as evident by both clinical and EEG findings. Of additional interest is the fact that this occurred in patients 1 and 2 even though prior treatment with CBZ did not result in this complication. (Disclosure: Grant: Novartis, Ortho-McNeil; Consulting: GlaxoSmithKline, Novartis, Elan, UCB Pharma, Ortho-McNeil; Honoraria: Elan, UCB Pharma.)

2.231

LEVETIRACETAM-RELATED AGGRESSION

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Rationale: The present study examines aggressive behavior in patients who received levetiracetam (LEV) for seizure disorder. **Methods:** We retrospectively reviewed medical records of patients who received LEV for seizure disorder at our epilepsy center between January 2000 and Febraury 2002. We included all patients who received LEV for epilepsy but did not receive any additional antiepileptic drugs (AEDs) during the period of aggressive behavior development. Aggressive behavior is defined here as any significant hostility, verbal, or physical aggression against people or properties as reported by patients, family, caregivers, or school teachers. At the same time, this aggressive behavior must be temporarily correlated with initiation or maintenance periods of LEV therapy, and it required the reduction or discontinuation of LEV and resolution of aggression. Patients who developed any form of psychosis were not included in this study **Results:** We identified 460 patients who received LEV for localization-related epilepsy or generalized epilepsy who fulfilled these criteria for inclusion or exclusion. Age range is 2–84 years, with mean age of 35 years; 240 female (52%) and 220 male subjects (48%). Eighteen patients (3.9%, nine females and nine males) displayed aggressive behavior requiring the reduction or discontinuation of LEV. Four males and three females have had a history of aggression in the past (including a female and a male with hypothalamic hamartoma), and four males and six females developed de novo aggression during the treatment period. The mean age of females who developed aggression was 38.9, and for males, 19.1 years. **Conclusions:** LEV-related aggression is observed in 3.9% of patients and nearly equally affecting males and females. However, females are more likely than males to develop new-onset aggression during treatment, whereas males are more likely to develop aggression at a much youger age than females.

2.232

SINGLE-CENTER 7-YEAR EXPERIENCE OF OXCARBAZEPINE EXPOSURE DURING PREGNANCY

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Rationale: Oxcarbazepine (OCBZ) is rapidly and almost completely metabolized to its active metabolite, 10-hydroxy-10,11-dihydrocarbamazepine (MHD) by a hepatic cytosolic arylketone reductase in humans. CBZ has a similar structure but undergoes oxidation to form an epoxide metabolite that has been attributed to its adverse-event profile including teratogenicity. OCBZ has been marketed in Argentina since 1990 for the treatment of newly diagnosed and poorly controlled patients with epilepsy. Because an epoxide metabolite is not present with OCBZ, the pregnancy outcomes of patients taking OCBZ were reviewed. **Methods:** Our comprehensive epilepsy center has gathered information on 91 pregnancies through an Epilepsy Pregnancy Registry since 1995 for patients exposed to antiepileptic drugs (AEDs). Forty-two of these patients were taking OCBZ during their pregnancies, 25 with monotherapy and 17 in combination with other AEDs. **Results:** No minor or major malformations were recorded in the OCBZ monotherapy group. Likewise, in a subgroup of pregnancies exposed to a combination of OCBZ and a benzodiazepine (BZD), no malformations were noted. One cardiac malformation (ventricular septal defect) was recorded in a neonate exposed in utero to OCBZ/phenobarbital (PB) polytherapy, and another PB-related cardiac malformation was recorded in a case of PB monotherapy. No neural tube abnormalities were seen. All epileptic female patients of childbearing age were given folate supplement prophylaxis. **Conclusions:** In our experience, OCBZ monotherapy was not associated with any fetal malformations. Al-

though we have reviewed a large number of pregnancies, it is still insufficient to draw any definitive conclusions. We encourage all physicians to actively participate with their respective large-scale epilepsy pregnancy registries. (Disclosure: Salary: Dr. Carrazana is an employee of Novartis Pharmaceuticals; Honoraria: Dr. Rabinowicz has received honoraria from Novartis Pharmaceuticals within the past 5 years.)

2.233

OLIGOHYDROSIS AND FEVER IN CHILDREN TAKING THE ANTIEPILEPTIC DRUG ZONISAMIDE

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Rationale: This presentation alerts prescribers of antiepileptc drugs (AEDs) to a potentially life-threatening side effect of the recently approved AED, zonisamide (ZNS). ZNS is an AED developed and first marketed in Japan. It was approved in the United States in March 2000 for adjunctive treatment of partial seizures in adults. ZNS has a sulfonamide side chain in common with the protypical carbonic anhydrase inhibitor, acetazolamide (AZM). In addition to its ability to inhibit carbonic anhydrase, ZNS exhibits in vitro, both sodium and calcium (T-type) channel-blocking properties. In 11 years of development and marketing in Japan, >50 cases of the potentially serious adverse event oligohydrosis/fever have been reported with ZNS use in pediatric patients, some resulting in heat stroke and hospitalization. ZNS is not approved in the United States for pediatric use. Nevertheless, considerable off-label use exists. The purpose of this study was to determine whether cases of oligohydrosis/fever have been reported in the U.S., and if so, to characterize them. **Methods:** We conducted a search of the Food and Drug Administration (FDA) Adverse Event Reporting System for reports of oligohydrosis/fever associated with ZNS use. Patient demographics, concomitant drugs, and ZNS dosing and duration of treatment were summarized from the identified cases. The U.S. reporting rate for oligohydrosis was calculated using prescription data compiled from IMS Health National Prescription Audit and patient demographic data from IMS Health National Disease and Therapeutic Index. **Results:** Five patients were identified as having oligohydrosis with or without fever. The three U.S. reports described a 6-month-old boy, a 9-month-old boy, and a 4-year-old girl. These children were receiving ZNS as monotherapy in doses ranging from 5.7 to 17 mg/kg (mean, 11.5 mg/kg). The duration of therapy to onset of oligohydrosis ranged from 10 days to 4 months. The 6-month-old boy was reported to have a temperature of 41°C. Body temperature was not specified in the other cases. Two of three patients improved on discontinuation of ZNS. The 6-month-old boy improved after ZNS discontinuation, but had not recovered completely. The estimated number of ZNS prescriptions dispensed by retail pharmacies in the U.S. (March 2000–May 2001) was 77,000, of which 27% appeared in the younger than 16-year-old group. Therefore, the U.S. reporting rate for oligohydrosis for this age group is calculated as 1.8/1,000 pediatric-years. **Conclusions:** Children may develop oligohydrosis and fever during ZNS use. This potentially serious adverse event must be considered in the differential diagnosis of fever in a child being treated with ZNS. Discontinuation of ZNS may be the only necessary intervention.

2.234

DO ALLERGIC REACTIONS TO SULFONAMIDE ANTIBIOTICS PREDICT ALLERGY TO ZONISAMIDE?

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Rationale: The package insert for zonisamide (Zonegran; ZNS) states: "Zonegran is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or Zonegran." However, no direct evidence is available to support this statement. Because ZNS is structurally stereospecifically different from sulfonamide antibiotics, the cross-reactivity is not known. The objective of this report is to review our experience with patients who have a history of hypersensitivity to sulfonamides and were treated with ZNS. **Methods:** All patients seen at the Minnesota Epilepsy Group are asked to report any allergies. The type of allergic action is then clarified (e.g., rash, urticaria, angioedema). Fifteen adults and children who reported "sulfa" allergy as a rash had also been treated with ZNS. The allergic reaction to sulfonamide antibiotic was investigated through review of medical records and patient contact, for validation. Charts were reviewed for cross-hypersensitivity reactions. **Results:** Despite the report of rash caused by sulfonamide antibiotics in all 15 patients, in only eight could we find good supportive evidence to validate this reaction. There were four male and four female subjects aged 9–78 years. Median age was 25 years. No rash or allergic reaction of any type occurred in these eight patients. Seven patients continue treatment with ZNS with benefit. One discontinued after 3 months because of lack of improvement in seizure control. No hypersensitivity reaction to ZNS was seen in any of the 15 patients reporting rash. **Conclusions:** These numbers are small, but the stereospecific structure of ZNS is different from that of sulfonamide antibiotics. This may decrease the risk for hypersensitivity and cross-reaction. Patients with intractable epilepsy and a history of rash from "sulfa" drugs may benefit from a cautious trial of ZNS. (Disclosure: Honoraria: Yes.)

2.235

FEW PATIENTS KNOW ABOUT POTENTIAL BONE-HEALTH ISSUES WITH ANTIEPILEPTIC DRUG USE

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Rationale: We surveyed the neurology clinic population at Henry Ford Hospital to determine if patients knew the potential adverse effects of antiepileptic drug (AED) use on bone health and preventive interventions. We wanted to know if there were significant differences based on gender, race, or the indication for AED use (epilepsy vs. other). **Methods:** An anonymous, voluntary "1-minute" survey was offered to every patient seen at two sites of the Henry Ford Neurology Clinic for 3 consecutive weeks in April 2002. Three groups were identified: those with AED exposure for epilepsy, those with AED exposure for reasons other than epilepsy, and those with no prior AED exposure. Replies from those with no AED exposure were used to compare fracture rates. Questions included specific AEDs used, whether health providers discussed bone health, recommended calcium/vitamin D or weight-bearing exercise, patient compliance with recommendations, incidence of fractures, race, age, and gender. Responses were put in a database, and analysis was performed with Pearson Correlations (Statistica). **Results:** The 173 surveys were returned; 18.7% of surveys had some missing responses, but only two were excluded from analysis because of the lack of essential data; 69% were completed by women; 59.6% were white, and 32.7% were African American; 23% of responders had epilepsy, while 17.5% took AEDs for other reasons. Those with AED exposure for reasons other than epilepsy were as likely to be informed about bone-health issues as those with AED exposure for epilepsy, but the rates were quite low for both groups (14.3 vs. 23.1%; $p = 0.94$). Those with AED exposure for reasons other than epilepsy were also as likely to be informed of preventive interventions against bone loss. African Americans likewise were as likely as whites to be given information about AED bone loss (13.3 vs. 22%; $p = 0.26$), but less likely to be told about preventive interventions with calcium/vitamin D (6.7 vs. 43.9%; $p = 0.003$). Fracture rates did not differ based on gender, race, age, or rationale for AED use. An increased incidence of fracture was not seen in those taking AEDs. If patients were told to take supplements, they were significantly more

likely to do so ($p < 0.001$). **Conclusions:** Relatively few patients taking AEDs know the potential adverse effects of these medications on bone health. Significantly fewer African Americans were advised to take adequate calcium and vitamin D for prevention by their health care providers despite similar fracture rates to whites taking AEDs. This survey highlights the need for greater patient education in bone health, especially because patients are significantly more likely to take supplements if advised to do so.

2.236

INTERACTION STUDIES WITH TOPIRAMATE IN THE PENTYLENETETRAZOL AND MAXIMAL ELECTROSHOCK SEIZURE MODELS

Graeme J. Sills, Elaine Butler, George G. Thompson, and Martin J. Brodie (Department of Medicine & Therapeutics, University of Glasgow, Glasgow, Scotland)

Rationale: Refractory epilepsy is a significant clinical problem that requires the development of a rational basis for the use of existing antiepileptic drugs (AEDs), particularly in polypharmacy regimens. There is emerging evidence to support the efficacy of particular combinations of AEDs, although definitive clinical studies are difficult to perform. Experimental seizure models can be employed to identify potentially beneficial combinations for future evaluation in this patient population. The following studies were designed to investigate potential pharmacodynamic interactions between topiramate (TPM) and a range of established and modern AEDs. **Methods:** Adult male ICR mice were pretreated with single doses (and combinations) of TPM (5, 25, 125 mg/kg) and adjunctive agent by intraperitoneal injection. The following adjunctive drugs were employed: phenobarbital (PB; 2, 10, 50 mg/kg), phenytoin (PHT; 2, 10, 50 mg/kg), primidone (PRM; 4, 20, 100 mg/kg), carbamazepine (CBZ; 2, 10, 50 mg/kg), ethosuximide (ESM; 25, 125, 625 mg/kg), sodium valproate (VPA; 40, 200, 1,000 mg/kg), clobazam (CLB; 0.2, 1, 5 mg/kg), vigabatrin (VGB; 10, 50, 250 mg/kg), lamotrigine (LTG; 0.5, 2.5, 12.5 mg/kg), felbamate (FBM; 10, 50, 250 mg/kg), gabapentin (GBP; 5, 25, 125 mg/kg), tiagabine (TGB; 0.2, 1, 5 mg/kg), and levetiracetam (LEV; 10, 50, 250 mg/kg). Anticonvulsant effects of single doses and combinations were determined in the pentylenetetrazol (PTZ) and maximal electroshock (MES) seizure models at 1 h after dosing. **Results:** In the PTZ test, TPM was without significant effect. In contrast, PB, PRM, ESM, VPA, FBM, and TGB all increased the latency to the first generalised seizure induced by 85 mg/kg PTZ. Combinations of TPM and active adjunctive drug were universally effective in the PTZ test. In addition, combinations of TPM with CLB, LTG, and LEV were anticonvulsant, despite the inactivity of the constituent compounds when administered alone. In the MES test, TPM reduced the incidence of tonic seizures in a dose-dependent manner. PB, PHT, PRM, CBZ, VPA, CLB, LTG, FBM, and TGB were similarly effective, as were all combination treatments. **Conclusions:** The findings of these exhaustive studies suggest that combinations of TPM with LTG and LEV may demonstrate anticonvulsant synergism and merit further detailed investigation in more appropriate model systems and with recourse to more quantitative mathematical analysis. [Supported by The RW Johnson Pharmaceutical Research Institute (Springhouse, PA, U.S.A.).] (Disclosure: Salary: None; Grant: GlaxoSmithKline, Janssen-Cilag, Sanofi-Synthelabo, The RW Johnson Pharmaceutical Research Institute, UCB Pharma; Equity: None; Consulting: GlaxoSmithKline, Janssen-Cilag, Pfizer, UCB Pharma; Ownership: None; Materials: None; Stock: None; Royalties: None; Honoraria: GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi-Synthelabo, UCB Pharma.)

2.237

OBJECTIVE ASSESSMENT OF RETINAL FUNCTION IN PATIENTS TAKING VIGABATRIN

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Rationale: Vigabatrin (VGB) has been reported to produce bilateral visual field defects in >30% of patients using subjective ophthalmologic techniques. We report the use of a new objective test of retinal function in this patient population. **Methods:** Retinal function was investigated in 57 treated patients (32 currently taking VGB, 25 never taken VGB) with localisation-related epilepsy using a new high-resolution imaging technique (wide-field multifocal electroretinogram, mfERG). The groups were matched for seizure control and duration of epilepsy (VGB: 17 m/15 f; median age 37 years; median duration 20 years; control: 12 m/13 f; median age, 37 years; median duration, 20 years). The mfERG results were compared with a normative data set (120 healthy drug-free controls) in respect of bilateral abnormalities in the timing of responses. Additional investigations included Humphrey visual field analysis (static perimetry) and fundoscopy. **Results:** Of the 32 patients taking VGB, 15 had moderate or severe bilateral abnormalities on Humphrey visual field assessment, whereas 12 had significant delays in mfERG responses from both eyes. Those with abnormal mfERGs took a greater median VGB dose (3 vs. 2 g daily) for longer (9 vs. 7 years) and, therefore, had a higher median drug burden (6,048 vs. 4,368 g) than unaffected patients. Therapeutic drug monitoring confirmed compliance with VGB treatment. Of the 25 controls, Humphrey visual field assessment was abnormal in one, unreliable in one (multiple fixation losses), and was abandoned in two because of poor tolerance. Bilateral mfERG retinal abnormalities were not detected in any of these patients. **Conclusions:** Wide-field multifocal ERG provides an objective assessment of retinal function that is independent of the patient's ability to perform visual field perimetry. This investigation is well tolerated and does not have the inherent variability and poor reproducibility of subjective visual field testing. This technique can be used to detect retinal dysfunction in treated epilepsy patients and affords the opportunity to determine progression or regression. (Supported by The Ross Foundation.)

2.238

TOPIRAMATE INDUCES MORE WEIGHT LOSS IN OBESE AS COMPARED WITH OVERWEIGHT EPILEPSY PATIENTS OLDER THAN 50 YEARS

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Rationale: Topiramate (TPM) is an effective anticonvulsant (AED) with a broad spectrum of action across seizure types. Weight loss has often been reported as a side effect during treatment with TPM. However, in 2000, NIH publicly reported that 60% of Americans are overweight or obese with body mass index >25 and 30, respectively. Thus, weight loss in epilepsy patients may reflect weight normalization, and actually improve other concomitant medical problems such as diabetes. Although weight loss associated with TPM has been studied in the general epilepsy population (MEDLINE search [66-10/5/01] indicates 35 publications; key words: weight loss and TPM), little is known about the frequency, benefits, and permanence of weight loss in the elderly seizure population treated with TPM. **Methods:** Retrospective chart review of routine clinical care of patients taking TPM for the treatment of seizures in a VA epilepsy clinic. Sample consisted of veterans older than 50 who needed treatment with TPM for their epileptic seizures and were evaluated at the Neuro-Seizure clinic of the Audie L. Murphy VA hospital in San Antonio, TX. Titration schedule and dose modification was dictated by routine clinical care. However, the most common titration schedule used was to start with initial dose of 25 mg at bedtime, and 25-mg increases every other week using a twice-daily schedule until the clinically desired dose was achieved. Mean follow-up was 12.2 months **Results:** TPM was prescribed for 21 patients older than 50 who had epileptic seizures, most often, complex partial seizures. Fourteen patients were between ages 50 and59, two patients were between ages 60 and 69, three patients were between ages

70 and 79, and two patients were older than 80 (range, 50–81). Body mass index (BMI) was calculated using a weight obtained during the initial clinic visit when TPM was prescribed, and again at 3–5 months and 12–15 months after beginning treatment. Seventeen of 21 patients reported taking TPM at the follow-up visits. Two of those 17 patients were excluded for worsening of concomitant medical conditions unrelated to TPM treatment. One patient was diagnosed with colon cancer and malignant ascites. A second patient had a change in chemotherapy for preexistent breast cancer. At second follow-up, the six patients who had initial BMI >30 (obese; range, 31–39) had lost 3.26 BMI units (±2.93 SEM). In contrast, nine patients with initial BMI <29 (range, 23–29) only had lost an average of 0.55 BMI units (±0.90 SEM). A one-tailed *t* test for the difference between these two small groups revealed p value of 0.05. **Conclusions:** TPM was well tolerated in elderly epilepsy patients (81%) at 1 year, and it was associated with weight loss in seizure patients older than 50 who were overweight or obese. The weight loss was more significant in obese patients as compared to overweight patients at 12 months after starting TPM for seizure control. This is an interesting trend that deserves further study using a larger sample size and a prospective design. (Disclosure: Grant: Johnson & Johnson Research Pharmaceutical Institute, NINDS; Consulting: Ortho-McNeil Pharmaceuticals.)

2.239

THE EFFECT OF ZONISAMIDE ON WEIGHT

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Rationale: To determine the effect of zonisamide (ZNS) on weight in adults with epilepsy in a clinical practice. Obesity is a major health issue in the United States (U.S.). For persons with epilepsy, antiepileptic drugs (AEDs) may contribute significantly to to weight. ZNS is a relatively new AED in the U.S. market, and was associated with weight loss in phase III clinical trials. **Methods:** The MINCEP database, of >2,500 people with epilepsy, was searched for treatment with ZNS. Only adults (16 years or older) who were started on ZNS from 2000 onward were considered for the study (n = 103). Seventy-four charts were randomly reviewed for baseline weight (W_0), weight while taking ZNS (W_{ZNS}), ZNS dosages and blood levels, concomitant AEDs and their blood levels. A total of 29 women (mean age, 33 years; range, 16–52 years) and 24 men (mean age, 36 years; range, 16–61 years) had complete data. Length of treatment ranged from 3 to 24 months; mean, 11 months. Student's *t* test and $\chi 2$ statistics were used. **Results:** Overall mean W_0 and W_{ZNS} was 76.78 ± 20.0 kg and 73.76 ± 20.0 kg ($p < 0.001$). Mean W_0 and W_{ZNS} for women were 71.7 ± 21.0 kg (range, 44.4–136 kg) and 67.8 ± 18.8 kg (range, 40.6–134 kg) ($p < 0.005$). Mean W_0 and W_{ZNS} for men were 82.9 ± 17.2 kg (range, 54.1–128.8 kg) and 80.9 ± 19.4 kg (range, 53–135.5 kg) ($p = 0.079$). Twenty-three women (79%) and 15 men (62%) had weight loss of ≥1 kg by $\chi 2$ (NS). Absolute weight difference and percentage of weight loss from baseline were calculated. Weight losses ranged from –1.3 kg to –28.9 kg (mean, –5.5 kg) for women and –1.1 kg to –12 kg (mean, –5.1 kg) for men in those who had weight loss. The mean percentages of weight loss for women and men were 7.1 ± 5.5% and 6.56 ± 4.7%, respectively ($p = 0.76$). All three patients receiving ZNS monotherapy had weight loss (mean, –4.5 kg). Fifty patients were taking ZNS with two to four other AEDs. The most commonly used concomitant AEDs were sodium valproate (VPA; 22), carbamazepine (CBZ; 21), and levetiracetam (LEV, 20). Four of 11 men (36%) and eight of 11 women (73%) who were taking VPA had weight loss (NS). **Conclusions:** Absolute weight loss is a significant effect of ZNS. In addition, women had a significant decrease in absolute weight after initiation of ZNS. The effect of ZNS on weight loss appears to be independent of concomitant AEDs. Additional analysis regarding dose, drug levels, and gender differences will be presented. (Supported by MINCEP Epilepsy Care.)

2.240

THE AUSTRALIAN REGISTRY OF ANTIEPILEPTIC DRUGS IN PREGNANCY: MULTIVARIATE LOGISTIC REGRESSION ANALYSIS DEMONSTRATING AN INCREASED RISK FOR VALPROATE, WITH A DOSE-DEPENDENT RELATION

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Rationale: Many women with epilepsy who become pregnant need to take antiepileptic drugs (AEDs) to prevent the potentially harmful effects of seizures. However, retrospective studies have demonstrated an increased chance of having a child with a birth defect (BD) in these women. It is uncertain how much of this risk is directly caused by the AEDs and whether certain drugs or drug combinations are associated with a greater risk. **Methods:** An Australia-wide, prospective, voluntary, telephone-interview–based, observational register enrolled three groups of women: those with epilepsy taking AEDs, those with epilepsy not taking AEDs, and those taking AEDs for a nonepileptic indication. The pregnancy outcomes are evaluated by follow-up interviews and by reference to hospital and treating doctors' records. **Results:** In the first 30 months of the study (until December 2001), 333 eligible women have been enrolled, with all states and territories being represented; 293 pregnancies had been completed, of which 254 (86.7%) have been a healthy live birth; 19 (6.5%), a live birth with a birth defect; four, an induced abortion because of a detected malformation on ultrasound; one, a premature labor with a stillbirth; and 11 (3.8%), a spontaneous abortion. Of completed pregnancies, 269 were exposed to at least one AED during the first trimester [carbamazepine (CBZ), 124; valproate (VPA), 96; lamotrigine (LTG), 52; clonazepam (CZP), 20; phenytoin (PHT), 19; vigabatrin (VGB), seven; gabapentin (GBP), nine; topiramate (TPM), six; tiagabine (TGB), two; primidone (PRM), two; acetazolamide (AZM) and diazepam (DZP), one]. The incidence of birth defects in relation to each specific AED was VPA (16.7%), PHT (10.5%), LTG (7.7%), and CBZ (3.2%), none of which was significantly different from women with epilepsy not taking an AED (4.3%; $p > 0.05$). However, multivariate logistic regression analysis found VPA exposure to be independently associated with the occurrence of BDs (OR, 4.6; $p = 0.03$). Additionally, the dose of VPA taken was higher in pregnancies with BDs compared to those without (mean, 2,081 vs. 1,146 mg; $p < 0.0001$). The incidence of folate supplementation being taken before conception did not differ for pregnancies with or without BDs (69.6 vs. 66.4%; $p > 0.05$). **Conclusions:** The model for the Australian Pregnancy Register has proved successful, with strong enrollment from all regions. The study is prospective and includes reference to all new AEDs approved in Australia over the past decade. Results to date provide evidence that exposure to VPA during the first trimester may be independently associated with a higher risk of an infant/fetus with a birth defect, particularly at higher doses. [Supported by unrestricted grants from the The Epilepsy Foundation of Victoria, The Epilepsy Society of Australia, Pfizer Pharmaceuticals, Aventis Pharma, Sanofi-Synthelabo, Novartis Pharmaceuticals, Janssen-Cilag, GlaxoSmithKline, and UCB (Belgium).] (Disclosure: Grant: Study supported by unrestricted grants from The Epilepsy Foundation of Victoria, The Epilepsy Society of Australia, Pfizer Pharmaceuticals, Aventis Pharma, Sanofi-Synthelabo, Novartis Pharmaceuticals, Janssen-Cilag, GlaxoSmithKline, and UCB.)

2.241

ACUTE, INTERMITTENT, AND RELAPSING CONFUSIONAL STATUS WITH TIAGABINE TREATMENT

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Rationale: Tiagabine (TGB) is a specific inhibitor of γ-aminobutyric acid (GABA) recapture and is effective as add-on therapy in refractory partial epilepsy. Several cases of nonconvulsive status have been described, reversible after stopping TGB. Question remains open about the etiology of such status: nonconvulsive status, toxic encephalopathy, or both. We described the EEG clinical evolution of five patients with acute and intermittent confusional status in three of them. **Methods:** Five partial epilepsy patients (four women, aged 22–38 years) have been treated according to a slow up-titration of TGB (5 mg/day/week) as monotherapy in one case and add-on therapy in the others [two carbamazepine (CBZ), two valproate (VPA), two topiramate (TPM), one lamotrigine (LTG)]. All patients have simple and complex partial seizures, three secondary to mesiotemporal sclerosis (one right), one to holoprosencephaly, and one to corticotemporal trauma. Comedication remained unchanged during the titration and the treatment with TGB. **Results:** Five partial epilepsy patients had confusional status in three cases. At the beginning of the treatment, there was no problem. However, after the dose of 30–60 mg/day (0.6–0.75 mg/kg/day), they presented a progressive and chronic confusion in two cases, and acute, intermittent, and relapsing in the three other cases. There was no concomittant sudden seizure control. The confusion started relatively abruptly 1–2 h after TGB intake and disappeared spontaneously after 2–3 h. This happened twice or thrice a day, more severely at the end of the day. When the patient was confused, for all of them, EEG was characterized by a high-amplitude delta wave EEG without (true) spikes. TGB was then progressively downtitrated, and all symptoms disappeared under the dose of 30–40 mg/day while for another patient, the situation (clinical and EEG) was dramatically improved by benzodiazepine (BZD) injection. For these patients, TGB was further continued with lower doses (20–30 mg/day) without specific problems. **Conclusions:** We presented five patients developing confusion when TGB was progressively increased. In the literature, such cases are presented as nonconvulsive status. However, some of these cases could be related to a toxic encephalopathy, as previously described with VPA. In this case, the use of BZD is rarely helpful. Probably confusion related to TGB treatment is secondary to several mechanisms including nonconvulsive status and/or toxic encephalopathy. These mechanisms are important to know, because therapeutic approach could be quite different.

2.242
CONTINUED USE OF ZONISAMIDE AFTER DEVELOPMENT OF RENAL CALCULI

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Rationale: The incidence of development of renal calculi with zonisamide (ZNS) is ~4%. Most often these are assymptomatic, but they may be symptomatic in ~1.2% of patients. ZNS is often discontinued after the development of renal calculi. There is no information available about the safety of the continued use of ZNS in patients. **Methods:** A retrospective chart review was performed at two academic epilepsy centers (Baylor College of Medicine Comprehensive Epilepsy Center in Houston, Texas and Rush Epilepsy Center in Chicago, Illinois). Patients with epilepsy who developed renal calculi after ZNS and continued to use it after their development were included. **Results:** Three patients who met these criteria were identified. All three were diagnosed with medically intractable partial seizures. Please refer to Table 1 for patient demographics. Patient 1 developed severe flank pain, and the ZNS was discontinued after a diagnosis of renal calculi was made. Seizures became very frequent after discontinuing ZNS. ZNS was restarted after attempts at controlling seizures with other medications were unsuccessful. A renal ultrasound was performed after 4 months and demonstrated no renal calculi. Patient 2 also elected to continue treatment with ZNS due to significant reduction in seizure frequency. A renal ultrasound was performed after 4 months and demonstrated no renal calculi. Patient 3 had previously developed renal calculi with TPM and also had a family history. He elected to continue treatment with ZNS because of a >90% reduction in seizure frequency with ZNS. **Conclusions:** ZNS is indicated for adjunctive therapy for partial seizures in adult epilepsy patients. The development of renal calculi often results in discontinuation of the medication. We present three patients who elected to continue treatment with ZNS despite development of symptomatic renal calculi and who have since remained assymptomatic despite continued treatment. All three patients elected to continue treatment because of a significant reduction in seizure frequency with ZNS. Renal ultrasounds were performed in two patients 4 months after the development of calculi, and both demonstrated no recurrence. This indicates that development of renal calculi should not be considered a contraindication to continued use of ZNS and that continued use may be safe in some patients. This also supports the effectiveness of ZNS in patients with medically intractable epilepsy. (Disclosure: Consulting: Elan Pharmaceuticals; Honoraria: Elan Pharmaceuticals.)

2.243
EFFECT OF TOPIRAMATE ON THE CHANGES OF INTERLEUKIN-1β, TUMOR NECROSIS FACTORα, AND NITRIC OXIDE IN SERUM AND CEREBROSPINAL FLUID IN EPILEPSY PATIENTS

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Rationale: To study the probable mechanism of topiramate (TPM) in the pathogenesis of epilepsy. **Methods:** The levels of interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), and nitric oxide (NO) production of nitrite (NO_2) in serum and CSF of 48 epilepsy patients and 27 normal subjects were measured with radioimmunoassay and fluorometric method. **Results:** The levels of IL-1β, TNFα, and NO_2 in serum and CSF were significant higher than those in normal subjects ($p < 0.01$).Treatment with TPM decreased the levels of IL-1β, TNFα, and NO_2 in serum and CSF of epilepsy ($p < 0.05$ or $p < 0.01$), but still higher than normal subjects ($p < 0.01$). Combined treatment with TPM and flunarizine (FNR), serum IL-1β, TNFα, and NO_2 in epilepsy were not significantly different from the normal subjects ($p > 0.05$), but the levels of TNFα and NO_2 in CSF were still higher than those in normal subjects ($p < 0.05$ or $p < 0.01$). **Conclusions:** The pharmacologic effect

TABLE 1. *Patient demographics*

Patient no.	Age (yr)	Epilepsy classification	Seizure onset	ZNS + AED	ZNS dose (mg/day)	Seizure frequency before ZNS	Seizure frequency with ZNS
1	43	Symptomatic generalized	Multifocal	Valproic acid, diazepam	400 mg/day	4–5 GTCs/week	Seizure free except in setting of fever or infection
2	20	Localization related	Left parietal	Oxcarbazepine	700 mg/day	4–5 secondarily GTCs/week	>50% reduction
3	28	Localization related	Supplementary motor	Carbamazepine	600 mg/day	3 secondarily GTCs/night	Seizure free except when noncompliant with meds or alcohol related (3–5/month)

of TPM is associated with the pathogenesis of epilepsy, and this effect will be enforced as it combines with the flunarizine. (Supported in part by China Janssen Pharmaceutical.)

TABLE 1. *Changes of serum IL-1β, TNFα, and NO_2*

Group	No.	IL-1β (ng/ml)	TNFα (mg/ml)	NO_2 (nmol/ml)
Epilepsy	48	7.19 ± 1.49^a	6.34 ± 0.62^a	42.64 ± 8.12^a
Epilepsy + TPM	42	$6.56 \pm 1.42^{a,b}$	$5.74 \pm 0.57^{a,b}$	$34.53 \pm 7.87^{a,b}$
Epilepsy + TPM + FNR	17	4.37 ± 1.34^c	4.26 ± 0.56^c	29.92 ± 6.53^c
Control	27	3.76 ± 1.03^a	4.12 ± 0.34	29.23 ± 5.64

Compared with control, $^a p < 0.01$; compared with epilepsy group, $^b p < 0.01$.

TABLE 2. *Changes of serum IL-1β, TNFα, and NO_2 in CSF*

Group	No.	IL-1 ± gb (ng/ml)	TNFα (mg/ml)	NO_2 (nmol/ml)
Epilepsy	48	8.89 ± 1.24^a	7.94 ± 1.21^a	8.64 ± 1.12^a
Epilepsy + TPM	33	$7.87 \pm 1.18^{a,c}$	$7.04 \pm 1.07^{a,c}$	$6.53 \pm 0.87^{a,c}$
Epilepsy + TPM + FNR	12	5.66 ± 0.97^c	$6.34 \pm 0.86^{a,c}$	$4.68 \pm 0.82^{b,c}$
Control	27	5.56 ± 0.85	4.62 ± 0.30	4.23 ± 0.44

Compared with control, $^a p < 0.01$, $b p < 0.05$; compared with epilepsy group, $^c p < 0.01$.

Non-AED/Surgical Treatment

2.244
A CROSS-SECTIONAL STUDY OF BONE DENSITY IN CHILDREN TREATED WITH THE KETOGENIC DIET

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Rationale: Osteoporosis is increasingly recognized to occur in patients with epilepsy (both men and women) and in children with chronic disabilities. Older-generation antiepileptic medications (AEDs) are known to to cause osteopenia/osteoporosis through various mechanisms. Little is known about the effects on bone health of the newer AEDs or the ketogenic diet (KD). It has been postulated that the KD could have adverse effects on the bone health by leaching of the bone mineral content to compensate for the acidosis and by direct effects on vitamin -D metabolism. The effects of the KD on bone health were assessed using a cross-sectional study approach. **Methods:** A cross-sectional study was designed using two groups of children, before and 12–24 months into the KD treatment. Group one was about to start the KD, and group two had been treated with the traditional 4:1 KD (with a multivitamin with minerals, calcium, and phosphorus supplements) for 12–24 months. Demographics, seizure history, weight, and height were collected. Changes in bone density were determined using dual energy x-ray absorptiometry (DXA QDR, Hologic 2000). The lumbar spine was assessed for bone area, bone mineral concentration, and bone mass density. Comparisons were made using Z-score averages, two-sample *t* test, and analysis of variance testing. **Results:** The two groups were similar in age, gender distribution, number of AEDs exposed to before the measurement, and percentage cerebral palsy. Group one (children who were about to start the KD) weighed less and were shorter than expected for their age. The group had a relative osteopenia of ~1 standard deviation. Group two showed similar weight and height characteristics, but the boys had a significantly worse osteopenia despite a 50% reduction in the number of AEDs. See Table 1. **Conclusions:** Children with intractable epilepsy are smaller and shorter than their age-matched controls. A pattern of decreased bone density was observed in the KD group; even though they consumed fewer AEDs; this was significant in the boys. Prospective longitudinal studies are needed to evaluate the many different effects on growth and nutrition in children with intractable epilepsy and chronic disabilities who are treated with the KD. (Supported by K23 RR 16074 NIH.)

TABLE 1. *Data for group I before starting KD and group II 12–24 months into the KD treatment*

Variables (mean)	G I total	G I boys	G I girls	G II total	G II boys	G II girls
No.	36	20	16	20	10	10
Age (yr)	7.2	6.8	7.8	7.0	7.9	6.1
No. AEDs at measurement	2.5	2.5	2.4	1.25	1.2	1.3
No. AEDs before measurement	7.6	8.1	7.1	7.0	7.8	6.2
Cerebral palsy (%)	56	40	75	55	50	60
Weight Z score	–0.38	0.08	–0.96	–0.44	–0.56	–0.32
Height Z score	–0.86	–0.11	–1.80	–1.44	–1.51	–1.36
BMD Z score	–1.17	–1.22	–1.10	–1.68	–2.19**	–1.18

2.245
MONITORING THE KETOGENIC DIET: IS THERE A STANDARD?

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Rationale: To determine whether there are common standards of care practiced by the ketogenic diet (KD) programs in the United States. **Methods:** A survey of 26 questions was developed by our ketoteam. The survey was then mailed to 50 registered dietitians (RDs) in epilepsy centers using the KD across the United States to assess what standards they follow. An initial response rate was analyzed after a 3-week period. **Results:** The survey was returned by 14 of 50 centers (28%). In general, the response of the survey shows that there are indeed no consistent standards of care followed. RDs answered some categories similarly, but there are a variety of areas that differ in the monitoring process. Examples of differences include (a) routine monitoring of laboratory results, (b) initiating or tapering of the diet, (c) assessment of calorie and protein needs, and (d) nutritional supplements prescribed. Additional monitoring variations are illustrated in the two tables. **Conclusions:** The American Dietetic Association (ADA) has developed standards of care for monitoring the nutritional status of various diseases of the pediatric population such as renal disease, diabetes, etc. By following these standards, RDs are able to assess patients in a consistent manner and to provide optimal recommendations based on the disease. The responses of the survey indicate that there is great variation in how the KD is monitored and assessed among epilepsy programs in the United States. The KD limits calories, protein, and micronutrients, which could lead to severe side effects. Therefore, the development of standards of care for the management of the KD across the United States would provide great benefit to this population. Further research and collaborating discussion among ketogenic programs

is needed in effort to develop such standards. (Supported by NIH 1K23RR16074.)

TABLE 1. *Preketogenic diet screening*

Areas screened	Yes	No	Nonapplicable
Complete lipid profile	35.7%	42.9%	21.4%
Prealbumin	14.3%	64.3%	21.4%
Zinc	7.1%	71.5%	21.4%
Magnesium	21.4%	57.2%	21.4%
Carnitine profile	28.6%	50.0%	21.4%
Swallowing dysfunction	57.1%	21.5%	21.4%
Reflux issues	42.9%	35.7%	21.4%

TABLE 2. *Ketogenic diet practices*

Common practices	Yes	No	Other	No response	Nonapplicable
Provide education classes before ketogenic diet	35.7%	28.6%	7.1%	7.1%	21.4%
Provide glucometer training for parents/ caregivers	7.1%	64.3%			28.6%
Restrict fluids on diet	42.9%	35.7%			21.4%
Restrict protein on diet	35.7%	42.9%			21.4%
Restrict calories on diet	50.0%	21.4%		7.1%	21.4%

2.246

EARLY- AND LATE-ONSET COMPLICATIONS OF KETOGENIC DIET IN INTRACTABLE EPILEPSY

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Rationale: Antiepileptic efficacy of ketogenic diet (KD) has been proved, but low tolerance and various complications still limit the wide application of this treatment. We studied the extent of early- and late-onset complications to evaluate the exact limitation and to provide the method to overcome complications of the KD. **Methods:** One hundred seventeen intractable childhood epilepsy patients treated by KD from October 1995 to October 2001 at the Department of Pediatrics and Epilepsy Center at Sang-gye Paik Hospital were involved. Mean age of the patients at the beginning of the KD was 67.0 ± 60.9 months (range, 7 months to 16 years), and mean duration of KD was 12.6 ± 10.4 months (range, 1–43 months). Early- and late-onset complications were reviewed, as well as their outcomes. **Results:** Most common early complication was gastrointestinal symptoms such as nausea/vomiting and diarrhea associated with gastritis and fat intolerance, noticed in 46 cases (39.3%). Other early complications during the first 2 months of KD were hypertriglyceridemia in 27 patients (23.1%), transient hyperuricemia in 27 patients (23.1%), symptomatic hypoglycemia in nine patients (7.7%), lipoid pneumonia in six patients (5.1%), hypomagnesemia in six patients (5.1%), and various infectious diseases in eight patients (6.8%). Late complications after 2 months of KD were gastrointestinal symptoms in 34 patients (29.1%), various infectious diseases in 23 patients (19.7%), hypercholesterolemia in 23 patients (19.7%), hypertriglyceridemia in 22 patients (18.8%), osteoporosis in 18 patients (15.4%), hypomagnesemia in 14 patients (11.9%), hyperuricemia in nine patients (7.7%), hepatitis in seven patients (5.9%), hypoproteinemia in five patients (4.3%), chronic hypokalemia without acute dehydration in five patients (4.3%), renal stone, iron-deficiency anemia, and aspiration pneumonia each in two patients (1.7%), cardiomyopathy, secondary hypocarnitinemia, acute pancreatitis, and symptomatic hypoglycemia each in one patient (0.9%). Twenty-one patients stopped KGD due to complications depite their therapeutic efficacies. The causes of discontinuation were serious infectious illnesses in nine patients, gastrointestinal intolerance in eight patients, severe osteoporosis, persistent hypomagnesemia with tetany, cardiomyopathy, and lipoid pneumonia due to aspiration each in one patient. Growth retardation was noticed in 41 patients among 65 patients maintained >6 months, but only five patients remained growth retardation after discontinuation. Most of early- and late-onset complications were transient and successfully managed by conservative treatments. KD-related deaths were presumed in four cases. The causes of deaths were sepsis in two patients, cardiomyopathy and lipoid pneumonia each in one patient. **Conclusions:** Most KD complications are transient and can be easily managed with various conservative managements, but life-threatening complications should be closely monitored during follow-up. (Supported by Sang-gae Hospital.)

2.247

CALORIE REQUIREMENT AT KETOGENIC DIET INITIATION

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Rationale: The ketogenic diet (KD) comprises three main components: restricted calories, high proportion of fat, and fluid restriction. Lack of efficacy often is attributed to excessive caloric consumption as indicated by excessive weight gain (although other factors can also cause decreased efficacy, like noncompliance, excess fluids, unrecognized carbohydrate). Calories prescribed at initiation of KD are calculated based on recommended daily allowance (RDA) for age and weight. However, caloric needs can be measured using oxygen consumption and carbon dioxide production (indirect calorimetry). Accurate measurement of caloric need at diet onset is likely to prevent excess weight gain (or loss) during KD therapy. **Methods:** Twenty-one patients (8 months–69 years) who were able to complete indirect calorimetry were started on the KD; 20 had intractable epilepsy. One (69 years) had a dementing illness, polyglycosan body disease. Average age was 9.1 years. Initial calorie requirement was calculated based on RDA for age and weight. Indirect calorimetry was performed using a commercial device to measure oxygen consumption and carbon dioxide production. The calories prescribed at KD initiation were based on the results of calorimetry. **Results:** The caloric needs based on RDA ranged from 20 to 57 kcal/kg (average, 46). The caloric needs calculated from calorimetry ranged from 22 to 101 (average, 53). Seven of the 21 patients had a difference between the measured and RDA-estimated calorie requirement ≥25%. Three of seven had calorimetry-based values less than RDA values. Six of these seven patients maintained weight within 300 g at first follow-up visit (22–163 days). Across the entire group of 21 patients, the average weight change was –200 g (±1.3 kg). For 13 patients (at first follow-up), urine ketones were reported as usually "large." For five, ketones were consistently in the "moderate-to-large" range. **Conclusions:** Indirect calorimetry testing to measure each individual's calorie requirements allowed adjustment of the KD prescription at diet initiation instead of at follow-up; 33% of patients started on the KD had calorimetry-based calorie requirements substantially (±25%) different from RDA-based values. For most of these patients, weight was stable between diet initiation and first follow-up. Accurate prescription of the daily calorie requirement at initiation of KD usually results in stable weight at follow-up. When patient weight is stable between visits, it eliminates a variable to which either lack of KD antiseizure efficacy or adverse effects might be attributed.

2.248

OXIDATIVE METABOLISM OF ^{13}C-LABELED KETONES IN HUMAN BRAIN

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Rationale: The antiepileptic action of the ketogenic diet is not well defined. Furthermore, dietary management is often empiric, evaluated through its efficacy and measurement of plasma ketones. To better understand the diet's mechanism of action, more data are needed on how the brain uses ketones. This study uses ^{13}C-labeled ketones and in vivo magnetic resonance (MR) spectroscopy to evaluate how β–hydroxybutyrate (BHB) is used in the brain of healthy adults. **Methods:** Under an IRB-approved protocol, four healthy overnight-fasted adults were studied; i.v. catheters were placed in both antecubital fossa veins, and 200 m*M* sodium [2,4-$^{13}C_2$]-D-BHB was bolus infused at 16.7 ml/min × 20 min and then maintained at 22 μ*M*/kg/min × 100 min. A Bruker Biospec 2.1-T human MR system and a ^{13}C (22.55 MHz) surface coil with quadrature ^{1}H (89.64 MHz) decoupling coils were used for all studies. As previously described, a localized adiabatic ^{13}C-[^{1}H] polarization transfer sequence was used for detection of ^{13}C, resulting in a sample volume of 6 × 4 × 6 cc selected from the occipital-parietal lobes (Shen et al. 1999). **Results:** The increase in plasma BHB is rapid and is accompanied by a near-simultaneous increase in brain BHB. From the four subjects, the achieved plasma concentration of BHB was 2.25 ± 0.24 m*M* with an apparent brain concentration of 0.18 ± 0.06 m*M* measured at the end of the infusion. Fig. 1 demonstrates the ^{13}C labeling of the amino acid pools acquired during the 60- to 120-min period of a 2-h infusion study from a volunteer. The positions of glutamate, glutamine, and aspartate are well resolved. The anticipated point of ^{13}C entry in the amino acid pools is glutamate-4 (from oxidative degradation of [2,4]-$^{13}C_2$-BHB) with subsequent labeling into glutamine-4 and glutamate-3 (neurotransmission and metabolism). The relative labeling of glutamate-4, glutamine-4, and glutamate-3 were 6.78 ± 1.71%, 5.68 ± 1.84%, and 5.91 ± 1.70%. **Conclusions:** The steady-state BHB measurement of 0.18 ± 0.04 m*M* is consistent with that determined in earlier studies using nonlabeled D-BHB infusions (Pan et al., 2001), at ~0.2 m*M*. Because of contributions from brain and nonbrain components (vascular, CSF), this value is an upper bound-to-the-brain BHB concentration. The distribution of ^{13}C label seen in glutamate and glutamine resembles that for glucose. Analysis of the glutamate-4 and glutamine-4 labeling using a metabolic model based on interacting neuronal and astrocytic pools suggests that under these conditions, BHB consumption is preferred by the neuronal compartment by at least a factor of 1.85. This suggests that with regard to ketogenic diet therapy, ketones may provide a fuel that is preferentially earmarked for neuronal consumption, thereby bypassing the astrocytic metabolism hypothesized with glucose consumption (Magistretti et al., 1996). [Supported by NIH R01 NS40550-1, P01 NS39092, R01 NS37527 and the Charles A. Dana Foundation .]

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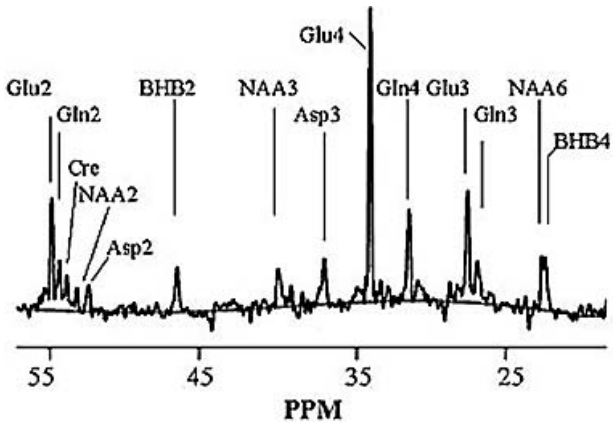

2.249
VAGUS NERVE STIMULATION IN RETT SYNDROME
Rebecca J. Schultz and Angus A. Wilfong (Pediatric Neurology, Baylor College of Medicine, Houston, TX; Pediatric Neurology, Texas Children's Hospital, Houston, TX)

Rationale: At the end of this activity the participants should be able to describe the effectiveness and tolerability of vagus nerve stimulation for the treatment of medically refractory epilepsy in Rett syndrome. **Methods:** Four females with Rett syndrome and medically refractory symptomatic generalized epilepsy, aged 1.5–14.5 years, had a vagus nerve stimulator implanted. Two of the subjects have received vagus nerve stimulation (VNS) for 3 months, one for 1 year, and one for 2 years. Neuropsychological testing including assessments of mood and alertness, the number and dosage of antiepileptic medication (AED), percentage decrease in seizure frequency, and utility of magnetic activation were assessed. **Results:** All four subjects demonstrated improved mood and alertness within the first month of VNS. The dosage of AED was reduced in all four subjects. The mean percentage decrease in seizure frequency was 69.5% at 1 month and 79.2% at 3 months. In the two subjects undergoing VNS for 1 year, the mean percentage decrease in seizure frequency was 83.5%. In the subject undergoing VNS for 2 years, the mean percentage decrease in seizure frequency was 100%. In all four subjects, magnetic activation of the VNS aborted or diminished the duration of seizures 50% of the time. **Conclusions:** VNS appears to be an effective long-term treatment for medically refractory epilepsy in Rett syndrome. Additional benefits of VNS in Rett syndrome are improved mood and alertness; these benefits occur independent of reduction in medication or decrease in seizure frequency. (Supported by Cyberonics.) (Disclosure: Grant: Cyberonics; Honoraria: Cyberonics.)

2.250
PHOTODYNAMIC THERAPY FOR EPILEPSY: BEHAVIORAL ANALYSIS
Nicholas A. Scott, Krithi Ravindranath, Kawanaa D. Carter Valerie Coon Lee Rognlie-Howe, Benjamin Edwards, Graca Vicente, and Edie E. Zusman (Neurological Surgery, University of California, Davis, Davis, CA)

Rationale: Photodynamic therapy (PDT) has been used in treatment of some forms of cancer, to target abnormal tissue with a photoactive dye that is preferentially taken up by tumor cells. PDT combines the uptake of a photosensitizing agent with exposure to laser light; the consequent excitation of the photosensitizing compounds causes the release of singlet oxygen (a free radical) that results in cytotoxicity. Cells that preferentially take up the dye are killed, with limited damage to the surrounding normal tissue. Application of this treatment for epilepsy may allow clinicians to selectively label and kill cells involved in seizure generation, leaving normally functioning brain unharmed. The objective of the current study was to determine the safety of PDT in a rat model of epilepsy. Specifically, we examined performance on a behavior that is thought to depend on intact hippocampal function, after injection of photosensitizing dye and laser exposure in kindled rats. **Methods:** The study was composed of four groups of eight animals each. Group A was a naïve control, Group B received a unilateral craniectomy and sham laser application. Groups C and D were implanted with bipolar stimulating electrodes in the perforant path, and were subsequently kindled (three consecutive stage 5 seizures). Animals in this group received injections of 5-aminoluvelinic acid (ALA), an FDA-approved photosensitizing agent, followed by one induced generalized seizure on the day of laser treatment. Group C, in addition, received a unilateral craniectomy and sham laser application, whereas Group D received a unilateral craniectomy followed by 10 min of laser treatment (laser wavelength of 635 nanometers; laser positioned 2.3 cm from the surface of the brain). After a 1-week recovery period, all animals underwent a behavioral battery which included the Morris Water Maze (MWM) (dependent on intact hippocampal function) and an inclined-plane evaluation. **Results:** Statistical analysis of performance on the MWM task indicated that there were no significant dif-

ferences between animals that received laser treatment and control animals [$F = 0.920$, ($df = 3, 27$), $p = 0.445$, between groups]. In addition, there were no differences across groups on the inclined-plane assessment. **Conclusions:** Preliminary data suggest that unilateral PDT in this model of epilepsy does not impair hippocampus-mediated spatial learning as measured by the MWM. Further, this therapeutic modality does not cause significant motor weakness, as determined by the inclined-plane test. Conclusions regarding PDT safety await further behavioral (and histologic) analysis. (Supported by C.U.R.E. Bronte Foundation.)

2.251

THE INCIDENCE AND MANAGEMENT OF CARNITINE DEFICIENCY IN CHILDREN ON THE KETOGENIC DIET

Rhonda R. Werner, Beth Zupec-Kania, Mary L. Zupanc, and Lori Arentz (Comprehensive Epilepsy Program, Children's Hospital of Wisconsin, Milwaukee, WI; Pediatric Neurology, Medical College of Wisconsin, Milwaukee, WI)

Rationale: The ketogenic diet (KD) has been used as a therapy for epilepsy since the 1920s. Recently, it has been used more frequently as an alternative therapy for children with medically refractory epilepsy. As with other epilepsy therapies, the KD has been associated with treatment side effects, including a secondary carnitine deficiency. Potential reasons for this deficiency may include an inadequate intake of carnitine, a greater demand on carnitine use, or an increase in the renal excretion of carnitine conjugates (De Vivo DC et al. L-carnitine supplementation in childhood epilepsy: current perspectives. *Epilepsia* 1998; 39:1216–25). At the end of this presentation, the participants will better under stand the incidence of carnitine deficiency in children on the KD and the response to carnitine supplementation in those children who are identified as being carnitine deficient. **Methods:** A retrospective chart review was done for 20 children between 6 months and 15 years who were started on the KD. There were nine children who received their nutrition enterally and 11 children who were orally fed. **Results:** Three (43%) of the enterally fed children and eight (73%) of the orally fed children developed a carnitine deficiency (free carnitine <20 μM). The decreases in free carnitine levels were manifested 1–6 months after starting the diet. The carnitine-deficient children were on a KD ratio of 3:1 to 4:1. Two of the enterally fed children who were taking valproate (VPA) had a carnitine deficiency at the onset of the diet. Of the children with carnitine deficiency, 10 were started on carnitine supplementation (30–63 mg/kg/day), and two had the diet discontinued because of lack of efficacy. Seven of the children who received supplementation had normalization of free carnitine levels after initiation of carnitine; one child had normalization of free carnitine after supplementation was increased from 30 mg/kg/day to 43 mg/kg/day. Two of the children did not receive follow-up carnitine levels because of discontinuation of the diet. Additionally, after 1 month on the diet, one (8%) of the oral feeders developed a symptomatic carnitine insufficiency (acyl/free ratio >0.4) characterized by an increase in seizures and lack of energy. One of the children with carnitine deficiency, and the child with carnitine insufficiency (on 5 mg/kg/day) described improved energy and alertness after supplementation. **Conclusions:** Of the children on the KD, 61% developed a carnitine deficiency, with the greater portion (73%) of these children receiving their nutrition orally as opposed to enterally (43%). The discrepancy between orally fed and enterally fed children could be related to the fortification of carnitine in the enteral formula. All of the children that had follow-up carnitine levels after supplementation had improved free carnitine levels. Children on the KD should have a baseline carnitine level and regular monitoring of their carnitine levels so that supplementation can be initiated when appropriate. Additional research is needed to determine if there is a clinical response related to symptoms of carnitine deficiency after supplementation in children who are carnitine deficient secondary to the KD.

2.252

IS A FAST NECESSARY WHEN INITIATING THE KETOGENIC DIET?

Elaine C. Wirrell, Husam Z. Darwish, Christine Williams-Dyjur, Marlene Blackman, and Valerie Lange (Pediatric Neurology, Alberta Children's Hospital, Calgary, Alberta, Canada)

Rationale: At the end of this activity, the participant should consider initiation of the ketogenic diet without a preceding fast. To determine time of onset of ketosis and efficacy when the classic ketogenic diet is initiated at full calories without a prior fast in children with epilepsy. **Methods:** Retrospective hospital and neurology clinic chart review of all 14 children commenced on the classic ketogenic diet at full calories without a prior fast between January 1, 1997, and May 31, 2001, to determine time to ketosis, time to good ketosis (urine ketones >80 mg/dl), and success of the diet. **Results:** Median age at diet initiation was 63 months (25–75%ile, 47–149 months). There were seven girls and seven boys. Four had symptomatic generalized epilepsy while the remainder had partial seizures ± secondary generalization. Twelve of 14 children suffered seizures on a daily basis before the ketogenic diet. Six were commenced on the diet as outpatients while eight were admitted to hospital. No patients were fasted. All admitted patients were started on a 1:1 ketogenic ratio at full calories for the first 24 h and advanced to a 3–4:1 ratio over 3–4 days, while outpatients were started on a 1–2:1 ratio and similarly advanced. Thirteen of 14 patients were successfully started on the diet, with one developing vomiting and food refusal during the initial hospitalization but after ketosis was established. One child was lost to follow-up after initial hospital discharge. Information regarding time to ketosis was determined for all inpatients. Mean time to onset of ketosis was 33 h (range, 17–48) and to good ketosis, 58 h (range, 40–84). Five of 12 children (42%) experienced success with the ketogenic diet, and all of these had their antiepileptic medications either withdrawn ($n = 3$) or decreased ($n = 2$). **Conclusions:** The ketogenic diet can be effectively initiated without a fast in children with epilepsy. Time to ketosis and diet efficacy is similar to protocols that utilize a fast.

2.253

LEVETIRACETAM MONOTHERAPY FOR ADULTS WITH EPILEPSY

Taoufik M. Alsaadi and Catherine Thieman (Neurology, UC Davis, Sacramento, CA; Neurology, UC Davis, Sacramento, CA)

Rationale: Levetiracetam (LEV) has been approved as adjunctive treatment for adults with partial onset seizures. We wished to evaluate our experience with LEV as monotherapy. At the end of this analysis, we expect LEV can be used effectively as monotherapy in adults with new-onset seizures and difficult-to-control epilepsy. **Methods:** We retrospectively reviewed the charts of all of our patients with a confirmed diagnosis of epilepsy who tried LEV monotherapy. Patients began LEV either as first-line therapy or were converted to LEV monotherapy after failing their prior antiepileptic medications (AEDs). We reviewed demographic data, diagnostic evaluation for epilepsy, seizure types, and seizure frequency before and after initiation of LEV monotherapy. Adverse events (AEs) while taking LEV were noted. **Results:** We identified 28 patients, ages 18–78 (mean, 39.5) with history of partial seizures with and without secondary generalization. The duration of epilepsy ranged from 1 to 30 years (mean, 10 years). Eight of these patients began LEV as first-line therapy, three of whom had liver disease. Twenty patients were converted to LEV monotherapy after they failed their initial trials of AEDs, which included phenytoin (Dilantin), carbamazepine (Tegretol), valproate (Depakote), lamotrigine (Lamictal), and topiramate (Topamax; mean, 2.3). Of the 28 patients, 25 (89%) of the patients continued on LEV monotherapy for ≥6 months. Nine of the 25 (36%) were seizure free. Three patients who began LEV monotherapy were seizure free, whereas the remaining six patients who began LEV as add-on therapy and converted to monotherapy became seizure free. Of the remaining patients, seven of 25 (28%) had >50% seizure reduction, and seven of 25 patients had >75% reduction of seizures. The remaining two patients had no significant change in seizure frequency. The total dosages used to control seizures were 1,000–4,000 mg/day (mean, 2,053 mg/day). Four of 28 patients (14 %) reported agitation at the start of treatment, of whom three discontinued therapy in 2 weeks at dosages <500/ day. No other AEs were reported. **Conclusions:** LEV monotherapy can be effective and well tolerated in adults with new-onset and difficult-to-control epilepsy. A prospective, large, double-blind study is needed to confirm this finding.

2.254

ADJUNCTIVE ZONISAMIDE AS IMMEDIATE TREATMENT OF BIPOLAR DISORDER OUTPATIENTS

Claudia F. Baldassano, S. Nassir Ghaemi, Christos Ballas, and Alan Lyman (Department of Psychiatry, University of Pennsylvania, Philadelphia, PA; Cambridge Hospital, Cambridge, MA; Beth Israel Hospital, New York, NY)

Rationale: Zonisamide (ZNS; Zonegran) is a broad-spectrum anticonvulsant (AED) approved in the United States for the adjunctive treatment of partial seizures in adults with epilepsy. ZNS demonstrates multiple mechanisms of action, including blockage of voltage-sensitive sodium channels, reduction of voltage-dependent T-type calcium currents, and reduction of glutamate-mediated synaptic excitation. A number of AEDs are currently used to treat bipolar disorder, suggesting mechanistic similarities between bipolar disorder and epilepsy. Furthermore, a kindling theory of bipolar disorder exists, similar to the kindling model of epilepsy. The objective of the present study was to evaluate the effectiveness of ZNS as adjunctive treatment in refractory bipolar disorder. **Methods:** This retrospective chart review included 20 outpatients meeting DSM-IV criteria for bipolar-spectrum disorder (type I, type II, not otherwise specified, and cyclothymia) who were treated with ZNS. Clinical response was based on physician-rated Clinical Global Impression scale (CGI) and Global Assessment of Functioning scale (GAF) scores after 4 weeks of ZNS treatment, as compared with baseline. **Results:** Preliminary analysis was performed on eight ZNS-treated patients; six patients had depression, and two patients experienced rapid cycling. Five patients were women, and three were men with a mean age of 42 ± 5 years. All patients were taking other psychotropic medications when ZNS was added. All eight patients had previously failed at least three adjunctive treatments for bipolar disorder. Mean GAF score significantly improved from baseline (42 ± 3.9) to week 4 (54 ± 4.5; $p = 0.05$ from paired *t* test). Mean CGI score improved slightly from 4.8 ± 2.5 at baseline to 3.8 ± 3.2 at week 4, but this improvement was not statistically significant. Based on CGI scores of ≥2, five patients (62.5%) were considered responders to ZNS. ZNS was well tolerated, with sedation being the most commonly reported adverse event (n = 3; 37.5%). No patients discontinued ZNS because of adverse events. **Conclusions:** These results suggest that ZNS may be an effective adjunctive treatment in refractory bipolar patients. ZNS was also well tolerated in these patients. Although this was a small, open-label study, its results indicate that further research is warranted to investigate the use of ZNS in bipolar disorder.

2.255

RAPID TITRATION OF LEVETIRACETAM IS EFFECTIVE AND WELL TOLERATED

Alton E. Bryant III (Epilepsy Unit, Roper Hospital, Charleston, SC)

Rationale: At the end of this activity the participants should be able to discuss how to initiate levetiracetam (LEV) therapy quickly, safely, and effectively. **Methods:** Eleven patients (nine inpatients, two outpatients) received rapid initiation of LEV therapy: a dose of 3,000 mg/day by the third day of therapy. All patients had partial-onset seizures with or without secondary generalization. LEV was dosed at 500 mg b.i.d. on day 1, 1,000 mg b.i.d. on day 2, and 1,500 mg b.i.d. on day 3. This rapid titration was indicated because of poor seizure control or unacceptable side effects on the previous AED regimen. The majority of patients underwent simultaneous discontinuation of one or two concomitant AEDs. **Results:** Ten of the 1 patients tolerated rapid initiation of LEV with minimal or no side effects. Four patients became seizure free with LEV therapy. No patient experienced worsened seizure control, despite the fact that most patients had one or two concomitant AEDs discontinued. One patient experienced hallucinations, and LEV was stopped. She was the oldest patient (63 years) and was the only patient who experienced status epilepticus before treatment. She may have had postictal psychosis. One patient had experienced postictal psychosis twice in the past, but he tolerated rapid initiation of LEV therapy without difficulty and became seizure free. **Conclusions:** LEV is a recently introduced AED that offers desirable pharmacokinetic qualities: no clear drug/drug interactions, no metabolism by the P450 enzyme system, and no significant protein binding. Pharmacokinetics are linear and steady state is achieved rapidly. Prescribing information recommends a gradual titration with the maximum recommended dose reached after 1 month of therapy. This gradual titration limits the usefulness of LEV in circumstances that require rapid control of seizures or rapid withdrawal of other, poorly tolerated AEDs. As described, rapid titration of LEV is effective and well tolerated by most patients.

2.256

TREATMENT PERSISTENCE WITH NEW ANTIEPILEPTIC DRUGS: LEVETIRACETAM, OXCARBAZEPINE, TOPIRAMATE, AND ZONISAMIDE

Joyce A. Cramer, Grant Follansbee, and James Vermilyea (Psychiatry, Yale University School of Medicine, New Haven, CT; Statistics, Aderis, Boston, MA)

Rationale: At the end of this presentation, participants will be able to discuss the use of treatment persistence as a patient-reported treatment outcome. Treatment persistence is considered a global measure of the acceptability of treatment based on efficacy, adverse effects, and convenience. Four new antiepileptic drugs (AEDs) were compared using this global measure. **Methods:** Patients who started a new prescription for levetiracetam (LEV; n = 766), oxcarbazepine (OCBZ; n = 1,208), topiramate (TPM; n = 4,544), or zonisamide (ZNS; n = 358) in January–February 2001 were followed up for prescription refills for 12 months at a national retail pharmacy chain. Persistence was defined as time from the index prescription to the last month a prescription was filled. Kaplan–Meier analyses of days to discontinuation were based on use of <50% of prescribed doses, with Wilcoxon $\chi 2$ tests between strata. **Results:** Mean treatment persistence rates were LEV, 8.3 ± 4.1 months; OCBZ, 7.3 ± 4.2 months; TPM, 8.0 ± 4.1 months; and ZNS, 7.8 ± 4.2 months. LEV persistence was significantly longer than OCBZ for all patients, and adjusting for age (both $p < 0.0001$). Kaplan–Meier analyses (excluding ZNS because of small numbers) also showed significantly longer time to discontinuation for LEV than TPM ($p = 0.018$) and OCBZ ($p < 0.0001$). Twelve-month discontinuation rates were significantly lower for LEV than OCBZ ($p < 0.0001$) and TPM ($p = 0.0002$). **Conclusions:** These data demonstrate significant differences in treatment persistence for patients prescribed a new AED. In contrast to patients participating in clinical trials, this analysis represents long-term open use of new AEDs in a nationwide population. Continuation of the index AED suggests patient satisfaction with efficacy, tolerability, convenience, or all aspects of treatment. Additional analyses will explore patterns of treatment crossover and use of concomitant AEDs. (Supported by UCB.) (Disclosure: Consulting: Elan, GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer, UCB; Honoraria: GlaxoSmithKline, Johnson & Johnson, Novartis, Pfizer, UCB.)

2.257

EVALUATION OF THE EFFICACY AND SAFETY OF FIRST MONOTHERAPY IN NEWLY DIAGNOSED ELDERLY PATIENTS WITH PARTIAL-SEIZURE EPILEPSY

Piotr Czapinski and Ewa Czapinska (Epilepsy and Migraine Treatment Centre, Cracow, Poland)

Rationale: Within the last decade, epidemiologic studies have demonstrated an increased epilepsy prevalence in patients older than 65 years. Elderly patients are difficult to treat, because they already undergo many therapies that facilitates adverse-effect and drug-interaction occurrence. Thus, there is no consensus whether, in this age group, classic or new-generation antiepileptic drugs (AEDs) should be used. The aim of the study was to compare the efficacy and safety of eight drugs employed in epilepsy treatment in the elderly. **Methods:** The study included 175 elderly patients (mean age, 72.2. years) with partial seizure epilepsy, who were treated with one of the following drugs: valproate (VPA), carbamazepine (CBZ), phenytoin (PHT), oxcarbazepine (OCBZ), lamotrigine (LTG), gabapentin (GBP), tiagabine (TGB), or topiramate (TPM). The follow-up period was 24 months. The measure of treatment efficacy was the percentage of seizure-free patients at the termination of therapy, whereas the measure of safety

was the percentage of exclusions due to unacceptable adverse effects. **Results:** The results are presented as the following percentage values: patients who have undergone the 24-month follow-up, seizure-free individuals, and exclusions due to adverse effects. VPA: n = 2, 871, 475, 017, 9. CBZ: n = 2, 466, 768, 7,525, 0; PHT: n = 20, 45, 066, 635, 0; OCBZ: n = 18, 88, 975, 05, 6; LTG: n = 18, 55, 670, 027, 7; GBP: n = 20, 90, 066, 65, 0; TGB: n = 26, 88, 569, 67, 7; TPM: n = 21, 47, 670, 042, 9. **Conclusions:** AEDs when employed in the elderly do not differ in their efficacy after a 24-month follow-up. GBP, OCBZ, and TGB are best tolerated by this age group, and they should be considered while treating elderly patients with numerous other medical problems.

2.258

RANDOMIZED CONTROLLED TRIAL OF ZONISAMIDE FOR TREATING OBESITY

Kishore M. Gadde, Deborah M. Franciscy, and H. Ryan Wagner II (Obesity Clinical Trials Program, Duke University Medical Center, Durham, NC)

Rationale: Zonisamide (ZNS) is a novel antiepileptic drug (AED) that possesses serotonergic and dopaminergic activity in addition to blockade of sodium and calcium channels. Weight loss was observed with ZNS treatment in epilepsy clinical trials. In the current investigation, we evaluated the efficacy and safety of ZNS in the treatment of obesity. **Methods:** Sixty obese subjects were assigned to receive zonisamide or placebo (1:1 ratio) in a randomized, double-blind fashion for 16 weeks in addition to a slightly hypocaloric (500 kcal/day deficit) diet. ZNS dosing was flexible with a maximum of 600 mg/day. Continuation of the same treatment for an additional 16 weeks was optional for the study participants. **Results:** Using the available data for all randomized subjects with the last observation carried forward, the ZNS group lost, on average, more body weight than the placebo group (5.98 ± 0.82% vs. 1.02 ± 0.40%; $p < 0.0001$) during the 16-week period. A random coefficient regression for weight change, with effects for age, race, gender, BMI, and percentage body fat, estimated that ZNS treatment over the 16-week study duration was associated with a 4.99-kg greater weight loss over placebo treatment ($p < 0.0001$). Seventeen of 30 subjects in the ZNS group and three of 30 in the placebo group lost ≥5% weight ($p < 0.0003$) at week 16. Of the 37 subjects who entered the extension phase, 36 completed week 32. Ten of 19 ZNS subjects and none of the placebo subjects lost ≥10% weight at week 32 ($p < 0.0004$). ZNS subjects had a mean weight loss of 9.37 ± 1.64% at week 32 compared with 1.82 ± 0.73% for placebo subjects ($p < 0.0001$). The following measures of the Impact of Weight on Quality of Life (IWQOL) scale improved more significantly in the ZNS group over the placebo group: Health ($p < 0.0030$), Work ($p < 0.0051$), Mobility ($p < 0.0019$), and Activities of Daily Living ($p < 0.0005$). ZNS was tolerated well with minimal side effects. **Conclusions:** ZNS was significantly more effective than placebo as an adjunct to hypocaloric diet in the treatment of obesity. Subjects receiving ZNS continued to lose weight in the extension phase with significant improvement of quality of life. (Supported by Elan Biopharmaceuticals.) (Disclosure: Grant: Elan Biopharmaceuticals.)

2.259

ZONISAMIDE IS EFFECTIVE IN THE TREATMENT OF MYOCLONUS STATUS EPILEPTICUS AND MYOCLONUS IN JAKOB-CREUTZFELDT DISEASE

Gautam Ganguly, M.D., Scott Selco, M.D./ Ph.D and David Y. Ko, M.D. (Dept. of Neurology, USC- LAC Medical center, Los Angeles, CA; Dept. of Neurology, USC- LAC Medical center, Los Angeles, CA; Dept. of Neurology, USC–LAC Medical center, Los Angeles, CA)

Rationale: Jakob–Creutzfeldt disease (CJD) is a form of acquired spongiform encephalopathy that results in rapidly progressive cognitive decline, involuntary movements such as myoclonus, and pyramidal and extrapyramidal involvements, which ultimately lead to grave outcome. The myoclonus can be very prominent and worsens in severity with disease progression. There have been recent reports of CJD presenting as nonconvulsive status epilepticus (Schwinn PJ, et al. Jakob-Creutzfeldt disease presenting as non-convulsive status epilepticus. *Epilepsia* 2001;42(suppl 7):146–7). In addition, the myoclonus of CJD is often refractory to most of the antiepileptic medications (AEDs) other than benzodiazepines (BZDs). Zonisamide (ZNS), a novel AED, has been reported to be effective in the treatment of the often refractory myoclonic seizures seen in progressive myoclonic epilepsy; therefore, it was thought that ZNS may be effective in treating the myoclonus of CJD. This report describes two patients with CJD and intractable myoclonus who were recently treated with ZNS. **Methods:** Retrospective chart analysis was performed for two patients diagnosed with CJD admitted to University of Southern California (USC) University Hospital between 2000 and 2001. **Results:** Two patients, a 58-year-old man and 72-year-old woman, had similar complaints of sudden and rapid decline in cognition, diminished attention span, speech disorders, excessive myoclonic jerks, and gait and balance problems. The patients were admitted to local hospitals and then transferred to USC. The 72-year-old female patient had continuous myoclonus, which caused her to continuously fall. At the local hospital, she was treated with valproic acid (VPA), followed by carbamazepine (CBZ), both of which were ineffective. On transfer, video telemetry EEG monitoring showed the patient to be in myoclonic status epilepticus. She was started on ZNS, and the myoclonus was markedly reduced. The 58-year-old man had classic stimulus-sensitive myoclonus and was also given ZNS, resulting in decreased myoclonus. Both patients were evaluated for the 14-3-3 protein at the National Prion Center at Case Western University; the female patient was negative, and the male patient was positive. The male patient's hospital course was very short, and his brain autopsy showed spongioform changes characteristic of CJD. The female patient had a skin biopsy for Lafora bodies and other tests for progressive myoclonic epilepsy, which were negative. **Conclusions:** Myoclonus in CJD can be varied in presentation from classic stimuli-sensitive myoclonus to myoclonic status epilepticus, which is refractory to other AEDs, but both types appear to respond well to ZNS.

2.260

ASSOCIATION BETWEEN ANTIEPILEPTIC DRUG USE AND BIPOLAR DISORDER IN NURSING HOME ADMISSIONS

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Rationale: At the end of this presentation, participants should be able to describe factors associated with the use of antiepileptic drugs (AEDs) by nursing home (NH) admissions with bipolar disorder, with/without epilepsy/seizure disorder (Epi/Sz). In a previous multivariate analysis of epilepsy and AED use among NH elderly, we found a strong association between AED use and bipolar disorder (manic depression). Little research exists about the use of AEDs in the treatment of elderly NH residents with bipolar disorder. Frontline therapy includes antimanic agents (e.g., lithium) and AEDs used as mood stabilizers [e.g., valproic acid (VPA)]. Because lithium is associated with increased adverse drug reactions among elderly, VPA in particular, as well as other AEDs [gabapentin (GBP), lamotrigine (LTG), carbamazepine (CBZ), and topiramate (TPM)] are often the treatment of choice. The purpose of this study was to examine the prevalence of and factors associated with AED treatment of NH admissions with bipolar disorder, including Epi/Sz as a comorbidity variable. **Methods:** Subjects were all elderly (N = 10,318), ≥65 years, admitted to 510 NHs located in 31 states during January through March 1999. Data sources included the Minimum Data Set, a federally mandated, standardized assessment form, and medication orders for all prescription drugs at admission. In

a logistic regression analysis, AED use was the dependent variable; covariates included comorbidities, comedications, demographics, clinical characteristics, and functional capabilities. **Results:** Of the 10,318 NH admissions, AED prevalence was 7.77%. In the multivariate analysis of factors associated with any AED use, bipolar disorder had an odds ratio (OR) of 10.87; the second highest OR after Epi/SZ disorder. Further analysis of the admissions cohort showed that the prevalence of bipolar disorder was 1.1% (n = 113). Of these, 93% (n = 105) did not have Epi/SZ as a comorbidity; 30% of the 105 admissions with bipolar disorder had AED use, including VPA (n = 21), GBP (n = 6), CBZ (n = 3), GBP and CBZ (n = 1), and GBP and VPA (n = 1). Eight others with bipolar disorder also had a comorbidity of Epi/SZ; their AED use included CBZ (n = 1), PHT (n = 2), VPA (n = 3), PHT/GBP (n = 1), and PHT/VPA (n = 1). **Conclusions:** Little is known about the pharmacoepidemiology of AEDs used as either single or adjunctive therapy for bipolar disorder. Prevalence of bipolar disorder was 1.1% among NH admissions, 1/3 of whom had AED treatment. The majority (66%) of admissions with bipolar disorder without Epi/SZ were being treated with VPA. In the presentation we will discuss additional multivariate relations between demographic, clinical, and functional variables associated with AED use among NH elderly with bipolar disorder. (Supported by NIH-NINDS grant P50-NS16308.) (Disclosure: Honoraria: Ilo Leppik, Abbott Laboratories, Novartis, Pfizer.)

2.261

A NATIONAL PATIENT SURVEY OF MEDICATION COMPLIANCE

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Rationale: Participants will understand the link between medication compliance and breakthrough seizures. The objective is to determine the predictors of inadequate medication compliance and association with seizures. **Methods:** Questionnaires were distributed in neurologists offices asking epilepsy patients for their responses to 10 questions. Completed questionnaires were returned anonymously by mail. Bivariate and multivariate analyses and logistic regressions were performed. **Results:** Responses from 661 patients taking AEDs showed that 71% missed doses (mean, 1.99; SD, 1.97/month); 45% had a seizure after a missed dose. Patients who missed doses were more likely to have been taking AEDs >5 years ($p < 0.01$). Patients who had a seizure after a missed dose were more likely to be taking more than seven tablets daily ($p < 0.01$). The number of AED doses ($p = 0.01$) and number of missed doses ($p = 0.02$) were associated with seizures after a missed dose. Logistic regression was performed with number of years taking seizure medications, number of AED tablets, number of AED doses, number of all medications, and number of all tablets. The results indicated that (a) a larger number of AED tablets taken was associated with a 43% increase in the odds of a seizure after a missed dose ($p = 0.02$), (b) increasing the number of times per day AEDs were taken (qd, b.i.d., t.i.d., q.i.d.) increased the odds of a seizure after a missed dose by 36% ($p = 0.04$), and (c) each increase of one missed dose per month was estimated to increase the odds of a seizure after a missed dose by 11%. **Conclusions:** These data demonstrate the importance of using simple AED treatment regimens and the smallest number of doses and tablets to be taken daily to avoid breakthrough seizures. (Supported by Bertek.) (Disclosure: Consulting: Bertek.)

2.262

EXPRESSION OF MULTIPLE DRUG RESISTENCE GENES IN REFRACTORY EPILEPSY

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Rationale: Most patients with epilepsy are effectively treated with antiepileptic drugs (AEDs); however, ~10–20% of them are pharmacoresistant. The mechanisms involved in AED resistance are not fully understood. Multiple drug resistance (multiple DR) is mediated at the cellular level by low abundance transporters expressed in normal endothelial cells (EC) and perhaps in "epileptic" astrocytes. Refractory epilepsy is characterized by overexpression of specific multiple DR mechanisms in EC.We investigated the expression of multiple drug resistance (MDR1), multiple drug resistance–associated (MRP1-6), cisplatin resistance-associated (CRA), and lung resistance (LRP) genes/proteins in astrocytes as well as EC isolated from epileptic brain. In addition, immunostaining was performed on tissue sections. It was our objective to study the patterns of expression and distribution of multiple DR proteins in epileptic brain. **Methods:** The methods used to investigate the expression of multiple DR genes were RT-PCR and Western blot on "epileptic" astrocytic and endothelial cells. ECs from intracranial aneurysms, umbilical cord and astrocytes from nonpathologic origin were used as controls. Immunofluorescence was performed on brain tissue from patients with refractory epilepsy. **Results:** In endothelial cells, RT-PCR and protein analysis revealed MDR1 expression only in pathological samples. Comparable expression of MRPs, CRA, and LRP occurred in all endothelia tested. RT-PCR analysis revealed that both MDR1 and LRP were expressed in astrocytes from surgical resections; MRP1 was present, but the other five members of multidrug resistance-associated protein family were not. Western blot experiments confirmed a high expression of MDR1 protein in astrocytes from epileptic brain compared to astrocytes from nonpathological origin. Moreover, MRP1 and LRP were present only in astrocytes from epileptic brain, even though their expression was much lower than MDR1. **Conclusions:** We conclude that multiple drug resistance gene overexpression is not an exclusive property of "epileptic" ECs, but may rather represent an endothelial and glial response to a variety of pathological or physiological conditions. Thus, outwitting the endothelial blood–brain barrier may not be sufficient to overcome multiple DR since parenchymal cells are also likely to be involved. (Supported by HL51614, NS143284, and NS38195.)

2.263

LEVETIRACETAM ENHANCES MARKEDLY THE SEIZURE SUPPRESSION OF OTHER ANTIEPILEPTIC DRUGS IN AMYGDALA-KINDLED RATS

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Rationale: We have recently demonstrated that levetiracetam (LEV; Keppra) markedly enhances the anticonvulsant properties of various antiepileptic drugs (AEDs) in audiogenic susceptible mice [Matagne et al. *Epilepsia* 2001;42(suppl 7):82]. The current study investigated whether a supraadditive pharmacodynamic interaction also exists between LEV and several classic AEDs in amygdala-kindled rats, a preclinical model mimicking partial epilepsy in humans. **Methods:** All experiments were conducted in fully amygdala-kindled male Sprague–Dawley rats (350–550 g; n = 8). LEV and the classic AEDs were administered i.p. 60 and 30 min, respectively, before testing. Anticonvulsant effects were assessed by protective ED_{50} values against secondarily generalized motor seizures (score 3, 4, or 5 on the Racine's scale). Changes in the anticonvulsant potency ratio were expressed by the ratio between the ED_{50} value of the AED alone and the ED_{50} value obtained when combining different doses of a classic AED with one of two fixed doses of LEV (17 and 108 mg/kg). **Results:** Combining the lowest fixed dose of LEV (17 mg/kg) with valproate, clonazepam, phenobarbital, and carbamazepine produced an increase in their anticonvulsant potency by a factor of 3, 4, 4, and 2, respectively. This increase was more important with the highest fixed dose of LEV (108 mg/kg), which produced factors of 9, 8, 4, and 2, respectively. **Conclusions:** The present study confirms previous preclinical observations in audiogenic susceptible mice by showing that LEV markedly enhances the seizure suppression of various AEDs in amygdala-kindled rats. This supraadditive pharmacodynamic interaction suggests that the future medical management of partial epilepsy could benefit from combination therapy with LEV. (Supported by UCB S.A. Pharma Sector.) (Disclosure: Salary: UCB S.A.)

2.264

STATUS EPILEPTICUS–INDUCED CHANGES IN P-GLYCOPROTEIN EXPRESSION IN THE RAT BRAIN

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Rationale: P-glycoprotein (PGP) encoded by multidrug resistance-1 gene (mdr-1) has been implicated in antiepileptic drug (AED) resistance in both epilepsy patients and animal models. We examined whether status epilepticus (SE) results in alterations of PGP immunoreactivity in the rat brain at a time when the standard AED fosphenytoin (FPHT), which is known to be regulated by PGP, fails to control seizures. **Methods:** SE was induced in adult Wistar rats by either LiCl (3 mEq/kg) and pilocarpine (60 mg/kg) or by 30-min perforant-path stimulation through chronically implanted electrodes. PGP immunohistochemistry was examined using anti-mdr-1 polyclonal antibodies (Chemicon) in the coronal sections of paraformaldehyde-fixed brains from the rats killed 40 min, 3, 6, 12, and 24 h after SE induction. FPHT (50 mg/kg) was injected i.v. before, 10 min, 40 min, or 3 h after SE induction. **Results:** In naive rats, PGP was confined to capillary endothelial cells diffusely throughout the brain. In both models of SE, PGP staining in the capillaries decreased at 40 min and was undetectable by 6 h. Simultaneously, PGP-positive astrocytes (identified by GFAP colabeling) appeared and increased in number, reaching maximal levels at the 12-h point. PGP- positive astrocytes were located throughout the brain, including abundant staining in the hippocampus, cortex, and thalamus. The effectiveness of a standard dose of FPHT in controlling PPS seizures significantly decreased 40 min after SE induction compared to both pre- and early posttreatment. FPHT administration during the third hour of SE failed to affect seizures. **Conclusions:** SE is accompanied by a progressive increase of PGP in astrocytes, which in contrast to the endothelial cell fraction, is known to contribute to the extrusion of xenobiotics from the brain. These changes parallel the failure of FPHT, suggesting that seizure-induced astrocytic PGP expression may contribute to the AED resistance in SE. The reported data are useful for understanding the mechanisms of drug-resistance in epilepsy. [Supported by VHA Research Service (C.G.W.), grant NS 13515 from NINDS (A.M., C.G.W.), and DAPA foundation (R.S., D.S., L.M.).]

2.265

BLOOD AND CEREBROSPINAL FLUID KINETICS OF CARBAMAZEPINE AND LEVETIRACETAM DURING LONG-TERM ADMINISTRATION TO RATS: CARBAMAZEPINE BUT NOT LEVETIRACETAM EXHIBITS AUTOINDUCTION

Philip N. Patsalos and Helen C. Doheny (Clinical and Experimental Epilepsy, Institute of Neurology, London, England)

Rationale: Autoinduction is an important consideration in epilepsy treatment and is a characteristic of numerous antiepileptic drugs (AEDs) including carbamazepine (CBZ), phenytoin, phenobarbitone, valproate, and lamotrigine. Autoinduction by CBZ can be considered by far the most important clinically. AEDs that are not autoinducers are preferred because they exhibit linear kinetics and consequently make treatment strategies simpler. This study was designed to determine and compare the blood and cerebrospinal fluid (CSF) kinetics of CBZ and the new AED lrevetiracetam (LEV) during 7 consecutive days of continuous administration to freely behaving rats. **Methods:** Under halothane anaesthesia, male Sprague–Dawley rats (300–350 g) had a catheter placed in the internal jugular vein for blood sampling, a cannula in the cisterna magna for CSF sampling, and an osmotic minipump in the peritoneal cavity. Minipumps were set to deliver CBZ (2 and 4 mg/kg/h) or LEV (8 and 16 mg/kg/h) at 48 h after surgery and continue drug delivery for 7 consecutive days thereafter. Blood and CSF samples were collected at 30-min intervals for 6–9 h on days 1, 2, 4, 6, and 7. Samples were analysed for CBZ, carbamazepine-epoxide (CBZ-E), and LEV content using high-performance liquid chromatography. **Results:** CBZ was rapidly absorbed from the peritoneal cavity with peak concentrations in blood and CSF occurring 4 and 6 h later, respectively. Peak blood CBZ-E concentrations occurred at 24 h, whilst for CSF, it was 9 h. Both CBZ and CBZ-E exhibited dose proportionality. On day 2, CBZ concentrations declined substantially and significantly (by 50–75%) and continued to decline during the subsequent 5 days. CBZ-E concentrations showed a precipitate decline on day 4. Like CBZ, LEV was also rapidly absorbed from the peritoneal cavity with peak blood and CSF concentrations occurring by 9 h and concentrations were dose dependent. However, in contrast to CBZ, steady-state LEV concentrations showed no evidence of decline during the subsequent 6 days of LEV administration. **Conclusions:** The significant decline in blood and CSF concentrations of CBZ and CBZ-E by the second day of CBZ administration is an indication of the potent autoinduction characteristics of CBZ. In contrast steady-state blood and CSF LEV concentrations did not change during 7 days of continuous LEV administration, suggesting that LEV is not associated with autoinduction. (Supported by National Society for Epilepsy.) (Disclosure: Honoraria: UCB Pharma.)

2.266

THE KINETICS OF TIAGABINE IN BLOOD AND EXTRACELLULAR FLUID FRONTAL CORTEX AND HIPPOCAMPUS: A MICRODIALYSIS STUDY

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Rationale: Previously we investigated the kinetic interrelationship of tiagabine (TGB) in cerebrospinal fluid (CSF) and showed that TGB appeared rapidly in the CSF compartment and that blood concentrations reflected CSF values (Ratnaraj et al., 2000). In this study, we have further investigated the kinetics of TGB by monitoring extracellular fluid (ECF) concentrations in the frontal cortex and hippocampus of freely behaving rats using microdialysis. **Methods:** Sprague–Dawley rats weighing 300–350 g (n = 5) were used. Under halothane anaesthesia, a catheter was placed in the internal jugular vein for blood sampling and microdialysis probes were implanted stereotactically into the hippocampus and frontal cortex for monitoring of the ECF. Two days later, TGB (40 mg/kg) was administered i.p. Blood samples (100 μl) were collected at 15-min intervals for the first hour and at 30-min intervals for a further 6 h. Microdialysate samples (flow rate, 2 μl/min) were collected at 10-min intervals for 2 h. Blood and ECF TGB content were determined by HPLC. **Results:** TGB serum concentrations rose rapidly after i.p. TGB administration (Tmax, 16 ± 0.3 min) with Cmax values of 27,754 ± 2,000 n*M*. In contrast, Tmax values for ECF frontal cortex and hippocampus were 41 ± 5 and 34 ± 3 n*M,* respectively. Recovery corrected Cmax values for frontal cortex were 266 ± 10 n*M,* and for the hippocampus, they were 291 ± 11 n*M*. TGB half-life values in serum, ECF frontal cortex, and hippocampus were 50 ± 2.6, 174 ± 32, and 133 ± 9 min, respectively. **Conclusions:** TGB rapidly enters brain ECF with concentrations peaking somewhat later than that in serum. As TGB ECF concentrations are similar in both the frontal cortex and the hippocampus, the brain distribution of TGB does not appear to be region specific. However, ECF half-life values in both the frontal cortex and the hippocampus are threefold greater than that of serum, and this may be an important consideration in the therapeutics of TGB. (Supported in part by the National Society for Epilepsy.)

2.267

CHARACTERIZATION OF TOPIRAMATE-ASSOCIATED WEIGHT CHANGES IN ADULTS WITH EPILEPSY

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Rationale: Many antiepileptic drugs (AEDs) can cause clinically significant weight changes, particularly weight gain. Even though weight change is a common occurrence and has potential health implications, AED-related weight changes are not well characterized. Clinically significant weight loss has been observed in patients with epilepsy being treated with topiramate (TPM) adjunctive therapy and

monotherapy. Data from epilepsy clinical trials were analyzed to characterize TPM-associated weight loss. **Methods:** Clinical trial data (double-blind and open-label studies) from adult patients were analyzed. The 1,319 patients with refractory epilepsy (most receiving TPM adjunctive therapy) had body weight measurements at baseline and during TPM treatment. Body-weight changes and absolute body weight were calculated at various periods for the population overall and for patient subgroups stratified by dose, baseline body weight, and BMI. Relations between weight change and pertinent clinical laboratory analytes were also assessed. **Results:** Of the 1,319 patients included in the analyses, 65% were male; mean age was 36 years (range, 19–74 years). Most patients received TPM in addition to carbamazepine and/or phenytoin; <20% of patients received valproate cotherapy. Weight was reduced in 85% of patients receiving TPM; mean body weight change was –3.8 kg (4.6% of baseline weight). Relative to baseline weights, the mean change was –9.6 kg (8.4%) for patients >100 kg and –3.2 kg (4.2%) for patients ≤100 kg. In the subgroup of patients for whom body mass index (BMI) could be calculated, patients with BMI ≥27 showed a mean weight loss of 7.4 kg (7.8%); with BMI <27, mean weight loss was 3.1 kg (4.4%). Weight loss was observed within the first 3 months of treatment. During long-term treatment (≥2 years), 45% of patients lost ≥5% of their baseline weight; 20% lost ≥10%. In patients treated for ≥2 years, weight continued to decrease through 18 months, and weight loss was maintained to ≥24 months. Weight loss varied according to dose. Patients receiving <200 mg/day TPM lost 2.2% of baseline weight compared with 3.7% in those receiving 200–399 mg/day TPM and 4.4% with 400–599 mg/day TPM. Changes in plasma glucose, total cholesterol, and blood pressure correlated with weight changes. **Conclusions:** Up to 85% of adults lost weight without dietary changes while receiving TPM adjunctive or monotherapy for epilepsy. TPM-associated weight loss depends upon dose, duration of treatment, and baseline weight/BMI. Weight loss is gradual, continues for ≤18 months, and then plateaus. Analyses of clinically relevant data suggest that weight loss may be accompanied by changes in lipid profile, glycemic control, and blood pressure. (Supported by Johnson & Johnson Pharmaceutical Research & Development.) (Disclosure: Grant: Cyberonics, Elan, Novartis, Ortho-McNeil Pharmaceutical/Johnson & Johnson, Pfizer/Parke-Davis, UCB; Equity: GlaxoSmithKline, Ortho-McNeil Pharmaceutical/Johnson & Johnson, Pfizer/Parke-Davis; Consulting: GlaxoSmithKline, Novartis, Ortho-McNeil Pharmaceutical/Johnson & Johnson, Pfizer/Parke-Davis, UCB; Honoraria: Novartis, Ortho-McNeil Pharmaceutical/Johnson & Johnson, Pfizer/Parke-Davis, UCB.)

2.268

INFLUENCE OF VALPROATE AND PHENYTOIN ON ESTROGEN-STIMULATED CELL GROWTH IN THE HUMAN BREAST CANCER CELL LINE MCF-7.

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Rationale: Disturbances in the estrogen pathway seen in women with epilepsy are, at least in part, induced by antiepileptic drugs (AEDs). Valproate (VPA) induces hyperandrogenism, while phenytoin (PHT) reduces estrogen and progesterone levels. The sites of action of these disturbances are still not completely known. If this can be related to an antiestrogen effect similar to the effects of antiestrogenic substances used in cancer therapy, this would be an important clinical observation. The aim of the study was therefore to evaluate if VPA or PHT reduced estrogen-stimulated cell growth in the estrogen-dependent human breast cancer cell line MCF-7. **Methods:** MCF-7 cells were grown in phenol red–free Dulbecco's modified Eagle's medium supplemented with 10% charcoal-dextran treated fetal bovine serum. Cell growth was measured as μg DNA after 6 days of coexposure to 30 p*M* 17β-estradiol and VPA or PHT at different concentrations. The findings were compared to cell growth in cultures without drug. **Results:** PTH, 100 μ*M,* reduced estrogen-stimulated cell growth by 55%. VPA reduced cell growth by 47% and 62% at 250 and 500 μ*M,* respectively. No increased cell death or reduced metabolism was observed after 24-h exposure of MCF-7 cells to 500 μ*M* VPA. **Conclusions:** VPA and PHT decrease cell growth in the human breast cancer cell line MCF-7 at clinically relevant serum concentrations. This opens new therapeutic perspectives in the treatment of patients with estrogen-sensitive tumors and the findings should be explored further.

2.269

LONG-TERM ANTICONVULSANT EFFECT OF LEVETIRACETAM

Archana Shrestha, Rhonda Debello, Jacquelyn Funk, Michael Johnson, and Mark Spitz (Neurology and Neurodiagnostics, University of Colorado Health Sciences Center, Denver, CO)

Rationale: A few anticonvulsants (AEDs) have been reported to have persistent long-term effects despite their discontinuation. This effect goes beyond their normal pharmacokinetics. This has not been shown clinically for some of the newer AEDs. We report on cases of persistent long-term anticonvulsant effect of levetiracetam (LEV) after its cessation. **Methods:** This was a retrospective review of patients from January 2001 to March 2002 in the Epilepsy Monitoring Unit at the University of Colorado Hospital. The AEDs of all the patients were stopped on the first day of hospitalization. Only the patients with temporal lobe epilepsy were included in the study, and patients who were taking valproic acid, barbiturate, or benzodiazepine were excluded. All the patients receiving LEV monotherapy or polytherapy with other AEDs were selected. These patients were then matched for age, sex, and frequency of seizures with patients taking other single or multiple AEDs. The hospital day to onset of their first seizure was noted. If a patient did not have a seizure during the 5-day hospitalization, then they were assigned a value of day six to onset of seizure. The two groups were then compared using a two-tailed, independent variable *t* test. **Results:** The two groups were matched for age, sex, and frequency of seizures. In addition to LEV, other AEDs patients were taking included phenytoin, carbamazepine, topiramate, lamotrigine, and zonisamide. There were equal number of patients receiving monotherapy and polytherapy in the two groups. The Lev group (n = 7) had a mean of 4 days to onset of first seizure and a median of 6 days (range, 2–6 days). The non-LEV group (n = 7) had a mean of 2.1 days with a median of 2 days to onset of first seizure (range, 1–3 days). This resulted in a p value of 0.08. There were three patients in the LEV group who had no seizures during the hospitalization, and all the patients in the non-LEV group had seizures **Conclusions:** After the discontinuation of AEDs, the LEV group had a later day to onset of their first seizure than the non-LEVgroup with three patients not having any seizures at all. Although the p value of 0.08 was not statistically significant, it is trending toward significance. Also, the patients without seizures were assigned the most conservative value of day 6 to onset of seizure. This only occurred in patients in the LEV group, and likely underestimated the actual day to onset of first seizure, thereby decreasing the significance of the difference between the two groups. Despite stopping the LEV, patients tended to remain seizure free for several days beyond. The exact mechanisms of LEV are just beginning to be elucidated, but this study shows that the efficacy of LEV appears to go beyond its pharmacokinetic effects.

2.270

EFFECT OF TOPIRAMATE ON DIABETIC CONTROL AND WEIGHT IN DIABETIC PATIENTS

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Rationale: As the prevalence of diabetes mellitus increases, neurologists can expect to see more patients with both epilepsy and diabetes. Although AED effects on neuroendocrine function and/or body weight could influence metabolic abnormalities associated with diabetes, the impact of AEDs on diabetes has not been widely reported on, despite the fact that AEDs have been used to treat pain in patients with painful diabetic polyneuropathy. Many AEDs are associated with weight gain, which can increase the risk of type 2 diabetes. Topiramate

(TPM) has been associated with weight loss and improvements in metabolic parameters (e.g., glucose, insulin, lipids) in adults. In an animal model of diabetes mellitus, TPM had antidiabetic effects independent of body-weight changes. Nearly 900 diabetic patients with peripheral polyneuropathy were treated with TPM in three double-blind, placebo-controlled studies to evaluate the effects of TPM on neuropathic pain, thereby providing the data we report here on diabetic control and weight in TPM- and placebo-treated patients. **Methods:** Adults (18–75 years) were eligible for randomization if they had painful diabetic peripheral polyneuropathy for ≥6 months and Hb_{A1c}<11% for ≥3 months before randomization. After a baseline period of ≤28 days, patients were randomized to treatment with placebo or TPM 100, 200, or 400 mg/day. Duration of double-blind treatment was 18–22 weeks (titration to target dose, 6–10 weeks; maintenance, 12 weeks). **Results:** Across the three studies, 384 patients were randomized to placebo, 253 to TPM 100, 372 to TPM 200, and 260 to TPM 400 (TPM total, 885). Most patients had type 2 diabetes (placebo, 82%; TPM, 81%). Mean Hb_{A1c} among TPM-treated study completers was reduced 0.4–0.5%, TPM 100; 0.7–0.8%, TPM 200; and 0.5–0.6%, TPM 400; in the placebo groups, mean changes were between –0.2 and +0.2%. Hb_{A1c} changes were statistically significant for TPM vs. placebo. Among study completers, the proportion of patients with ≥0.5% and ≥1.0% reductions in Hb_{A1c} levels were placebo, 32% and 15%, respectively; TPM 100, 55% and 18%; TPM 200, 57% and 38%; TPM 400, 62% and 50% (TPM overall, 57% and 38%). Mean body weight was increased 0.3–0.9% in the placebo group and reduced 2.1–5.1% with TPM, depending on TPM dose. Changes in Hb_{A1c} correlated poorly with changes in weight. The most common adverse events in TPM-treated patients (≥5% incidence vs. placebo) were paresthesia (placebo, 5% vs. TPM, 12%), nausea (7% vs. 12%), somnolence (4% vs. 10%), anorexia (3% vs. 10%), fatigue (11% vs. 16%) and weight loss (1% vs. 7%). **Conclusions:** In diabetic patients, TPM improves diabetic control as measured by Hb_{A1c} levels. Because reductions in Hb_{A1c} levels do not correlate with TPM-induced weight loss, the effect of TPM on glycemic control appears to be independent of weight loss. The favorable weight and metabolic profile of TPM, combined with its effectiveness against partial and generalized seizures, make TPM a particularly beneficial option for the growing number of diabetic/overweight patients with epilepsy. (Supported by Johnson & Johnson Pharmaceutical Research & Development.) (Disclosure: Salary: Johnson & Johnson Pharmaceutical Research & Development.)

2.271

THE KINETICS OF PHENYTOIN IN BLOOD, CEREBROSPINAL FLUID, AND BRAIN EXTRACELLULAR FLUID AFTER INTRAVENOUS PHENYTOIN AND FOSPHENYTOIN

Xiaolan Wang and Philip N. Patsalos (Department of Clinical and Experimental Epilepsy, Institute of Neurology, London, England)

Rationale: Fosphenytoin (FosPHT) has been designed to overcome some undesirable characteristics of phenytoin (PHT) so that its use in the treatment of seizures and status epilepticus is more practical. However, the kinetic interrelationship of PHT in blood CSF and brain extracellular fluid (ECF) after i.v. FosPHT is unknown. This study was designed to determine this interrelation and to compare with that obtained after i.v. PHT. **Methods:** Male Sprague–Dawley rats (300–350 g) were anaesthetised with halothane and a catheter placed in the internal jugular vein for the iv infusion of PHT or FosPHT and for blood sampling and a cannula in the cisterna magna for CSF sampling. Microdialysis probes were implanted stereotactically into the hippocampus and frontal cortex for monitoring of the ECF. Two days after surgery rats were administered i.v. PHT or FosPHT (30 mg/kg or 60 mg/kg). Blood, CSF and ECF were collected concurrently from the freely moving rats at various intervals for 6 h. Samples were analysed for PHT content using high-performance liquid chromatography. **Results:** Plasma PHT Cmax values increased dose-dependently after PHT and FosPHT i.v. administration. However, AUC and t1/2 values increased disproportionately to dose. After PHT administration, the PHT free fraction varied between 0.25 and 0.31, whilst after FosPHT administration, it varied between 0.26 and 0.31. Overall the pharmacokinetic parameters for PHT in the blood compartment after PHT and FosPHT administration were indistinguishable. PHT was rapidly detectable in the CSF compartment. Mean Tmax values varied between 9 and 13 min and were neither dose nor formulation dependent. However, although CSF AUC and t1/2 values increased disproportionately to dose after PHT administration, as observed for plasma, values increased dose dependently after FosPHT administration. PHT was detectable in ECF at time of first dialysate sample (10 min) after PHT and FosPHT administration. However, Tmax values (29–34 min) were significantly greater than that of CSF. Although ECF AUC and t1/2 values were comparable to those in the hippocampus and there was no difference between PHT and FosPHT administration, t1/2 values were twofold greater than those seen in blood and CSF. **Conclusions:** The kinetics of PHT after i.v. PHT and FosPHT in blood, CSF and ECF of the hippocampus and frontal cortex are indistinguishable. However, PHT blood concentrations may not necessarily reflect concentrations in the ECF and the site of drug action. (Supported in part by Parke-Davis and by the National Society for Epilepsy.)

2.272

VASCULAR CONSEQUENCES OF CORTECTOMIES FOR EPILEPSY

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Rationale: Cortectomies can cure refractory epilepsy in selected patients. However, cortical resections may inevitably be associated with arterial brain infarction. The goal of this study was to characterize patterns of brain infarction associated with specific types of cortectomies. **Methods:** Preoperative and postoperative MRIs were analyzed in 50 consecutive patients undergoing cortectomy. Based on the classic microvascularization studies of Lazorthes, cortectomies were divided into five categories and the pattern of ensuing brain infarction was studied. Each patient was assessed for associated neurologic deficit. **Results:** Simple gyrectomies (type 1) were associated with subtle linear or no subcortical infarctions. Multiple gyrectomies (type 2) were associated with pyramidal infarctions that reached the ventricle. Insulectomies (type 3) and operculectomies (type 4) were associated with infarctions that could reach the corona radiata and the corticospinal tract. Orbitofrontal resections (type 5) could be associated with lenticulostriate infarctions. Most adverse clinical consequences occurred with type 3, 4, or 5 resections. Fortunately, postoperative neurologic deficits were either transient or mild in most patients studied. **Conclusions:** Each type of cortectomy is associated with a specific and predictable pattern of brain infarction, the consequence of which must be considered before surgery. The present classification permits an estimation of the risk of postoperative neurologic morbidity in candidates for cortectomy.

2.273

PATTERNS OF INTRACRANIAL SEIZURE PROPAGATION

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Rationale: Little is known about pattern of seizure propagation. We studied routes and patterns of spread of complex partial and secondarily generalized tonic–clonic seizures on intracranial EEG to identify ictal features. **Methods:** We divided the seizures into seven categories according to the zone of onset: three frontal zones (medial, lateral, and orbital) two temporal zones (mesial and lateral), and the parietal and occipital lobes. We recorded latency of seizure spread to another lobe in the same hemisphere—ipsilateral propagation time (IPT), and latency of spread to opposite hemisphere—contralateral propagation time (CPT). All patients had EEG recorded with depth and/or subdural electrodes depending on clinical needs. **Results:** There were a total of 115 seizures in 40 patients. The number of seizures from the seven zones were 10, 13, eight, 30, 21, 15, and 18, respectively. Mean IPT by

zone: mesial frontal 1.6 s (range, 0.2–8 s), lateral frontal, 8.15 s (range, 6–22 s), orbitofrontal, 47.4 s (range, 0.4–15 s), mesial temporal, 14.6 (range, 1–47 s), lateral temporal, 17.9 (range, 0.2–57 s), parietal, 7.8 (0.4–15 s), occipital, 18.2 (range, 0–42 s). Mean CPT by zone: mesial frontal, 0.35 s (range, 0.2–1 s), lateral frontal, 13.7 s (range, 0.4–35 s), orbitofrontal, 41.5 s (range, 9.8–92 s), mesial temporal, 34 s (range, 1–195 s), parietal, 23.3 s (range, 2–54 s), occipital, 35.4 s (range, 27–41 s). Preferred route of spread of two thirds of the seizures in each category: mesial frontal to contralateral mesial frontal, lateral frontal to ipsilateral temporal lobe, orbitofrontal to contralateral frontal lobe, mesial temporal to ipsilateral lateral temporal, lateral temporal to ipsilateral mesial temporal, parietal to frontal lobe and occipital to temporal lobe. **Conclusions:** The site at which seizures originate determine propagation latency and routes of spread. This is determined by anatomic connections. Knowledge of spread pattern can help in interpreting seizure localization.

2.274

THE REOPERATION TECHNIQUE FOR RECURRENT EPILEPSY

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Rationale: Surgical treatmnt is an effective method for intractable epilepsy patients, but recurrent epilepsy after the first operation occurs with some patients.We are trying to find the reasons that caused the unsatisfactory outcomes, and trying to find some better ways to solve the problems. **Methods:** Twenty-seven cases with recurrent epilepsy, 11 cases first treated with gamma-knife and X-knife, two cases with stereotactic lesion destruction, 14 cases with craniotomy and surgically invasive treatments; all patients had a reoperation based on the first surgical experiences and the pre-reoperation comprehensive evaluation. The epileptogenic foci, having a relation with the first operation, had been found with ECoG monitoring during the second operation. The reoperations were mainly to eliminate or to resect the epileptogenic areas; when these areas were located in the functional cortexes, the bipolar coagulation technique could be used, the output power was 4 U, the duration 1–2 s at interval 5 mm apart (the bipolar coagulator is made in Sweden). **Results:** The early effects of the reoperation are followed up for only 3–5 months, all patients had a lesser seizure attacks than preoperation, and the later effects are uncertain. **Conclusions:** The surgical treatments for the patients with refractory epilepsy are not only to resect the epileptic foci, but also to eliminate the epileptogenic areas completely. (Supported by Beijing Surgical Institute.)

2.275

TEN YEARS' EXPERIENCE WITH MULTIPLE SUBPIAL TRANSECTION IN THE TREATMENT OF LANDAU–KLEFFNER SYNDROME

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Rationale: To examine the clinical course and long-term management of patients after multiple subpial transection (MST) for Landau–Kleffner syndrome (LKS). **Methods:** LKS, acquired epileptic aphasia, is a syndrome that, although rare, has profound effects on speech and behaviour. The epilepsy in the syndrome is neither prominent nor troublesome. Since first described in 1957, little effective treatment has been available. Morrell devised the surgical treatment of LKS, deducing correctly that LKS was a manifestation of secondary epileptogenesis and therefore would be amenable to this surgical procedure. Between 1992 and 2002, 10 patients were investigated and operated on on the Denmark Hill site with a presumptive diagnosis of LKS. All patients had severe speech disturbance, eight of the 10 were mute or virtually so before surgery. Six patients had a severe behaviour disorder. All of the patients were investigated appropriately, within the limits of their behaviour disorder. These included MRI, speech and language assessment, and neurophysiological tests of secondary epileptogenesis. All patients had carotid amytal tests, and in two patients, it was necessary to use intracranial electrodes. The last two patients operated on had magnetic source imaging. **Results:** All of the patients underwent MST with electrocorticographic control. In eight cases, the operation was on the left side; in two cases, on the right side. There were no significant complications from the surgery except for a transient hemiparesis in the first patient that resolved within 1 week. In three patients, there was evidence of relapse with deterioration or halting of speech reacquisition and the reappearance of ESES in the EEG. In one case, this resolved spontaneously; in the other two, a further operation was required 2 years and 1 year after the first. In one patient, that was probably a wrong selection; there was no improvement. All the other patients showed improvements in seizure control and behaviour. With a follow-up of 1–5 years in nine patients, there was complete seizure freedom in two patients (Engel 1A) but significant improvement to Engel 3A or better in six of the remaining seven. In one case, speech did not return; in the remaining seven patients for whom follow-up data are available, there was a significant and sustained improvement in speech as a result of the surgery. **Conclusions:** In appropriately selected cases of LKS (acquired epileptic aphasia), multiple subpial transection will improve speech, behaviour and seizure control.

2.276

OUTCOME OF EPILEPSY SURGERY IN MENTALLY HANDICAPPED CHILDREN

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Rationale: Children with severe epilepsy are often mentally retarded. In the majority of these patients, epilepsy is drug resistant, and epilepsy surgery (ES) may offer a solution. However, it is said that the efficacy of ES with regard to seizure reduction is unpredictable in patients with intractable epilepsy and mental retardation (MR) because of the diffuse character of the underlying brain disorder (Engel J Jr, Shewmon DA. *Surgical treatment of the epilepsies.* New York: Raven, 1999:23–24). Therefore, in many centers, children with MR are considered to be unfeasible for ES. The aim of this study was to assess the value of ES in these children in terms of both seizure reduction and quality of life. **Methods:** Twelve children with drug-resistant epilepsy with an IQ <70 were studied. Hemispherectomy was performed in five; callosotomy in two, and resection in five patients. Postoperative seizure control was expressed in the Engel classification. Quality of life was assessed by retrospective file analysis focused on the domains of self-care, mobility, cognitive and emotional functioning, well-being, and health and social interaction, as well as by validated structured interviews. Follow-up was ≥2 years. **Results:** Seizure control: Engel 1A was found in eight; Engel 2A in two, and Engel 3 in two patients. Comparison of postoperative IQ with preoperative IQ did not show any improvement or deterioration. In the two patients with Engel 3 (both treated with callosotomy), no improvement of quality of life was found. In the other 10, quality of life measurements showed an impressive improvement after surgery in all domains. **Conclusions:** Seizure control and quality of life significantly improved after epilepsy surgery in patients with MR. In our opinion children with drug-resistant epilepsy should be considered for ES, regardless of their IQ.

Nursing/Psychosocial/Health Services

2.277

IMPROVED DOCUMENTATION AND TRIAGE OF PATIENT TELEPHONE CALLS TO AN EPILEPSY CENTER

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Rationale: Complex, multidisciplinary epilepsy center offices receive a high volume of patient telephone calls. Our five neurologists see an average of 270 patients in clinic a month. We average 20 to 30 patient telephone calls for advice to our registered nurses a day. Documentation of patient telephone calls, nursing assessment, and physician assessment and advice is required. The objective of this poster is to present specific triage guidelines and computer-generated forms that were developed to ensure appropriate handling and documentation of patient telephone calls. **Methods:** A team of registered nurses and neurologists met to develop guidelines for our specific patient population. Nursing guidelines for seizure activity, medication dosing, side effects, allergic reactions and headaches were created. These guidelines include general information, assessment questions, care advice and triage instructions. Computerized Call Back Forms were developed for our receptionist to document the reason for the call, requested call back time and to update demographic information. Nursing Telephone Encounters were created to document the presenting problem, current medications, guideline used, recommended disposition and patient/caller understanding and intended action. The physicians also use this form to document their assessment and advice. Links to computer generated prescription forms and pharmacy fax cover sheets were designed. The forms were implemented as part of an internal practice management database developed at the Regional Epilepsy Center using a commercial database program. **Results:** The guidelines and forms were implemented in November 2001. Nurses report that the guidelines and forms have improved patient care by creating more thorough and uniform assessment and documentation of patient problems and concerns. Also the guidelines have been useful in training new nursing staff. Physicians prefer the printed forms that are specific to our patient population and find the chronological history of medication doses to be very helpful. The printed prescriptions and pharmacy fax cover sheets are easier and quicker to create and read. **Conclusions:** Response to patient telephone calls has been standardized and streamlined with the new system. User feedback has resulted in revisions to the forms, and new guidelines are being developed to address additional patient concerns and problems. Data concerning type of telephone call, daily volume and response turnaround times are now easily compiled and analyzed to help determine staffing needs and monitor quality of care. This system has been beneficial in meeting regulatory documentation requirements and in developing a paperless record-keeping system.

2.278

FACTORS ASSOCIATED WITH ACADEMIC ACHIEVEMENT IN CHILDREN WITH RECENT-ONSET SEIZURES

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Rationale: Children with epilepsy are at great risk for learning and academic achievement problems in school. Studies of children with chronic epilepsy have not discerned the causes for these problems. Moreover, no previous studies have investigated factors associated with academic achievement in children with recent-onset seizures to examine when and where academic problems arise. This unique sample of children with recent-onset seizures provides important data to examine academic functioning during the initial period after the onset of the seizure condition and the progression of problems. The purpose of this study was to identify factors related to academic achievement in children with recent-onset seizures. At the end of this activity the participants should be able to identify factors associated with academic achievement in children with recent-onset seizures. **Methods:** Baseline data were collected from parents, children, and teachers within 6 weeks of the child having a first recognized seizure and then again ~12 months later. Subjects were 109 children with new-onset seizures, their mothers, and their teachers. Data were analyzed using multiple regressions to predict academic achievement (Teacher Rating of Performance and Total Battery scores). **Results:** Regression results showed that parent expectations, child adaptive competency, externalizing behavior, and teacher expectations accounted for a significant amount of the variance in Teacher Rating of Performance (Adjusted R2, 0.599) and SES, parent expectations, and child adaptive competency accounted for a significant amount of the variance in Total Battery scores (Adjusted R2, 0.734). **Conclusions:** The most critical finding was that psychosocial variables (parent expectations, child adaptive competency, externalizing behavior, teacher expectations, SES) were more strongly associated with academic achievement than seizure variables, which suggests that when a child is having problems in school, psychosocial factors in addition to factors related to the seizures must be clinically assessed. Identification of the factors associated with academic achievement in children early in the course of the disorder will enable development and implementation of appropriate interventions at a time when they can have the greatest impact. (Supported by NS22416.)

2.279

PREDICTING AND PREVENTING INJURIES BY CONSIDERING SEIZURE CLASSIFICATION

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Rationale: It is often assumed that those caring for people with epilepsy educate them adequately about preventing injuries due to seizures. However,when we reviewed our patient population we discovered several differant areas in which we could have prevented injury. By the end of this activity we should be able to prevent some injuries by educating our patients of the association between their individual seizure type and what injuries have happened to other people with the same seizure type. **Methods:** We did a retrospective review of 500 outpatient records and interviewed 50 of these same patients in the clinic or by telephone about whether or not they have ever been injured during of a seizure. We included only adult and adolescent patients with a video-EEG–confirmed diagnosis and included only those injuries which specifically happened since the time of their video-EEG. Only those injuries were included which happened during seizure activity as described in the video-EEG findings. **Results:** We found a variety of injuries with each seizure type. Patients also unknowingly did things which increased their risk of injury during a seizure. We have compiled a list of safety recommendations which we will now use to educate our patients. Some of our patients did not remember the initial safety teaching we offered them and these recommendations will be added as we reeducate them. **Conclusions:** In conclusion, when offering epilepsy education to patients and caretakers, the type of seizure may be a predictor of certain situations which would put that person at risk for injury.

2.280

ELECTRONIC SCREEN GAME–INDUCED SEIZURES: RECOMMENDATIONS FOR PREVENTION AND RISK OF RECURRENCE

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Rationale: Electronic screen games (ESGs) and computer activities are frequent facets in a child's daily life and may potentiate seizures. We reviewed our outpatient clinical records for the past 3 years to determine appropriate guidelines for parents/patients to follow after an ESG-induced seizure. **Methods:** We reviewed 324 patient charts that had a diagnosis of generalized epilepsy from July 1999 through April 2002. Thirteen patients were identified as having ESG-induced seizures. We reviewed their clinical presentation, EEG findings, epilepsy diagnosis, clinical course, and obtained follow up. **Results:** Twelve of the 13 patients were available for follow-up. Patients' ages ranged from 9 to 18 years (mean, 12.2 years); nine boys and two girls. Two of the 12 were diagnosed with absence seizures but presented with a generalized tonic–clonic (GTC) at the time of the ESG-induced seizure. Both of these patients are seizure free with antiepileptic drugs (AEDs).

Seven had a single GTC seizure that was triggered by an electronic stimulus. Three of these patients are seizure free without medication and have continued to avoid the stimulus. The remaining four are well controlled on a single AED. The remaining three patients have intractable mixed generalized seizures, are taking multiple AEDs, and continue to have recurrent ESG-induced seizures if they are exposed to the stimulus. **Conclusions:** The most common seizure type in our patient population with ESG-induced seizures was GTC seizures. The risk of recurrence was low if patients complied with avoidance of the trigger and followed treatment recommendations. The patients who continued to have ESG-induced seizures had intractable mixed generalized seizures and remain taking multiple AEDs.

2.281

EFFICACY AND TOLERABILITY OF THE KETOGENIC DIET IN THE VERY YOUNG: ONE CENTER'S EXPERIENCE

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Rationale: When multiple antiepileptic medications (AEDs) fail or produce undesirable side effects in treating intractable epilepsy, the ketogenic diet can be an effective treatment option. Through the review of this poster, participants will be able to discuss the results of one center's retrospective study regarding safety, efficacy, and tolerability of the ketogenic diet in children younger than 2 years. **Methods:** A retrospective medical record review was conducted of ketogenic diet patients who were younger than 2 years when the diet was initiated, between August 1995 and March 2002. For each patient, seizure frequency and duration, AEDs, adverse effects, and parent comments were collected for the last clinic visit prior to diet initiation, the date of initiation, and the most recent clinical evaluation. The data collected before diet initiation was compared to the most recent clinical evaluation data and the results were assessed. **Results:** Seventeen children (nine boys and eight girls) younger than 2, with intractable epilepsy were placed on the ketogenic diet. Two were on the diet for <1 month, so they were excluded from the study. Of the 15 children remaining, six (40%) became essentially seizure free, and an additional eight (53.3%) had a >50% reduction in seizure frequency compared to baseline. One child (6.7%) had no change in seizure frequency long term, but did have a significant reduction of AEDs. In all cases, there were concomitant reductions in AEDs. The majority of parents reported improvement in seizure frequency and duration, increased levels of alertness, activity, and improved cognitive function. There were no serious adverse effects such as kidney stones, hypoproteinemia, acidosis, hemolytic anemia, or marked increases in liver function tests. Two children died as a result of other medical complications, but the ketogenic diet was not considered a factor. **Conclusions:** The results demonstrate that children under 2 years of age had a reduction in seizure frequency without experiencing any adverse effects. Most children in this retrospective study were either tapered off all AEDs or had a significant reduction in the number of AEDs needed. Thus, the ketogenic diet should be considered a safe, effective, and well-tolerated therapy for treating young children with intractable epilepsy.

2.282

"TAKING CHARGE OF EPILEPSY": THE DEVELOPMENT OF A STRUCTURED GROUP INTERVENTION FOR ADOLESCENTS WITH EPILEPSY AND THEIR PARENTS

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Rationale: Previous research demonstrates that children and adolescents with chronic health conditions such as epilepsy are at an increased risk for negative psychosocial outcomes including social isolation, affective disorders, and decreased quality of life. Although the increased risk has been recognized for some time, little research has been conducted examining the outcome of psychosocial interventions for adolescents with epilepsy. This presentation will provide the partcipants information concerning the development, implementation and impact of a structured group treatment program for adolescents with epilepsy and their parents. **Methods:** The program "Taking Charge of Epilepsy" was initially developed by two of the authors (J.A., K.B.) and previous psychology interns with input from the local chapter of the Epilepsy Foundation of America (EFA) in response to a perceived need within the local community for an educational/support group for adolescents with epilepsy. The initial version of the group was just for adolescents . Subsequently, the format was modified and structured group meetings were designed so that the parents and adolescents participated in concurrent meetings 1 h weekly for 6 weeks. Session topics included epilepsy information, medical treatment, and psychosocial well-being/adjustment. Between sessions, all participants completed daily seizure/thought logs which were utilized during presentation of a cognitive–behavioral model of the interaction between thoughts and mood. **Results:** Nine adolescents age 13–18 years completed the screening. Five (two boys and three girls) qualified and were enrolled. Of these, one participant did not complete the program due to a family illness. After the final session, all participants completed an anonymous evaluation form including Likert-type scale items and open-ended questions. Overall level of satisfaction with the group was high. A nonparametric analysis indicated significant findings for two items: "Did the groups meet your expectations?"and "Were the subjects covered in the sessions helpful to you?" Responses to open-ended questions indicated that parents and adolescents valued the interaction with other participants and the support provided by the group. In addition, several respondents indicated particular topic areas covered in the sessions as what they liked most about the groups. **Conclusions:** Both adolescent and parent participants responded positively to participation in the group sessions. Social interaction with other participants and factual information presented in group were most commonly indicated as valued by the participants. The adolescents varied greatly in age (13–17 years) as well as developmental level. Overall cognitive level and degree of independence from parents may influence the applicability of the group for some adolescents. Ongoing efforts will need to incorporate or respond to differential level of parental dependency. This data were collected through an ongoing research project. Additional subjects will be enrolled prior to the AES meeting and new analyses will be conducted. (Supported by American Epilepsy Foundation/Shire.) (Disclosure: Grant: Epilepsy Foundation of America/ Shire.)

2.283

QUALITY OF LIFE IN EPILEPSY: TOWARD A COMPREHENSIVE AND UTILITARIAN DEFINITION

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Rationale: Quality of life is increasingly being recognized by epilepsy professionals as a construct with tremendous potential as a measure of treatment outcome, and as a model for developing and planning services. In order to have utility in outcome and evaluation research, or in service planning, quality of life must be defined in a way that is meaningful, consistent, and comprehensive. The purpose of the present study was to further explore the utility of the quality of life construct as a multi-dimensional and multi-domain concept, the utility of the construct for researchers and professionals, and its meaning among people with epilepsy. At the end of this activity, participants will be able to discuss the quality-of-life construct in terms of its definition, current status, and both the potential and the problems associated with its utility for researchers and professionals working with people with epilepsy. **Methods:** In the autumn of 2001, 200 37-item surveys were mailed to people on the mailing lists of Ohio and Kentucky Epilepsy Foundation chapters. The survey included questions related to the respondents′

quality of life, their definition of quality of life, and the factors that promote and detract from quality of life. Forty-six completed surveys were returned. Using open and axial coding techniques, a multidimensional (objective and subjective perspectives), and multidomain structure of quality of life emerged from the data analysis. **Results:** Domains that were consistently identified by the participants as central to the quality of life included work and productivity, social support, physical health, religion/spirituality, autonomy/independence, leisure activities, security, mental health, and educational status. While general, rather than epilepsy-specific factors were reported to contribute to quality of life, epilepsy-specific factors related to seizures, seizure worry, and medication effects were reported to detract from quality of life. The results provide increased understanding of the quality of life construct as it is understood and experienced among adults with epilepsy. **Conclusions:** To the extent that it can be shown to be meaningfully and consistently defined and understood, quality of life represents a construct with tremendous potential in epilepsy service planning and outcome research. The present study highlights this potential by demonstrating the consistency of this construct in terms of domains associated with quality of life, and the general and epilepsy-specific factors that contribute to and detract from quality of life ratings among adults with epilepsy. This broader conceptualization of quality of life than is typically used among epilepsy researchers and professionals has implications for the future use of the quality of life construct in both clinical and nonclinical settings. (Supported by University of Kentucky Research Foundation.)

2.284

SIMILARITIES AND DIFFERENCES BETWEEN CAMPS FOR CHILDREN WITH EPILEPSY

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Rationale: Camps designed for children with epilepsy have been advocated as a means to promote social interactions and adaptive behaviors, however there is no uniform model even among Epilepsy Foundation (EFA) affiliates and other sponsoring organizations. We seek to understand the variability among camps in their design, goals, management of disabilities, staff to camper ratio, number of campers, opportunities for campers to advance in leadership roles, and the number of counselors with epilepsy. Future study may shed light on the most effective means to achieve social and behavioral goals. **Methods:** We identified 31 camps through EFA and other disability organizations. We telephoned camp directors or senior staff to ascertain models of care for children with epilepsy in 2001. We asked 38 specific open ended questions regarding the camp design, their goals, composition of campers and counselors, management details, budgets, programs, and benefit to campers. **Results:** Results from 31 camps for children with epilepsy demonstrated four primary designs: (a) epilepsy-only camps, (b) children integrated into a regular camp, (c) children attending with siblings or parents, (d) children mixed with children with other disabilities and chronic health conditions. In this sample, 52% of camps were designed for children with epilepsy only, 19% had a few children with epilepsy integrated with many children without epilepsy, 19% children with epilepsy with family members (16% siblings and 3% parents) and 10% placed children with epilepsy with children having other chronic health conditions. 50% of camps had clearly defined goals to build self-esteem, independence and/or socialization. 25% of camps used developmental and chronological ages to organize bunks. 52% of camps offered opportunities for campers to advance into leadership roles such as counselors in training. Only 50% of camps had counselors with epilepsy on their staff. The staff to camper ratio varied between camps: 12% (2:1), 19% (1:1), 54% (1:2 or 3), 8% (1:4 or 5) and 4% (1:10). Also the number of campers varied between camps: 38% camps (<29 campers), 35% (30–49), 12% (50–69), and 15% (>70). **Conclusions:** There is significant variability in the organizational structure and design of camps for children with epilepsy. Our previous research demonstrates a condition-specific camp for children with epilepsy can improve adaptive behaviors and increase socialization. Further analysis is necessary to evaluate which design and management factors are most relevant to promote a positive change. Greater consistency between camps may also be helpful to families and referring healthcare providers and for future research opportunities.

2.285

EPILEPSY AND EMPLOYMENT: THE EFFECT OF EPILEPSY ON EMPLOYMENT AND EMPLOYMENT DETERMINANTS AMONG ADULTS WITH EPILEPSY

Malachy L. Bishop and Chase Allen (Special Education and Rehabilitation Counseling, University of Kentucky, Lexington, KY)

Rationale: People with epilepsy continue to experience higher rates of unemployment and underemployment relative to people without epilepsy. The purpose of the present study is to further the understanding of the factors that affect employability and predict employment status among adults with epilepsy. **Methods:** Binary logistic regression and $\chi 2$ analyses were used to evaluate the relationship between employment status and demographic variables, including gender, age, rural versus urban dwelling, and education, and epilepsy-related variables, including seizure frequency, antiepilepsy medication (AED) use, years since diagnosis, and seizure type. Data for the analysis were collected from 146 adults with epilepsy, through Epilepsy Foundation chapters in Wisconsin, Kentucky, and Ohio. **Results:** A number of variables , including gender, number of AEDs used, seizure frequency, and perceived interference of seizures in daily functioning were significantly associated with employment status. Possession of a driver's license was also positively associated with employment status. **Conclusions:** The results of this study contribute to the comprehensive understanding of the effects of epilepsy on employment. The findings are important for the development of effective employment-related services and have implications for professionals working to improve the quality of life of people with epilepsy, and specifically, for addressing the barriers to employment faced by people with epilepsy. This study will be presented in the context of a series of recent studies aimed at understanding the barriers to employment and improving the employment situation for people with epilepsy. (Supported by University of Kentucky Research Foundation.)

2.286

THE IMPACT OF CARING FOR A CHILD WITH EPILEPSY: A PARENT'S PERSPECTIVE

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Rationale: Although many parents encounter stressors while raising a child with epilepsy, little is known about how parents are affected by this experience. The objective of this investigation was to explore parents' perceptions of the social, emotional, financial, and spiritual impact that results from caring for a child with epilepsy. **Methods:** Participants were 25 parents (seven men; 18 women) whose child was admitted to a children's inpatient epilepsy unit for evaluation and treatment. Parents ranged in age from 25 to 48 years. Most participants who completed the questionnaire were married ($n = 18$) including six married couples. The participants' children with epilepsy (10 boys; nine girls) ranged in age from 1 to 18 years (median, 7 years). Time since seizure onset ranged from newly diagnosed to 15 years (median, 4 years). The children experienced one to multiple seizure types. Seizure frequency ranged from one to hundreds per week. Children were treated with mono- or polyanticonvulsant (AED) therapy. Parents were asked if they were willing to complete a survey that included checklists, open-ended and scaled score questions regarding family demographics, stressors, and the impact of caring for a child with epilepsy. Parents were excluded if medical staff reported that comprehension of the questionnaire may have been difficult due to language or cognitive abilities. **Results:** Many parents (48%) noted an increase in tension with their spouse/partner due to caring for their child with epilepsy, while 28% noted that their relationship had been strengthened. Simi-

larly, 32% reported feeling a close relationship with their child; however, parents tended to treat their child with epilepsy differently (e.g., overprotective). Of those parents with additional children, 44% noted fewer opportunities to provide them time or attention. Relationships with extended family members were primarily described as supportive (52%), yet a majority of parents (84%) reported a marked change in their social life (e.g., less free time, spend most time with their family). Taking time off from work was the most frequently cited change noted by parents employed outside the home (57%). A majority of parents (60%) also noted a change in their family′s financial circumstances due to expenses related to the child′s care. 72% reported that caring for a child with epilepsy resulted in increased stress or symptoms of depression or anxiety; however, most parents (80%) described themselves as doing "OK" or able to cope with stress more effectively. Of those parents who noted a change in their spirituality, 57% stated their experiences had deepened their faith. When asked to describe the most stressful part about caring for their child with epilepsy, 44% noted the uncertainty associated with their child's illness. Finally, 60% of parents reported feeling moderately overwhelmed with the care their child with epilepsy requires. **Conclusions:** These results suggest that parents of children with epilepsy experience marked social, emotional, financial and spiritual changes as a result of caring for their child with epilepsy. Although these results are based on a limited number of participants and are considered preliminary, these findings have implications for the type of services these families may require. In addition, these results may help healthcare providers appreciate the experiences of families.

2.287

THE BENEFITS OF A CAMP DESIGNED FOR CHILDREN WITH EPILEPSY: EVALUATING ADAPTIVE BEHAVIORS IN A 3-YEAR STUDY

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Rationale: Children with epilepsy as a group have more behavioral problems and social isolation than children without epilepsy. Anecdotal reports and limited evidence suggest that children with epilepsy can benefit from attending a camp dedicated to their specific condition. Camp Great Rock is a condition-specific camp that positively affects children with epilepsy. We prospectively studied children attending this dedicated camp and measured change in four domains over the past 3 years. **Methods:** Children attending Camp Great Rock, a 7-day, overnight camp were evaluated for changes in adaptive behaviors. The number of campers was: 1998: 44, 1999: 55, and 2000: 64. An average of 49% of the campers had epilepsy only; 40% had epilepsy and learning disabilities; 9% had mild mental retardation (MR) and epilepsy; 2% were children of counselors. Return campers were evaluated longitudinally over 3 years. A modified Vineland Adaptive Behavior Scale was used to assess social interactions including (responded appropriately to positive statements; showed a consistent friend preference; and initiated topics of interest); cooperation (participated in activities; helped with chores; and helped other campers in need) communication (labeled feelings; expressed anger appropriately; expressed thoughts and concerns) and responsibility (changed clothes when dirty; and straightened bunk without reminders). For each camper pre- and posttest scores were obtained for each question on the first and last day of camp by two counselors. A mean score was derived for each of the 27 questions that contributed to the four functional categories. A paired-sample *t* test was performed to compare the pre- and posttest values for each of the mean scores. **Results:** Significant improvement in social interaction for all 3 years was consistently found: 1998: 33% of behaviors; 1999: 50%; and 2000: 67% ($p < 0.05$). Overall improvement in socialization was observed in each of 3 years ($p < 0.01$ to 0.0001). In the domain of cooperation, significant improvement ($p < 0.05$) was seen in 1998 (40%), 1999 (40%), and in 2000 (80%). In communication, significant improvement ($p < 0.05$) was observed in 1998 (40%) and in 2000 (60%). In the domain of responsibility, little change was observed. Returning campers (50%) showed a significant overall improvement in social interaction from postcamp 1 year to precamp the next, for the 3 years. Cooperation improved significantly in 1999–2000 for return campers. **Conclusions:** Adaptive behaviors are important for all children and more so for children with epilepsy. Specialty camps designed for children with epilepsy can positively increase adaptive behaviors and improve social interactions. Notable was the significant and consistent improvement in social interaction in all 3 years. Furthermore, the benefit was sustained from year to year for return campers. (Supported by Pediatric Clinical Research Center, Children's Hospital.)

2.288

EPILEPTIC PATIENTS' ATTITUDES ON DRIVING IN PERU

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Rationale: A seizure is the most common cause of loss or rejection of driving licenses for medical reasons, but there is variability in how physicians and the authorities who regulate driving approach this issue including empiric, clinical, and statistical data. We wanted to know the opinions and attitudes of epilepsy patients about this controversial issue. **Methods:** A questionnaire regarding driving was given to ambulatory adult epilepsy patients evaluated in a neurological referral center ($n = 104$). **Results:** Patients had a mean age of 27.8 years; a mean duration of seizures of 10.7 years; and mean seizure frequency of one each 4.2 months; 85% were receiving regular antiepileptic drugs (AEDs). Twenty-five percent had driving licenses. Driving was an extremely important issue for 30%; important for 60%; and not important for 10%. Of 81% who were driving; 29% had had an accident. The cause was seizures in 45%; between them 25% had drunk alcohol. **Conclusions:** Driving is an important issue for epilepsy patients, and many of them work in driving activities.

2.289

NEUROTICISM INFLUENCES PATIENTS' COMPLAINTS ABOUT MEMORY

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Rationale: Neuroticism, widely accepted as a prominent component of the "5-factor model of personality" (McCrae and Costa, 1990), refers to a pattern of negative affect and associated behaviors including anxiety, hostility, depression, impulsiveness, and vulnerability. Neuroticism has been shown to correlate with increased stress, poor health, and increased symptom reporting. Epilepsy patients' self-reports of poor memory are sometimes not consistent with their neuropsychological test scores. To account for this, it was hypothesized that Neuroticism, rather than objective neuropsychological test performance, would be significantly associated with patient-reported memory problems. **Methods:** Seventy-three consecutive patients, admitted for monitoring on a surgical epilepsy center, were assessed. All patients were administered the negative affects portion of the Positive and Negative Affect Scale (PANAS) as a measure of neuroticism. Subjective report of memory was assessed using the memory questions from the Quality of Life in Epilepsy–89 (QOLIE-89). Objective memory performance was obtained using the Rey Auditory Verbal Learning Test. Three memory performance variables were studied: immediate memory, rate of learning, and delayed recall. Age, level of education, and Full-scale IQ scores were also entered as predictor variables. Data were analyzed through linear regression analysis. **Results:** Regression analyses revealed that only the Neuroticism score (PANAS) predicted the QOLIE-89 memory items. Objective memory test performances (immediate recall, rate of learning and delayed recall), age, education, and Full-scale IQ scores were not significant predictors of patients' subjective memory ratings. To substantiate this finding, two groups were created (High, Low Neuroticism) based on a median split of scores. Between-groups comparisons (one-way analysis of variance) revealed those in

the High Neuroticism group endorsed having significantly greater memory complaints on all self-report items. In contrast, no between-groups differences were seen on any neuropsychological measure of memory. **Conclusions:** Subjective and objective memory functioning are independent in patients with epilepsy. Neuroticism is an important influence upon patients' reports of subjective memory functioning. High Neuroticism can lead to a discrepancy between self-report and objective findings. Screening for Neuroticism is an important consideration when evaluating the contribution of epilepsy to patients' self-report of poor memory.

2.290

THE IMPACT OF AGE AT SEIZURE ONSET ON OCCUPATION AND EDUCATION

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Rationale: Employment status has been shown to improve after epilepsy surgery, but in many cases, not to the extent that one might expect in seizure-free patients. Psychosocial factors have been implicated to explain poor occupational status. The aim of this study is to investigate the influence of age of seizure onset before and after education completion on employment status in epilepsy surgery candidates. **Methods:** We studied 355 patients with epilepsy that were admitted to the video-EEG monitoring unit between June 1997 and June 2001. The patients were 15–77 years old (mean, 37.05 years; SD, ±11.65); 51.3% were female. The sample was divided in two groups according to whether the age at seizure onset occurred before or after they completed their education. Groups were compared considering highest educational and occupational level achieved and current employment status or major day activity. Data were obtained from the 89-item QOL questionnaire developed at the Cleveland Clinic Foundation. Educational and occupational levels were classified on a scale from 1 to 8 where 1 corresponded to the highest level of education and occupation and 8 to the lowest. The $\chi 2$ and t test were used for comparison among groups. **Results:** A total of 199 patients (56.1%) had seizure onset before they completed education and 112 (31.5%) afterward. The mean occupational level in patients with seizure onset before education was completed was significantly lower (5.07) than those whose seizures started after (4.27; t test = 0.001). Unskilled employees [30 patients (17.9%)] and patients who never worked [18 patients (10.7%)] were more likely to have seizure onset before completion of education ($\chi 2 = 16.40$; $p = 0.022$). Patients with seizure onset after completion of education were significantly more likely to be disabled [24 patients (21.8%)], retired [five patients (4.5%)], or homemakers [22 patients (20%)], while students [31 patients (15.8%)] were more likely to have had seizure onset before completion of education ($\chi 2 = 19.07$; $p = 0.004$). No differences were found for the mean educational level (mean, 0.13; t test = 0.482) or the level of education achieved between the two groups ($\chi 2 = 10.11$; $p = 0.182$). **Conclusions:** Patients with seizure onset before education completion achieve lower occupational status. Seizure onset after education is completed leads to more disability and early retirement. The impact of education status in patients with seizures deserves further study.

2.291

HISTORY OF ABUSE DURING CHILDHOOD AFFECTS PSYCHOSOCIAL ADJUSTMENT IN ADULTHOOD IN PATIENTS WITH EPILPESY

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Rationale: This study examines the question of whether or not reporting a history of abuse during childhood is associated with increased psychosocial problems in adulthood as evaluated by the Washington Psychosocial Seizure Inventory (WPSI). We discuss the various impacts of abuse during childhood on psychosocial functioning as an adult in epilepsy patients. **Methods:** Detailed psychosocial interviews were conducted with 192 patients as a regular part of long-term EEG monitoring on an inpatient epilepsy unit. History of physical, sexual, emotional abuse, or no abuse before age 18 was obtained. Of the 192 patients examined, 106 reported no abuse, 63 reported abuse in one of the three abuse categories (26 physical, 23 sexual, 14 emotional), and 23 reported abuse in all three categories. Patients' WPSI scores for each scale were obtained, and the groups were compared to determine significant differences in scores across the groups. Mean eduacation, age, intelligence, as well as seizure diagnosis, were taken into account as well. **Results:** The results showed that there were significant differences on six of the eight WPSI clinical scales between patients who did and who did not report abuse in childhood. Patients with any type of reported abuse history before age 18 showed more difficulty in Family Background ($p < 0.0001$), Emotional Adjustment ($p < 0.001$), Interpersonal Adjustment ($p < 0.01$), Adjustment to Seizures ($p < 0.001$), Medicine and Medical Managment ($p < 0.05$), and Overall Psychosocial Functioning ($p < 0.001$), as reported on the WPSI. The statistically significant finding on the Family Background scale is of particular interest because of the large differences between all three groups. This represents an external validation of the WPSI Family Background scale. Furthermore, this scale was able to differentiate between patient groups with no abuse, one area of abuse, and more than one area of abuse. No other WPSI scale was able to make this differentiation statistically. Finally, reported abuse in even one of the three areas (physical, sexual, emotional) was associated with diminshed psychosocial functioning in adulthood with no evidence for differences in psychosocial functioning in adulthood depending on the area of abuse in childhood. **Conclusions:** Patients who reported any type of abuse during childhood in the psychosocial interview by the epilepsy social worker reported increased difficulty with adjustment and functioning in adulthood compared to those without an abuse history. This shows us that among our patients, childhood abuse is having a long-term impact on psychosocial functioning. With the growing poularity of offering comprehensive epilepsy services, this information is useful in creating a successful treatment plan for patients that addresses not only the medical aspects of epilpesy, but also the social and emotional aspects as well.

2.292

THE IMPACT OF SUMMER CAMP ON IMPROVING SELF-ATTITUDE IN CHILDREN WITH EPILEPSY

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Rationale: One third of all epilepsy is present in children. Self-attitude in children is negatively influenced by the presence of epilepsy. A weeklong overnight summer camp exclusively for children with epilepsy offers an opportunity to feel less estranged from their peers, and provides an opportunity to increase self-attitude. We set out to determine whether this camp experience could improve the self-attitude of children with epilepsy. **Methods:** We used the Child Attitude Toward Illness scale (CATIS; Austin and Huberty, 1993). The CATIS is a 13-item questionnaire appropriate for children aged 8–17, which measures a child's favorable or unfavorable attitude toward having a chronic illness. Each question was scored on a five point scale with higher scores indicating more positive attitudes. The CATIS was mailed with an accompanying cover letter and instruction sheet for both precamp and postcamp periods. The letter requested that parents or guardians help the child by clarifying the questions being asked (if necessary), but to refrain from influencing their answers. The 21 children ranging in age from 10 to 15 years completed the CATIS before camp and 19 completed it after camp; unfortunately, only 11 children completed both the pre- and postcamp questionnaires. **Results:** Inter-item reliability of the CATIS was found to be high, the standardized

item alpha equaling 0.79. An average of the CATIS items was thus calculated to be used in subsequent analyses. A *t* test was performed with the 11 children comparing pre- and postcamp CATIS responses, which revealed a nonsignificant numeric trend toward improved self-attitude after attending camp [3.55 vs. 3.80, $t(10) = 1.78$, $p = 0.105$]. We hypothesized that the lack of significance may have been due to two factors. First, the small sample size likely limited our power to detect significant differences. Second, we wondered whether just the anticipation and excitement of going to camp could have played a role in improving self-attitude. To explore this hypothesis, we sent out CATIS questionnaires to a control group of 11 similarly aged children with epilepsy who did not attend the camp. A one-way analysis of variance comparing the 21 precamp responses to those of the control group revealed significant differences demonstrating that those children anticipating camp reported higher levels of self-attitude than those who were not going to camp [3.55 vs. 2.89, $F(1, 30) = 11.35$, $p = 0.002$]. **Conclusions:** These results suggest that a weeklong summer camp may be able to improve self-attitude in children with epilepsy. Further, this improvement may be observed prior to attending camp, presumably due to the positive anticipation felt by the child. Additional research with larger samples will be needed to confirm these preliminary findings. (Supported by Donations to Camp Wee-Kan-Tu: A Camp for Champs.)

2.293

IMPACT OF A GROUP INTERVENTION ON THE QUALITY OF LIFE OF ADOLESCENTS WITH EPILEPSY

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Rationale: With advances in medical technology and the ability to successfully manage chronic health conditions, there has also been increasing interest in the impact of these conditions on the lives of individuals. A large body of literature exists documenting the often deleterious effects of chronic health conditions and their treatments on the quality of life of youth. Relatively little literature has investigated the impact of group psychosocial treatment for adolescents with chronic health conditions. The present study reports preliminary data on the impact of a group psychosocial intervention for adolescents with epilepsy and their parents on quality of life as measured by the Quality of Life for Adolescents with Epilepsy (Cramer, et al., 1999; QOLIE-AD-48) **Methods:** Pre and Postintervention ratings of quality of life using the QOLIE were obtained from adolescents with epilepsy and at least one of their parents participating in a six- session (weekly) structured cognitive–behavioral group intervention. All of the adolescents were being treated with antiepileptic medications while they participated in the group and some continued to experience seizures. Certain items on the QOLIE address symptoms or general health states that an intervention of this type would not be expected to impact even if successful (e.g., "In the past 4 weeks, how often has your health limited heavy activities such as running, participating in very active sports (such as gymnastics, roller-blading, skiing?"). Therefore, before analysis of the data, the researchers identified "critical items" on the QOLIE for analysis in addition to the derived subscales and total score. **Results:** Using paired samples *t* tests, no significant pre- to posttreatment changes were found across the QOLIE subscales or total score. Due to the limited sample size ($N = 4$), we performed a nonparametric sign analysis. When we looked at the type of change (e.g. positive/higher ratings on posttest, negative/lower ratings on posttest, no change) observed on the eight subscales and the overall score, there was a significant trend toward positive change ($\chi 2 = 11.9$, $p = 0.003$). Of a possible 35 opportunities for a postintervention change in subtest or total score across the four subjects, 21 were observed in a positive direction, nine in a negative direction, and no change was observed in five instances. A similar trend was observed for type of change on the "critical items" ($\chi 2 = 15.34$, $p < 0.001$) with many instances of no change occurring when the adolescent selected the highest level response at the time of the pretest, therefore providing a ceiling effect in which there was no room for further improvement. **Conclusions:** The preliminary data demonstrates a potential positive effect on adolescent quality of life as measured by the QOLIE from participation in a structured group psychosocial intervention for adolescents with epilepsy and their parents. The small sample size is an obvious limiting factor of the study. However, these data was collected through an ongoing research project. Additional subjects will be enrolled prior to the AES meeting and new analyses will be conducted. (Supported by Epilepsy Foundation of America/Shire.) (Disclosure: Grant: Epilepsy Foundation of America and Shire.)

2.294

PERCEPTIONS AND ATTITUDES TOWARD EPILEPSY: A COMMUNITY SURVEY OF INDEPENDENT HEALTHY OLDER ADULTS IN METROPOLITAN PHOENIX, ARIZONA

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Rationale: The number of older adults with epilepsy is increasing, and the highest incidence and prevalence of seizures is within this population. There is limited to no information regarding how independent older adults perceive and comprehend seizures and epilepsy. Phoenix is home to one of the largest populations of older adults in the United States. This information will be used to develop educational tools to further promote understanding of epilepsy within this population. On completion of this activity, participants will have a better understanding of older adults' perceptions of seizures. **Methods:** Independent older adults completed a survey consisting of 28 questions regarding personal perceptions and attitudes about epilepsy. Surveys were conducted at various older adult community centers in metropolitan Phoenix in April 2002. Older adults (older than 60 years) without a history of seizures or epilepsy were included. The survey assessed knowledge of first aid for seizures and understanding of this condition compared with other chronic diseases. **Results:** The 104 surveys were completed by 32 male and 72 female participants, ages 60–99. The average age of respondents was 77. Most were familiar with seizures or epilepsy by either knowing somebody (67%) or having witnessed a seizure (69%). A sizeable minority of respondents had significant misperceptions about epilepsy. Twenty-eight percent either considered epilepsy a form of mental illness or were uncertain if it represented one. Eight percent believed that seizures were contagious. Only 53% were able to correctly identify various symptoms of different seizure types. A concerning majority of respondents had misunderstandings about seizure first aid. Sixty-nine percent were uncertain as to how to help someone with a seizure either suggesting or being uncertain that something needs to be placed in the mouth or that the individual should be held down during a seizure. Several differences emerged between male and female responders regarding who they would tell about having seizures. Thirty-seven percent of men and 25% of women would tell a family member. Fourteen percent of females would tell a friend and 19% would tell anyone, while only 2% and 9% of male respondents would tell a friend or anyone, respectively. Fifty-six percent of all respondents would not tell their doctor. When epilepsy was compared to other medical conditions, such as arthritis, cancer, diabetes, pulmonary and heart disease, 7% of respondents feared chronic seizures most. Forty-eight percent indicated that they were not completely familiar with epilepsy. There were significant psychosocial misperceptions in the respondents. Forty-seven percent either were uncertain or believed that individuals with seizures should not live independently. Fifty-one percent were uncertain or believed that individuals with seizures should not have children. Nearly one-third (29%) were uncertain if people with seizures were violent. **Conclusions:** Older adults in Phoenix, Arizona, have misperceptions about seizures and epilepsy, which may be indicative of how many older Americans view this condition. A larger popu-

lation based study is needed to further define how to best structure community educational programs about epilepsy in older adults.

2.295
ATTITUDES OF ELEMENTARY AND MIDDLE SCHOOL TEACHERS TOWARD STUDENTS WITH EPILEPSY: PRELIMINARY RESULTS OF A KENTUCKY STUDY
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Rationale: Teachers' attitudes about their students have the potential to affect students' success in school, and thus, the individual's success and achievement after leaving school. The broad goal of the present line of research is to increase understanding of the effects on educational and employment success of teachers' negative attitudes and incorrect assumptions about epilepsy. A related goal is the development of educational and informational training programs for educators of students with epilepsy. In order to develop effective training programs, it is necessary to make the programs' foci appropriate to identified problem areas. At the end of this activity, participants will have an understanding of the current research regarding the relation between educational experiences and later psychosocial and vocational success, and will have the opportunity to discuss development of appropriate and effective teacher training concerning working with students with epilepsy. **Methods:** A questionnaire was used to assess teacher attitudes toward persons with epilepsy. An indirect, error-choice attitude measurement scale, the "Test of Knowledge about Epilepsy" scale, was used to assess teacher attitudes. In addition, the questionnaire requested demographic information and information about professional preparation. The questionnaire was sent to 1,000 randomly selected elementary and middle school teachers in the state of Kentucky. Data collection for this project is currently ongoing. **Results:** Preliminary results from this ongoing study will be presented. Data from 100 respondents will be presented with an exegesis of the relation between teacher attitudes toward students with epilepsy. The comparison will focus on attitude differences that arise based on differences among teachers with respect to rural versus urban school-setting, years of teaching experience, teacher gender and age, teacher preparation, and teacher knowledge and understanding of epilepsy. **Conclusions:** The impact of the elementary and middle school educational experience on future academic, social, and vocational experiences is not currently well understood. Neither are the relations between teacher attitudes and teacher demographic and experiential variables. This study represents an effort to increase and expand the current understanding so that effective teacher training and educational programs may be developed. (Supported by University of Kentucky Research Foundation.)

2.296
PRELIMINARY DATA EVALUATING A WEB-BASED PATIENT RESOURCE
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Rationale: The epilepsy service at Massachusetts General Hospital (MGH) has instituted a Web-based resource (PatientWeb) specifically designed for its patients. The goal of PatientWeb is to improve access to the epilepsy service, allow patients to interact with each other if they choose, and access educationa materials that the epilepsy service has reviewed and "certified" as useful and accurate material. The design of PatientWeb has evolved from an analysis of the MGH epilepsy public Web-forums and feedback from patient of the epilepsy service ambulatory clinic. In previous studies, the issues of greatest interest to patients were treatment options, natural history of illness and to share personal experiences. For this study, we analyzed user activity of PatientWeb to determine resources used after initial training on the system. **Methods:** We analyzed user logs of the first 21 enrolled users of PatientWeb. We looked at computer user log files for the first 2 months to determine who logged on after training and which resources they accessed. We further examined use of individual library articles to determine those of greatest interest to our patients. **Results:** After training, 16 of the 21 users logged onto the system and posted messages to their providers. Ten of the 16 users accessed the library. Each of the 10 patients reviewed at least one article on specific medications. Other articles accessed included; general principles of medical management of seizures (five), medication side effects (four), relaxation therapy (five), memory issues (three), and surgical treatment of epilepsy (four). Users spend an average of 6 min on an article, the longest time spent was 30 min. **Conclusions:** Although the user logs only show if a patient has accessed the library, they do not show if the user has actually read the information. However, this preliminary data shows that users do access the system, and the majority of patients utilize the system to communicate with their providers. The level of use of the library was less than anticipated, thus demonstrating that static information certified by providers is not of the greatest interest to users. (Supported by National Library of Medicine.)

Pregnancy/Gender Issues

2.297
A SYSTEMATIC REVIEW OF LONG-TERM DEVELOPMENTAL OUTCOMES IN CHILDREN EXPOSED TO ANTIEPILETIC DRUGS IN UTERO
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Rationale: A systematic review summarisng the existing evidence for the potential adverse effects of antiepileptic drugs (AEDs) on the development of children born to mothers with epilepsy. **Methods:** A systematic search of Medline (from 1966) and Embase (from 1988) to December 2001 was conducted to identify case–control and prospective controlled cohort studies of the developmental outcome in children born to mothers with epilepsy. An adapted version of the Newcastle-Ottowa scale for nonrandomised studies was used for qualitative assessment. Data were extracted from each study for developmental outcomes in children exposed to AEDs per se, monotherapy (MT), and polytherapy (PT) regimens compared to nonexposed children in the general population. **Results:** Twenty-four prospective cohort-controlled studies were identified. After qualitative assessment, two studies were excluded, and only 14 were found to be independent studies, with the remainder reporting further follow-up of a related cohort. The population studied, age at follow-up, drug exposure in utero, and assessment of the children varied widely amongst the studies, making a quantative summary of the data difficult. Whilst the majority of studies examined children between the ages of 8 months and 3.5 years, eight studies looked at children in the preschool or school age. Most studies reported the effects of AED exposure per se or MT and PT regimens in general without reference to specific regimens. Four of 7 studies showed a poorer developmental outcome in children exposed to PT in utero in both early and later years compared to MT regimens. Eight studies had data on children exposed to MT in the younger age group, and five in the older age group. The numbers exposed were small with most exposures being to phenytoin (PHT) or carbamazepine (CBZ). Only one study included a significant number of children exposed to valproate (VPA). The results of the studies were conflicting. Among eight studies of PHT exposure, one study showed an adverse effect for PHT in early development, and three, an advesre effect in later life. Of the five studies of CBZ exposure in utero, two studies suggested an adverse effect on development in the first years of life, while three studies including older children failed to show a difference. In the one study of VPA exposure in utero, there was a poorer outcome in the first 3 years of life. Few studies icluded data on how common these adverse effects were. **Conclusions:** On the basis of

current studies, conclusive evidence regarding the relative risks of specific AEDs are fraught with limitations. There is a need to ground advice to women of reproductive age on high-quality evidence.This has vital implications for the design and reporting of studies of the longer-term risks of AED exposure in utero. (Supported by University Department of Neurological Science, University of Liverpool.)

2.298
SEIZURE FREQUENCY DURING PREGNANCY AND PUEPERIUM

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Rationale: Patients with epilepsy have been estimated to constitute 0.3–0.7% of all pregnancy. Patients with epilepsy are at substantial risk for a variety of complications during pregnancy. The objectives are (a) to evaluate the changes in seizure frequency during pregestational, pregnancy, and puerperium periods, and (b) to identify factors related to increase in seizure frequency. **Methods:** We followed up 50 pregnant women with epilepsy prospectively. The mean age was 25 years (range, 16–45), and the mean duration of epilepsy was 11 years (range, 7 months–37 years). Nine had symptomatic, 35 had probably symptomatic, and six had idiopathic epilepsies. All patients were evaluated every 60 days. Forty-seven were keeping with the same pregestational antiepileptic drug (AED). Three had no AED therapy. Drug dosages were increased to control tonic–clonic seizures in seven patients. Forty-one patients were taking monotherapy and six taking two AEDs. The subjects were classified according to seizure frequency into six groups based on modified report of Milan study (Canger et al., 1982). **Results:** The seizure frequency in 23 patients (46%) remained unchanged, in 14 (28%) worsened, and in 13 (26%) improved. Comparison of seizure frequency among prepregnancy, gestational, and puerperium periods showed no difference (Friedman, $p = 0.073$). We found no significant correlation in seizure frequency during pregnancy and risk factors such as type of seizure and epilepsy, etiology, age, duration of epilepsy, prepregnancy seizure frequency, type of AED and its serum levels, and electroencephalogram abnormalities. None of patients had status epilepticus. **Conclusions:** Gestational and puerperium periods did not influence seizure control.

2.299
THE IMPACT OF EPILEPSY ON WOMEN: A COMMUNITY-BASED SURVEY

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Rationale: The differential impact of epilepsy on women is complex and there have been no large community-based surveys addressing this issue. **Methods:** A survey was mailed to persons with epilepsy (PWE) and to persons with no chronic ailments (NoProb). Subjects had been identified from a prior survey of 180,997 individuals from the National Family Opinion (NFO) database. The survey included demographic factors, a measure of quality of life (QOLIE-31) and the Centers for Epidemiological Studied-Depression (CESD) questionnaire. Results were balanced to the U.S. Census. **Results:** We identified 775 persons with epilepsy and 341 with NoProb. Women with epilepsy were 47.1% of the PWE group. Seizure control, measured by time to last seizure and self-reported seizure severity, was similar between men (M) and women (W). Self-reported cause of epilepsy was similar between men and women except for a lower rate of head injury (26.7% M, 20.1% W). A diagnosis of depression was seen in 33.1% of W compared to 27.3% of M with epilepsy. On the CESD scale, 31.2% of W showed scores consistent with ongoing major depression compared to 19.2% of M; 6.8% of M saw a psychiatrist in the past month versus 3.2% of W. On the QOLIE, W showed slightly lower scores than M on every subscale with overall scores of 60 (W) versus 64.9 (M). W were also more likely to have household incomes <$30,000 (54.6% of W compared to 46.0% of M). **Conclusions:** In this large, population-based survey, women showed similar levels of seizure control, but depression was more severe and quality of life slightly worse, compared to men. Socioeconomic status was slightly worse for women with epilepsy. (Supported by GlaxoSmithKline.) (Disclosure: Salary: D.E.B. is an employee of GlaxoSmithKline, who funded this project; Consulting: I have been consultant to Abbott Pharmaceuticals, Novartis, OrthoMcNeil, Hoechst Marion Roussel, Wallace Laboratories, Parke Davis, and GlaxoSmithKline; Honoraria: I have received honoraria for speaking from Abbott Laboratories, Novartis, OrthoMcNeil, Hoechst Marion Roussel, Wallace Laboratories, Parke Davis, GlaxoSmithKline, and UCB Pharma; Other: All of these listed companies have also sponsored educational programs which I have conducted, they have all supported the Chili cook-off I hold annually for the Epilepsy Medication Fund.)

2.300
FACTORS INFLUENCING AGE AT MENOPAUSE IN WOMEN WITH EPILEPSY

Cynthia Harden, Douglas Labar, Barbara Koppel, Blagovest Nikolov, Avril Dwyer, Nalini Rivera, and Andrew Herzog (Comprehensive Epilepsy Center, Weill Medical Center of Cornell University, New York, NY; Department of Neurology, New York Medical College, New York, NY; Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA)

Rationale: We have observed that a group of women with epilepsy who had an early onset of menopause (last menses at 37–45 years) generally had more frequent seizures than women with epilepsy who had a later-onset menopause (last menses at 50–56 years). Other investigators have also suggested that women with epilepsy have an increased risk of premature menopause (Klein et al., *Epilepsia* 2001). We sought to further explore the age of menopause and factors associated with early onset of menopause in women with epilepsy. **Methods:** Sixty-eight women with epilepsy who were naturally menopausal (≥1 year since last menstrual period) were surveyed by interview and chart review for reproductive characteristics, epilepsy history, and other known factors that affect the onset of menopause. Subjects were obtained from four urban academic medical centers. Subjects were categorized into one of three broad seizure-frequency groups; seizure frequency was estimated over the course of the subject's epilepsy. Group 1 was <20 seizures in lifetime, Group 2 was >20 seizures in lifetime and fewer than one seizure/month, and Group 3 was more than one seizure/month. Statistical analysis was performed using bivariate correlations (Pearson and Spearman), one-way analysis of variance, and univariate General Linear Model. **Results:** Fifteen women were in Group 1 (mean age, 55 years), 25 women were in Group 2 (mean age, 54 years), and 28 women were in group 3 (mean age, 52 years). The mean age of last menses was significantly different between groups ($p = 0.042$); Group 1, 49.9 years, Group 2, 47.7 years, and Group 3, 46.7 years. The age at last menses did not change in the subsets of subjects having onset of epilepsy before 42 years ($n = 49$) or onset of epilepsy at older than 42 years ($n = 14$). The number of enzyme-inducing antiepileptic drugs (EIAEDs) ever used for ≥1 year significantly negatively correlated with age of last menses (more EIAEDs used correlated with lower age of last menses) and positively correlated with seizure frequency group. Age at onset of epilepsy also significantly negatively correlated with seizure group (earlier age onset correlated with higher seizure frequency group) and positively correlated with age of last menses. When factoring in these two confounders, the mean age at menopause in each seizure-severity group did not change: Group 1, 50 years, Group 2, 47.5 years, Group 3, 46.5 years. Four subjects had premature ovarian failure (onset of menopause before age 42). Three were in the highest seizure-frequency group, and one was in the intermediate group. No other factors had significant effects on age at last menses including cigarette use, number of pack-years, race, number of children, age of last child, number of total AEDs, or number of years of any "classic" AED. **Conclusions:** Seizure frequency may affect the age at menopause, causing it to decrease from a population norm of 50

years to as much as 3 years earlier. The use of EIAEDs may also contribute to this effect. These findings cannot clarify whether central nervous system factors or direct ovarian factors are most important in the relation of epilepsy to menopause. Further evaluation is needed to rule out confounding effects. (Supported by NIH National Institute of Neurological Diseases and Stroke, R01 NS38473.)

2.301
ASSOCIATION OF SEIZURES WITH ESTROGEN-REPLACEMENT THERAPY IN MENOPAUSE
Pavel Klein (Department of Neurology, Georgetown University Hospital, Washington, D.C.)

Rationale: Estrogen hormone-replacement therapy is widely used in menopause to prevent the consequences of chronic low-estrogen state, such as osteoporosis and increased risk of cardiovascular ischemic disease. Estrogens potentiate excitatory cellular function in limbic structures, induce seizures, and lower seizure threshold in animal models of seizures and facilitate interictal epileptiform discharges and seizures in epileptic women (1). A questionnaire survey suggested that hormone-replacement therapy may exacerbate seizures during perimenopause or menopause (2). One case of Premarin-related seizures in menopause has previously been reported (3). Here, I report two cases of estrogen-related seizures in menopause. **Methods:** The subjects were two women referred for evaluation of possible seizures. The evaluation included standard clinical, EEG and neuroimaging assessment, and reproductive endocrine histories. **Results:** Case 1: A woman without seizure risk factors had four partial seizures with secondary generalization during 2 years of treatment with an oral contraceptive at the age of 28–30. Seizures ceased after discontinuation of the contraceptive. She was well until the age of 53 when, 1 year after her last period, she was treated with Premarin for hot flushes and sweating. Four weeks later, she had a seizure. Examination and EEG were normal. Magnetic resonance imaging (MRI) scan of the brain showed several 1- to 3-mm foci of high T2 signal intensity, suggestive of small-vessel ischemic changes, including one in the left hippocampal region. Premarin was stopped. One more seizure occurred 1 year later. Gabapentin (GBP), 300 mg, b.i.d., was started. No further seizures have occurred during a 4-year follow up. Case 2. A 32-year-old woman had a history of episodes of dizziness, intense fear, anxiety, and altered awareness, which began 1 year after menarche. The episodes occurred mainly during the week before menstruation. They stopped during pregnancy at the age of 28. At the age of 32, she developed irregular menses and menorrhagia, for which she undewent hysterectomy and bilateral oophorectomy. Estrogen-replacement therapy was started after hysterectomy. One month later, the spells recurred. Two weeks later, she had a major clonic seizure. Neurologic examination and computed tomography examination of the brain were normal. EEG showed independent bitemporal spikes, left greater than right. Phenytoin was started. Seizures persisted. They stopped shortly after discontinuation of estrogen-replacement therapy. **Conclusions:** Unopposed estrogen therapy in menopause may activate seizures in women with hormonally sensitive partial seizures, even if the seizures have been quiescent for many years. This finding should be considered before instituting estrogen-replacement therapy in menopausal women with a history of epilepsy.

2.302
CHARACTERISTICS OF LIFETIME FRACTURES IN MENOPAUSAL WOMEN WITH EPILEPSY
Barbara Koppel, Blagovest Nikolov, Douglas Labar, Nalini Rivera, Avril Dwyer, and Cynthia Harden (Department of Neurology, New York Medical College, New York, NY; Comprehensive Epilepsy Center, Weill Medical College of Cornell University, New York, NY)

Rationale: Fracture rate is increased in persons with epilepsy. Contributing factors include fractures during seizures, fractures due to clumsiness or falling, which may be a reflection of effect of medication neurotoxicity, and fractures due to decreased bone density. We sought to determine the characteristics of lifetime fractures in a group of menopausal women with epilepsy, to assess the impact of these contributing factors. **Methods:** Women with epilepsy who were in natural or surgical menopause were surveyed for the history of documented skeletal fractures, whether they occurred before or after antiepileptic drug (AED) treatment, or before or after menopause, the site of fracture, and the setting in which it occurred (seizure, "clumsiness," or accidental). Descriptive statistics were used in the analysis. **Results:** Fifty menopausal women with epilepsy were surveyed. The mean age was 54.4 years (range, 44–64; SD, 5.6). Mean age of menopause was 46.2 years (range, 23–59; SD, 6.0). Ten women had undergone hysterectomy (20%) and 31 women had undergone bone mineral density evaluations (62%). Thirty-three total lifetime fractures were reported; 30 subjects had none, 13 had one, five had two, one had three, and one had four. Eleven fractures occurred before AED treatment and before menopause; seven of these were accidental, one was due to a seizure, and two were due to clumsiness. Most fractures occurred in the upper extremity; one was a skull fracture. Twelve fractures occurred with AEDs but before menopause; six occurred during seizures, four were related to clumsiness, and two were called accidental. Of these, five fractures occurred in the upper extremity, and four in the lower extremity. Nine fractures occurred with AEDs during menopause; six were due to clumsiness and two were during seizures (data missing for one). Eight of these fractures occurred in the lower extremities, but were not hip fractures. None occurred off AEDs during menopause (data missing for one fracture altogether). **Conclusions:** Most fractures after the onset of epilepsy and onset of AED treatment were related to either seizures or clumsiness (possible AED neurotoxicity), compared to fractures before AED treatment in the premenopausal group, in which most fractures were reported as accidental. During menopause on AED treatment, most fractures were in the lower extremities, compared to the premenopausal group not taking AEDs, in which most fractures were in the upper extremities. These data indicates that after the onset of AED treatment, accidental fractures are much less frequent than those likely related to epilepsy, either AED toxicity or seizures themselves. (Supported by NIH, National Institute of Neurological Diseases and Stroke, R01 NS38473.)

2.303
PREGNANT WOMEN WITH EPILEPSY TAKING OLDER ANTICONVULSANTS MUST HAVE DRUG LEVELS CHECKED FREQUENTLY TO AVOID SEIZURES
Kaarkuzhali B. Krishnamurthy, Diane T. Sundstrom, Janet M. Beaudoin, and Elaine Kiriakopoulos (Women's Health in Epilepsy/Comprehensive Epilepsy Center, Beth Israel Deaconess Medical Center, Boston, MA; Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA)

Rationale: After attending this presentation, clinicians will learn to monitor anticonvulsant levels of older drugs more frequently than recommended by current guidelines to avoid the occurrence of breakthrough seizures in women with epilepsy during pregnancy. **Methods:** Thirty-five women with epilepsy were followed up during 44 pregnancies as part of the Women's Health in Epilepsy program from July 1994 through April 2002. All women were scheduled to see an epilepsy physician and an epilepsy nurse specialist at monthly intervals from the discovery of the pregnancy until the 36th week of gestation. Trough anticonvulsant (AED) levels were ordered monthly from the beginning of pregnancy until week 24, biweekly from week 25–35, and weekly from week 36 until delivery. Data analysis was limited to those pregnancies that occurred while the mother was taking any one of the AEDs under study [phenobarbital (PB), phenytoin (PHT), carbamazepine (CBZ), or valproic acid (VPA)] in monotherapy for the duration of her pregnancy. AED levels were examined along with requirements for adjustments of doses and the occurrence of seizures. **Results:** Of the 44 pregnancies reviewed, four were prematurely terminated, eight were excluded due to polypharmacy, three were in women taking no AEDs, and five were in women using newer AEDs, and one patient was lost to follow-up. Of the remaining 23 pregnancies, six were in women taking PB, six were in women taking PHT, eight were in women taking

CBZ, and three were in women taking VPA. Of these, four of six pregnancies with PHT and four of six pregnancies with PB required more than four adjustments of dose during the pregnancy to maintain levels in the patient's optimal range (i.e., in the range of levels shown to be associated with the patient remaining seizure free). Half of all pregnancies on these two agents were associated with breakthrough seizures when AED levels fell below the patient's therapeutic range. Five of eight pregnancies in six women taking CBZ similarly required adjustment of AED doses more than 4 times during the pregnancy; two of these women (accounting for four pregnancies) had breakthrough seizures when levels dropped. By contrast, only one of the pregnancies occurring in women taking VPA monotherapy was associated with dramatic alterations in blood level. **Conclusions:** Women with epilepsy taking older AEDs are at risk for breakthrough seizures due to alterations in AED levels. AED levels must be monitored more frequently than current recommendations would suggest to avoid seizures during pregnancy and the attendant risks of adverse pregnancy outcome. Reasons for this might include the tendency for older AEDs to be dependent on hepatic P-450 enzymatic system for metabolism; activation of this system occurs during pregnancy.

2.304

INITIAL EXPERIENCE WITH THE IRISH EPILEPSY AND PREGNANCY REGISTER

Brenda Liggan, Cora Flynn, Maire White, Jim Morrow, and Norman Delanty (Department of Clinical Neurological Sciences, Irish Epilepsy and Pregnancy Register, Beaumont Hospital, Dublin, Ireland; Department of Neurology, Royal Victoria Hospital, Belfast, Northern Ireland, United Kingdom)

Rationale: This presentation describes the initial experience with the prospective Irish Epilepsy and Pregnancy Register. This is part of a worldwide effort gathering prospective data to determine the safest strategies for the treatment of women with epilepsy who are pregnant or planning to become pregnant. The Irish Epilepsy and Pregnancy Register was initiated in May 2001, and has close links with the U.K. Register, which is based in Belfast. Its main aims are (a) to establish the relative safety of anticonvulsant drugs (AEDs) with reference to major malformations in the offspring of women with epilepsy, (b) to establish whether seizure frequency is related to adverse outcome in pregnancy, (c) to monitor the rate of preconceptual folic acid administration in women with epilepsy and whether this beneficially affects outcome, and (d) to educate people about epilepsy and pregnancy by giving preconceptual, pregnancy, and postpregnancy advice. **Methods:** This is a prospective register of all women with epilepsy in Ireland who become pregnant. It is run by a research nurse and is based at the Clinical Research Centre at Beaumont Hospital in Dublin. All neurologists, general practioners, and obstetricians in the country are informed of the register and are invited, after informed consent, to enroll their patients in the register. Relevant information is gathered in a systematic manner and stored on a database. Pregnancy outcome is determined at 3 months after the expected date of delivery. **Results:** To date, there are 79 prospectively registered pregnancies with 21 full-outcome reports to the Irish Epilepsy and Pregnancy Register. Thus far, there has been a wide exposure to a variety of AEDs in monotherapy [e.g., with carbamazepine (CBZ), phenytoin (PHT), valproate (VPA), and lamotrigine (LTG)]. Various AED combinations reported include treatment with the following drugs: CBZ, clonazepam, gabapentin, LTG, levetiracetam, oxcarbazepine, phenobarbital, PHT, primidone, VPA, and vigabatrin. **Conclusions:** The Irish Epilepsy and Pregnancy Register is an ongoing long-term project. The register will continue to give advice to women with epilepsy who may or may not be taking AEDs, and will continue to enroll pregnant women with epilepsy. It is envisaged that the scope of the register will be widened to assess the cognitive and neuropsychological development of children born to mothers with epilepsy in Ireland. (Supported by The Irish Brain Research Foundation and the Monkstown Hospital Trust.)

2.305

BONE HEALTH IN EPILEPSY: FOLLOW-UP OF METABOLIC BONE DISEASE

Joyce Liporace, Sevie Shuman, Maromi Nei, and Michael R. Sperling (Neurology, Jefferson Medical College, Philadelphia, PA)

Rationale: At the end of this presentation, participants will begin to uderstand how bone density changes over time in epilepsy patients with metabolic bone disease. **Methods:** Epilepsy patients followed up at the Jefferson Epilepsy Center found to have metabolic bone disease on a prior dual-energy x-ray absorptiometry (DEXA) scan were offered a follow-up DEXA scan after a minimun of 1 year from the inital screening. Yearly interval change of bone mineral density (BMD) at the hip and lumbar spine were evaluated, along with treatment of bone disease, and the relation to menopause. Osteopenia was defined as a T score less than –1 SD, and osteoporosis was defined as a T score less than –2.5 SD compared to gender-matched controls at their peak bone mass. **Results:** Fourteen patients had serial DEXA scans, including 12 women and two men. Age ranged from 32 to 68 years, mean, 46.9. Two patients were black, 12 were white. Six women were postmenopausal. Nine patients had partial epilepsy, three had generalized epilepsy. Duration of epilepsy was 2–46 years, mean, 27.5 years. Monthly seizure frequency was none to six; nine pateints were seizure free. There was one smoker. Four patients had osteoporosis, and 10 had osteopenia identified on the initial scan. Repeat scans were obtained after 12–31 months (mean, 20.5) on the same type of machine. Repeated DEXA revealed that three had osteoporosis, eight had osteopenia, and three had normal bone health. Yearly interval change revealed stable/improved BMD in eight of 14 (57%) patients. The yearly mean interval change in BMD was 3% at the lumbar spine and 5.7% at the hip. Of the six with a decline in BMD, four were postmenopausal. The yearly mean interval change in the postmenopausal women was –2.3% at the spine and –0.8% at the hip. All patients were supplemented with 1,200–1,800 mg calcium and 800 IU of vitamin D after the inital abnormal scan. Two received Fosamax. One patient had her AED changed due to concerns about bone health, but the majority did not. **Conclusions:** While epilepsy patients are at greater risk for bone loss, they may also gain bone quickly. Calcium and vitamin D supplementation typically stablize/improve bone health in epilepsy patients with bone disease, despite on-going treatment with AEDs. Postmenopausal women are at greatest risk for continued decline in bone health. Additional studies are needed to determine if bone health may normalize after longer treatment duration or with bisphosphonate therapy. We suggest serial DEXA scans at 18-month intervals in patients with abnormal bone health.

2.306

AN EVALUATION OF KNOWLEDGE OF WOMEN'S ISSUES IN EPILEPSY: A SURVEY OF HEALTH CARE PROFESSIONALS

Lucretia Long (Neurology, The Ohio State University, Columbus, OH)

Rationale: Recent data evaluating the knowledge of healthcare issues in women with epilepsy (WWE) supports a lack of knowledge concerning a variety of related topics. While there are multiple educational resources available for WWE, they rightfully expect health care professionals (HCPs) to be knowledgeable and to disseminate relevant information. Although previous authors have focused on this topic, the current survey may be more relevant as it includes a broader range of topics, does not contain questions perceived to be misleading, and emphasizes pertinent clinical concepts rather than percentages or specific terms. **Methods:** A variety of health care professionals employed at a large tertiary care center were approached to complete an anonymous one-page, 13-item knowledge of womens issues and epilepsy (KOWIE-2) questionnaire. The KOWIE-2 was modified from a previous survey developed for patients (KOWIE-1). Content validity was established by allowing field experts to evaluate the survey prior to data collection. To eliminate questions that were misleading or difficult to comprehend, the survey was pilot tested. There was no incentive for

participation; it was completely voluntary. **Results:** Sixty-eight of 120 surveys were completed. Twenty-five percent of respondents were neurologists (n = 17), 13.2% OB/GYN physicians (n = 9), 32.3% nurses (n = 22), 10.3% were social workers (n = 7), 3% internists (n = 2), 13.2% were medical students (n = 9), and the remaining 3% were included under other (n = 2). The mean total correct score for all disciplines was 41.2% with an interquartile range and SD of 18.1–64.3% and 23.1%, respectively. Nurses (28.3% correct) and social workers (30.2% correct) were least knowledgeable, whereas neurologists obtained the highest percentage correct (61.4%). Approximately 20% of all respondents believed that WWE should stop taking their AEDs when becoming pregnant, and 21% did not know the importance of taking folic acid before conception. Seventy percent did not know that women taking AEDs could breast feed. Forty percent were unaware of the effects of enzyme-inducing antiepileptic drugs (EIAED) on BCPs. Other low scores pertained to the association between VPA and polycystic ovaries (10% correct), the hemorrhagic disorder associated with EIAEDs (21% correct), the effect of primary AEDs on bone mass (30% correct), and the potential correlation between endogenous hormones and seizures (40% correct). As expected, HCPs with greater exposure to WWE (more than six patients per month) were more knowledgeable than those with fewer exposures. In terms of perceptions, <50% were "comfortable treating pregnant WWE," 80% felt that pregnant WWE should be evaluated by a neurologist, and 78% were interested in learning more about WWE. **Conclusions:** HCPs are not knowledgeable about concepts related to WWE. Although neurologists obtained the highest percentage correct, they did not respond accurately to ~40% of the included questions. This study supports the need to better educate those treating and evaluating WWE. The lack of awareness in nurses and social workers is an important finding as these providers play a pivotal role in patient education. Improving the knowledge of HCPs in general may enhance the awareness of WWE, leading to improved outcomes.

2.307

SAFETY OF GABAPENTIN TREATMENT DURING PREGNANCY

Georgia Montouris (Neurology, The Comprehensive Epilepsy Care Center for Children and Adults, P.C., St. Louis, MO)

Rationale: The objective of this study was to assess the safety of gabapentin (GBP) exposure in human pregnancy. **Methods:** Prospective and retrospective data were collected from 51 pregnancy outcomes among 39 women exposed to GBP during either a current pregnancy (42 outcomes) or a previous pregnancy (nine outcomes) resulting in 44 live births. Data collected included maternal demographics, diagnosis, treatment, and complications; and fetal complications and outcomes. **Results:** The percentage of live births in this study exceeded that seen in the general population (87 vs. 62%) with fewer miscarriages (11.3 vs. 16%) and abortions (2 vs. 22%). The major malformation rate in this cohort was 4.5% (two of 44 live births). This is slightly above the range seen for the general population (2–4%). The rate of minor malformations in this group was 2.0% (one of 44 live births). Overall, in untreated women with epilepsy, the range for malformations is 4–8%), and for treated women with epilepsy, 5–10%). In the general population, the percentage of babies born with very low birth weight (defined as 3 lb 4 oz) is 1.5%, but no babies in this group were born at this weight. Maternal complications were minimal. Three women experienced complications. The rate of hypertension/eclampsia was two in 46 live births (ratio, 0.043), essentially identical to that observed in the general population for hypertension/eclampsia of 44 in 1,000 live births (ratio, 0.044). The rate of cesarean section was 10.9%, much lower than the 22.9% seen in the general population. **Conclusions:** GBP exposure during pregnancy did not lead to an increased risk for adverse maternal and fetal events in this study. However, because of the small number of patients examined in this study, additional data from more pregnancies and outcomes are needed. (Supported by Pfizer, Inc.) (Disclosure: Grant: The author has received a research grant for this project from Pfizer, Inc., and is a principal investigator for Pregabalin drug trials for Pfizer, Inc.; Consulting: The author serves as a consultant for Pfizer, Inc.; Honoraria: The author is a member of a national speakers bureau sponsored by Pfizer, Inc.)

2.308

EPILEPSY SEVERITY AND REPRODUCTIVE CHARACTERISTICS IN MENOPAUSAL WOMEN WITH EPILEPSY

Blagovest Nikolov, Douglas Labar, Laura Ponticello, Novette Green, Nalini Rivera, Avril Dwyer, and Cynthia Harden (Comprehensive Epilepsy Center, Neurology, Weill Medical College of Cornell University, New York, NY)

Rationale: We sought to determine historic factors associated with epilepsy severity and reproductive characteristics in menopausal women with epilepsy. **Methods:** We surveyed menopausal women with epilepsy from four urban academic medical centers by interviewing the subjects and reviewing the charts. Subjects were categorized into one of three broad epilepsy-severity groups. Epilepsy-severity groups were determined by estimation of seizure frequency over the entire duration of epilepsy as follows: Group 1, <20 lifetime seizures; Group 2, >20 lifetime seizures but <1 seizure/month; Group 3, >1 seizure/month. Women with both natural and surgical menopause were included. Statistical methods used were one-way analysis of variance, Pearson bivariate correlation, and cross-tabulation with $\chi 2$. **Results:** Sixty-nine menopausal women with epilepsy were included. Subjects by epilepsy group were Group 1, n = 15; Group 2, n = 25, Group 3, n = 28. The average number of children borne was not significantly different between epilepsy severity groups. Total number of antiepileptic drugs (AEDs) ever used (each AED taken for >1 year) and total number of enzyme-inducing AEDs ever taken correlated with epilepsy severity by group ($p < 0.001$ for total AEDs and $p = 0.002$ for EIAEDs). **Conclusions:** These results suggest that of this population of women treated in urban academic epilepsy centers, those with more severe epilepsy are receiving more AED treatment trials, which is an indirect measure of the patients' both seeking and obtaining adequate epilepsy care. However, the number of children borne does not seem to be influenced by, or to have any influence on epilepsy severity. (Supported by NIH, National Institute of Neurological Diseases and Stroke, R01 NS38473.)

2.309

LAMOTRIGINE CLEARANCE MARKEDLY INCREASES DURING PREGNANCY

Page B. Pennell, Jean Q. Montgomery, Sandra D. Clements, and Donald Jeffrey Newport (Neurology, Emory University School of Medicine, Atlanta, GA; Psychiatry, Emory University School of Medicine, Atlanta, GA)

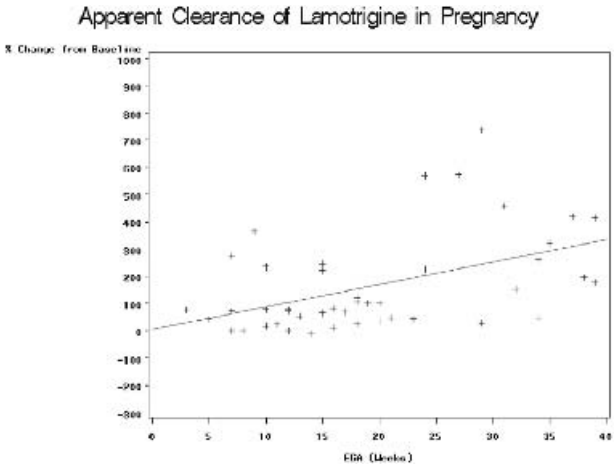
Rationale: One of the paramount goals of management of pregnant women with epilepsy is optimal seizure control; 20–37% will experience increased seizures. A major factor is the physiologic alterations in antiepileptic drug (AED) metabolism that accompany the pregnant state. Lamotrigine (LTG) is ~55% protein bound and is metabolized predominantly by glucuronic acid conjugation. Preliminary reports suggest that LTG clearance may increase early during pregnancy. At the end of this presentation participants should be able to describe the extent and pattern of increased clearance of LTG during pregnancy. **Methods:** Nine patients receiving LTG monotherapy for epilepsy were studied. All patients had baseline LTG concentration measurements obtained before conception or ≤7 weeks estimated gestational age (EGA), were compliant with medications and blood draws, did not have significant emesis, and were not on any interacting medications. Each patient underwent trough LTG concentration measurements at least monthly. Total LTG concentrations were utilized since LTG is not highly protein-bound. Apparent Clearance (AC) values were calculated as daily dose (mg)/concentration (mg/L). Three patients consistently

had weight measurements to allow for calculation of Relative Clearance (daily dose (mg/kg)/concentration (mg/L)). **Results:** Forty-four LTG concentration samples were obtained in the nine women during pregnancy, excluding the baseline samples. AC for each sample was calculated and reported as percentage change from that individual patient's baseline AC (Fig. 1). The samples from all nine women were also grouped together by each trimester and by overall pregnancy and reported as mean percentage change from baseline with standard deviations (Table 1). LTG AC values began to increase very early in pregnancy and steadily and dramatically trended upward to a maximum at term. One patient demonstrated >700% increase in AC (Fig. 1). Relative (weight-adjusted) clearance was also calculated for three patients and demonstrated the same trend of increased clearance with EGA. **Conclusions:** Our findings of progressively increased LTG clearance throughout pregnancy contradict the previous report of LTG AC increasing in the first trimester only (*Epilepsia* 2000;41(suppl 7):246). The extent of increased LTG clearance during pregnancy is far greater than that described with the older AEDs and probably reflects its relatively unique metabolic pathway. Given these findings that alterations in LTG clearance occur substantially yet unpredictably during pregnancy, monthly LTG level monitoring during pregnancy and the postpartum period may be warranted. (Disclosure: Consulting: Dr. Pennell has received consulting fees from GlaxoSmithKline; Honoraria: Dr. Pennell has received honoraria from GlaxoSmithKline.)

TABLE 1. *Apparent clearance (daily dose/[serum]) of lamotrigine during pregnancy*

Percentage change from baseline [mean (SD)]			
1st Trimester	2nd Trimester	3rd Trimester	Overall
92.4 (110.2)	121.2 (137.7)	315.4 (213.6)	164.3 (177.8)

n = 44 samples, excluding baseline samples.



2.310

PERIMENSTRUAL SEIZURE EXACERBATION IN NONOVULATORY PERIMENARCHEAL GIRLS SUGGESTS THAT PROGESTERONE WITHDRAWAL IS NOT THE ONLY FACTOR RESPONSIBLE FOR PERIMENSTRUAL CATAMENIAL SEIZURE EXACERBATION

Sanjiv Sahoo and Pavel Klein (Neurology, Georgetown University Hospital, Washington, D.C.)

Rationale: Three types of catamenial epilepsy have been described. The commonest type, type I, is exacerbation of seizures perimenstrually (i.e., just before or after the onset of menstruation). It has been suggested that fall in serum levels of progesterone premenstrually is the factor responsible for perimenstrual seizure exacerbation. Animal models of catamenial epilepsy support this postulate. Following menarche, menstrual cycles are anovulatory for one to several years in the majority of girls. The ovary produces little progesterone during anovulatory cycles. In the present study, we describe several postmenarcheal girls with anovulatory cycles, little ovarian progesterone secretion and perimenstrual seizure exacerbation. We suggest that factors other than progesterone withdrawal may contribute to perimenstrual seizure exacerbation in some women with catamenial epilepsy. **Methods:** Five postmenarcheal girls aged 12–17 with remote symptomatic partial complex seizures. ILAE seizure classification was used. Catamenial (perimenstrual) exacerbation of seizures was documented with a 3-month prospective seizure diary. Midluteal (menstrual cycle day 20–22) serum progesterone level was checked during ≥1 month of documented perimenstrual seizure exacerbation. **Results:** Seizures occurred significantly more frequently on menstrual cycles day (−3) to (+3) in all girls. Seizures occurred exclusively perimenstrually (menstrual cycle day [−3] – [−1]) in one girl and mainly premenstrually in another girl. In the remaining girls, seizures occurred with a twofold or greater daily frequency perimenstrually compared with other menstrual cycle phases. Three of five girls had irregular menses, two of five had regular menses; one girl had late luteal dysphoric syndrome, another girl had significant perimenstrual somatic symptoms. None of the girls had pre- or perimenstrual insomnia or hypersomnia. Midluteal serum progesterone levels ranged from 0.1 ng/ml to 1.7 ng/ ml. Midluteal serum estrogen levels ranged from 39 to 68 pg/ml. **Conclusions:** Perimenstrual exacerbation of partial complex seizures can occur in the context of anovulatory cycles and minimal ovarian progesterone secretion. In this context, perimenstrual seizure exacerbation is unlikely to be due to falling serum progesterone levels. Addional, as yet unknown factors, may therefore be implicated in the pathogenesis of perimenstrual seizure exacerbation.

2.311

DO WOMEN WITH EPILEPSY HAVE AN INCREASED FREQUENCY OF MENSTRUAL DISTURBANCES?

Sigrid Svalheim, Erik Tauboll, Tone Bjornenak, Line S. Roste, Tore Morland, Erik R. Saetre, and Leif Gjerstad (Department of Neurology, Rikshospitalet, University of Oslo, Oslo, Norway; Department of Neurology, Telemark County Hospital, Skien, Norway; Department of Neurology, Ullevaal Hospital, University of Oslo, Oslo, Norway)

Rationale: Menstrual disorders, reduced fertility, and sexual problems have been reported to be more frequent in women with epilepsy than in the general population. However, most investigations concerning menstrual disturbances in epilepsy patients are hampered by a small number of patients and often based on selected materials. We therefore wanted to investigate the frequency of menstrual disturbances in a larger population of female epilepsy patients and possible factors influencing this frequency. **Methods:** A retrospective, questionnaire study of a cohort of female outpatients, aged 18–45 years, was conducted. Each patient chose a close friend who served as individual control to optimize matching regarding age and lifestyle. Menstrual disturbances were defined as periods of <22 days or >35 days, or bleeding duration of >8 days, or a variation of >4 days between two consecutive menstrual periods. **Results:** Answers were received from 265 patients and 142 controls. In the epilepsy group, 56.6% had partial and 36.6% generalized epilepsy. In 6.8% of the patients, we were unable to classify the epilepsy type. Mean age was 32.3 years in the patient group and 32.0 years the control group. Body mass index (BMI) was 24.3 in the patient and 24.1 in the control group. Menarche age was 13.1 in patient and 13.0 in controls; 48% of the patients had menstrual disturbances compared to 29.7% in the control group ($p < 0.004$). Menstrual disturbances were seen in 50.7% of patients with generalized compared to 47.8% in patients with partial epilepsy (not significant). **Conclusions:** The investigation confirms that women with epilepsy have an increased frequency of menstrual disturbances compared to women without epilepsy. There was no difference between patients with generalized versus partial epilepsy. BMI or menarche age did not differ. (Supported by the Norwegian branch of IBE.)

December 10, 2002
Platform Session E: Basic Science 2
3:30 p.m.–5:30 p.m.

E.01
SELECTIVE VULNERABILITY OF CA1 ORIENS/ALVEUS INTERNEURONS TO KAINIC ACID–INDUCED SEIZURES

Nathalie Sanon, Martine Pascale Emond, Jean-Claude Lacaille, and Lionel Carmant (Physiology, Université de Montréal, Montreal, QC, Canada; Pediatrics, Ste-Justine Research Center, Montreal, QC, Canada)

Rationale: Kainic acid (KA)-induced seizures are a model of the mesial temporal lobe epilepsy syndrome. KA causes a prolonged acute seizure followed by a latent phase of a few weeks followed by chronic recurrent seizures. The mechanisms involved in epileptogenesis during the latent phase remain unclear. In adult animals, pyramidal cell loss and synaptic reorganization are thought to underlie this process, but in immature animals this is not consistently seen despite more severe acute seizures. We have observed a selective vulnerability of CA1 oriens/alveus (OA) interneurons to KA-induced seizures in both groups. The goal of the present study is to further delineate the subgroups of interneurons susceptible to KA-induced seizures and assess if this selective vulnerability is due to differential acute effects of kainate. **Methods:** Prolonged seizures were induced with two intraperitoneal injections of KA (6.75 mg/kg) at 1-h interval in postnatal day 20 (P20) and P30 rats. Control rats received a saline solution. Animals were observed for 40 days for recurrent seizures. We then performed immunohistochemical studies with glutamic acid decarboxylase (GAD), parvalbumin (PV), and somatostatin (SS) staining. A second group of naive animals were killed at P30 for electrophysiologic studies. Transverse brain slices were prepared. Responses of CA1 interneurons were monitored with whole-cell patch-clamp recordings in current-clamp mode. We recorded membrane potential and cell input resistance before, during and after a 5 μM KA application for a period of 10–15 min. In some experiments, we blocked Na+ channels with tetrodotoxin (TTX), 1 μM, AMPA receptors with GYKI52466, 30 μM, and non-*N*-methyl-D-aspartate (NMDA) receptors with CNQX, 20 μM. In experiments where calcium imaging was performed simultaneously, cells were dialyzed with intracellular solution containing the fluorescent cell-impermeable calcium indicator: Oregon Green Bapta-1 (50 μM). **Results:** At P20, we observed a significant and selective loss of CA1 GAD-positive interneurons (60%) but an even more severe loss of PV- (88%) and SS- (90%) positive cells. In P30 animals, we observed a reduction of 55, 65, and 67%, respectively. Cell loss was present in OA layers but none was seen in pyramidale or R-LM layers. Electrophysiologic studies comparing interneurons in OA (vulnerable) and in R-LM (resistant) showed that both populations responded to KA with similar levels of depolarization and input resistance decrease. These responses were also equally blocked by GYKI52466 and CNQX, suggesting an implication of AMPA receptors. Similarly, in calcium imaging experiments, Ca^{2+} elevations were not significantly different in both cell groups following KA application. **Conclusions:** The vulnerability of CA1 cells in the KA model involves similar subgroups of interneurons in juvenile and mature animals, which supports a key role for the loss of interneurons in epileptogenesis. Furthermore, this selective vulnerability may not be due to a differential sensitivity to KA involving direct acute effects on membrane potential, input resistance or intracellular Ca^{2+} elevation. (Supported by Savoy Foundation for Epilepsy.)

E.02
DENTATE GRANULE CELL DISINHIBITION AND HYPEREXCITABILITY IN AWAKE RATS DURING THE FIRST WEEK AFTER KAINATE-INDUCED STATUS EPILEPTICUS; THE SOURCE OF VARIABILITY IDENTIFIED

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Rationale: Status epilepticus (SE) in rats produces widespread brain damage, variable patterns of hippocampal cell loss, mossy fiber sprouting (MFS), and spontaneous seizures of unknown origin. We reported that granule cell disinhibition and hyperexcitability developed immediately after kainate (KA)-induced SE, and were closely correlated with hilar cell loss. Restoration of inhibition, rather than hyperexcitability, coincided with MFS (1). Our suggestion that MFS is inhibitory rather than epileptogenic was addressed in a recent study that concluded that inhibition recovers in the first days after SE, before MFS (2). **Methods:** Rats were implanted bilaterally with stimulating electrodes in the perforant pathway and recording electrodes in the granule cell layers. SE lasting 6–8 h was reliably induced in awake rats by KA (10 mg/kg, i.v.; n = 13). Spontaneous and evoked granule cell activity were recorded, and histologic analysis was subsequently performed. **Results:** Rats varied in terms of the time spent generating granule cell discharges during KA-SE. Rats exhibiting granule cell discharges ~65% of the time during behavioral SE (n = 5) immediately exhibited multiple granule cell population spikes and paired-pulse disinhibition. Subsequent histologic analysis showed extensive hilar cell loss and dense MFS. Conversely, rats exhibiting similar behavioral SE, but discharging only 10–30% of the time (n = 8) exhibited single or double population spikes, minimal granule cell disinhibition, minor hilar cell loss, and minimal MFS. The latter group exhibited rapid restoration of paired-pulse inhibition, whereas the former exhibited a prolonged disinhibitory state throughout the week after SE. Spontaneous population spikes, multiple evoked spikes, and long-latency discharges often attributed to MFS in bicuculline-treated hippocampal slice preparations were observed in awake rats before MFS (Fig. 1). **Conclusions:** We attribute the rapid recovery of paired-pulse inhibition in minimally affected animals to a compensatory mechanism operant in relatively normal tissue. In rats with extensive hilar cell loss, granule cell pathophysiology did not recover before MFS. Thus, we attribute the rapid recovery of inhibition in the study of Hellier et al. (2) to the fact that none of their 17 animals exhibited the degree of multiple spiking and disinhibition described in our previous (1) or present studies. We conclude that despite similar behavioral SE among animals, granule cell discharges and hilar cell death occur unreliably and unpredictably. When granule cell discharges occur consistently during KA-SE, hilar cells die, prolonged disinhibition results immediately, and the restoration of inhibition corresponds temporally with MFS. [Sloviter RS. *Neurosci Lett* 1992;137:91–6; Hellier JL, Patrylo PR, Dou P, Nett M, Rose GM, Dudek FE. *J Neurosci* 1999;19:10053–64.(Fig.1).] (Supported by NINDS grant NS18201.)

E.03
RECURRENT LIMBIC SEIZURES DO NOT CAUSE PROGRESSIVE HIPPOCAMPAL LOSS IN A RAT MODELS IN LIMBIC EPILEPSY

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Rationale: It is debated whether intermittent seizures cause progressive neuronal loss. Studies have provided conflicting results, but uncertain clinical histories and seizure severities have confounded the results. In this study we examine this issue using two rat models of limbic epilepsy (kindling and post–status epilepticus chronic limbic epilepsy). The two models allow for a standardized method of seizure induction and the ability to document numbers of seizures accurately. **Methods:** Adult Sprague–Dawley rats were divided into three groups: controls (n = 17), kindled (n = 12), and chronic limbic epilepsy (CLE) (n = 14). All rats received bipolar electrodes in the mid ventral hippocampus. The controls were not stimulated. The kindled animals were divided into a low frequency (one to two stimuli/day, 3 times/

week) or high frequency (eight stimuli/day, 3 times/week). The CLE rats underwent a period of electrically induced status epilepticus, after which they developed spontaneous recurrent seizures. Seizure frequency was documented by continuous EEG monitoring. CLE rats were divided into low frequency (low seizure number) and high frequency (high seizure number). All rats were also divided by age: 6 months after the first stimulation divided young and old rats. At predetermined intervals rats were perfused and prepared for histologic analysis of the ventral hippocampus, which included Timm staining for mossy fiber sprouting as well as stereologic analysis (cell counts and regional cross-sectional areas). **Results:** In general, kindled animals did not differ significantly from controls other than with an increase in cross-sectional area in many of the hippocampal regions. Timm staining was not significantly increased in kindled rats, and there was no relation between frequency or age and the degree of sprouting. The CLE animals had significant neuronal loss in multiple regions, but there was no relation between age or seizure frequency. Timm staining was greater in older rats and in rats with higher frequencies. **Conclusions:** In these rat models of limbic seizures, there is no evidence for progressive neuronal loss with increasing seizure frequency, although mossy fiber sprouting is increased in older CLE animals and in CLE animals with higher seizure frequencies. The findings support the hypothesis that the majority of neuronal loss occurs is a result of an initial insult rather than of a cumulative consequence of recurrent seizures. [Supported by NINDS grants NS25605 (E.B.) and NS38992 and NS 02808 (G.M.).]

E.04
PROGRESSIVE SEIZURE-INDUCED LOSS OF γ-AMINOBUTYRIC ACID INTERNEURONS PROVIDING AXO-AXONIC AND AXO-SOMATIC INHIBITION IS CRITICAL FOR SPONTANEOUS SEIZURES AND INTRACTABILITY

Thomas Sutula, Sue Osting, Julia Shanton, Josh Hagen, Simone Dustin, and Umit Sayin (Department of Neurology, University of Wisconsin, Madison, WI)

Rationale: Stereologic methods and markers of apoptosis have provided evidence that repeated brief seizures are sufficient to induce neuronal death (Kotloski et al. *Prog Brain Res* 2002;135:95–110). Apoptotic damage is observed after a single evoked seizure in the dentate gyrus (Bengzon et al., 1997), and is detected throughout the hippocampus after repeated secondary generalized (class V) seizures (Pretel et al., 1997; Zhang et al., 1998). Cumulative neuronal loss resembling hippocampal sclerosis is eventually observed. If γ-aminobutyric acid (GABA) interneurons are among neurons undergoing seizure-induced loss, alterations in the balance of inhibition and excitation induced by poorly controlled seizures could increase susceptibility to additional seizures and potentially contribute to intractability. After 100 evoked class V seizures, kindled rats develop spontaneous seizures, which are associated with loss of inhibition in the dentate gyrus, as demonstrated by loss of paired pulse inhibition and alterations in the kinetics of evoked granule cell IPSCs (Sayin et al. *Soc Neurosci Abstr* 1998;24:1205). In this study, the effect of repeated seizures on interneurons labeled by GAD65, the 65-kDa isoform of glutamic acid decarboxylase and synthetic enzyme for GABA, was evaluated after 30 and 100 evoked class V seizures evoked by kindling. Subclasses of interneurons labeled by GAT-1 (the neuronal GABA transporter) and CCK, which provide axo-axonic and axo-somatic inhibitory inputs, were also evaluated. **Methods:** Rats received olfactory bulb stimulation to evoke kindled seizures using standard techniques. Nonisotopic in situ hybridization with digoxygenin labeled riboprobes for GAD65 were used to label GABA interneurons. Profile counts of GAD65 labeled interneurons per unit area were obtained in the hilus of the dentate gyrus at a standard temporal location along the septotemporal axis, and were compared to batch processed age-matched controls. Conventional immunohistochemistry for GAT-1 and CCK and stereological methods were used to examine these interneuron subclasses. **Results:** Profile counts for GAD65-labeled interneurons were decreased by ~25% compared to controls after 30 class V seizures, and by ~35% after 100 class V seizures ($p = 0.0002$, analysis of variance), which indicated that seizures induce gradually progressive loss of GABA interneurons. After 100 class V seizures, there was ~33% loss of CCK interneurons and extensive loss of GAT-1 expression in both the hippocampus and dentate gyrus, but loss of CCK or GAT-1 was not detected at earlier stages. Stereologic assessment revealed that the CCK subclass was reduced along the entire septotemporal axis of the hippocampus. **Conclusions:** Repeated brief seizures induce gradually progressive loss of GABA interneurons after as few as 30 seizures. The emergence of spontaneous seizures is associated with loss of the CCK and GAT-1 subclasses, which provide axo-axonic and axo-somatic inhibition that is an important control over propagation of synchronous activity. As GAT-1 and CCK subclasses are also reduced in the human epileptic hippocampus, seizure-induced loss of these interneuron subclasses appears to be a critical step in development of intractable temporal lobe epilepsy. (Supported by NINDS RO1-25020.)

E.05
NEUROKININ B MOBILIZES SPARE *N*-METHYL-D-ASPARTATE RECEPTORS AND TRIGGERS STATUS EPILEPTICUS

Claude G. Wasterlain, Hantao Liu, Andrey M. Mazarati, and Roger A. Baldwin (Neurology, UCLA School of Medicine, Los Angeles, CA; Research, VA GLAHS, Los Angeles, CA)

Rationale: Previous studies showed that peptide neuromodulators play an important role in status epilepticus (SE). Tachykinins are proconvulsants, while galanin, dynorphin and, to a lesser extent, somatostatin and neuropeptide Y act as endogenous anticonvulsants. In this study we examined the mechanism by which the tachykinin neurokinin B triggers seizures and SE. We found that intrahippocampal injection of neurokinin B (NKB) induces extensive receptor trafficking, which mobilizes excitatory glutamate receptors to the cell surface. Blocking these receptors was very effective in stopping SE. **Methods:** SE was induced either by intrahippocampal injection of NKB or by intermittent electrical stimulation of the perforant path. Seizures were monitored by EEG telemetry-videotape. Double-label immunofluorescence staining used fluo-NKB imaging of NK3 receptors, or antibodies to synaptophysin, a marker of the presynaptic apparatus, or to NMDA receptors. Confocal microscopy was utilized to reveal the subcellular distribution of receptors. **Results:** Intrahippocampal injection of NKB or its agonist senktide caused dose-dependent seizures. One nmole induced electrographic seizures for 24 ± 5 min. In perforant path–induced SE, pretreatment with the selective NK3 receptor antagonists SR142,801 (1 nmol) or L-769,927 (2 nmol) prevented the development of SE. Treatment of established SE with 100–200 nmoles reduced Se duration from 485 ± 45 min to a few minutes. Immunocytochemical studies showed that, in control hippocampi, most NMDA receptors in CA3 pyramidal cells did not colocalize with synaptophysin, which outlined the cell surface, but were internalized in cell soma or proximal dendrites. Thirty minutes after NKB injection, most of these spare receptors had been mobilized to the cell surface, and colocalization with synaptophysin had increased fivefold. Treatment of established, diazepam (DZP)-refractory SE with NMDA blockers (either systemic or intrahippocampal) was very effective in terminating SE. **Conclusions:** These results suggest that NKB plays an important proconvulsant role in SE. NKB or SE-associated trafficking of NMDA receptors may increase the number of active excitatory receptors on the neuronal surface and play a key role in the maintenance phase of SE. Other data suggest that NKB-associated receptor trafficking alters $GABA_A$ receptors in the opposite direction (endocytosis), reducing their number during the initiation phase of SE. The effectiveness of NMDA blockers in stopping DZP-refractory SE suggests that agents that block NMDA-receptor trafficking of function should be investigated as therapeutic agents in SE. (Supported by VA Research Service and by grant NS13515 from NINDS.)

E.06
REDUCED INHIBITION IN EXPERIMENTAL HETEROTOPIC GRAY MATTER

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Rationale: At the end of this activity participants should understand alterations in cortical circuitry that occur in an experimental model of

neuronal heterotopia. Syndromes of neuronal heterotopia have a strong association with epilepsy but the underlying mechanisms are poorly understood. We used in utero irradiation to produce heterotopic gray matter in rats to study circuit abnormalities in these displaced neurons. Previous studies from this laboratory showed a selective impairment of inhibition in normotopic, dysplastic cortex in this modelm (Zhu and Roper, 2000). This study was undertaken to determine if similar alterations in inhibitory synaptic transmission were present in heterotopic cortex in irradiated rats. **Methods:** Pregnant rats were exposed to 225 cGy of external γ-irradiation on gestational day 17 (E17). Offspring were killed for testing at postnatal days 21–28; 300-μm-thick hemispheric slices were obtained at the level of the anterior commissure and placed in a submersion-type recording chamber. Pyramidal cells in areas of heterotopic gray matter were identified using infrared, differential interference contrast microscopy and compared to layer II/III pyramidal cells from control animals. The whole-cell voltage-clamp technique was used to record spontaneous and miniature inhibitory (IPSCs) and excitatory (EPSCs) postsynaptic currents. EPSCs were recorded in the presence of the GABA-A receptor antagonist, picrotoxin (50 μ*M*), and IPSCs were recorded in the presence of CNQX (10 μ*M*) and AP5 (50 μ*M*). Five-minute continuous recordings were analyzed and compared between heterotopic and control pyramidal neurons. Group values were compared using the *t* test with significance defined as $p < 0.05$. **Results:** The average frequency of spontaneous IPSCs was significantly reduced in heterotopic pyramidal neurons (4.12 ± 0.39 Hz, $n = 18$) compared to control pyramidal neurons (7.44 ± 0.58 Hz, $n = 18$). The average frequency of miniature IPSCs was also significantly reduced in heterotopic pyramidal neurons (2.23 ± 0.35 Hz, $n = 15$) compared to control pyramidal neurons (3.33 ± 0.27 Hz, $n = 16$). There were no differences in amplitude and kinetics of spontaneous and miniature IPSCs between heterotopic and control pyramidal neurons. There were no differences in frequency or amplitude of spontaneous and miniature EPSCs between the two groups. **Conclusions:** Irradiation at E17 produces a selective and lasting impairment of inhibition in heterotopic pyramidal neurons. Coupled with similar findings from normotopic, dysplastic cortex in this model, these results demonstrate a pervasive effect on inhibition throughout all putative neocortical structures. The current work further defines the scope of the profound and deleterious effect of a single, in utero injury on subsequent cortical development. [Supported by a grant from NINDS (NS35651).]

E.07
THALAMOCORTICAL OSCILLATIONS IN A GENETIC MODEL OF ABSENCE EPILEPSY

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Rationale: The neocortex and thalamus generate brain rhythms that are observed during sleep and in some pathologic conditions such as absence seizures. Several studies have analysed the mechanisms of thalamocortical synchronization in vivo and in vitro. However, it is as yet unclear how reciprocal thalamocortical network interactions contribute to absence seizures. Here, we addressed this issue by thalamocortical slices obtained from epileptic (>160 days old) WAG/Rij and age-matched, nonepileptic control (NEC) rats. **Methods:** We used field-potential recordings in an in vitro thalamocortical slice preparation (Tancredi et al. *J Neurophysiol* 2000;84:1093–7). To increase neuronal excitability, and thus to cause the appearance of spontaneous field potential activity in vitro, we applied medium containing low concentrations of the K^+ channel blocker 4-aminopyridine (4-AP, 0.5–5 μ*M*). **Results:** Sequences of fast (intraburst frequency, 10–16 Hz) and slow (5–8 Hz) spindle-like oscillations (SLOs) were recorded in WAG/Rij slices during application of 4-AP. In contrast, only fast SLOs (9–16 Hz) were seen in NEC slices. Moreover, in WAG/Rij slices, slow SLOs were of larger amplitude and reflected a larger degree of synchronization than fast SLOs. Slow SLOs were not seen after surgical separation of cortex and thalamus; under these conditions fast SLOs continued to occur in thalamus only. Fast and slow SLOs disappeared in all areas of the WAG/Rij slice during thalamic application of the excitatory amino acid receptor antagonist kynurenic acid; by contrast, fast SLOs were still recorded in the ventrobasal complex when kynurenic acid was applied to the cortex. **Conclusions:** Our data demonstrate for the first time that highly synchronized, slow SLOs are induced by 4-AP in WAG/Rij, but not in NEC slices. This slow activity, which may represent an in vitro hallmark of thalamocortical epileptogenicity, requires the function of reciprocally connected thalamic and cortical networks. (Supported by Canadian Institutes of Health Research and Savoy Foundation.)

E.08
IDENTIFICATION OF SEIZURE-RESISTANT ZEBRAFISH MUTANTS

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Rationale: Genetic factors are known to play a significant role in the development of epilepsy. With recent progress in human and mouse genetics, it is now clear that mutations can predispose an individual to seizure activity. Identification of gene mutations that confer enhanced seizure susceptibility or a frank epileptic phenotype has greatly increased our understanding of epilepsy. However, mutations that would confer seizure resistance remain undiscovered. To more efficiently identify seizure-resistant mutations, we have developed a forward genetic screening strategy in zebrafish. Here we describe our early efforts to characterize pharmacologically induced seizures in zebrafish larvae, and report our initial identification of several resistant mutants. **Methods:** For induction of seizures, zebrafish larvae (*Danio rerio*) were exposed to a common convulsant agent (pentylenetetrazole, PTZ). For electrophysiologic seizure studies, zebrafish larvae were immobilized in agar and placed on the stage of an upright microscope. A field recording electrode containing 2 m*M* NaCl (2–5 MΩ) was placed in the tectum under visual control. Electrical activity was monitored using a patch-clamp amplifier in current-clamp mode. In all experiments, PTZ was directly added to the Ringer's bathing medium at a saturating concentration. Wild-type and ENU-mutagenized zebrafish larvae (6–8 days old) were used in all studies. **Results:** High-frequency interictal-like electrographic seizure activity (burst duration, ~650 ms; burst amplitude ~1 mV) was observed during the first 15–30 min of PTZ exposure in all electrophysiologic trials. After 45 min of PTZ exposure interictal- and ictal-like electrographic seizure activity (burst duration, ~5 s; burst amplitude, ~6 mV) was consistently observed ($n = 49$). Electrographic seizure-like activity was abolished by the addition of valproic acid, ethosuximide, tetrodotoxin, kynurenic acid, or CNQX/APV to the bathing medium. During PTZ exposure, freely moving wild-type fish were observed to undergo three distinct stages of seizure-like behavior, as described previously (Baraban et al. *Epilepsia* 2001;42:3.017). Wild-type zebrafish exposed to PTZ exhibited "status-like" seizure activity, and >98% of all wild-type fish died within 24 h of PTZ exposure. Similar seizure-like behaviors were observed in zebrafish mutants exposed to PTZ. To date, we have identified 12 families that carry seizure-resistance mutations. **Conclusions:** Here we demonstrate that a common convulsant agent (PTZ) can be used to reliably induce seizures in zebrafish. These PTZ-induced seizures appear to have a behavioral, electrophysiologic, and pharmacologic profile that is identical to that previously reported in rodents. Further, the initial identification of seizure resistant zebrafish mutants using our forward genetic screening strategy demonstrates that this is a powerful system to discover genes that may prevent, rather than ameliorate, epilepsy. [Supported by Epilepsy Foundation of American (Holden Targeted Investigation Program) and the National Institutes of Health.]

December 10, 2002
Platform Session F: Neuropharmacology 1
3:30 p.m.–5:30 p.m.

F.01
VALPROATE IRREVERSIBLY AFFECTS FOLLICULAR STEROIDOGENESIS IN ISOLATED OVARIAN FOLLICULAR CELLS, LEADING TO INCREASED TESTOSTERONE AND PROGESTERONE AND REDUCED ESTRADIOL SECRETION

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Rationale: Long-term valproate (VPA) treatment has been shown to induce hyperandrogenism and polycystic ovaries in women with epilepsy. There is an intense, ongoing debate on whether this is related to the drug itself or to the epileptic activity. The aim of the study was to investigate the possibility of a drug-induced effect of VPA on steroidogenesis by studying the effect of VPA on steroid secretion from isolated follicular cells. **Methods:** Small and medium follicles were obtained from pig ovaries collected respectively at days 8–10 and 14–16 of the estrus cycle. Theca and granulosa cells were collected from follicles and cultured as a coculture in one well. Cells were cultured for 24, 48, or 72 h with VPA 100 or 250 μg/ml. To show whether the effect of VPA was reversible, the medium was changed to fresh medium without drugs for an additional 24, 48, or 72 h. **Results:** VPA added to the culture medium caused a significant reduction of estradiol secretion with concomitant increase in both testosterone and progesterone secretion by small follicles. In medium-sized follicles, 100 μg/ml of VPA was without effect on estradiol secretion, whereas 250 μg/ml caused a small, but statistically significant decrease. The effects of VPA on steroid-secretion patterns were irreversible independent of concentration, exposure time, and time of restoration after drug exposure ≤72 h in both small and medium follicles. **Conclusions:** The study shows a direct effect of VPA on steroidogenesis in isolated ovarian follicular cells, resulting in increased testosterone and progesterone, and decreased estradiol secretion. The effects are achieved at therapeutic serum concentrations. It was not possible to reverse the steroidogenic effects of VPA by removing the drug from the cell cultures.

F.02
ANTICONVULSANT USE IN ELDERLY WOMEN INCREASES THE RATE OF HIP BONE LOSS

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Rationale: Anticonvulsant drug (AED) use may result in lower bone mineral density (BMD). Available studies are compromised by use of cross-sectional design, selection bias, lack of adequate controls, and lack of adjustment for other determinants of BMD. We tested the hypothesis that continuous AED use in elderly women increases rates of hip bone loss even after adjustment for other determinants of bone loss. **Methods:** We assessed current AED use using an interviewer-administered questionnaire at the fourth, fifth, and sixth examinations in a cohort of 4,202 elderly women participating in the Study of Osteoporotic Fractures. We verified use from medication containers and classified type of medication from product brand or generic names obtained from containers using a computerized medication dictionary. We categorized women according to their reported AED use as continuous users (use at all three examinations), partial users (use at one or two), or nonusers (no use). Hip BMD was measured at the fourth examination and an average of 4.4 years later at the sixth by dual x-ray absorptiometry. Mean annual percentage change in total hip BMD (THBMD) and its four subregions was calculated by category of AED use. All results were adjusted for the following characteristics measured at the fourth examination: age, health status, total calcium intake (dietary plus supplemental), vitamin D supplement use, estrogen use, body mass index, and THBMD. **Results:** Forty (0.92%) women were continuous AED users, 68 (1.6%) partial users, and 4,094 nonusers. All continuous AED users took phenytoin, carbamazepine, phenobarbital, or primidone; three took additional valproate. The average rate of decline in THBMD in the overall cohort steadily increased from –0.70%/year in nonusers to –0.94%/year in partial users to –1.17%/year in continuous users (p for trend = 0.006). Findings were similar at subregions of the hip, although results reached significance only at the intertrochanteric region. **Conclusions:** AED use in elderly women is associated with increased rates of hip bone loss, even after adjustment for other determinants of bone loss. Continuous users have the highest rates of loss. Assessment of AED use should be included in the clinical evaluation of osteoporosis risk in older women. (Supported by grants AG05407, AR35582, AG05394, AR35584, and AR35583 from the Public Health Service.)

TABLE 1. *Changes in findings*

Category of AED use	Mean annual change in THBMD (95% CI) adjusted as described (%)
Nonusers (n = 4,094)	−0.70 (−0.74 to −0.66)
Partial users (n = 68)	−0.94 (−1.25 to −0.63)
Continuous users (n = 40)	−1.17 (−1.58 to −0.77)

F.03
COMPARISON OF OUTCOMES IN PATIENTS WITH JUVENILE MYOCLONIC EPILEPSY TREATED WITH LAMOTRIGINE, TOPIRAMATE, ZONISAMIDE, OR LEVETIRACETAM

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Rationale: Juvenile myoclonic epilepsy (JME) is typically, but not always, responsive to valproate (VPA), but not all patients respond. VPA is associated with adverse effects, like tremor, weight gain, sedation, and menstrual irregularities, often resulting in discontinuation. Newer antiepileptic drugs (AEDs) [e.g., lamotrigine (LTG), topiramate (TPM), zonisamide (ZNS), and levetiracetam (LEV)] are associated with fewer adverse effects. However, data describing the newer AEDs for JME and direct comparisons in JME are lacking. A retrospective chart review of patients with JME in our clinic, treated with one of these AEDs, is ongoing. Preliminary results are reported in this abstract. **Methods:** A search of the epilepsy clinic database at UAB was done using the terms JME, myoclonic, absence, and generalized tonic–clonic seizures. Inclusion criteria are age older than 15 years, administration of a new AED, a diagnosis of JME, and initiation of a new AED in our clinic. Exclusion criteria are concurrent administration of more than one new AED, except for <12-week transition to another drug, and insufficient documentation of seizure frequency. Outcomes evaluated are frequency of myoclonic (MYO), absence (AB), and generalized tonic–clonic (GTC) seizures, doses of VPA, adverse effects, administration of other AEDs, weight, and new AED discontinuation. Comparisons are made between treatment before initiation of the new AED (data from up to three clinic visits before new AED start) and treatment with the new AED. If the new AED is discontinued, data for up to three clinic visits after discontinuation are evaluated. **Results:** Sixty-eight patients are evaluated at this point. Of these, 21 were excluded for no new AED, 17 for no JME diagnosis, and nine for concomitant administration of more than one new AED. Data from 21

TABLE 1. *Comparison of seizure frequencies*

Drug	Baseline MYO (days/wk)	New drug MYO (days/wk)	Baseline AB (seizures/mo)	New drug AB (seizures/mo)	Baseline GTC (seizures/mo)	New drug GTC (seizures/mo)
LTG	0.39	1.14	0.05	0.08	0.15	0.13
TPM	0.3	0.63	0	0	0.54	0.03
ZNS	0.9	1.65	0.38	0.36	1.14	0.17

patients (11 LTG, six TPM, and four ZNS) are included in the preliminary comparison. Myoclonic seizures increased 192% for LTG, 110% for TPM, and 83% for ZNS. GTCs decreased 13% for LTG, 94% for TPM, and 85% for ZNS. Absence seizures increased with LTG and decreased with ZNS. Mean daily VPA doses increased 5% for LTG and decreased 26 and 6% for TPM and ZNS, respectively. Weight decreased 6% for LTG, 25% for TPM, and increased 2% for ZNS. **Conclusions:** Preliminary analysis of patients receiving LTG, TPM, or ZNS for JME indicates that administration of LTG is associated with an increase in MYO, AB, and GTC seizures. Additionally, there is an increase in VPA doses after initiation of LTG. TPM and ZNS are associated with a decrease in AB and GTC seizures and a decrease in VPA doses. There appears to be a smaller increase in MYO with TPM and ZNS compared to LTG. LTG may be less effective in this group of JME patients compared to TPM and ZNS. (Supported by Elan Pharmaceuticals.)

F.04

EFFECTIVE LEVITERACETAM DOSES AND SERUM CONCENTRATIONS: AGE EFFECTS

Ilo E. Leppik, John O. Rarick, Thaddeus S. Walczak, Teresa A. Tran, James R. White, and Robert J. Gumnit (Research, MINCEP Epilepsy Care, Minneapolis, MN)

Rationale: The objective was to evaluate age differences in leviteracetam (LEV) doses and levels in a large clinical population. Age differences have been demonstrated for many antiepileptic drugs (AEDs). Preliminary data from registration studies suggested LEV doses needed to be higher in children and lower in elderly. This study was done to examine doses and concentrations in a large clinical practice evaluating for age effects. **Methods:** The MINCEP database of >2,500 persons with epilepsy was searched for treatment with LEV. Concentration data was available for 470 individuals. Of these, 418 had dose data, and 371, weights. Many patients had multiple visits, and the highest doses were chosen for analysis. For analysis they were divided into three groups: 18 years and younger, 19–64 years, and 65 years and older. **Results:** For the 18 years and younger (n = 29), the mean highest dose was 1,993 mg/day or 32.8 mg/kg/day. For 19–64 (n = 373), the mean highest dose was 2,611.3 mg/day or 35.3 mg/kg/day. For ≥0.93/l/kg/day (n = 16) the mean highest dose was 1,765.6 mg/day or 23.0 mg/kg/day. Corresponding LEV levels were 26.2 ± 15.1 μg/ml for 18 and younger (n = 23); 29.6 ± 17.3 μg/ml (n = 335) for 19–64, and 24.7 ± 16.9 μg/ml for 65 and older (n = 13). The mean highest dose for female subjects was 2,436 mg/day (range, 250–7,000), and for male subjects was 2,647 mg/day (range, 275–5,000). But in terms of mg/kg/day, the mean highest was 35.8 for females and 33.4 for males. Apparent clearance was calculated by dividing the daily dose in mg/kg by the level in μg/ml. For 18 and younger, it was 1.25/l/kg/day; for 19–64 it was 1.19/l/kg/day; and for 65 and older, was 0.93/l/kg/day. Beacause of the wide variability, none of the differences was statistically significant. **Conclusions:** The mean dose of LEV in this population was ~2,500 mg/day, but the range was large. Although females received lower daily doses, their doses were higher than males on a mg/kg basis. The apparent clearance was greatest in persons younger than 18 years and lowest in in those older than 65 (~26% greater). It appears the concentrations of 29 μg/ml with 1 SD of 17.2 are associated with the highest doses attained in a clinical setting, and thus a range of 12–46 μg/ml could be considered effective for most persons with epilepsy. (Supported by MINCEP Epilepsy Care.)

F.05

LONG-TERM EFFICACY AND TOLERABILITY OF PREGABALIN IN PATIENTS WITH PARTIAL SEIZURES

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Rationale: Pregabalin (PGB) is an alpha$_2$-delta ($\alpha_2\delta$) ligand that exhibits analgesic, anxiolytic, and anticonvulsant activity. A double-blind, placebo-controlled, 41-center trial has demonstrated the efficacy, tolerability, and safety of adjunctive treatment with PGB in patients with medically refractory partial epilepsy. This current study reports the long-term efficacy and tolerability of PGB. **Methods:** All consenting patients completing the double-blind trial (Study 1008-009) were immediately enrolled in an open-label extension study (Study 1008-010) allowing continued exposure to PGB. In addition, de novo patients with medically refractory partial-onset seizures who fulfilled eligibility criteria were directly enrolled into the open-label study. During the open-label phase, adjunctive treatment with PGB was optimized via flexible titration of doses ≤600 mg/day. Patients who took at least one dose of PGB during open-label were included in the intent-to-treat population (ITT). Patients who completed the double-blind study took at least one open-label dose of PGB, and provided prospective baseline and open-label seizure diary data were considered evaluable patients for efficacy analyses. The efficacy of those patients who remained in the study for ≥1 year was evaluated by both the responder rate (defined as the percentage of patients with a ≥50% reduction in seizure frequency during open-label treatment compared to baseline) and by the percentage change from baseline in seizure frequency. **Results:** Of the 454 patients who participated in the study, 257 (57%) were evaluable for efficacy analyses, and 195 (43%) were de novo. Of all evaluable patients, 170 were exposed to PGB for ≥1 year and followed up as a cohort. The mean patient age was 38.8 years (range, 15–82 years) with a mean duration of epilepsy of 26 years. Study patients presented with highly refractory epilepsy as evidenced by their mean and median prospective baseline seizure rates of 24.4 and 11.2 seizures/month, respectively, and that ~27% of the patients were taking one, 45% taking two, and 28% taking three or more concurrent AEDs at entry to open-label. Responder rates calculated over 84-day periods in the first year of open-label ranged from 47 to 52% for the 1-year cohort, and 38 to 51% for evaluable patients. Median percentage change from baseline also calculated over 84-day periods in the first year of open-label ranged from 46 to 51% for the 1-year cohort, and 39 to 50% for the evaluable group. The most frequent adverse events were generally CNS related and mild to moderate in intensity. Serious adverse events were infrequent. The maximum patient exposure was 166 weeks for ITT patients. Approximately 50% of PGB patient-day exposure occurred at 600 mg/day, indicating continued tolerability and benefit at higher doses of PGB. **Conclusions:** Long-term add-on therapy with PGB is safe and well tolerated in patients with refractory partial seizures, with half of PGB exposure at 600 mg/day. The efficacy of PGB is sustained with no evidence for the development of tolerance after 1 year of treatment. (Supported by Pfizer Global Research and Development.)

F.06

ZONISAMIDE REDUCES SEIZURE FREQUENCY OVER TIME IN LONG-TERM CONTINUATION STUDIES

Jacqueline A. French and Alissa D. Ruelle (Neurology, University of Pennsylvania, Philadelphia, PA; Operations Programming, Statprobe, Inc., Ann Arbor, MI)

Rationale: Most data regarding impact of new antiepileptic drugs (AEDs) is derived from randomized placebo-controlled trials of short duration. However, it is also important to assess the potential for long-term benefit from these agents. Zonisamide (ZNS) regulatory trials were initiated up to 16 years before FDA approval. From these, patients entered long-term follow-up studies, during which seizure calendars and adverse-event data were rigorously captured. **Methods:** After completion of regulatory trials with ZNS, patients were eligible to enroll in one of three long-term extension studies in Europe and the United States. Criteria for enrollment in the original trials included history of treatment-refractory partial seizures. During long-term extension medications could be added or eliminated. Monthly seizure calendars were rigorously maintained by patients and retrieved at quarterly study visits. Seizure data was maintained in a centralized database. Seizure frequency was assessed during the last 3 months of ZNS therapy, regardless of whether patients discontinued. This was compared to seizure rate at baseline, and at the time they initially attained their target dose, to determine whether tachyphylaxis occurred. **Results:** The 381 patients entered extension studies. Data available from these patients included demographics, discontinuation (d/c) rates, and reason for d/c. One European study was excluded from seizure outcome analysis, because substantial seizure data was missing. Therefore, 251 of 381 patients were eligible for analysis of seizure frequency over time. Mean duration of epilepsy before ZNS was 21.8 years. Median baseline seizure frequency was nine per month. Including those that d/c'd, mean duration of ZNS therapy was 2.9 years (range, 0.2–16). Retention rate after 4.5 years of therapy was 28%; 142 of 381 (37%) patients were taking fewer concomitant AEDs at the end of ZNS exposure than at baseline. Fifty-four were taking ZNS monotherapy for a mean of 671 days. Specific reasons for d/c included adverse events in 13.7%, and lack of efficacy in 37.2%. Seizure analysis (n = 251): There was a median 38% reduction in seizures from baseline once target dose was reached. At the time of last evaluation (including patients who discontinued) there had been a median 61% partial seizure reduction from baseline. Of pts who d/c'd, only 13% had an increase in seizures in the last 3 months of ZNS rx compared to baseline. Of those remaining on ZNS, 30 were seizure free at the last evaluation (11.3% of cohort). **Conclusions:** ZNS is effective as long-term therapy. There is no evidence of tachyphylaxis. With long-term exposure, there appears to be a continued reduction in seizure frequency over time. (Supported by Elan Pharma.)

F.07

TOPIRAMATE: EFFECTIVE AS MONOTHERAPY IN DOSE–RESPONSE STUDY IN NEWLY DIAGNOSED EPILEPSY

Santiago Arroyo, Liza Squires, Steven Wang, and Roy Twyman (Neurology, Medical College of Wisconsin, Milwaukee, WI; Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ)

Rationale: A superiority design showing a significant difference between treatments is the highest standard for proof of efficacy and a requirement for drug approval in some countries. One approach to safely achieving such a standard for antiepileptic drug (AED) monotherapy in newly diagnosed epilepsy is to directly compare two doses: a modestly effective dose and one presumed to be a maximally effective dose, using a seizure-related end point to protect patients. However, such a design has yet to be successful in newly diagnosed epilepsy. We undertook a multicenter double-blind study comparing 50 and 400 mg/day topiramate (TPM) in adults and children with newly diagnosed epilepsy, using time to first seizure as the primary end point. **Methods:** Children (≥25 kg) and adults with newly diagnosed epilepsy (≤3 months); (one to two partial or GTC seizures during 3-month retrospective baseline) were eligible, as were untreated patients with recurrent epilepsy. Although temporary/emergency use of one AED before study entry was allowed, the AED was discontinued during a 7-day open-label run-in with 25 mg/day TPM. After randomization to 50 or 400 mg/day TPM, patients continued double-blind treatment until their first seizure or the study ended 6 months after the last randomization. Because statistical power in a survival analysis depends on the number of patients who have seizures, study enrollment continued until 108 patients had their first seizure. Patients exiting due to a seizure could enter the open-label extension. **Results:** The 470 patients were randomized to TPM 50 (n = 234) or TPM 400 (n = 236). Median age was 22 (6–83) years; 32% were older than 16 years, and 50% were female subjects. Median time since epilepsy diagnosis was 1 month. Kaplan–Meier estimates for time to first seizure showed a highly significant (p = 0.0002) treatment effect favoring TPM 400. Covariate analyses showed no interaction with age, gender, region, baseline weight, baseline seizure type, baseline AED use, or time since epilepsy diagnosis. With TPM 400, the estimated seizure-free rate at 6 months was 83% versus 71% for TPM 50 (p = 0.005), at 1 year, 76% and 59% (p = 0.001), respectively. The most common adverse events were paresthesia, 23%; headache, 19%; upper respiratory infection, 16%; dizziness, 13%; somnolence, 12%; weight loss, 11%; fatigue, 11%; and loss of appetite, 10%. During treatment ≤786 days (median, 266 days), 11% withdrew due to adverse events (TPM 50, 6%; TPM 400, 17%). **Conclusions:** TPM is the first AED to show, in a randomized double-blind trial, a strongly significant dose–response effect as monotherapy in adults and children with newly diagnosed epilepsy. This study demonstrates the feasibility of safely achieving the highest standard for proof of AED efficacy as initial therapy in this population. The 6-month and 1-year seizure-free rates for both doses compare very favorably with the 6-mo and 1-year seizure-free rates (6 months, 35–48%; 1 year, 53–61%) reported in double-blind studies with other AEDs in newly diagnosed epilepsy. In this study, TPM 400 was selected to show superiority over TPM 50. In a comparative study of likely initial target doses in newly diagnosed epilepsy, TPM 100 mg was at least as effective as 600 mg carbamazepine and 1,250 mg valproate, but better tolerated. The study reported here confirms the usefulness of TPM as first-line therapy in newly diagnosed epilepsy. (Supported by Johnson & Johnson Pharmaceutical Research & Development.) Discussion of Unlabeled/Unapproved Uses: Topiramate is currently not approved for use as monotherapy.

F.08

RAPID TOPIRAMATE DOSE ESCALATION IN CRITICALLY ILL PATIENTS

Denise H. Rhoney, Lisa L. Larive, Dennis Parker, Jr., Kellie R. Murry, Aashit Shah, and William M. Coplin (Pharmacy Practice, Wayne State University College of Pharmacy, Detroit, MI; Neurology, Wayne State University College of Medicine, Detroit, MI; Neurological Surgery, Wayne State University College of Medicine, Detroit, MI; Clinical Affairs, Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ)

Rationale: Topiramate (TPM) is an antiepileptic drug (AED) proven effective for partial seizures (CPSs) and generalized tonic–clonic seizures (GTCs). It is suggested that TPM dosing be slowly titrated (over 8 weeks) as too rapid titration has been associated with dose-related cognitive dysfunction. This dosing regimen is not practical in critically ill patients requiring rapid seizure cessation. The rationale of this prescribing practice was (a) to provide an adjunct to refractory seizures (in an effort to spare the use of high-dose barbiturate therapy), and (b) to provide an alternative to critically ill patients experiencing adverse events to other AED used for seizure prophylaxis. The purpose of this report is to describe patient tolerability to rapid TPM initiation for seizures in critically ill patients. **Methods:** After human investigation committee approval, a search of our hospital database flagged charts in which TPM was prescribed in the intensive care unit. **Results:** The median age was 62 (34–92) years with five female and two male patients. Admission diagnosis included: traumatic brain injury (two), hemorrhagic stroke (two), ischemic stroke (one), and status epilepticus (two). Only two patients had a history of a premorbid seizure disorder. TPM was initiated a median of 3.5 (2–11) days after acute seizure onset. All patients were receiving at least one other AED (median, two; range, one to three) before TPM initiation, primarily phenytoin and

valproic acid. Two patients received a TPM bolus dose of 1,200 mg, and one patient received 800 mg per gastric tube. The median TPM maintenance dose was 1,000 (400–1,200) mg/day per gastric tube, and this was achieved 1.5 (1–4) days after initiation. All patients expressed clinical seizure activity (three CPSs, three GTCs, one CPS with secondary GTC), and sic of seven displayed epileptiform discharges (EDCs) on EEG before TPM initiation. Clinical seizure activity had dissipated in six of seven patients 2 (1–5) days after TPM administration; in one patient, clinical seizures did not stop with adjunctive TPM, but there was no EEG evidence of seizure activity. All patients showed no EDCs on EEG within 2–5 days of TPM initiation. Approximately 50% of patients required supplemental administration of either lorazepam, midazolam, or propofol after TPM was started. None of the patients required high-dose barbiturates. One patient experienced hallucinations after TPM was started, but TPM therapy was continued. At discharge, three patients went to a rehabilitation facility, one went home, one went to a nursing home, and two died. All patients discharged to home, rehab, or nursing home continued on TPM therapy either alone or with other AEDs. For one of these patients, TPM was stopped as an outpatient due to acral paresthesias. **Conclusions:** In this report, rapid TPM dose escalation was found to be well tolerated in critically ill patients. Rapid TPM administration appears to result in rapid cessation of both clinical and EEG seizure activity in combination with other AEDs. Further safety, efficacy, and pharmacokinetic studies of TPM rapid dose initiation are warranted in a controlled intensive care unit setting. This information should provide practictioners with initial experience with the use of rapidly administering TPM in critically ill patients. (Discussion of Unlabeled/Unapproved Uses: Topiramate is indicated for type of seizures in this study although the rapid titration schedule described is not a labeled dosing schema.)

December 10, 2002
Platform Session G: Adult Epilepsy
3:30 p.m.–5:30 p.m.

G.01
POSTTRAUMATIC SEIZURES AND STEROIDS

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Rationale: Epilepsy is a common consequence of severe traumatic brain injury (TBI). Clinical trials involving antiepileptic medications (AEDs)f or the prevention of late posttraumatic seizures have been disappointing. Intravenous (i.v.) steroids are often administered after TBI to reduce cerebral edema. We investigated the effect of i.v. steroids administered in the immediate post-TBI period on the development of late posttraumatic seizures and epilepsy. At the end of this activity participants should be able to discuss the relationships between TBI, steroids, and seizures. **Methods:** We searched a database of 404 TBI patients for exposure to i.v. steroids within a week of their TBI. Exposure to any type or dose of steroid was considered significant, although most patients received ≥10 mg of dexamethasone (Decadron). Steroid treatment was divided into occurring less than, or greater than, 24 h after the TBI. A backward stepwise selection method was used to control for patient demographics and injury severity. Using this model we identified five variables that were associated with the development of late (>1 week after injury) posttraumatic seizures. These variables were nonreactive pupils, cortical contusions, intracranial hemorrhage, subdural hematoma, and seizures within 1 week of the TBI. Analysis was performed while controlling for these variables and any interactions via a multivariate Cox model. **Results:** Patients receiving steroids ≤24 h after their TBI were 1.5 times more likely to develop a first late seizure than those that did not receive steroids ($p = 0.14$). This trend did not apply to second late seizure development ($p = 0.48$; Hazard Ratio, 1.3). Patients receiving steroids >24 h after their TBI were 1.2 times more likely to experience a first late seizure ($p = 0.44$), and 1.3 times more likely to experience a second late seizure ($p = 0.49$) than those that did not receive steroids. **Conclusions:** Treatment with i.v. steroids in the immediate (≤24 h) post-TBI period may contribute to the development of a first late seizure. This is consistent with animal data showing hippocampal irregularities after glucocorticoid exposure. No trend was seen regarding the development of a second late seizure. Steroid exposure >24 h after a TBI did not affect late seizure development.

G.02
THE COMBINED DEXAMETHASONE/CRH TEST AS A BIOLOGIC MARKER FOR THE DISCRIMINATION OF PATIENTS WITH EPILEPSY AND PSYCHOGENIC SEIZURE DISORDERS

Jörg Wellmer, Till Perrey, Astrid W. Zobel, and Christian E. Elger (Department of Epileptology, University of Bonn, Bonn, Germany; Department of Psychiatry, University of Bonn, Bonn, Germany)

Rationale: Therapeutic strategies in epilepsies differ fundamentally from those in psychogenic disorders. However, differentiation between epileptic (ESs) and psychogenic seizures (PSs) often proves difficult. Semiologic differences may be negligible; negative long-term EEG recordings do not exclude the presence of epileptic events. Valid biologic markers are lacking. After the observation that chronic ESs influence the function of the hypothalamic–pituitary–adrenocortical system, including the secretion of steroids, we investigated if the combined dexamethasone/CRH-test (Dex/CRH-test) is a sensitive marker for the discrimination of epilepsy patients from those with exclusive PSs. **Methods:** Between May 2001 and April 2002, 37 patients admitted to the Department of Epileptology for either surgical or conservative treatment of chronic epilepsy or differential diagnosis of seizures were included into the study. Patients were divided into two groups: Inclusion criterion for the ESs group was the validation of habitual ESs by ictal EEG ($n = 33$). Patients with successful suggestive provocation of typical events and absent ictal and interictal epileptiform activity in long-term EEG monitoring under antiepileptic drug (AED) withdrawal were attributed to the PSs group ($n = 4$). With an established Dex/CRH-test protocol (Heuser et al. *J Psychiatr Res* 1994;28:341–56), after a single oral dose of 1.5 mg dexamethasone at 11 p.m., between 3 p.m. and 4.15 p.m. the following day, five blood samples were taken from the patients to measure the basal cortisol level as well as the response to i.v. application of 100 μg CRH. Results were plotted against time. In the ESs group, result analysis included statistical evaluation of the effect of time since last seizure, actual seizure frequency, and interictal discharge activity. **Results:** In the ESs group, maximum cortisol levels (MCL) and area under the cortisol response curve (AUC) were significantly higher than in the PSs group (ESs: mcl 19.8 ± 6.2 μg/dl; AUC, 1,117 ± 365; PS, MCL 5.2 ± 2.3 μg/dl; AUC 289 ± 113, unpaired *t* test: $p < 0.001$). Cut-off values of 8μg/dl for MCL and 450 for AUC allowed good discrimination [diagnostic accuracy, 97.3% (95% CI, 92.1–102.5%, $\chi 2$: $p < 0.001$), each]. No significant influence of the other clinical parameters on the cortisol response was found. **Conclusions:** The combined Dex/CRH-test is a promising tool for the discrimination of patients with chronic epilepsy from those experiencing only PSs. In the present sample, we did not find any influence of the seizure-to-test latency or the actual seizure frequency on the cortisol response. This, as shown for other steroids in chronic epilepsy, can be due to a loss of reactivity of the endocrine feedback regulation as an effect of chronic epileptic discharges. Further examinations will be necessary to show if the test also allows discrimination between patients with newly manifested ESs or oligoepilepsies and those having exclusively PSs. (Supported exclusively by internal grants of the Department of Psychiatry, University of Bonn.)

G.03
EFFECT OF ESTROGEN-CONTAINING ORAL CONTRACEPTIVES ON SEIZURE FREQUENCY IN WOMEN WITH EPILEPSY

Julio Cantero and Pavel Klein (Neurology, Georgetown University Hospital, Washington, D.C.)

Rationale: The effect of hormonal contraceptives on seizure frequency in women with epilepsy is ill understood. There have been

anecdotal reports off worsening of seizures in isolated cases, but the accepted belief is that estrogen-containing contraceptives do not affect seizures. However, there are few data to support or refute this belief. In animals and in some human studies, estrogens have been shown to exacerbate seizures. The purpose of this study was to evaluate the effect of estrogen-containing oral contraceptives (OCs) on seizures in women with epilepsy. **Methods:** One hundred forty-two consecutively evaluated women with epilepsy aged 14–55 years underwent reproductive endocrine interviews. Women with severe cognitive impairment were excluded; 21% women had primary generalized epilepsy (PGE), and 79% had localization-related epilepsy (LRE). Questions included exposure to OCs, type and duration of OC treatment and seizure frequency, severity and any changes in antiepileptic drugs (AEDs) during OC exposure. Women older than 55 years were excluded to maximize the accuracy of recall of reproductive history. Epilepsy evaluation included EEG and, when normal, sleep-deprived EEG or LTEEG with minisphenoidal electrodes, and magnetic resonance imaging (MRI). ILAE seizure classification was used. Patients with possible nonepileptic seizures were excluded; 67% of the women were interviewed on more than one occasion. Women whose answers concerning seizure frequency and severity during OCs exposure varied at different interviews were arbitrarily classified as not affected by OCs. **Results:** Of patients, 44% never used OC. Among past and present OC users, duration of use ranged from 2 months to 14 years; 22% of past OC users did not recall the brand or type of OC used; 21% of estrogen OC users (12% of all women) experienced worsening of seizures during use of estrogen-containing Ocs; 62% of estrogen OC users experienced no change in seizure frequency or severity during OC use; 17% of estrogen OC users were unsure whether seizure freqeucy and/or severity changed during OC use. In two patients, seizures began shortly after initiation of contraceptive use. There was no difference in the effect of estrogen-containing OCs on seizures among women with LRE and PGE. **Conclusions:** Estrogen-containing OCs exacerbate seizures in possibly $\leq$20% of women with epilepsy who use them. This should be considered when counseling women with epilepsy on contraception. A prospective controlled study is needed to corroborate the results of this retrospective study.

G.04

NONLESIONAL TEMPORAL LOBE EPILEPSY WITHOUT HIPPOCAMPAL ATROPHY: VARIANT OF MESIAL TEMPORAL LOBE EPILEPSY OR DISTINCT CLINICOPATHOLOGIC SYNDROME?

Ross P. Carne, Terence J. O'Brien, Rodney Hicks, Michael Murphy, Christine Kilpatrick, Penny McKelvie, Andrew Kaye, and Mark Cook (Victorian Epilepsy Centre, Department of Neurosurgery, St. Vincent's Hospital, Melbourne, Victoria, Australia; Department of Neurology, Royal Melbourne Hospital, Melbourne, Victoria, Australia; PET Department, Peter MacCallum Cancer Institute, Melbourne, Victoria, Australia)

Rationale: Aim: To determine whether nonlesional temporal lobe epilepsy (TLE) without hippocampal sclerosis (HS) on magnetic resonance imaging (MRI) represents a variant of, or a different clinicopathologic syndrome from that of mesial TLE (MTLE). Most patients with medically refractory nonlesional TLE have the syndrome of MTLE associated with typical findings of HS on MRI. However, a significant group of patients with well-lateralized temporal lobe seizures on ictal EEG, often with significant focal temporal hypometabolism on positron emission tomography (PET), do not have HS on MRI. The underlying pathophysiologic basis of this syndrome is uncertain. **Methods:** The clinical, EEG, fluorodeoxyglucose (FDG)-PET, histopathology, and surgical outcome of 15 consecutive nonlesional patients without HS on MRI (HS-) were compared with 15 consecutive patients with typical HS (HS+). **Results:** The HS- group less frequently had a history of a remote symptomatic neurologic insult (13% vs. 58%, $p < 0.05$), and this occurred at an older age (median, 18.5 vs. 2 years, $p < 0.05$). Febrile convulsions were only seen in the HS+ group (42%). The ictal EEG pattern in the HS- group more frequently showed a focal delta rhythm (58 vs. 10%, $p < 0.05$), compared with a focal theta rhythm in the HS+ group (60 vs. 25%, $p = 0.20$). Blinded review of the FDG-PET scans detected unilateral focal hypometabolism in 100% of both groups, but its pattern did not differ between the groups. Nine patients in both groups have had epilepsy surgery with no significant difference in outcome (67 vs. 89% seizure free, $p > 0.05$) despite most of the HS- patients having a hippocampus-sparing procedure. **Conclusions:** We conclude, based on the clinical, EEG, pathology, and surgical outcome differences identified, that nonlesional TLE without HS may be a distinct surgically remediable clinicopathologic syndrome, rather than being a part of the spectrum of MTLE. (Supported by Epilepsy Fellowship Sanofi-Synthelabo.)

G.05

REFLEX-WRITING SEIZURES IN TWO SIBLINGS WITH JUVENILE MYOCLONIC EPILEPSY

Rosanna Chifari, Ada Piazzini, Vincenzo Sgro', Raffaele Canger, and Maira Paola Canevini (Regional Centre of Epilepsy, San Paolo Hospital, Milano, Italy)

Rationale: There have been very few reports on reflex epilepsy induced by writing, indicating that such reflex seizures may be very rare, even though, like many rare disorders, they may be underdiagnosed. The pathophysiologic mechanism of this curious disorder is actually unknown, and controversy remains whether writing epilepsy should be included among localization-related epilepsies or it represents a peculiar form of idiopathic generalized epilepsy with seizure precipitate by specific modes of activation. Here we report on two sisters with juvenile myoclonic epilepsy (JME) where writing activity triggered epileptic myoclonic jerks of right arm and hand **Methods:** The patients are two girls of 20 and 18 years of age. Both girls are right-handed, the product of a normal pregnancy, delivery, with normal psychomotor development. At the age of 14 and 13 years, respectively, they began to experience early-morning seizures while awaking, which were characterized by myoclonus in both arms. Their interictal EEG showed normal background activity and rare generalized spike–wave complexes. A diagnosis of idiopathic generalized epilepsy was made, treatment with valproate (VPA), at the dosage of 400 mg/day), was started, and almost complete control of seizures was achieved. After 3–4 years, they began to present rare myoclonic jerks occasionally triggered by writing. Both patients underwent porlonged video-EEG monitoring using writing tasks of increasing difficulty that required a parallel increased degree of concentration. **Results:** In both patients, on video-EEG monitoring, depicted reflex epileptic myoclonus triggered by writing. Most important, myoconic jerks were more easily triggered by writing that required a higher degree of concentration. Conversely, in both patients, other cognitive tasks, such as reading, typing, thinking, and calculation never elicited any seizures or myoclonus. VPA was effective in controlling both spontaneous and reflex epileptic seizures. **Conclusions:** The results of this study further support the notion that "praxis-induced" reflex epilepsy precipitated by specific stimuli occurs in the context of idiopathic generalized epilepsy. Our results also illustrate that writing tasks are more effective in eliciting seizures when they require higher levels of concentration and mental elaboration.

G.06

STATUS EPILEPTICUS IN THE ELDERLY POPULATION

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Rationale: Status epilepticus (SE) is a serious medical condition associated with significant morbidity and mortality. Few studies have addressed this condition in the elderly. We examine characteristics of SE in this population. **Methods:** For this prospective study, data were obtained from the NIH Greater Richmond Metropolitan Area Status Epilepticus database. The elderly group ($n = 382$) was defined as age 60 and older. The adult group ($n = 318$) was defined as aged 16–60 years. **Results:** A total of 382 cases, age 60 or older, were available for analysis. Of these 54% were female and 61% nonwhite; 57% had no history of seizures, and 71% had no history of SE. Generalized con-

vulsive seizures accounted for 63%, partial convulsive 27%, and nonconvulsive 10% of cases. Acute CNS events accounted for the largest etiology (42%), followed by remote symptomatic (24%), and hypoxic–anoxic (13%). The overall mortality rate was 38% with a 27% mortality for ages 60–69, 37% mortality for ages 70–79, and a 42% mortality for ages 80 and older. Differences were seen when comparing the adult (16–60 years of age) and elderly populations (60 years and older): more elderly cases (65%) had SE without seizure history than was seen in adults (44%); partial convulsive seizures were more common in the elderly (27%) than in the adult group (17%); and there was a significantly greater mortality in the elderly group, 23 versus 38% ($\chi 2 = 19$, $df = 1$, $p < 0.0001$). **Conclusions:** Elderly patients with SE represent a distinct population with unique characteristics. Most of the patients had no history of seizures or SE and had a relatively high rate of nonconvulsive SE. Mortality was significantly higher in the elderly population than was seen in the nonelderly adult group. (Supported by NIH PO1 NS25630.)

G.07
HEART-RATE INCREASE IN OTHERWISE SUBCLINICAL SEIZURES IS DIFFERENT IN TEMPORAL VERSUS EXTRATEMPORAL EEG SEIZURE PATTERN

Sabine Weil, Stephan Arnold, Ilonka Eisensehr, and Soheyl Noachtar (Neurology, University of Munich, Munich, Germany)

Rationale: To investigate the heart rate in patients with otherwise subclinical seizures in relation of the localization of the epileptogenic zone. **Methods:** We reviewed the data base of our Epilepsy Monitoring Unit for the term "subclinical seizure" in all patients with focal epilepsies. The term subclinical seizure was defined as EEG seizure pattern not associated with any disturbance of consciousness, sensory phenomena or motor functions. Twenty-two patients (10 male, 12 female patients) were identified, in whom ictal EEG and videos could be retrieved for analysis. Heart rate before and during the EEG seizure pattern was analyzed in these patients and correlated to localization and duration of the seizure patterns. Heart rate was calculated from RR distances in the ECG channel. Heart rate was plotted depending on time. Responding curves were fitted to calculate the point of maximum velocity of heart-rate increase. Increase of heart rate >1.8 times and an increase of velocity >50% were considered significant. **Results:** Of the 22 patients with subclinical seizures, 13 patients had temporal and nine patients had extratemporal seizure patterns (frontal $n = 8$, occipital $n = 1$). Ictal heart-rate increase >50% was observed more often in patients with temporal EEG seizure patterns (61%, eight of 13) than in those with extratemporal seizure patterns (11%, one of nine; $p < 0.018$). There was no correlation between duration of seizure patterns and change of heart rate (Mann–Whitney test, $p = 0.261$) or lateralization of the EEG pattern. There was no significant decrease of heart rate during seizures. **Conclusions:** We conclude that pure ictal tachycardia can be induced by spread of epileptic seizure activity to the temporal cortex and is not secondary to physical or psychic stress factors during seizures. Our findings support cortical representation of autonomic function such as heart rate in the temporal lobe region.

G.08
PREDICTORS OF LONG-TERM OUTCOME IN PATIENTS WITH NONEPILEPTIC SEIZURES

Allan Krumholz, Olukemi F. Ajayi, Elizabeth Barry, and Lawrence G. Seiden (University of Maryland Epilepsy Center, Department of Neurology, University of Maryland School of Medicine, Baltimore, MD)

Rationale: Although video-EEG monitoring has proven to dramatically increase the ability of clinical epileptologists to correctly diagnose inidividuals with nonepileptic seizures, prognosis and therapy for such patients have not been as well studied and remain controversial. We analyzed a large group of patients with well-documented nonepileptic seizures to determine factors useful for predicting long-term prognosis and guiding management. At the end of this activity the participants whould be able to discuss factors that predict outcome and prognosis in indivividuals with nonepileptic seizures. **Methods:** We reviewed all epilepsy monitoring unit admissions to the University of Maryland Epilepsy Center from 1989 to 1995. All patients with video-EEG documented nonepileptic seizures were identified and characterized in terms of age; sex; seizure duration, type, and frequency; associated psychopathology; and outcomes. In particular, outcomes were determined at follow-up of ≥1 year. Outcomes were graded as "excellent," "good," "fair," and "poor" based on cessation of seizures and function measures. Patient and seizure characteristics were correlated with outcome using contingency analysis ($p \leq 0.05$). **Results:** A total of 568 patients were monitored from 1989 to 1995. Of these, 150 individuals (18%) were confirmed to have nonepileptic seizures by video-EEG monitoring. Among these 150 patients with nonepileptic seizures, 80 (53%) could be adequately characterized, had no evidence of active coexisting true epileptic seizures, and had >1 year of follow-up. Significant predictors of outcomes included: age (individuals younger than 18 had the best outcomes); nature of nonepileptic seizures [individuals with nonconvulsive events were more likely to become event free (excellent outcome), while individuals with convulsive manifestations were more likely to have poor outcomes]; duration of nonepileptic seizure disorder (patients with seizures for ≤3 months had the best prognosis, and those with events for <1 year still had better prognoses than those with nonepileptic seizures going on longer before diagnosis); and the severity and nature of associated psycholopathology (patients classified with more severe psychiatric disorders such as somatization disorders, personality disorders, or major affective disorders had poorer outcomes than individuals judged to have less severe psychopathology including anxiety, stress, or coping disorders, and misinterpretation or elaboration of physiologic events). **Conclusions:** Our findings demonstrate factors that predict or influence outcome and prognosis in patients with nonepileptic seizures. These include the age of the patient, duration of the nonepileptic seizure disorder before correct diagnosis, nature of the events, and associated psychopathology. Early diagnosis is confirmed to be important in outcome. In particular, nonepileptic seizure patients diagnosed within 1 year of onset have a better prognosis than those diagnosed later, and individuals diagnosed at younger than 18 years have better outcomes than older subjects. In addition, because associated psychopathology significantly influences outcomes, it also warrants further study and attention to develop better strategies for improving the prognosis for patients with nonepileptic seizures. (Supported by grant from the Rosen Foundation.)

December 10, 2002
Platform Session H: Surgery
3:30 p.m.–5:30 p.m.

H.01
LONG-TERM SEIZURE OUTCOME AFTER STANDARD VERSUS TAILORED TEMPORAL RESECTION: A CORRELATION WITH EXTENT OF RESECTION

Andres M. Kanner, Lincoln Ramirez, Leyla deToldeo-Morrell, and Walter W. Whisler (Neurological Sciences, Rush Medical College, Chicago, IL; Neurosurgery, University of Wisconsin, School of Medicine, Madison, WI; Neurosurgery, Rush Medical College, Chicago, IL)

Rationale: Anterotemporal lobectomy is the most common operative procedure used to treat epilepsy. It can be performed either as a standard resection (SR) or as a tailored resection (TR). Historically, epilepsy centers have adopted one but not both techniques. Current opinion holds that SR generally removes more tissue, especially from mesial and basal temporal lobe, and this results in a better seizure control. Data comparing seizure outcome in SR and TR have been difficult to interpret because centers differ not only with respect to choice of surgical technique, but also with respect to criteria for patient selection. For this reason we designed a two-center study comparing SR and TR in which patient selection at each center was the same. We focused on seizure outcome after SR or TR and correlated this outcome with the extent of temporal resection. **Methods:** We compared 30 SR patients and 30 TR patients. Each cohort had 15 patients with a left-

sided focus and 15 with a right-sided focus. Each patient had a nonlesional unilateral anterotemporal seizure focus. The SR cohort received their care at the University of Wisconsin Epilepsy Program where at the time SR was the procedure of choice. The TR cohort received their care at the Rush Epilepsy Center where at the time TR was the procedure of choice. Patient selection was identical at each center. Achieving this objective was facilitated by the fact that the same epileptologist (A.M.K.) held faculty positions at different times in both centers. The minimal follow-up period was 7 years. Approximately 6 months after surgery, patients underwent a brain magnetic resonance imaging (MRI) to establish the extent of temporal resection. To measure the extent of this resection we used Awad's semiquantitative method (*Epilepsia* 1989). We used Engel's classification to assess postsurgical seizure outcome (IA, no sz, no auras; IB, only auras; IC, sz after discontinuation of AED; ID, nocturnal sz; II, rare sz; III, >90% sz reduction; IV, <90% sz reduction). Neuropathologic diagnosis was obtained for all patients. Logistic regression was used to test dichotomous variables, and analysis of variance was used to test continuous variables. **Results:** Patients who underwent SR had significantly greater tissue removal of mesial and basal structures than did patients who underwent TR ($p = 0.0001$). Despite this, no significant difference in seizure outcome was seen between SR and TR when all patients in one cohort were compared as a group to those in the other cohort (see Table 1). However, when the comparison was restricted to class 1A alone (vs. IB+IC+ID+II+III+IV), there was a statistical trend favoring patients who underwent SR ($p = 0.07$). **Conclusions:** Seven years after surgery to control anterotemporal epilepsy, the results of SR or TR are comparable, although there is a statistical trend favoring class IA outcomes after SR. This trend may be related to the fact that more mesial and basal temporal tissue is removed during SR than is removed in TR.

TABLE 1. *Number of patients in each outcome class*

Outcome class	1A	1B	1C	1D	II	III	IV
Standard resection	18	3	2	5	1	0	1
Tailored resection	11	8	5	3	2	0	1

H.02

OUTCOME OF PEDIATRIC EPILEPSY SURGERY: A 10-YEAR FOLLOW-UP STUDY

L. D. Hamiwka, P. Jayakar, T. Resnick, G. Morrison, J. Ragheb, P. Dean, C. Dunoyer, and M. Duchowny (Comprehensive Epilepsy Center, Miami Children's Hospital, Miami, FL; Comprehensive Epilepsy Center, Miami Children's Hospital, Miami, FL; Comprehensive Epilepsy Center, Miami Children's Hospital, Miami, FL; Comprehensive Epilepsy Center, Miami Children's Hospital, Miami, FL; Comprehensive Epilepsy Center, Miami Children's Hospital, Miami, FL; Comprehensive Epilepsy Center, Miami Children's Hospital, Miami, FL; Comprehensive Epilepsy Center, Miami Children's Hospital, Miami, FL; Comprehensive Epilepsy Center, Miami Children's Hospital, Miami, FL)

Rationale: Surgery is now well established in the management of selected pediatric patients with medically resistant epilepsy. However, there is limited information about very long-term seizure outcome after surgical treatment. We present our experience regarding seizure status in children 10 years after excisional procedures and corpus callosotomy. **Methods:** Children were identified from the Miami Children's Hospital Epilepsy Surgery database, and surgical charts were reviewed. We recorded the following parameters: seizure type, neuroimaging, seizure status at 2, 5, and 10 years and pathologic diagnosis. Follow-up data were obtained through clinic visits or by telephone interview. Seizure outcome was classified according to Engel's criteria. **Results:** From a cohort of 93 children operated on between 1980 and 1992, we identified 59 children who were alive and had data at 10 years after surgery. Age at surgery ranged from 5 months to 18 years (mean, 8.7 years). Fifty-three (90%) had partial seizures and underwent excisional procedures [23 (39%) temporal, 23 (39%) extratemporal, seven (19%) hemispherectomy], and six (10%) had generalized seizures and underwent corpus callosotomy (complete, three; anterior 2/3, three). Pathological information was available in 51 cases: cortical malformation, 25 (49%), encephalomalacia, seven (14%), tumor, 12 (24%), hippocampal sclerosis, two (3%), infection, four (8%), nonspecific, one (2%). At 2-year follow-up, 27 (46%) were seizure free, 21 (36%) showed worthwhile improvement, and 11 (18%) were marginally improved or unchanged. At 5-year follow-up, 18 (31%) were seizure free, 23 (39%) showed worthwhile improvement, and 18 (30%) were marginally improved or unchanged. At 10-year follow-up, 20 children, eight temporal and 12 extratemporal (34%) were seizure free, 23 (39%) showed worthwhile improvement, while 16 (27%) were unchanged. Seizure freedom was higher among lesional (65%) when compared to nonlesional (35%) cases. Five of six children who underwent callosotomy were unchanged at 10-year follow-up. Forty-five children (76%) remained on anticonvulsant treatment. Relapse rates were highest in the first 2 years after surgery. **Conclusions:** Approximately one third of children who undergo excisional procedures are seizure free at 10 years. Children with a lesion on neuroimaging were more likely to remain seizure free. A favorable outcome was independent of underlying pathology. In contrast, no child who underwent callosotomy was seizure free. Relapse rates were highest within the first 2 years after surgery, declined until 5 years, and plateaued thereafter. Seizure freedom at 5 years after surgery is a good predictor of permanent seizure remission.

H.03

OUTCOME OF SURGICAL TREATMENT FOR MEDICALLY REFRACTORY TEMPORAL LOBE EPILEPSY AMONG PATIENTS SELECTED USING NONINVASIVE STRATEGY IN A DEVELOPING COUNTRY

Bhaskara R. Malla, Radhakrishnan Kurupath, Padmavathy N. Sylaja, Joseph Cherian, and Ravi M. Rao (Comprehensive Epilepsy Care, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India; Comprehensive Epilepsy Care, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India; Comprehensive Epilepsy Care, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India)

Rationale: Epilepsy surgery is a well-established treatment for selected patients with medically refractory epilepsy. Epilepsy surgery was considered, until recently, an expensive high-tech therapy restricted to the industrialized world. The recent recognition that a majority of patients with medically refractory partial seizures have surgically remediable syndromes that can be identified by relatively simple noninvasive studies has resulted in the evolution of epilepsy surgery programs in developing countries. During the last 6 years, the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, India, has developed a comprehensive program for the evaluation and management of persons with medically refractory epilepsy. Based on this program, we wish to report our experience with determination of surgical candidacy for epilepsy surgery and propose a pragmatic cost-effective strategy applicable to developing regions of the world. At the end of this presentation, the participants should be able to assess the quality and cost-effectiveness of a noninvasive presurgical evaluation and understand the development of epilepsy surgery program in a country with limited resources. **Methods:** From March 1995 through December 2001, 358 patients underwent anterior temporal lobectomy (ATL). These patients were selected for ATL based on a noninvasive protocol, comprising history, interictal scalp EEG, magnetic resonance imaging (MRI), ictal video scalp EEG, and neuropsychological data. Information obtained through neuropsychological assessment and Wada test were considered complementary. All patients underwent craniotomy and standard ATL, which included 5–6 cm of lateral neocortical resection, anterior two thirds of hippocampus, and lateral two thirds of the amygdala along with uncus and parahippocampal gyrus under general anesthesia without electrocorticography. We determined the siezure outcome using seizure-outcome scoring for each 12-month period after surgery. Psychological, psychiatric, educational, and employment status were also evaluated. **Results:** The 358 ATL patients comprised 183 men and 175 women; mean age, 25.6 years; median duration of epilepsy, 15 years. The preoperative MRI and/or histopathology of the resected specimens among the first 300 cases revealed mesial temporal sclerosis in 240,

neoplastic lesions in 28, and dysplastic and nonspecific changes in 32 patients. Among the 213 patients who completed 2-year follow-up, 77.9% had Engel class I outcome. The quality of life remarkably improved in seizure-free patients. The average cost per patient for presurgical evaluation and ATL was Indian Rupees 47,000 (US$, 1,200). Comparable post operative changes in the neuropsychology and quality of life were seen. **Conclusions:** Our experience from a comprehensive epilepsy surgery center from a developing region indicates that epilepsy surgery is not only possible but can be undertaken in a cost-effective way. The epilepsy surgery centers in developing countries should initially restrict their surgical candidacy to patients who can be selected using locally available relatively inexpensive and noninvasive technologies and in whom an excellent postoperative outcome can be predicted. (Supported by SCTIMST.)

H.04

TIMING OF EPILEPSY SURGERY DOES NOT ALTER SEIZURE OUTCOME

Gregory D. Cascino, Denise M. Cambier, Max R. Trenerry, Jeffrey W. Britton, Terrence D. Lagerlund, Cheolsu Shin, Elson L. So, Frank W. Sharbrough, Jeffrey R. Buchhalter, Frederic B. Meyer, and W. Richard Marsh (Neurology, Mayo Clinic, Rochester, MN; Neurology, Ohio State University, Columbus, OH; Psychiatry and Psychology, Mayo Clinic, Rochester, MN; Neurosurgery, Mayo Clinic, Rochester, MN)

Rationale: To investigate the effect of the timing of epilepsy surgery on seizure outcome in patients with intractable partial epilepsy undergoing a focal cortical resection. **Methods:** We performed a retrospective analysis of seizure outcome in 526 consecutive patients who were surgically treated for medically refractory partial seizures at Mayo Clinic, Rochester, MN, between 1988 and 1996; 479 patients had temporal lobe epilepsy. The mean age at surgery was 32 years (range, 3–69). The mean age at seizure onset was 13 years (range, 0–65). A modified Engel classification was used for seizure outcome. **Results:** The duration of epilepsy before surgery and the seizure outcome were available in 520 patients. The mean duration of epilepsy was 18.6 years (range, 0–56). The association between operative outcome and duration of epilepsy was not significant (Spearman's rho, $p = 0.417$). The patients were separated into three groups based on the timing of the operative procedure: Group I, duration of epilepsy ≤5 years ($n = 88$), Group II, duration of epilepsy 6–34 years ($n = 369$), and Group III, duration of epilepsy l35 years ($n = 63$). The outcome for the 3 groups was not significantly different (Kruskal–Wallis test, $p = 0.871$). The outcome in patients who underwent early surgery (Group I) and late surgery (Group III) were subsequently compared. The timing of surgery in these patients did not affect the outcome classification (Wilcoxon rank sum, $p = 0.639$). Finally, the associations between the age at seizure onset and outcome (Pearson correlation coefficient, $r = 0.01$), and the age at surgery and outcome (Pearson correlation coefficient, $r = –0.05$) were also not significant. **Conclusions:** Early surgery for epilepsy has potential putative beneficial effects on quality of life. The present series, however, failed to demonstrate that early surgery was more effective than later surgery in reducing seizure tendency. (Supported by Mayo Foundation.)

H.05

REOPERATION FOR EPILEPSY: A 10-YEAR REPORT (1990–1999) FROM THE SWEDISH NATIONAL EPILEPSY SURGERY REGISTER

Bertil Rydenhag, Kristina Malmgren, Ingrid Olsson, Hans Cason Silander, and Roland Flink (Epilepsy Research Unit, Institute of Clinical Neuroscience, Göteborg, Sweden; Department of Neuropediatrics, Institute for the Health of Women and Children, Göteborg, Sweden; Department of Neuroscience, Section for Clinical Neurophysiology, Uppsala, Sweden)

Rationale: To report outcome data following reoperation for pharmacoresistant epilepsy using the Swedish National Epilepsy Surgery Register. **Methods:** Epilepsy surgery in Sweden is performed at six centers, and data on all procedures are collected in a national register. This study includes 83 resective reoperations performed in 1990–1999, and with 2-year follow-up data available. The outcome data will be presented in relation to the postoperatively defined pathologic–anatomic diagnoses. Gangliogliomas ($n = 6$), dysembryoplastic neuroepithelial tumor (DNET; $n = 4$), low-grade astrocytomas ($n = 8$), and two cavernous hemangiomas constitute a lesion group. The remaining temporal ($n = 33$) and extratemporal ($n = 17$) resections had diagnoses such as gliosis or malformations. Multilobe ($n = 4$) and subtotal hemispherectomy reoperations ($n = 2$) are grouped together, while complete hemispherectomies ($n = 7$) are reported separately. **Results:** Reoperations for pathologically verified lesions were performed in 20 cases, 60% of the patients became seizure free, and 5% had >75% reduction of seizure frequency. If only ganglioglioma and DNET were grouped ($n = 10$), 70% of the patients became seizure free, and 10% had >75% reduction of seizure frequency following reoperation. The temporal lobe reoperations rendered 24% of the patients seizure free, and 18% had >75% reduction of seizure frequency. Extratemporal reoperations in a single lobe rendered 24% of the patients seizure free, and 12% had >75 % reduction of seizure frequency. The multilobe and subtotal hemispherectomy reoperations rendered 16% ($n = 1$) of the patients seizure free, and 16% ($n = 1$) had >75% reduction of seizure frequency. The complete hemispherectomies performed as a reoperation rendered by contrast 71% of the patients seizure free; the other 29% had no benefit. **Conclusions:** The data from the Swedish National Epilepsy Surgery Register show that reoperations for pharmacoresistant epilepsy in general has a worse outcome than the primary surgery. However, reoperations for residual lesions is highly beneficial. Especially ganglioglioma and DNET residuals should be considered for reoperation if seizures persist. It is also our view that total hemispherectomy as a reoperation is a different entity, because this procedure is sometimes performed as a staged procedure, with an initial callosotomy or multilobe resection. The outcome in this group is as good as expected for a primary procedure. (Supported by The Medical Faculty of the University of Göteborg.)

H.06

LOW-DOSE LINAC STEREOTACTIC RADIOSURGERY FOR THE TREATMENT OF MEDICALLY INTRACTABLE MESIAL TEMPORAL LOBE EPILEPSY

Stephan Eisenschenk, William A. Friedman, Robin L. Gilmore, Steven N. Roper, Frank J. Bova, Robert Amdur, Dawn Bowers, Ilona Schmalfuss, and Lorna Williams (Neurology, University of Florida, Gainesville, FL; Neurosurgery, University of Florida, Gainesville, FL; Radiation Oncology, University of Florida, Gainesville, FL; Clinical and Health Psychology, University of Florida, Gainesville, FL; Radiology, University of Florida, Gainesville, FL)

Rationale: Stereotactic radiosurgery (SRS) is used for the treatment of cryptogenic mesial temporal lobe epilepsy (MTLE) as an alternative to conventional anterior temporal lobectomy (cATL). Nonetheless, optimal dose and volume irradiated remain undetermined. We hypothesized that (a) optimal radiation dosing of SRS for MTLE may be less than current reports; (b) magnetic resonance spectroscopy (MRS) may demonstrate changes associated with seizure remission; and (c) MTLE treated with low-dose SRS would have better neuropsychological (NP) outcomes compared to cATL. The objective of the participant is to assess low-dose SRS for treatment of MTLE. **Methods:** Inclusion criteria: (a) Video-EEG: unilateral MTLE ictal onset; (b) neuroimaging: ipsilateral (IL) asymmetry of hippocampal volumes with reduced MRS NAA/Cr+Cho ratio; (c) NP testing: no disconcordant findings; and (d) Wada: adequate isolated contralateral hemispheric memory. Both patients received 15 Gy at the 70% isodose level via a 6-mV LINAC SRS device. The volumes irradiated corresponded to the area proposed for cATL for each patient (11 and 7.5 cc for patients 1 and 2, respectively). **Results:** Population: Two patients demonstrated left MTL seizure foci on video-EEG with concordant ipsilateral hippocampal atrophy, decreased NAA/Cr+Cho ratios, and NP profiles. Patients 1 and 2 are 25 and 13 months post-SRS, respectively. Outcome: Before SRS, patient 1 had complex partial seizures two to four times per week and one secondarily generalized seizure per month, and patient 2 had monthly seizure clusters of up to eight seizures. Post-SRS, seizure frequency

gradually declined with a dramatic improvement in control following radiation-induced changes on MRI. Patient 1 has remained seizure free for the past 8 months except for two seizures, both associated with a precipitate PHT level decline (8 μg/ml) from her baseline (18 μg/ml). Patient 2 had the same seizure frequency until 4 months post-SRS with a gradual decline thereafter, and has remained seizure free for the past 4 months. Neuroimaging: Serial MRI demonstrated radiation-induced changes at 14 and 4 months in patients 1 and 2, respectively, with improvement on subsequent images. Patient 1 demonstrated a further reduction in the NAA/Cr+Cho ratio (0.276) at 2 years post-SRS (baseline = 0.44) in the left hippocampus and no change on the right (baseline = 0.63; post-SRS = 0.648). NP testing: Patient 1 has had mild (not statistically significant) overall improvement compared to preop testing. No NP changes have been noted for patient 2. Adverse effects: No unexpected postop adverse effects except for the development of an outer right superior quadrantanopsia at 1 year post-SRS in patient 2. **Conclusions:** Preliminary results suggest that (a) 15 Gy SRS to the MTL corresponding to proposed cATL is adequate to produce seizure remission without significant adverse effects on cognitive function; (b) radiation-induced changes noted on MRI may herald seizure remission following SRS; (c) and further reduction of MRS NAA/Cr+Cho ratio may be a marker of seizure remission.

H.07

BASAL GLUTAMATE, γ-AMINOBUTYRIC ACID, GLUCOSE, AND LACTATE LEVELS IN THE EPILEPTOGENIC AND NONEPILEPTOGENIC BRAIN SITES IN NEUROSURGERY PATIENTS

Idil Cavus, Walid M. Abi-Saab, Michael Cassadey, Ralph Jackob, Robert S. Sherwin, John Krystal, and Dennis D. Spencer (Psychiatry, Yale University, New Haven, CT; Research and Development, Pfizer, Groton, CT; Medicine, Yale University, New Haven, CT; Neurosurgery, Yale University, New Haven, CT)

Rationale: The basal glutamate, γ-aminobutyric acid (GABA), glucose, and lactate levels in the epileptogenic and nonepileptogenic brain sites of patients with seizure disorder were compared using in vivo microdialysis to study the role of the major neurotransmitters and energy metabolytes in seizures. **Methods:** Patients with medically intractable seizure disorder undergoing presurgical evaluation to identify their seizure focus were implanted with microdialysis cathaters in the presumptive seizure focus and surrounding brain areas. The extracellular fluid (ECF) was sampled 5–60 h before any seizure activity. The basal glutamate, GABA, lactate, and glucose levels were measured using the zero-flow microdialysis technique and HPLC. Data from the epileptogenic area (identified with intracranial EEG obtained during spontaneous seizures) and the nonepileptogenic (quiet or propagated) brain areas were compared. **Results:** Twenty-seven patients with intractable seizure disorder were studied. Total of 16 microdialysis catheters were localized to the epileptogenic brain areas (hippocampus, eight; temporal lobe tumor, three; cingulate, three; motor cortex, two; frontoorbital cortex, one) and 24 catheters were in the nonepileptogenic sites (hippocampus, 13; Heschel gyrus, two; parietal cortex, two; amygdala, one; cingulate, four; frontoorbital cortex, one; and the insula, one). Basal ECF glutamate levels were markedly elevated in the epileptogenic brain sites versus the nonepileptogenic brain sites (15 $\mu M \pm$ 3.8 vs. 2.9 $\mu M \pm 0.3$, $p = 0.0003$). Eleven patients had one probe within the epileptogenic area and another in an unaffected area allowing for within-subject comparison. The basal glutamate level was consistently elevated within the epileptogenic sites in all 11 patients (11.8 $\mu M \pm 3.1$ vs. 2.9 $\mu M \pm 0.6$, $p = 0.008$). The basal glutamate levels in the nonepileptogenic areas were within the range of previously reported normal ECF levels. However, the ECF glutamate in the epileptogenic focus was at a neurotoxic range. Basal GABA, glucose, and lactate levels were measured in the same 11 patients. Lactate levels were also significantly elevated within the epileptogenic sites (6.5 ± 0.6 m*M* vs. 5.1 ± 0.4 m*M,* $n = 11$, $p = 0.02$). No significant difference was detected for GABA (epileptogenic 174.5 ± 39.3 n*M* vs. non- 119.03 ± 20.7 n*M,* $p = 0.17$) or glucose (2.03± 0.5 m*M* vs. 1.8 ± 0.3 m*M,* $p = 0.5$) levels. **Conclusions:** The epileptogenic brain areas were characterized with markedly elevated interictal basal ECF glutamate level within the neurotoxic range. The higher ECF glutamate levels suggest an increased glutamate release and/or inadequate glutamate uptake within the epileptogenic focus. Glutamate uptake is coupled to glucose and lactate metabolism. Glucose, being readily supplied by the bloodstream, was not depleted under basal conditions. The significant lactate increase may reflect an increased aerobic glycolysis to meet the energy demands of the elevated glutamate uptake. Our present finding of unchanged ECF GABA levels together with the previous reports of decreased total GABA are suggestive of decreased intracellular GABA levels in the epileptogenic areas. (Supported by NIH-PO1 NS39092-01 and BIRCWH 1K12DA14038-01 for I.Cavus.)

H.08

THE UTILITY OF FLUMAZENIL POSITRON EMISSION TOMOGRAPHY IN THE PRESURGICAL EVALUATION OF EXTRATEMPORAL VERSUS MESIAL TEMPORAL LOBE EPILEPSY

Lawrence N. Eisenman, Yonglin Pu, Mark A. Mintun, Nisha Vermani, Frank G. Gilliam, Hrayr P. Attarian, A. James Fessler, N. Edwin Trevathan, and Jeffrey G. Ojemann (Department of Neurology, Washington University; Mallinckrodt Institute of Radiology, Washington University; Department of Neurology, Washington University Medical School, St. Louis, MO)

Rationale: The purpose of this study was to explore the potential utility of flumazenil positron emission tomography (FMZ-PET) in the surgical evaluation of extratemporal or neocortical temporal epilepsy versus mesial temporal epilepsy patients using intracranial monitoring as the gold standard for localization of the epileptogenic zone. At the end of this activity, the participants should be able to discuss the use of FMZ-PET in the presurgical evaluation of epilepsy patients. **Methods:** Only patients who were already scheduled for (or previously underwent) intracranial monitoring were included in this study. Sixty-minute dynamic FMZ-PET images were acquired in all patients using a Siemens (Iselin, NJ) CTI ECAT EXACT HR tomograph after injection of 20–30 mCi of [^{11}C]flumazenil. Decisions for placement of intracranial EEG recording electrodes and any subsequent surgical resection ($n = 3$) were blinded to FMZ-PET results. 3-D gradient-echo high-resolution MRI of whole brain was also acquired for anatomic coregistration of FMZ-PET images. A summed FMZ-PET image using the data 16–60 min after injection was used for visual evaluation of focal areas of decreased FMZ uptake and measurement of an asymmetry index of FMZ binding between the area of decreased binding and the mirror area of the normal contralateral side. FMZ-PET interpretation was blinded to all clinical and electrical data. This research was performed under a protocol approved by the Washington University Institutional Review Board with informed consent from all subjects. **Results:** Eight patients were studied, four with mesial temporal epilespy and four with neocortical epilepsy. Clear, focal decreased FMZ binding was detected three of the four of the neocortical patients, and the fourth may have had some subtle decrease. These were located in the right frontal lobe, right posterior temporal lobe, and the right parietal and temporal lobes. The asymmetry indices were 46%, 21%, and 85%, respectively. In these three patients, the locations of the abnormal binding of FMZ corresponded to the focus of epileptogenicity found by intracranial EEG recordings. In the fourth patient; there were multiple epileptogenic zones within the region of subtly decreased flumazenil binding. Three of these four patients had normal MRI. Three had surgical resection, including two with normal MRI, with pathologic diagnosis of microdysgenesis in white matter, cortical gliosis, and neuronal dysplastic/dysmorphic changes in subcortical white matter, respectively. Intracranial monitoring revealed bitemporal onset of seizures in the remaining four patients. No localized abnormal FMZ binding was detected although a subtle bitemporal decrease could not be excluded in all four patients. **Conclusions:** In this small sample, FMZ-PET appears be able to localize the focus of epileptogenicity in patients with intractable neocortical epilepsy. FMZ-PET may have a role in surgical planning of patients with inconsistent results in MRI, FDG-PET, and extracranial EEG recordings. [Supported by the Charles A. Dana Foundation with additional support from NIH Training grant NS07205-20 (L.N.E.) and NINDS grant NS41272 (J.G.O.).]

December 11, 2002
Plenary Session 2: Neuroimmunology and Epilepsy
8:30 a.m.–11:00 a.m.

PL2.01
NEUROINFLAMMATION AS A MEDIATOR OF TISSUE INJURY AND REPAIR
Jack P. Antel (Neurology and Neurosurgery, McGill University, Montreal, QC, Canada)

Although regarded as a site of relative immune privilege, a central nervous system (CNS)-directed immune response can be initiated by cellular and humeral components of the adaptive immune system that have been activated by exposure to neural antigens or their molecular mimics in the systemic compartment (e.g., acute disseminated encephalomyelitis). Inflammatory responses in the CNS are now also recognized in concert with neuronal degenerative, ischemic, and traumatic disorders. These responses are likely initiated by constituents of the innate immune system (microglia, macrophages) that can detect injury or death of neural cells. Entry and persistence of a cellular immune response in the CNS are dependent on molecular interactions between the cells of the immune system and resident cells of the CNS. Passage of cells across the blood–brain barrier requires specific ligand-dependent adhesion to endothelial cells (ECs) with subsequent migration being directed by chemoattractants produced by resident cells (ECs, microglia, astrocytes). Having entered the CNS, lymphocytes will persist on interaction with antigen-presenting cells (APCs) that can deliver both signal 1 [antigen within the major histocompatibility complex (MHC) molecule groove] and signal 2 (costimulatory molecules, CD40; CD80/86). Microglia rather than astrocytes are the competent resident APCs within the CNS; their function is enhanced as the cells are activated. The presence of inflammation within the CNS can contribute both to tissue injury and repair. With regard to immune-mediated injury, autoreactive CD4 T cells are required to initiate the animal disorder experimental autoimmune encephalomyelitis (EAE). The actual tissue injury may, however, be mediated by a wide array of cells (T and B lymphocytes, monocytes) using a wide array of effector molecules including cytokines, proteases, and reactive oxygen species. Many of these soluble molecules can also be produced by the resident cells of the CNS. Selectivity of neural targets to such injury can reflect the properties of either the effector mediators (e.g., specific cytotoxic T cells, antibodies) or the target (e.g., expression of specific receptors or cell type–specific intracellular signaling pathways). With regard to tissue repair, the inflammatory response may be crucial for removing dead and damages tissue, allowing remodeling to proceed. Glial cells can serve to remove putative neurotoxins such as glutamate. Immune cells are potential sources of "trophic factors" required for recruitment and/or differentiation of progenitor cells. The presence and functional properties of an inflammatory response within the CNS reflect the dynamic interactions that occur between the cells and products of the immune system and the resident cells of the CNS. Potentially this dynamic interaction can serve as a target for therapeutic intervention.

December 11, 2002
Poster Session 3
11:00 a.m.–1:00 p.m.

Nonhuman Mechanism Studies

3.001
STATUS EPILEPTICUS IS NECESSARY BUT NOT SUFFICIENT TO REGULATE EPILEPTOGENESIS AND AXON GUIDANCE GENE EXPRESSION IN MOUSE HIPPOCAMPUS AFTER KAINIC ACID STATUS EPILEPTICUS
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Rationale: Synaptic reorganization after neural injury may form the basis of recurrent excitatory networks. Axon guidance cues including the semaphorins (sema) provide targeting information to axons along predetermined pathways during development. It is unclear which of these axon guidance cues participates in the formation of adaptive and maladaptive circuitry after neural injury. Class III sema ligands that bind to neuropilin 2 (NPN2)-containing sema receptors are selectively downregulated in CA1 pyramidal cells of hippocampus in mature rat brain during the epoch of synaptic reorganization after kainic acid (KA) status epilepticus (SE). This suggested the hypothesis that loss of the tonic activation of NPN2-containing sema receptors may lead to axonal sprouting from CA1 pryamidal cells and thereby promote epileptogenesis. To further investigate this hypothesis, we have studied of genetically defined strains of mice, which may lead to innovative approaches to the understanding of the molecular basis of synaptic organization and epileptogenesis. **Methods:** FVB/N mice but not C57Bl/6 mice have KA-induced cell death of CA3/hilar regions and synaptic reorganization (mossy fiber sprouting) despite equivalent behavioral seizures and comparable metabolic activation of hippocampal neurons (Schauwecker et al. *Exp Neurol* 2000). Using serial videotape recording sessions (60 h and 6 months after KA-SE), we determined rates of epileptogenesis (epilepsy defined as two or more observed seizures) in these strains after KA-SE. To determine whether axon-guidance gene expression is altered after KA-SE, in situ hybridization, immunoblot analysis, and immunocytochemistry of the semaphorin ligands and receptors (neuropilins) were performed in mouse hippocampus. **Results:** Despite equivalent duration (FVB: 198 min vs. C57Bl/6: 191 min) and severity (average seizure class: IV) of KA-SE, death of CA3b neurons was evident in FVB but not C57Bl/6 mice (FVB: 150 ± 15 cells/μm^2 vs. 85 ± 17 cells/μm^2; C57Bl/6 160 ± 25 cells/μm^2 vs. 167 ± 22 cells/μm^2) without any detectable CA1 pyramidal cell loss 7 days after KA-SE. Five of nine FVB mice (55 %) were observed to have a chronic epilepsy starting 4–8 weeks after KA-SE, whereas no C57Bl/6 mice ($n = 9$) so far have had any recorded spontaneous behavioral seizures. In concert with this finding, Sema 3F, NPN2, and NPN1 protein/mRNA content were decreased an average of 75% ($p < 0.001$) in CA1 neurons of FVB but not C57Bl/6 mice 7 days after KA-SE. In contrast, sema 3A, sema 3C, and sema 4C mRNA content were unaltered in all hippocampal subregions after KA-SE regardless of the strain. **Conclusions:** These data demonstrate that SE is necessary but not sufficient to regulate epileptogenesis and selected axon-guidance genes in mouse brain after KA-SE. Transcriptional regulatory complexes unique to the hippocampal neurons of the FVB/N mouse but not the C57Bl/6 mouse strain may underlie [define] its susceptibility to KA-SE–induced neural injury and subsequent generation of epileptic circuitry. (Supported by NINDS, AES, and Exelixis Pharmaceuticals.)

3.002
INFOLDINGS IN THE GRANULE CELL LAYER OF THE RAT DENTATE GYRUS AFTER STATUS EPILEPTICUS AND CHRONIC SEIZURES: A RESULT OF INCREASED NEUROGENESIS?
Russell E. Berger, Anne L. Sollas, Jeffrey H. Goodman, and Helen E. Scharfman (Center for Neural Recovery & Rehabilitation Research, Helen Hayes Hospital, West Haverstraw, NY; Pharmacology & Neurology, Columbia University, New York, NY)

Rationale: It has been shown that seizures increase neurogenesis of granule cells in the dentate gyrus. If the survival of new granule cells exceeds their death, one would expect that the granule cell layer would increase in size. To test this hypothesis, the dentate gyrus was evaluated morphologically in animal models of epilepsy. At the end of this activity the participants should understand changes that accompany sei-

zures in the rat dentate gyrus. **Methods:** Adult male Sprague–Dawley rats were injected with pilocarpine or kainic acid i.p., followed by diazepam (DZP) after 1 h of status epilepticus. Controls received identical treatment, except they received saline instead of a convulsant. Other rats were amygdala-kindled (≤50 kindled seizures) and perfused after the last kindled seizure. Immunocytochemistry was performed 1–10 months after status using antisera to calbindin D28K, a marker of granule cells, NeuN, a marker of adult neurons, and neuropeptide Y, a peptide expressed in γ-aminobutyric acid (GABA)ergic neurons, and in granule cells after seizures. Timm stain was used to examine sprouting. In some pilocarpine-treated rats, bromodeoxyuridine (BrdU) was injected (50 mg/kg i.p., once/day, on days 4–9 after status). Neurons born after seizures were visualized using antisera to BrdU and NeuN. **Results:** In the posterior half of the hippocampus, all pilocarpine- or kainic acid–treated animals (n = 35) showed infoldings. The folds were similar to gyri of the primate neocortex, but less extensive. These "microgyri" were mostly in the ventral blade. There was little evidence of changes in the width of the cell layer, extent of mossy fiber sprouting, or NPY staining along a microgyrus. There often were clusters of calbindin-immunoreactive neurons near infoldings, presumably ectopic granule cells born after seizures. BrdU-labeled granule cells were common in the microgyrus. Similar invaginations were obtained after amygdala kindling. In saline controls (n = 12), there was little sign of invaginations except in four animals, where small folds were present in the ventral blade at extreme posterior levels of the hippocampus. **Conclusions:** The results suggest that the granule cell layer of epileptic rats undergoes dramatic changes after repetitive seizures. In addition to the previously described reports of granule cell dispersion and increased neurogenesis, the granule cell layer appears to develop folds in the ventral blade. Like adult neurogenesis, the infoldings after seizures appear to reflect an increase in a phenomenon that is present at a low level normally. The observation of robust BrdU labeling along infoldings, previous reports that neurogenesis is greater in the ventral blade, and spatial association of calbindin-immunoreative granule-like hilar cells with the infoldings, raise the possibility that the invaginations develop as a result of increased numbers of granule cells that are born after seizures. This is analogous to the argument that neocortical gyri developed in primates because the number of neurons increased disproportionally to the increase in skull size. The corollary to this hypothesis is that seizure-induced neurogenesis is greater than seizure-related granule cell death, as least in some animal models of epilepsy. (Supported by NS 38285 and the Human Frontiers Science Program to H.E.S.) (Disclosure: Grant: Contract with Neuropace Inc.)

3.003
FAST RIPPLE RATE INDICATES THE SEVERITY OF EPILEPSY: COMPARISON OF TWO CHRONIC EPILEPSY MODELS

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Rationale: To investigate the relationship between severity of status epilepticus and severity of chronic epilepsy in two rat models. **Methods:** Self-sustained status epilepticus (SSSE) and kainic acid status (KASE) models of chronic epilepsy were compared in the following ways: severity of initial SE, characteristics of high-frequency oscillations (ripple and fast ripples), serum neuron-specific enolase (sNSE) assay during interictal period, and severity of chronic, recurrent spontaneous seizures. **Results:** The pattern of electrical activity during SE was similar in both models of epilepsy; however, the rate of seizures was higher during SSSE, and SE itself was longer. The level of sNSE after SSSE was significantly (35%) higher than after KASE, reflecting greater neuronal injury. There were no significant differences in the percentage of rats developing spontaneous seizures after SE; however, the mean rate of seizures per month in the SSSE group was 121 ± 13, and in the KASE group, 4.2 ± 2.7. The rate of EEG interictal spikes was significantly higher in the SSSE group as well as the rate of occurrence of high-frequency oscillations [Ripples and Fast Ripples (FRs)]. There was no difference in the amplitude distribution of high-frequency oscillations between the two models of epilepsy. In the KA group, Ripple oscillations were recorded bilaterally while FRs were found only in the dentate gyrus (DG) and entorhinal cortex (EC) ipsilateral to KA injection. In the SSSE group, both Ripples and FRs were found to be generated bilaterally in the DG and EC. In both models of epilepsy, FR oscillations were recorded at seizure onset. **Conclusions:** The severity of SE determines the severity of the epileptic seizures. The rate of occurrence and bilateral distribution of FRs within hippocampal–entorhinal circuitry correlates with the severity of epilepsy. (Supported by NIH grants NS02808, NS33310, NS11315, and NS01792.)

3.004
INTRINSIC OPTICAL SIGNALING REVEALS CHARACTERISTIC PATTERN OF PROPAGATION OF THE EPILEPTIFORM ACTIVITY WITHIN THE LYMBIC SYSTEM IN PILOCARPINE-TREATED EPILEPTIC RATS

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Rationale: The pilocarpine-treated rat is an excellent model system for mesial temporal lobe epilepsy (MTLE). In both situations, neuronal damage occurs in the CA3, dentate hilus, and entorhinal cortex (EC) layer III. Moreover, axonal sprouting and synaptic rearrangement have been described in limbic structures both in pilocarpine-treated animals and in MTLE. Hence, changes in limbic neuronal network function may take place in both conditions. We tested this hypothesis by using intrinsic optical signal (IOS) recordings along with histopathologic scoring. **Methods:** Infrared-darkfield video-microscopy techniques were employed in submerged hippocampus–EC slices obtained from rats injected with pilocarpine 16–23 days earlier and from age-matched controls. Averaged darkfield images after electrical stimuli were taken through an infrared videocamera, digitized, stored, and subtracted in real time. Slices were then stained for histopathologic scoring. **Results:** In pilocarpine-treated rat slices (n = 14), single-pulse electrical stimuli delivered in the medial EC induced changes in IOS that initiated close to the stimulation site and spread to the lateral EC and to the hippocampus. In addition, early changes in IOSs occurred in the CA1/subiculum area (which was presumably activated via the temporoammonic path). In contrast, in control rat slices (n = 10), only repetitive stimulation of the EC deep layers induced appreciable IOS changes that propagated to the hippocampus, reaching the dentate gyrus and later CA3/CA1. Histologic analysis showed damage in the dentate hilus of pilocarpine-treated rats, where almost all mossy cells disappeared and in CA3, where the lesion consisted of a 40–60% decrease in cell count. **Conclusions:** Our findings demonstrate an increase in excitability of the limbic system in pilocarpine-treated rats as well as that circuit reorganization may switch EC outputs from the classic trisynaptic modality to the monosynaptic temporoammonic path. These changes may sustain the epileptic activity seen in vivo in pilocarpine-treated rats, and perhaps in MTLE patients. (Supported by Canadian Institutes of Health Research and Savoy Foundation.)

3.005
INCREASED EXPRESSION OF BRAIN-DERIVED NEUROTROPHIC FACTOR INDUCES FORMATION OF BASAL DENDRITES AND AXONAL BRANCHING IN DENTATE GRANULE CELLS IN HIPPOCAMPAL EXPLANT CULTURES

Steve C. Danzer, Kristy R.C. Crooks, Donald C. Lo, and James O. McNamara, (Department of Medicine (Neurology), Duke University, Durham, NC; Department of Neurobiology, Duke University, Durham, NC; Department of Pharmacology, Duke University, Durham, NC; Department of Molecular Cancer Biology, Duke University, Durham, NC)

Rationale: During limbic epileptogenesis in vivo, the dentate granule cells (DGCs) exhibit increased expression of brain-derived neurotrophic factor (BDNF) followed by striking morphologic plasticities: formation of basal dendrites and sprouting of mossy fibers. These morphologic plasticities may underlie epileptogenesis. Since BDNF and its cognate receptor TrkB exert powerful morphoregulatory effects on diverse types of neurons, we hypothesized that increased expression of BDNF intrinsic to DGCs is sufficient to induce these plasticities. By assessing the role played by BDNF in inducing mossy fiber sprouting and basal dendrite formation, we hope to gain insight into the development of epilepsy in patient populations and to elucidate potential drug targets for therapeutic intervention. **Methods:** DGCs in hippocampal slice cultures made from P10 rat pups were transfected with BDNF + green fluorescent protein (GFP), nerve growth factor (NGF) + GFP, or GFP + empty vector control using particle-mediated gene transfer. All procedures conformed to NIH and Institutional guidelines for the care and use of animals. NGF served as a negative control as DGCs do not express the NGF recptor TrkA. Twenty-four hours after transfection, the slice cultures were fixed in paraformaldehyde, and neuronal processes were visualized using a Biorad MRC 600 confocal microscope. Confocal images were reconstructed using the Neurolucida system, and multiple neuronal parameters were assessed, including dendritic and axonal branch number and dendritic length. **Results:** Transfection with BDNF produced significant increases in axonal branch and basal dendrite number relative to NGF or empty vector controls. BDNF transfection also increased basal dendrite length. Increases in axonal and dendritic branch number were restricted to a region within 50 μm of the soma. Significantly, structural changes were prevented by the tyrosine kinase inhibitor, K252a, indicating that the BDNF effects are likely mediated by the BDNF receptor, TrkB. **Conclusions:** Repeated and/or prolonged focal hippocampal seizures promote limbic epileptogenesis, the process by which a normal brain becomes epileptic. The cascade of gene expression activated by focal hippocampal seizures includes marked increases of BDNF content in multiple neuronal populations including the DGCs. Pharmacologic and genetic interventions implicate a causal role for BDNF in epileptogenesis. Here we show that increasing expression of BDNF in DGCs is sufficient to induce the formation of basal dendrites and axonal sprouting. In conclusion, these morphologic consequences of increased BDNF expression may underlie the recurrent excitatory synapses demonstrated among DGCs in epileptic animals and thus may constitute one mechanism by which seizure-induced BDNF expression promotes limbic epileptogenesis. (Supported by NIH grants NS07370, NS32334, and NINDS grant NS17771. S.C.D. was supported by an NIH NRSA grant and the PhRMA Foundation.)

3.006
INJURING NEURONS INDUCES NEURONAL DIFFERENTIATION IN A POPULATION OF HIPPOCAMPAL PRECURSOR CELLS IN CULTURE

Marc A. Dichter, Henry C. Tseng, Stephen J. Rueegg, Margaret Maronski, and Judith B. Grinspan (Neurology and David Mahoney Institute of Neurological Sciences, University of Pennsylvania, Philadelphia, PA; Research Neurology, Children's Hospital of Philadelphia, Philadelphia, PA)

Rationale: Multipotent hippocampal precursor cells (HPCs) were identified in hippocampal cell cultures, but traditional neuronal differentiation factors were unable to induce differentiation into cells with neuronal phenotype. We attempted to determine if neuronal differentiation could be induced by injuring nearby mature neurons in the cultures. **Methods:** Cultures of dissociated rat hippocampal neurons were grown in serum-free conditions in the presence of platelet-derived growth factor-β. After 3 weeks, the cultures were first exposed to bromodeoxyuridine (BrdU) for 48 h and then were treated with excitotoxic concentrations of glutamate or *N*-methyl-D-aspartate (NMDA). Cultures were also treated with supernatants from injured cultures or with cell lysates from sonicated cultures [conditioned medium (CM) experiments]. Treated cultures were then allowed to survive for 48–96 h, and remaining cells were double stained for BrdU and neuronal markers (MAP2, TUJ1, neurofilament, GluR2/3). Small cells with neuronal appearance were also recorded with patch-clamp electrodes. **Results:** Within hours of neuronal injury or treatment with CM containing some unknown factor ("factor X"), HPCs began to extend processes and became positive for the neuronal marker MAP2. Over the next 48 h, staining intensified and processes became longer. Treated HPCs also stained for neurofilament, TUJ1, and GluR2/3. Patch-clamp recordings of the HPCs before differentiation revealed very small, glial-like sodium currents and larger potassium currents. After excitotoxic injury to the cultures or treatment with factor X, the differentiating HPCs exhibited larger sodium currents, and some also developed spontaneous synaptic potentials, indicating connections with nearby neurons. **Conclusions:** Injured or dying neurons can release a factor that promotes the differentiation of multipotent precursor cells into cells with neuronal phenotype. This may be related to the neoneuronogenesis seen in adult hippocampus after status epilepticus. The identification of factor X remains to be determined, as does the mechanism by which it induces neuronal differentiation. At the end of this activity, participants will appreciate a new mechanism for inducing neuronal differentiation in hippocampal progenitor cells that may play a role in epileptogenesis. (Supported by NS 24260.)

3.007
REGULATION OF MAJOR HISTOCOMPATIBILITY COMPLEX mRNA EXPRESSION IN THE DENTATE GYRUS DURING EPILEPTOGENESIS

Robert C. Elliott, Fulvio A. Scorza, and Daniel H. Lowenstein (Program in Brain Plasticity and Epilepsy, Harvard Medical School and Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA)

Rationale: Major histocompatibility complex (MHC) molecules are cell-surface glycoproteins that play an important role in the vertebrate immune system by presenting foreign antigens to T lymphocytes. These molecules have been detected in diverse neuronal populations in rodents, including neurons in the hippocampal formation, and have been shown to be potentially involved in brain plasticity (Corriveau et al. *Neuron* 1998;21:505–20; Huh et al. *Science* 2000;290:2155–9). Previous DNA microarray analysis in our laboratory of rat dentate gyrus gene expression found evidence for regulation of multiple MHC mRNAs during epileptogenesis. The objective of this study is to investigate further the possible involvement of MHC molecules in epilepsy-associated network reorganization. To do so, we have characterized the spatial and temporal patterns of MHC expression in the rat dentate gyrus following pilocarpine-induced SE. **Methods:** Adult male Sprague–Dawley rats (180–200 g) were given i.p. atropine methylbromide followed 20 min later by pilocarpine hydrochloride to induce status epilepticus (SE). Seizure activity was monitored behaviorally and terminated with diazepam (DZP) after 2 h of convulsive SE. Control rats received saline instead of pilocarpine. Animals were killed 3, 7, 14, and 28 days later, and perfusion-fixed brains were processed for nonradioactive in situ hybridization analysis of rat MHC class I and class II mRNAs. Digoxygenin-labeled in situ probes were transcribed from DNA templates generated by polymerase chain reaction (PCR) from neonatal or adult rat hippocampal cDNA libraries. **Results:** Our results show that mRNAs coding for MHC class I and class II molecules are differentially regulated during epileptogenesis. At 14 days after SE, MHC class I RT1.Aa and MHC class I RT1-RT44 were markedly increased when compared with saline-treated control animals, with scattered expression throughout the hippocampus and the highest increase in the dentate gyrus. In contrast, expression of MHC class II RT1.B-1 was downregulated throughout the dentate gyrus and pyramidal cell layers. More extensive in situ analysis of MHC class I RT1.Aa and MHC class II RT1.B-1 mRNAs indicated that these molecules are regulated over different time courses. Expression of MHC class I RT1.Aa peaks at 7–14 days after SE, and then returns to basal levels over the next 2 weeks, whereas MHC class II RT1.B-1 expression declines slowly following SE and remains decreased at 28 days after SE. **Conclusions:** The class I and class II families of MHC molecules consist of ≥20–30 related proteins with similar yet distinct functions in the immune system. Our results suggest that the various members are differentially regulated following SE, with particularly

marked differences in expression between class I and class II molecules. These findings support and extend previous evidence that MHC molecules are expressed in areas of ongoing neural plasticity and raise the possibility of a potential role for MHC molecules in mediating SE-induced network reorganization. [Supported by NIH RO1NS39950 and FAPESP (Brazil).]

3.008
MECHANISMS UNDERLYING SUPPRESSION OF NEUROGENESIS IN DEVELOPMENTAL EPILEPSY

Linda K. Friedman, Hongguang Liu, and Jaspreet Kaur (Department of Neuroscience, Seton Hall University/NJ Neuroscience Institute, South Orange, NJ)

Rationale: Dentate granule cell neurogenesis is stimulated by seizures in adult rats, but decreased in young pups. Corticosteroid (CORT) plasma levels increase significantly on postnatal (P) day 14 and again on P21, ages associated with a natural decline in neurogenesis. We hypothesized that elevated CORT plasma levels could be induced and sustained by perinatal seizures during the hyporesponsive period and contribute to inhibition of neurogenesis. **Methods:** Status epilepticus was induced with kainate (KA) once, twice, or three times at postnatal ages (P6, P9, P13, or P20, or P30) and rats were killed 48 h after the last seizure. Glucocorticosteroid levels were measured with radioimmunoassay (RIA). Neurogenesis was assessed by single and double labeling with bromodeoxyuridine (BrdU) immunohistochemistry. Electrographic activity (EEG) was recorded at P13, P20, and P30 in the presence and absence of a history of perinatal seizures induced by KA. **Results:** In control P6 animals, basal CORT levels were low (0.06 ± 0.1 mg/dl), increased steadily, and then rose sharply between P20 and P22 (4.07 ± 0.6 to 16.1 ± 0.46 mg/dl). At least three episodes of sustained status epilepticus within the first 13 days of postnatal life were required to suppress granule cell neurogenesis. Suppression was not due to cell death as chromatin stains only showed increased basophilia of inner cells lining the granule cell layers, in the absence of eosinophilia, argyrophilia, or TUNEL labeling. The EEG also showed no relationship between neurogenesis and duration of high-synchronous ictal activity at the postnatal ages examined. In contrast, endocrine studies showed sustained increases at 1 h after status epilepticus in circulating CORT levels following 1× KA on P6 (0.7± 0.1 to 2.40 ± 0.86 μg/dl) or 2× KA on P6 and P9 (10 ± 0.77 μg/dl). Following 3× KA on P6, P9, and P13 or P20, cumulative increases exceeded 10 μg/dl, and these were sustained even after 4–8 h. **Conclusions:** Perinatal seizures inhibit neurogenesis if (a) a certain number of seizures are first initiated during active phases of granule cell proliferation and migration, and (b) a minimal level of circulating plasma CORT is reached and sustained. It is proposed that control of dentate granule cell neurogenesis with early intervention by regulation of postictal CORT levels with CORT suppression may help prevent deleterious side effects of seizures in young humans. (Supported by NIH-NS-38069.)

3.009
BRAIN-DERIVED NEUROTROPHIC FACTOR–INDUCED NEUROPLASTICITY IS CRITICAL IN THE OCCURRENCE OF ORGANIZED RECURRENT HIPPOCAMPAL SEIZURES IN KAINATE-INJECTED MICE: A CONSEQUENCE OF A CONTROL OF HIPPOCAMPAL HYPERACTIVITY?

Christophe Heinrich, Yves Larmet, Christian Marescaux, Fumio Suzuki, and Antoine Depaulis (Faculte de Medecine, INSERM U398, Strasbourg, France; Faculte de Medecine, EA 3433, Strasbourg, France; Department of Anatomy, Shiga University of Medical Science, Otsu, Japan)

Rationale: Previous studies have reported that intrahippocampal injection of kainic acid in adult mice results, after a latent period of 15 days, in recurrent hippocampal epileptic discharges associated with cell loss in CA1 and hilus and dispersion of dentate gyrus granular neurons. In this model of mesial temporal lobe epilepsy (MTLE), a lasting overexpression of brain-derived neurotrophic factor (BDNF) mRNA has been observed in dispersed granule cells. According to previous reports, this increase of BDNF could trigger epileptogenesis. However, other data suggest that the overexpression of BDNF may constitute an endogenous regulatory mechanism able to restrain hippocampal epileptogenesis. The aim of our study was to clarify the consequences of BDNF overexpression on hippocampal epileptogenesis in the kainate mouse model. Therefore, in the present study, we determined (a) the time-course of hippocampal expression of BDNF during epileptogenesis, (b) the consequences of a blockade of BDNF expression, and (c) the consequences of an infusion of recombinant BDNF on epileptogenesis and granule cell dispersion. **Methods:** Adult C57/Bl6 mice were stereotaxically injected with 1 nmol of kainate (50 nl) in the right dorsal hippocampus and implanted with a bipolar electrode at the injection site. Hippocampal BDNF protein levels were measured with an enzyme-linked immunosorbent assay (ELISA). Long-term intrahippocampal infusions of BDNF antisense oligodeoxynucleotides (ODN) (0.5 nmol/h) or recombinant BDNF (0.85 μg/h) were performed during 7 days with miniosmotic pumps. **Results:** BDNF protein levels were significantly increased in the injected hippocampus during the first 3 weeks after kainate injection with a maximum at 16 days, as compared to contralateral side. During this period, dentate gyrus thickness rapidly increased, and recurrent epileptic discharges progressively developed in the injected hippocampus. A 7-day infusion of BDNF antisense ODN in kainate-treated mice prevented the dispersion of granule cells, but not the cell losses, and only continuous spiking activity was observed, as compared to animals infused with mismatch ODN. When kainate-treated mice were infused with human recombinant BDNF, a similar pattern of hippocampal sclerosis and epileptic discharges was observed, as in kainate- and PBS-treated mice. **Conclusions:** Our data confirm the key role of BDNF overexpression in the enlargement of granule cells. Moreover, these results support the hypothesis that BDNF overexpression and granule cell dispersion could participate in the organization of the hippocampal kainate-induced hyperactivity into recurrent epileptic discharges. (Supported by INSERM.)

3.010
MORPHOLOGIC CHARACTERIZATION OF NEWBORN DENTATE GRANULE CELLS IN EPILEPTIC AND CONTROL RATS USING A RETROVIRAL VECTOR EXPRESSING GREEN FLUORESCENT PROTEIN

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Rationale: At the end of this activity participants should be able to discuss the morphologic characteristics of epileptic and control newborn dentate granule cells (DGCs). The birth of new neurons in the adult rat dentate gyrus occurs throughout life and is known to increase significantly in the period immediately following a seizure event. Little is known of the fate of these newly generated neurons in the epileptic brain, specifically how ongoing seizure activity may affect the development and subsequent morphology of these cells and how their presence may contribute to the chronic epileptic state. The purpose of the present study was to study the morphology of these cells several weeks following their birth in control and epileptic animals. **Methods:** Five days after pilocarpine-induced status epilepticus (n = 3) or sham treatment (n = 3), a retroviral vector carrying a GFP transgene was injected into the subgranular zone of the dentate gyrus. Animals were allowed to survive 3–5 weeks after injection before transcardial perfusion with a 4% paraformaldehyde solution. Brains were sectioned and coverslipped with an anti-fade mounting medium containing a DAPI counterstain. **Results:** GFP+ cells within the DGC layer were selected for analysis using confocal microscopy at ×400–600. By 3–5 weeks after injection, GFP+ cells within the granule layer appeared fully differentiated, with complex dendritic arbors, oval somata and visible axons. For the most part, GFP+ DGCs appeared similar between control and epileptic rats. Distinguishing the two groups, however, was the observation that 27% (four of 15) of GFP+ cells in epileptic rats exhibited a

clear basal dendrite extending into the hilus. No GFP+ cells from control rats were observed to have this profile (none of 15). **Conclusions:** Observations of hilar basal dendrites are consistent with previous reports demonstrating the presence of this morphology in 5–12% of DGCs of epileptic rats (Ribak et al. *JCN* 2000;428:240; Buckmaster and Dudek. *J Neurophysiol* 1999;81:712). This phenotype could enhance recurrent excitation within the hippocampus and may contribute to the hyperexcitable state present in epileptic animals. However, given that newborn cells comprise only a small subset of the total population of DGCs, and the relatively low percentage of basal dendrites we found in GFP+ cells, it is unlikely newly generated neurons were the sole source of basal dendrites found in the DGCs of epileptic rats reported in previous studies. (Supported by NIH-NINDS grants NS-32403 and NS-38572 to D.A.C. NIH-R01-NS-39950 to D.H.L.)

3.011

EARLY-LIFE KAINATE SEIZURES INDUCE ECTOPIC GROWTH OF MOSSY FIBERS IN THE STRATUM ORIENS OF HIPPOCAMPAL AREA CA3

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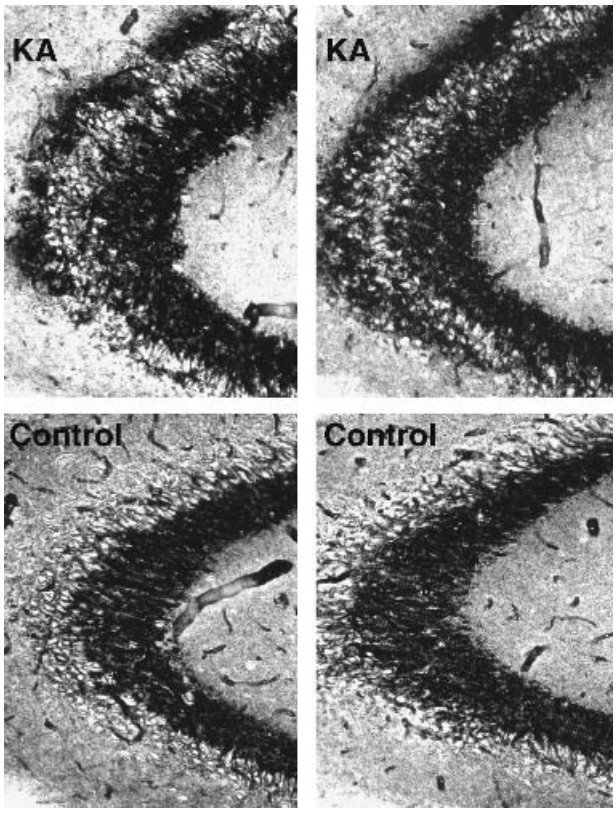
Rationale: Early-life seizures permanently decrease seizure threshold and increase the susceptiblity to seizure-induced cell death in adulthood. Even a single seizure in early life can cause long-lasting functional alterations in network circuitry despite the absence of acute neuronal injury. To determine anatomic correlates of this functional alteration, we subjected postnatal day (P) 15 rat pups to a single kainate (KA)-induced seizure and evaluated dentate granule cell mossy fiber sprouting by Timm stain at P30. **Methods:** Long–Evans male rats were injected with KA (3 mg/kg, i.p.) or saline at P15 and killed by transcardiac perfusion at P30. We prepared 40-μm coronal sections, 160 μm apart, spanning dorsal hippocampus between 2.8 and 3.8 mm ventral to bregma and processed the sections for Timm staining. Timm scores (0–5) were assigned to six hippocampal CA3 fields from three sections per brain and averaged for statistical analysis using Student's *t* test.



Results: At P15, KA induced status epilepticus lasting for 30–60 min in all rats. Evaluation of Timm staining at P30 showed a continuous dense laminar band of granules in the stratum oriens along the entire CA3 region in eight of 10 animals with prior exposure to KA at P15. In P30 control littermate rats, Timm-stainied granules in the stratum oriens were limited to the septal end of dorsal hippocampus ($n = 8$). No supragranular mossy fiber sprouting in the molecular layer of dentate gyrus was seen at P30 after kainate status at P15. The mean Timm score was significantly higher in the kainate-treated rats (4.1 ± 0.7) compared to controls (1.1 ± 0.9, $p < 0.0001$; Fig. 1). **Conclusions:** Early-life KA seizures at P15, without causing overt cellular injury, induce mossy fiber sprouting and aberrant innervation of basal dendrites of CA3 pyramidal neurons in the stratum oriens. Recurrent seizures in early life have been shown to cause mossy fiber sprouting in the CA3 pyramidal cell layer (Holmes et al. *Ann Neurol* 1998;44:845–57) as well as spine loss in apical dendrites of CA3 pyramidal neurons, possibly due to pruning and partial deafferentation induced by recurring seizures (Swann et al. *Hippocampus* 2000;10:617–25). Here we show that even a single prolonged seizure is sufficient to cause abnormal afferent targeting during second week of life at the time of active granule cell proliferation and axonal outgrowth. Pathologic connectivity change induced by seizures in the immature brain may provide a structural basis for the priming effect of early-life seizures for later epilepsy and seizure-induced neuronal injury. (Supported by KO8NS02068, RO1NS27984, RO1NS31718, and NIH2P30HD18655.)

3.012

AN IN VITRO SLICE MODEL OF NEUROGENESIS IN NEONATAL RODENT BRAIN

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Rationale: The ability to follow the development of an adult stem cell through its maturation into a functional neuron has many potential experimental applications. Dissociated cell culture lacks the extracellular matrix and support present in the intact brain, while in vivo analysis of stem cells only allows end-stage examination of cell fate. In these experiments, we attempted to follow neurogenesis from cell division, through migration and differentiation in slice cultures from rat or mouse brain to determine the normal process of neurogenesis in the dentate gyrus of the hippocampus occurs in vitro. **Methods:** Organotypic hippocampal slices cultures were prepared from P6 Sprague–Dawley rat brain or from P1 C57Bl6 mouse brain, according to Stoppini's method (*J Neurosci Methods* 1991;37:173–82) and grown for 14 or 28 days before being used in the experiments. Slices cultures were pulsed with 0.5 m*M* bromodeoxyuridine (BrdU), and media was replaced after 24 h. Slices were fixed at 2 weeks or 4 weeks and processed for BrdU and multiple labels immunofluorescence. Primary antibodies were chosen that recognize immature and mature astrocytes (S-100b polypeptide), immature neurons (b-tubulin, TUJ1), mature neurons (neuronal nuclear antigen clone A60, NeuN, and high-molecular-weight neurofilament, NFH), mature astrocytes (glial fibrillary acidic protein, GFAP), mature oligodendrocytes (RIP), and immature/mature astrocytes and oligodendrocytes (adenomatous polyposis coli tumor-suppresser gene, APC). **Results:** Confocal imaging revealed a high number of BrdU-labeled neural and glial progenitor cells throughout the slice. At 1 week after BrdU, no cell that had undergone cell division expressed mature neuronal markers including NFH or NeuN. However, by 3 weeks after BrdU pulse, NeuN-labeled cells began to appear in the granule cell layer of the dentate, indicating neuronal differentiation. **Conclusions:** These results demonstrate that neurogenesis occurs in the dentate gyrus of organotypic hippocampal slice cultures. This in vitro model offers the ability to finely control and manipulate microenvironmental conditions critical to proliferation, differentiation, and survival of neurons. The slice culture preparation may be useful in examining mechanisms of induction and manipulation of neurogenesis in models of neurologic disorders such as epilepsy. (Supported by NIH IK24NS02128. P.J.H. and M.K.M. are supported by the

Glaucoma Research Foundation and the Steve and Mary Kirsch Foundation.)

3.013
ECTOPIC HILAR MIGRATION OF DENTATE GRANULE CELL PRECURSORS AFTER PILOCARPINE-INDUCED STATUS EPILEPTICUS

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Rationale: Proliferation of neuronal precursors persists in the adult mammalian hippocampal dentate gyrus. Newborn neurons populate the dentate granule cell (DGC) layer, and their birth increases after seizure activity in the adult rat. Newly generated granule neuron-like cells also appear ectopically in the hilus after chemoconvulsant-induced status epilepticus (SE). We sought to determine the origin and phenotype of the hilar ectopic neurons generated in the adult rat pilocarpine model of temporal lobe epilepsy. This activity should enable the participant to discuss basic mechanisms of temporal lobe epilepsy. **Methods:** Adult rats received systemic pilocarpine to induce SE for 2 h. Proliferating cells were labeled with bromodeoxyuridine (BrdU) 7 days after SE, and animals survived an additional 2 h or 2, 7, 14, or 28 days. Immunostaining of coronal brain sections was performed using antibodies to BrdU, the DGC marker Prox-1, calbindin, and the immature neuronal markers doublecortin (DCx), collapsin response mediator protein-4 (CRMP-4), and polysialylated neural cell adhesion molecule (PSA-NCAM). BrdU- and Prox-1-immunoreactive (IR) cells in the dentate hilus were quantified at 14 and 35 days after SE and in saline-treated controls. **Results:** The number of BrdU-IR cells in the dentate hilus increased markedly between 7 and 14 days after SE, and were still present after 35 days. Hilar BrdU-IR cell number was significantly greater 14 and 35 days following pilocarpine-induced SE compared to controls ($p < 0.01$). Few DCx- or Prox-1-IR cells were found in the dentate hilus of controls or at 7 days after SE. By 14 days after SE, many DCx- and Prox-IR cells appeared in the dentate hilus. DCx-IR decreased at 35 days after pilocarpine treatment, but many Prox-1-IR cells persisted in the hilus. No calbindin-IR hilar granule-like neurons were seen at any time in pilocarpine- or saline-treated rats. CRMP-4, PSA-NCAM, and DCx immunostaining showed chains of cells with migrating neuroblast morphology extending from the inner DGC layer to the hilus. **Conclusions:** These data confirm previous findings of hilar ectopic granule-like neuron generation after SE. Moreover, the hilar ectopic neurons appear to migrate from the DGC layer to the hilus and differentiate into DGCs, as evidenced by expression of a DGC-specific marker. Additional study of this process may provide insight into the mechanisms of neuronal precursor migration and differentiation after injury, and their potential role in epileptogenesis. [Supported by NINDS NS02006 (J.M.P.) and NS35628, NS39950 (D.H.L.).]

3.014
SURVIVAL OF NEWBORN DENTATE GRANULE NEURONS AFTER AN EPISODE OF STATUS EPILEPTICUS DURING DEVELOPMENT

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Rationale: Seizures alter the rate of dentate granule neuron (DGN) neurogenesis. After status epilepticus (SE), there is a dramatic increase in the rate of DGN neurogenesis. It is not known what the consequences of increased DGN neurogenesis are for the development of epilepsy and if these newborn DGN persist. Prior studies have described a 20-fold increase in the rate of DGN neurogenesis 7 days after a bout of pilocarpine-induced SE in 3-week-old rats. Here we study the survival of these newborn DGN over time. At the end of this activity, the participant should be able to discuss the survival of DGN born after SE. **Methods:** We have induced SE in postnatal day 20 rats with an injection of lithium–pilocarpine, and labeled DGNs undergoing cell division with bromodeoxyuridine (BrdU) a thymidine analog, 4, 6,and 8 days after SE. The animals were then killed 1 week later on P34, and the number of BrdU-labeled cells within the dentate was quantified per square micron of dentate. **Results:** There was a 2.6-fold increase in the number of BrdU-labeled DGNs in the SE-treated animals as compared to control littermates (Li-Pilo-2.25×10^{-4} BrdU neurons/μm^2 (SE, $\pm 5 \times 10^{-5}$); Li-Saline, -0.87×10^{-4} (SE, $\pm 3.3 \times 10^{-5}$); Naïve, 1.1×10^{-4} (SE, $\pm 3.5 \times 10^{-5}$). **Conclusions:** In P20 rats 1 week after Li-Pilo–induced SE, the rate of DGN neurogenesis has been reported to increase 20-fold (Sankar et al. *Epilepsia* 2000;41:53–6). When followed over time the number of DGN born 1 week after SE decreased to only a 2.6-fold increase over controls. The current study suggests that the majority of the DGN born 1 week after SE do not persist. Studies are under way to understand the mechanism by which newly born DGN are lost after SE. [Supported by (A.B.K.) Child Neurology Foundation, NINDS-RO1-NS38595; (B.E.P.) Dana Brown Epilepsy Fellowship, Epifellows, NINDS-NS 07413.]

3.015
A NOVEL SPECIES OF MULTIPOTENT HIPPOCAMPAL PRECURSOR CELLS DETECTED IN RAT DISSOCIATED HIPPOCAMPAL CULTURES

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Rationale: New neurons are generated in the adult mammalian hippocampus at low levels under baseline conditions and with increased frequency after status epilepticus. Little is known about the nature of the precursors responsible for neoneuronogenesis. We attempted to identify precursor cells in cultures of embryonic rat hippocampus that might give rise to the new neurons and/or other hippocampal cell types. **Methods:** Cultures of dissociated rat hippocampal neurons were grown in serum-free conditions in the presence of platelet-derived growth factor-β (PDGF-β). After 3 weeks, the cultures were exposed either to brain morphogenetic protein (BMP) to stimulate astrocytic differentiation, or triiodthyronine (T_3) to stimulate oligodendrocytic differentiation or brain-derived neurotrophic factor (BDNF), fibroblast growth factor (FGF), or retinoic acid (RA) to stimulate neuronal differentiation. **Results:** After 3 weeks of culture, a population of PDGF-responsive, small, dark, multipolar cells appeared in the cultures. Similar cells could be seen in much lower numbers, and later, in cultures not treated with PDGF-B. These hippocampal precursor cells (HPCs) did not stain for markers of mature oligodendrocytes (ODCs), astrocytes (ACs), or neurons, but were stained with markers of glial precursor cells (A2B5, PSA-NCAM, NG2). After exposure to BMP, ~30% of these HPCs differentiated into ACs. Similiarly, addition of T_3 to the culture media led to the differentiation into mature ODCs of ~30% of the HPCs. Exposure to BDNF, FGF, or RA (three agents that have previously been shown to induce neuronal differentiation in neuronal stem cells) did not induce the differentiation of these HPCs into neurons. However, subsequent studies revealed that injuring mature neurons in the culture induced neuronal differentiation in these cells, although neither the specific factor involved nor the underlying mechanism of this induced neuronal differentiation has yet been identified. **Conclusions:** In 3-week-old dissociated rat hippocampal cultures, a group of previously undescribed HPCs displays the ability to differentiate into ACs, ODCs, and neurons, depending on the stimulus applied. Neuronal differentiation was not induced by application of traditional neuronal differentiating factors, although it could eventually be achieved by a novel mechanism. At the end of this activity, participants will be able to recognize an important new cell type in hippocampal cultures that may play a role in epileptogenesis. [Supported by NS 24260 (M.A.D.).]

3.016

EVIDENCE OF MONOSYNAPTIC EXCITATORY CONNECTIONS AMONG GRANULE CELLS BASED ON SIMULTANEOUS INTRACELLULAR RECORDINGS IN SLICES OF PILOCARPINE-TREATED RATS WITH MOSSY FIBER SPROUTING

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Rationale: In many animal models of epilepsy, the axons of dentate gyrus granule cells (mossy fibers) develop collaterals that innervate an abnormal lamina, the inner molecular layer. Whether sprouting leads to excitatory monosynaptic connections among granule cells has been a subject of great interest. This study was undertaken to examine the question with direct methods, using simultaneous recordings of granule cells in a slice preparation with mossy fiber sprouting. At the end of this activity the participants should be able to discuss new evidence for excitatory monosynaptic connections among granule cells in rats with mossy fiber sprouting. **Methods:** The pilocarpine model was used to examine mossy fiber sprouting in adult male Sprague–Dawley rats. Pilocarpine was administered (380 mg/kg, i.p.) 30 min after atropine (1 mg/kg). After 1 h of status epilepticus, diazepam (DZP) was injected (5 mg/kg, i.p.). All animals had spontaneous behavioral seizures. After 2–8 months, slices from the ventral hippocampus of one hemisphere were prepared with conventional methods. Simultaneous recordings of granule cells were made in a semisubmerged chamber using sharp microelectrodes (60–80 Mohms) filled with 4% Neurobiotin in 1 *M* K acetate. The opposite hemisphere was immersed in 4% paraformaldehyde. It was subsequently sectioned and stained with antisera to neuropeptide Y to confirm that sprouting occurred. **Results:** Of 873 pairs of granule cells, six pairs demonstrated monosynaptic connectivity. Thus, an action potential evoked in one cell by current injection through the recording electrode depolarized ($\leq$3.7 mV) the second cell. The depolarization began during the repolarization of the action potential of the first cell, a latency that is consistent with a monosynaptic event. These putative monosynaptic excitatory postsynaptic potentials (EPSPs) appeared to be excitatory because they failed to invert at membrane potentials depolarized to the reversal potential for chloride, and in some cases could trigger action potentials at depolarized potentials. Interestingly, the failure rate was extremely high (45–63%) when compared to other monosynaptic pathways examined with the same methods (0–40%). Pairs of presynaptic action potentials with short interspike intervals led to paired-pulse depression. When the recorded cells were filled with Neurobiotin, their morphology confirmed that they were granule cells. Several of the filled neurons had axon collaterals in the inner molecular layer with many varicosities. **Conclusions:** The results suggest that there are functional excitatory monosynaptic connections among granule cells in epileptic rats with mossy fiber sprouting. They also suggest that these synapses may be functionally weak because of their relatively high failure rate and frequency depression. These data support the hypothesis that new recurrent excitatory circuits develop in rats with mossy fiber sprouting, and may contribute to the hyperexcitability that often occurs when sprouting is present. The results are also consistent with studies that have demonstrated strong inhibition in the dentate gyrus despite the presence of mossy fiber sprouting. (Supported by NINDS 38285 to H.E.S.) (Disclosure: Grant: Contract with Neuropace Inc.)

3.017

FETAL HIPPOCAMPAL CA3 CELL GRAFTS INTO THE LESIONED CA3 REGION OF THE ADULT HIPPOCAMPUS INHIBIT ABERRANT SPROUTING OF DENTATE MOSSY FIBERS IN A RAT MODEL OF TEMPORAL LOBE EPILEPSY

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Rationale: Intracerebroventricular kainic acid (i.c.v. KA) administration in rat, a model of temporal lobe epilepsy, causes degeneration of hippocampal CA3 pyramidal neurons and dentate hilar cells, the target cells of dentate granule cell axons (mossy fibers). This leads to a robust but aberrant sprouting of mossy fibers into the deafferented dentate supragranular layer. As this sprouting is linked to an increased seizure susceptibility of the dentate gyrus, strategies that restrain mossy fiber sprouting into the dentate supragranular layer are of considerable significance. We hypothesize that grafting of specific fetal hippocampal cells into the CA3-lesioned adult hippocampus results in the formation of appropriate connectivity between grafted cells and the host dentate gyrus, which in turn leads to a durable suppression of aberrant mossy fiber sprouting into the dentate supragranular layer. **Methods:** Embryonic day 19 hippocampal CA3 or CA1 cells were grafted into the CA3 region of the adult hippocampus at 4 or 45 days after the i.c.v. KA administration, and the aberrant sprouting of mossy fibers into the dentate supragranular layer was quantified after 8–12 months of grafting using Timm histochemical staining. For comparison, the extent of mossy fiber sprouting was also quantified from "lesion-only" animals at 4–12 months after lesion. Graft axon growth into the deafferented sites of the lesioned hippocampus was analyzed using transplantation of fetal mouse hippocampal cells into the lesioned rat hippocampus and immunostaining for the mouse-specific antigen M6. **Results:** Fetal CA3 cell grafts placed close to the lesioned CA3 region received dense projections from the host mossy fiber bundle, whereas similarly placed CA1 cell grafts received no such projections. Further, in animals receiving CA3 cell grafts, the overall extent of aberrant mossy fiber sprouting was radically diminished, in comparison to the "lesion-only" animals. In contrast, in animals receiving CA1 cell grafts, the dentate supragranular layer mossy fiber sprouting was closer to lesion-only animals. Analyses of graft axon growth revealed robust graft efferent projections into the dentate supragranular layer in animals receiving CA3 cell grafts but not in animals receiving CA1 cell grafts. **Conclusions:** These results underscore that grafting of specific fetal hippocampal cells into the lesioned adult hippocampus can considerably inhibit the formation of aberrant circuitry by facilitating an appropriate restitution of the disrupted circuitry. These results have significance towards the development of cell transplantation therapy for temporal lobe epilepsy. [Supported by grants from the Department of Veterans Affairs (VA Merit Review Award to A.K.S.) and National Institutes of Health (NINDS R01 NS36741 to A.K.S.).]

3.018

SPROUTING OF CHOLINERGIC FIBERS IN THE DENTATE GYRUS AFTER RECURRENT NEONATAL SEIZURES

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Rationale: The basal forebrain cholinergic neurons, which are involved in the modulation of memory and susceptibility to seizures, heavily innervate the hippocampal formation and neocortex. However, it is still unclear whether seizures affect the cholinergic system. The goal of this study was to determine the effects of recurrent seizures in immature rats on cholinergic innervation of the CA1 and CA3 regions of the hippocampus and dentate gyrus (DG). **Methods:** Rat pups were submitted to recurrent seizures using flurothyl 5 times a day during 5 days from postnatal ages 0 (P0) to P4 and from P15 to P19, in a total of 25 seizures per rat. Age-matched controls were handled in a similar manner but not submitted to seizures. Animals from all age groups were killed at P45. Brain tissue sections at the level of the dorsal hippocampus and basal forebrain were processed for acetylcholinesterase (AChE) histochemistry and choline acethyltransferase immunohistochemistry. **Results:** Rats submitted to seizures from both P0 to P4 and P15 to P19 showed significantly greater density AChE-labeled fibers in the molecular layer of the DG than controls. No significant differences in the density of AChE-labeled fibers were found in the stratum oriens of the CA1 and CA3 regions between rats submitted to seizures and controls from both age groups. **Conclusions:** We found an increased density of AChE-labeled fibers in the molecular layer of the DG in rats that had a series of flurothyl-induced seizures during the early postnatal period. It remains unknown whether the sprouting of cholinergic fibers in the DG that follows recurrent seizures in immature rats contributes to cognitive impairment or increased susceptibility to

seizures. [Supported by a grant from NINDS to G.L.H. (NS27984). Dr. Silveira was supported by a research fellowship from the Epilepsy Foundation of America.]

3.019
INJURY-INDUCED AXONAL SPROUTING IS LACKING IN HIPPOCAMPAL SLICE CULTURES FROM trkB-DEFICIENT MICE

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Rationale: Epilepsy is a common consequence of traumatic brain injuries; its cause is unknown. Axonal sprouting is observed after many forms of CNS injury, and it has been hypothesized that this synaptic reorganization is a critical cause of posttraumatic epilepsy. A full test of this hypothesis requires the means to stop injury-induced axonal sprouting, but the factors that trigger sprouting after injury are unknown. Secretion of neurotrophins and expression of NT receptors is increased after many forms of CNS injury and can trigger axonal sprouting, even in mature tissue. We hypothesized that injury-induced NT secretion triggers axonal sprouting. **Methods:** Schaffer collateral transection in hippocampal slice cultures has been shown previously to result in a delayed sprouting of CA3 cell axons and in hyperexcitability. Furthermore, application of NTs triggers axonal sprouting by pyramidal cells in cultures maintained in vitro for >14 days. The role of NTs in injury-induced sprouting was therefore tested in hippocampal slice cultures prepared from postnatal day 5–7 mice in which the predominant CA3 cell NT receptor, trkB, has been replaced with a "floxed" trkB transgene, resulting in a 75% reduction in trkB expression (Xu et al. *Neuron* 2000;26:233). After 14 days in vitro, lesions were placed in the Schaffer collateral pathway at the border between areas CA3 and CA1 in cultures from wild-type and homozygous "knock-down" litter mates. Seven days later, cultures were fixed and processed for immunocytochemistry using an antibody against the growth-associated protein GAP-43. Previous work has shown that GAP-43 expression is substantially upregulated in newly sprouted axons after injury. **Results:** Decreased trkB expression had no adverse effects on the cytoarchitecture or health of the cultures. Large numbers of immunoreactive fibers, terminating in growth cones, were observed in lesioned wild-type cultures. Cultures from mice with decreased trkB expression, in contrast, displayed no or very few immunoreactive fibers. **Conclusions:** We conclude that Schaffer collateral transection fails to trigger axonal sprouting when the level of trkB expression by CA3 cells is below some critical level. Signaling via the trkB receptor, presumably in response to NTs secreted as a result of the tissue injury, is required for the induction of axonal sprouting by pyramidal cells after traumatic injury. This model system thus provides the experimental means to test the hypothesized role of axonal sprouting as a cause of posttraumatic epilepsy. (Supported by NINDS.)

3.020
NEUROSERPIN AND TISSUE-TYPE PLASMINOGEN ACTIVATOR MODULATE SEIZURE SPREADING AND CELL DEATH WITHIN THE LIMBIC SYSTEM

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Rationale: Neuroserpin (NS) is a selective inhibitor of tissue plasminogen activator (tPA) that is primarily expressed in neurons in the central nervous system (CNS) in areas involved with synaptic plasticity. The aim of the present study is to examine the role of tPA and its natural inhibitor in the brain, NS, in the modulation of seizure spreading and cell death in an animal model of limbic seizures. At the end of this presentation the participants should be able to discuss the role of NS as a potential new treatment modality for seizures. **Methods:** Adult Sprague–Dawley rats or mice, C57BL/6J, C57BL/6J-tPA-/-, C57BL/6J-PAI-1-/-, C57BL/6J-Plg-/- were injected unilaterally into the amygdala with KA, and with PBS or 16 μM recombinant NS into the ipsilateral hippocampus. Some animals also underwent corpus callosotomy. tPA activity and NS antigen within the limbic system were studied at different times by in situ zymography and immunofluorescence. tPA activity was also quantified in rats 1 h after KA by SDS-PAGE zymography. For quantification of seizure-induced cell loss, serial sections through the dorsal hippocampus were prepared and stained with hematoxylin–eosin. For clinical evaluation, animals were observed for 120 min, and seizure behavior was classified as follows: (a) myoclonic jerks involving the head and neck; (b) unilateral tonic–clonic activity in the limbs; (c) generalized bilateral tonic–clonic activity. Hippocampal local field potentials (EEG) were recorded for 15 min before injection of KA and PBS or NS and for 2 h thereafter using electrodes placed in the CA1 region of the hippocampus. **Results:** After the injection of KA, tPA activity and NS antigen increased within 10 min in the amygdala, by 30 min in the ipsilateral hippocampus, and by 60 min in the contralateral hippocampus. In the hippocampus, NS expression and tPA activity were found in the CA-2 and CA-3 layers. Injection of NS into the hippocampus in close proximity to the CA-2 and CA-3 layers immediately after KA injection into the amygdala prevented the clinical and electrographic generalization of seizures. Mice lacking tPA showed a significant delay in the propagation of the seizure activity and administration of NS did not further prolong this delay, suggesting that NS was acting through its inhibition of tPA activity. PAI-1–deficient mice did not exhibit any difference compared to wild-type animals, suggesting a specific role for NS in the CNS. Plasminogen-deficient mice showed a pattern of seizure spreading and a response to NS similar to wild-type animals. **Conclusions:** TPA mediates the spreading of kainic acid–induced seizures throughout the limbic system. Treatment with NS, the natural inhibitor of tPA in the brain, promotes cell survival and slows the progression of KA-induced seizures. (Supported by NIH grants HL55374 and HL55747 to D.A.L. and NS36477 to J.Y.W.)

3.021
MORPHOLOGIC PROPERTIES OF DENTATE GRANULE CELL MIGRATION IN THE NORMAL AND INJURED HIPPOCAMPAL FORMATION

Dong Mei Zhang and Daniel H. Lowenstein (Program in Brain Plasticity and Epilepsy, Harvard Medical School and Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA)

Rationale: The dentate gyrus of the hippocampus is unique in having a region of neuronal proliferation, termed the subgranular zone (SGZ), that continues to generate dentate granule cells (DGCs) throughout life. The nature of normal DGC migration and maturation, and the migration of newborn DGCs to ectopic locations following pilocarpine-induced status epilepticus (SE), is poorly understood. The aim of this study was to examine the morphology of DGCs and their patterns of migration in control versus SE animals. **Methods:** Adult male Sprague–Dawley rats (180–200 g) were given i.p. atropine methylbromide followed 20 min later by i.p. pilocarpine hydrochloride to induce SE. Seizure activity was monitored behaviorally and terminated with diazepam (DZP) after 2 h of convulsive SE. Control rats received saline instead of pilocarpine. From 14 to 28 days later, animals were killed, and immunocytochemistry was performed on coronal sections of the hippocampus using antibodies to the neural precursor marker doublecortin (DCX) and the mature neuronal marker NeuN. **Results:** In control rats, a subset of putative, recently born DGCs (labeled with DCX) were located at the SGZ and appeared as isolated, single cells or small clusters of cells with cell bodies and dendritic trees oriented horizontal to the main axis of the DGC layer. Some cells had basal dendrites. Another subset of cells at the SGZ had dendrites perpendicular to the DGC layer that extended toward the molecular layer; examples of cells intermediate between the horizontal and perpendicular orientation were seen as well. Labeled cells in the middle of the DGC layer typically had decreased DCX staining in the soma relative

to that seen in the dendrites. In pilocarpine-treated rats, an increased number of DCX-positive cells were observed in the SGZ, and many of these cells had basal dendrites that extended deep into the hilus. Other cell soma were located within the hilus or the molecular layer, with dendrites oriented opposite to the direction seen in cells located within the DGC layer. **Conclusions:** The reliance on static images of immature and mature DGCs does not provide direct evidence regarding the dynamic nature of DGC migration. Nonetheless, with this caveat in mind, the morphology and orientation of the DCX-positive cells observed in both the normal and pathologic states suggest that DGC dendrites may "guide" developing DGCs during the later stages of their migration into a final location. Anomalies in the interaction between dendrites and adjacent cells or the extracellular matrix may underlie the appearance of ectopic cells in certain pathological conditions. (Supported by NIH, RO1NS NS39950.)

3.022
CHRONIC IMPAIRMENT OF EXTRACELLULAR K^+ HOMEOSTASIS AFTER TRAUMATIC BRAIN INJURY IN THE RAT

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Rationale: Traumatic brain injury (TBI) results in acute pathophysiological changes of glial cells that are pro-seizuregenic. We have previously shown that, 2 days following fluid percussion injury (FPI), a clinically relevant model of TBI, rat hippocampal astrocytes are reactive, have decreased membrane potassium conductance that results in impaired extracellular K^+ homeostasis, which, in turn, contributes to abnormal neuronal excitability (1). However, it is not known how such acute impairment progresses over time after injury. We have assessed the efficiency of extracellular K^+ homeostasis in rat hippocampal slices at subacute and long-term times after moderate midline FPI. **Methods:** Moderate in vivo midline FPI was induced. Slices were obtained at 2 days, 2 weeks, and 1 month after FPI from post-FPI or age-matched sham-operated rats. K^+-selective microelectrodes were employed to measure K^+ accumulation and evoked field potentials in CA3 stratum pyramidale during antidromic Schaffer collateral stimulation at 0.05 Hz. Data are shown as mean ± SEM. **Results:** In posttraumatic hippocampal slices, we found that, during Schaffer collateral stimulation, the baseline $[K^+]_o$ is elevated by (a) 0.4 ± 0.04 m*M* 2 days after FPI ($n = 9$; $p < 0.01$), (b) 0.27 ± 0.04 m*M* at 2 weeks after FPI ($n = 9$; $p < 0.01$), and (c) 0.25 ± 0.02 m*M* 1 month after FPI ($n = 13$; $p < 0.01$), over the K^+ levels measured in similar manner in slices obtained from age-matched sham-operated rats 2 days, 2 weeks, or 1 month after surgery ($n = 12$, 6, and 8, respectively). **Conclusions:** Impaired extracellular K^+ homeostasis persists at long-term time points after TBI, paralleling glial cells reactivity, and contributes to chronic tissue hyperexcitability and seizure precipitation (2,3). [Supported by NIH NS 40823 (RD).]

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3.023
ERG CHANNELS AND REGULATION OF EPILEPTIC ACTIVITY: GLIAL MODULATION OF NEURONAL EXCITABILITY

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Rationale: Potassium homeostasis plays an important role in the control of neuronal excitability. Glial cells have been implicated in this ionic regulatory process by supporting the homeostatic regulation of the neuronal environment. In our previous in vitro studies of CNS glia in hippocampal slices, we found that ERG (ether-a-go-go) potassium channels are selectively localized in astrocytes. Electrophysiologic characterization of ERG channels suggested that they contribute to the modulation of extracellular potassium levels following neuronal activation, and thus may play a critical role in controlling excitability and epileptogenicity. We now examine long-term changes resulting from ERG channel blockade, to assess their role in the long-term modulation of excitability. **Methods:** Hippocampal organotypic cultures were prepared from 4- to 7-day-old neonatal Sprague–Dawley rats and maintained for 14 days before being used in the experiments. Recordings from hippocampal cultures were performed with a Biocell Interface multielectrode recording system. This system allows simultaneous stimulation and recording at multiple sites (up to eight different locations). The recording can be conducted over days, so that electrical activity within the hippocampal circuitry can be followed closely for long-term studies. CA1 field potentials evoked by stimulation of the Schaffer collaterals were recorded before, during, and after injection of 100 μ*M* dofetilide (a selective ERG channel blocker), on day 1 of the experiment. Additional recordings were collected, with the stimulation protocols repeated without drug administration, on days 2 and 3. A group of cultures treated with aCSF on day 1 was used as control. Paired pulses (PP; 0.1 Hz) were delivered to assess hippocampal network inhibition/facilitation using interstimulus intervals (ISIs) of 30, 70, and 150 ms. Tests were repeated for 3 consecutive days for long-term observation. **Results:** Baseline recordings showed the appearance of episodes of spontaneous bursting activity in the dofetilide-treated cultures on day 1; spontaneous burst activity was observed also on days 2 and 3. In contrast, the control group never showed any spontaneous field discharge. Population spike (PS) amplitude in CA1 increased significantly ($p < 0.005$, $n = 9$) on day 1 during and after the treatment with dofetilide, and in comparison to saline controls. PS amplitude remained elevated on days 2 and 3 after dofetilide treatment ($p < 0.05$, $n = 4$). While the PP ratio at the 30-ms ISI did not show significant changes on days 1 and 2, a significant increase in PP inhibition ($p < 0.001$) was observed on day 3. A slight but nonsignificant increase in facilitation was observed at the 70- and 150-ms ISIs on day 1. A significantly ($p < 0.001$) enhanced facilitation was observed on day 3 at 150-ms ISIs. **Conclusions:** Our results support the view that ERG channels contribute to the regulation of neuronal activation, presumably by their regulation of potassium homeostasis. These data also show long-lasting changes of the electrical activity following ERG channels blockade. Additional experiments are needed to explain the nature of these long-lasting changes. Because ERG channels are specific to glia, these data provide additional evidence for the critical role played by glia in controlling excitability of the neuronal population. (Supported by CURE.)

3.024
ASTROCYTE-SPECIFIC TUBEROUS SCLEROSIS COMPLEX-1 CONDITIONAL KNOCKOUT MICE II: SYNAPTIC PHYSIOLOGY AND POTENTIAL ROLE OF ABNORMAL GLUTAMATE HOMEOSTASIS

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Rationale: Tuberous sclerosis complex (TSC) is a multisystem genetic disease characterized by abnormal cellular proliferation and differentiation. Neurologic manifestations are usually quite severe and include epilepsy, developmental delay, mental retardation, and autism. While these features are generally attributed to dysfunction of neurons, we postulated a more central role for astrocytes in the pathophysiology of TSC. Our laboratory recently developed a mouse model of TSC utilizing Cre-LoxP technology to generate an astrocyte-specific conditional knockout of *Tsc1* (*Tsc1*^{GFAP} cKO). These animals have frequent seizures, hippocampal pathology and increased astrocyte proliferation (See accompanying abstract I). Our objective in this study was to explore astrocyte medicated mechanisms of epilepsy in TSC. We hypothesized that the loss of *Tsc1* in astrocytes triggers epileptogenesis via alterations of synaptic processing in the hippocampus. We further

hypothesized that this mechanism involves abnormal astrocytic glutamate uptake. **Methods:** Hippocampal brain slices from 1- to 3-month-old *Tsc1*^{GFAP} cKO and control mice were prepared for extracellular recordings using standard methods. Synaptic responses from CA3 and CA4 pyramidal layers were evoked by mossy fiber stimulation. Whole-brain and derivative astrocyte cultures were also used to study expression patterns of proteins critical for glutamate transport by Western blot and immunohistochemistry. **Results:** Electrical stimulation of dentate gyrus mossy fibers in control hippocampal slices produced paired-pulse facilitation in regions CA3 and CA4 as expected. Paired-pulse facilitation, however, was not seen in CA3 and CA4 regions from *Tsc1*^{GFAP} cKO mice. The convulsant 4-aminopyridine produced comparable epileptiform activity in *Tsc1*^{GFAP} cKO and control slices. To investigate a possible role of altered glutamate transport, we examined expression in derivative cell cultures and intact brain slices. We observed differential downregulation of glutamate transporter proteins in derivative cultured astrocytes from *Tsc1*^{GFAP} cKO mice. Whole-brain lysates and intact slices also had downregulation of glutamate transporters by Western blot and immunohistochemistry. **Conclusions:** *Tsc1*^{GFAP} cKO mice develop progressive epilepsy at an early age. Our data demonstrate abnormalities in hippocampal synaptic transmission and downregulation of astrocyte glutamate transporters. These results support a primary role for astrocytes in TSC epileptogenesis and suggest impaired glutamate homeostasis as one possible mechanism. [Supported by Tuberous Sclerosis Alliance (D.H.G., H.O., D.J.K., L.B.), NIH NS36996 (D.H.G.), NIH NS31535 & NS24279 (D.J.K.), NIH NRSA (E.J.U.), NIH 5K12NS0169004 (M.W.).]

3.025
SPATIOTEMPORAL ACTIVITY PATTERNS IN GLIOMA-INVADED NEOCORTEX

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Rationale: Gliomas very often cause seizures as one of their first symptoms. It is largely unknown which functional changes of neuronal activity are responsible for this, and to which extent the degree of tumor invasion correlates to the changes in neuronal excitabiltiy. This study addresses the question whether the spread of activity in neuronal networks is changed by neoplastic glial cells. **Methods:** Gliomas were induced in adult Wistar rats (n = 17) by stereotactic intracortical implantation of a C6 tumor cell line suspension (10 μl; cell concentration, $2 \times 10^5/\mu l$) stably transfected with GFP or LacZ. Gliomas were left to develop for 14–17 days. After this period, animals were killed, and coronal neocortical slices (500 μm) were made. Evoked (single electical stimuli, white matter), as well as spontaneous or triggered epileptiform activity (0-Mg^{2+}) was monitored using the voltage-sensitive dye RH 795. Age-matched animals (n = 6) served as controls. **Results:** Implantation of tumor cell suspension led to development of intracortical gliomas in all cases, with both solid tumors and a surrounding 200- to 300-μm-wide zone of dispersed invasion. Single electrical stimuli resulted in supragranular activation in control tissue. By contrast, in glioma-invaded slices, network activity generally extended also to infragranular layers. Whereas in control slices, spontaneous epileptiform activity could start in any area of the neocortex, initiation sites in glioma-invaded tissue were always paratumoral. **Conclusions:** These results show that glioma infiltration causes substantial alterations in network activity patterns. (Supported by DFG KO 1779/4-1.)

3.026
TRAUMATIC INJURY INDUCED TRANSCRIPTIONAL ALTERATIONS IN REACTIVE GLIA: A MICROCHIP STUDY IN ASTROCYTE-CULTURE MODEL

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Rationale: At the end of this activity, participants should be able to discuss which genes are induced by injury in astrocytes. Temporal lobe epilepsy (TLE) is characterized by cell loss, circuit rearrangements, reactive gliosis, and expression alterations of multiple genes. Reactive gliosis is manifested by increased number of astrocytes with aberrant morphology. The increased number and altered intrinsic astrocyte properties demonstrated in human epilepsy suggest a role of these cells in epileptogenesis. We assessed gene-expression alterations in a scratch-injury reactive glia model using microchip technology. **Methods:** Reactive glia were created by scratching purified mouse cortical astrocyte cultures with a dissection pin comb, and harvested 2 h, 2, and 7 days after injury (PI). Total RNA was isolated, cDNA synthesized, cRNA labeled and hybridized to murine genome U74Av2 arrays (Affymetrix). **Results:** High-density oligonucleotide arrays containing 12,473 gene probe sets were used to monitor injury-associated gene expression alterations. After 2-h PI (n = 4) 1.6% of gene probe sets exhibited altered expression levels, while 2 and 7 days PI (n = 3 each), 0.8% and 0.1% gene probe sets exhibited altered expression compared to control (n = 5). In 2-h PI astrocytes a twofold to 21-fold increase in expression was detected for transcription-related mRNAs including Nurr77, fosB, fra-1, LRG-21, Kruppel-like factor, Krox-20, Krox-24, GIF, NFIL/E4BP4, Nurr1, junB, Hox2.4, bHLH, c/EBP, PEBP2, ATF4, pip92, and mTGIF. Also induced were inflammation (griPGHS, cytokine A2), apoptosis (TDAG51, MyD116, caspase 9), injury (PAI-1), stress response (mafF, HSP70), signal transduction (SOCS1, stathmin-like protein RB3, Ldlr, serum inducible kinase, Ras-like GTP-binding protein), and growth factor genes (EGF-like growth factor, TGF, NGF). Downregulated genes included caspase 6 and pyruvate dehydrogenase kinase. In 2-day PI cultures, a twofold to sixfold increase in expression was detected for cell cycle (cyclin B1, Cdc25, Ki-67, Plk, Bub1, Mad2, Cenp-a, CHO1/MKLP1), and vesicular transport genes (rabkinesin-6). Decreased expression was detected for complement C1q B chain, colony-stimulating factor 1 receptor, G protein–coupled receptor. In 7-day PI cultures, altered genes included 4.6-fold increased metalloelastase and decreased heme oxygenase. **Conclusions:** This reactive glia culture model demonstrated a fast (within 2 h) complex genomic response to the injury. The identity of the genes exhibiting altered expression revealed that injury alters many aspects of cell physiology, including transcriptional regulation, signal transduction, stress responses, apoptosis, inflammation, and the cell cycle. At 2-h PI, 25% of genes with altered expression were transcription factors and immediate-early genes. These alterations were absent in astrocyte cultures 2 and 7 days after injury, and were replaced by changes in cell-cycle genes. This pattern of gene induction in reactive glia may facilitate TLE-associated reactive gliosis and affect epileptogenesis. [Supported by (D.A.C.) NS 32403, NS 38572; (P.G.H.) NS43142, NS37585.]

3.027
MULTIDRUG RESISTANCE PROTEIN-1 (MDR-1) IS ACUTELY ALTERED BY STATUS EPILEPTICUS IN THE DEVELOPING RAT BRAIN

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Rationale: MDR-1 has been implicated in antiepileptic drug (AED) resistance. Previous studies have shown the expression of these proteins in the developing rat brain. We examined changes in MDR-1 after status epilepticus (SE) and their possible role on the efficacy of treatment with phenytoin (PHT), administered as fos-phenytoin (FPHT). Our objective is to contribute to a greater understanding of the relation between MDR and seizures and the potential to alter the expression of these proteins as a new treatment strategy for SE and epilepsy. **Methods:** Two-week-old Wistar rat pups were pretreated with LiCl (3 mEq/kg) followed by pilocarpine (60 mg/kg) the next day to induce SE. Rats were perfused with paraformaldehyde at 1–2 h, 6 h, and 24 h after SE. Brains were cut, frozen, and examined for the presence of the MDR-1 isoform–like immunoreactivity (IR) using routine immunohistochemistry. Another group of rats were injected with FPHT 1 h after the start of SE. **Results:** Rat pups possessed extensive MDR-1 immunoreactiv-

ity in the brain capillaries. In those that underwent SE, however, the labeling seen in the microvasculature of the control animals was almost entirely absent after 1–2 h and remained so at 6 h. Immunostaining did not become readily visible in glial-like elements at any time point. Twenty-four hours after SE, MDR-1 expression returned to baseline. Those animals given the MDR-1–dependent drug, PHT, 1 h after SE, showed complete cessation of behavioral seizure activity within 20 min. **Conclusions:** The effectiveness of PHT during the early period of SE provide further evidence that MDR-1 may play a role in resistance to AED therapy. The finding that young animals may be more sensitive (i.e., responsive) to PHT after 1 h of SE may be due to the lack of SE-induced MDR-1 in glia that may serve to act as a drug sink in the mature animal. Since glial MDR-1 expression is not altered by SE in the immature animal that remained responsive to PHT under circumstances when PHT fails in the mature animal, inhibiting expression of this protein may be an area for a new treatment modality to restore responsivity to PHT when SE tends to become refractory to this drug. (Supported by The DAPA Foundation, NS13515 from NINDS and the Research Service of the VHA.)

3.028
DOES IMPAIRED POTASSIUM CLEARANCE CAUSE POST-TRAUMATIC HYPEREXCITABILITY?

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Rationale: After fluid percussion head injury, dentate granule cells demonstrate hyperexcitability (Toth et al., 1997; Santhakumar et al., 2000). One hypothesis is that impaired clearance of extracellular potassium contributes to posttraumatic hippocampal hyperexcitability. This study was conducted to compare the steady-state and activity-dependent changes in extracellular potassium concentration in the dentate gyrus of head-injured and control animals. **Methods:** Single-barrel ion-selective microelectrodes (ISME; 1–10 GΩ) with valinomycin-based potassium-selective membrane solution (Fluka) were used with field reference electrodes. Temporal characteristics of the ISME were determined by fast application switch using a nanostepper motor. The potassium concentration was measured in the granule cell layer in response to perforant path (orthodromic) or hilar (antidromic) stimulation in acute hippocampal slices from fluid percussion head injured (FPI) and control animals. γ-Aminobutyric acid (GABA) and glutamate receptor antagonists were used in some experiments. **Results:** First, there was no difference in the baseline potassium concentration in the granule cell layer between control and FPI animals 2 days, 1 week, and 1 month after injury. Second, the clearance of potassium increase evoked by orthodromic tetanic stimulation was not different between head-injured and control animals. Third, because calibration of the temporal characteristics showed that ISMEs had a latency of ~7ms to detect a 0.05 m*M* change in potassium concentration, ISMEs were used to compare single-shock stimulation-evoked rapid transient changes in extracellular potassium between FPI and control animals. Again, although the amplitude of the evoked extracellular potassium increase and field population response were significantly greater after FPI, the clearance of the evoked potassium increase was not statistically different between injured and control animals. Fourth, the clearance of exogenously applied potassium was not different between injured and control animals. Finally, the posttraumatic clearance of potassium increase, evoked by antidromic stimulation of the granule cells in the presence of ionotropic glutamate and GABA-receptor antagonists, was not statistically different from controls. Interestingly, although previous studies have used antidromic stimulation in ionotropic glutamate and GABA antagonists as a method to normalize action potential firing between injured and control groups, both the evoked field response and extracellular potassium increase in the dentate were significantly greater in the injured animals compared to controls. **Conclusions:** There is no increase in the steady-state extracellular potassium concentration in the dentate gyrus days or weeks after head injury. The clearance of both activity-dependent endogenously released and exogenously applied potassium is not different between the injured and control animals. Posttraumatic increase in amplitude of extracellular potassium in response to both orthodromic and antidromic stimulation is a consequence (and not a cause) of increased excitability after head injury. [Supported by NIH (NS35915) to I.S.]

3.029
A KETOGENIC DIET ENHANCES RESPIRATORY UNCOUPLING AND DECREASES REACTIVE OXYGEN SPECIES PRODUCTION IN MITOCHONDRIA ISOLATED FROM MOUSE CORTEX

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Rationale: We have previously observed that a ketogenic diet (KD) increases the survivability of Kcna1-null epileptic mice, suggesting possible neuroprotective effects. We asked whether this observation might be a consequence of enhanced fatty acid–induced respiratory uncoupling, leading to an inhibition of reactive oxygen species (ROS) production, which can be damaging to neurons. **Methods:** Normal C3Heb/FeJ mice were fed either the Bio-Serv F3666 KD or normal rodent chow for 10 days beginning at P21–23. The Keto-Site reflectance meter was used to measure blood D-β-hydroxybutyrate (BHB) levels. Synaptosomal mitochondria were prepared acutely from cortex of mice at P30–31. Mitochondrial uncoupling protein activity and ROS production were assessed through measurements of mitochondrial oxygen consumption and hydrogen peroxide production, respectively. **Results:** Mean BHB levels 1 day before killing were 1.2 and 0.68 m*M* for KD-treated and control diet-fed mice, respectively ($p < 0.05$). Mitochondrial uncoupling protein activity was increased by 70% in KD-treated compared to control diet-fed mice. Additionally, a KD reduced oligomycin-induced ROS production by 17% compared to normal diet-treated mice. **Conclusions:** An experimental KD increases mitochondrial uncoupling activity and decreases ROS production in the cortex of normal juvenile mice, suggesting that this dietary therapy may be neuroprotective as well as anticonvulsant. [Supported by NeoTherapeutics Fellowship (P.G.S.), NIH NS 32280 (O.S.), and NIH K08 NS 01974 (J.M.R.).]

3.030
ASTROCYTE-SPECIFIC TUBEROUS SCLEROSIS COMPLEX-1 (*TSC1*) CONDITIONAL KNOCKOUT MICE I: ABNORMAL NEURONAL ORGANIZATION AND SEIZURES

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Rationale: Patients with tuberous sclerosis complex (TSC) may develop a wide range of neurologic abnormalities, including epilepsy, mental retardation, cortical dysplasias, and astrocytomas. Many of the abnormal neurologic features of TSC could be due to a primary defect in astrocyte function. The objective of this study was to generate a mouse model of TSC-associated CNS abnormalities using an astrocyte-specific conditional knockout of the *Tsc1* gene. **Methods:** Two independent lines of astrocyte-specific *Tsc1* conditional knockout mice ($Tsc1^{GFAP}$ cKO mice) were generated using the Cre-LoxP system by expressing nuclear-targeted Cre recombinase under the control of the human glial fibrillary acidic protein (GFAP) promotor. $Tsc1^{GFAP}$ cKO mice were studied by video-EEG for characterization of seizures. Immunostaining for GFAP and conventional histologic techniques were used to examine for glial and neuronal abnormalities. **Results:** At birth, $Tsc1^{GFAP}$ cKO mice appeared normal compared to wild-type littermates. By 2 months of age, $Tsc1^{GFAP}$ cKO mice became less active, tended to assume a retracted posture, and exhibited paroxysmal movements resembling seizures. Video-EEG analysis confirmed that

Tsc1^{GFAP} cKO developed frequent clinical and electrographic seizures, usually characterized by tonic stiffening and clonus of the trunk or extremities without loss of upright posture. Electrographically, most seizures appeared to have simultaneous bilateral onset, but hippocampal depth recordings indicated focal onset for some seizures. Seizures were documented at 1 month of age, the earliest time examined. By 3–4 months of age, seizures became extremely frequent, interictal EEG showed a burst-suppression pattern, and all mice died of an uncertain cause. GFAP immunostaining demonstrated significant increases in astrocyte numbers, as a result of increased cell proliferation, throughout the brain, starting around 3 weeks of life and increasing progressively with age. Selective abnormalities of neuronal organization of hippocampal pyramidal neurons, primarily in the dentate hilar CA4 region, also developed and progressively worsened over a similar time course. **Conclusions:** Selective inactivation of *Tsc1* in astrocytes results in severe behavioral and neuropathologic abnormalities, most likely involving both astrocytic and neuronal functions. The phenotype of this mouse model suggests that seizures and other neuronal abnormalities in TSC could be due to a primary defect of *Tsc1* in astrocytes. Further work on *Tsc1*^{GFAP} cKO mice should yield important insights into the mechanisms by which astrocytic dysfunction may lead to abnormal neuronal excitability and seizures (see accompanying abstract II). [Supported by Tuberous Sclerosis Alliance (D.H.G., H.O., D.J.K., L.B.), NIH NS36996 (D.H.G.), NIH NS31535 & NS24279 (D.J.K.), NIH NRSA (E.J.U.), NIH 5K12NS0169004 (M.W.).]

3.031
FOCAL CORTICAL DYSPLASIA INDUCED IN THE NEWBORN RAT REDUCES THRESHOLD TEMPERATURES AND LATENCIES TO FEBRILE SEIZURES

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Rationale: Febrile seizures affect 2–5% of the pediatric population, and although simple febrile seizures are currently thought to be benign, studies have shown that 40–60% of patients with intractable mesial temporal lobe epilepsy (MTLE) have a history of prolonged febrile seizures. In models of febrile seizures induced in the immature rat it has been demonstrated that it is prolonged hyperthermia-induced convulsions that are associated with long-term changes in hippocampal excitability resulting in reduced seizure thresholds in adult subjects. Studies of specimens obtained from patients surgically treated for MTLE have demonstrated that between 10 and 80% had a cortical dysplastic lesion of the temporal lobe along with mesial temporal sclerosis. We therefore hypothesized that children with focal cortical dysplasia are more likely to have reduced seizure thresholds and febrile seizures that are prolonged or atypical. **Methods:** Pregnant Sprague–Dawley rats were conditioned 1 week before parturition to minimize mortality due to postoperative neglect of the offspring. Surgical freeze lesions were induced in the neocortex of pups at P1 by applying a frozen probe, previously cooled in liquid nitrogen, to the exposed calvarium of anesthetized subjects. Convulsions were then induced at P10. Pups were placed into a large plexiglass container and were exposed to a stream of moderately heated dry air until they had generalized convulsions evidenced by tonic–clonic movements of the upper and lower limbs with loss of the righting reflex. The core temperatures of all subjects were continually monitored throughout the period of hyperthermia. The threshold temperature and latency to jaw myoclonus (JMC), hind-limb clonus (HLC) and generalized convulsions (GC) were recorded including the duration of the postictal phase. Comparisons were made between lesioned, sham-operated, and naive control subjects. **Results:** Baseline temperatures at P10 were 35.0 ± 0.91°C with no differences between the groups. Seizures were induced in 100% of subjects exposed to hyperthermia. The seizures were characterized by episodes of freezing interspersed with periods of hyperkinesis followed at higher temperatures by JMC with tonic neck and forelimb flexion, HLC, then GC, successively. This was followed by a period of postictal depression characterized by prolonged immobility, hyporeactivity, and reduced exploratory behavior. Lesioned pups exhibited reduced threshold temperatures to HLC, 36.9 ± 1.41°C, versus controls, 38.8 ± 1.71 ($p < 0.05$) and GC, 40.4 ± 1.86°C versus controls, 42.3 ± 0.95°C ($p < 0.001$); reduced latencies to HLC, 127.90 s ± 81.9 versus controls, 290.61 ± 166.25 s ($p < 0.05$), and GC, 403.1 ± 29.44 s versus controls, 525.8 ± 30.33 s ($p < 0.05$); and a prolonged period of postictal depression, 938.7 ± 96.91 s versus controls, 461.8 ± 52.22 s ($p < 0.001$). **Conclusions:** Febrile seizures in the presence of focal cortical dysplasia occur at lower threshold temperature and shorter latency followed by postictal depression of a longer duration than that seen in controls. These findings demostrate that febrile seizures in the presence of cortical dysplasia are atypical and hence may contribute to the progression to MTLE. (Supported by The Saint Justine Research Foundation, Saint Justine Hospital, Montreal, Quebec, Canada.)

3.032
UPREGULATION OF GLUTAMATE-RECEPTOR EXPRESSION IN RAT CEREBRAL CORTEX WITH NEURONAL MIGRATION DISORDERS

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Rationale: Neuronal migration disorders (NMDs) such as cortical dysplasia and microdysgenesis constitute the main pathologic substrate of medically intractable epilepsy in human. This study is designed to investigate the changes in expression of glutamate-receptor subtypes in an experimentally induced NMD in rats. **Methods:** NMD lesion was produced by intrauterine irradiation (240 cGy) on E17 rats, and then 10-week-old rats were used for the study. The pathologic and immunohistochemical findings for glutamate-receptor subunit proteins (NR1, NR2A/B, GluR2, GluR3) on NMD cortex were correlated with development of behavioral seizures and EEG abnormality, which induced by kainic acid provocation. Spontaneous seizure was uncommonly occurred in NMD rats (5%), however, most of the rats developed seizures after an administration of kainic acid (90%). Prevalence, duration, and clinical stage of seizures were significantly increased in NMD rats compared with controls. **Results:** Brains taken from irradiated NMD rats show microcephaly, thinning of cortex, blurring of the gray- and white-matter junction, and hypoplasia or agenesis of corpus callosum. Loss of lamination, neuronal heterotopia in the subpial gray and white matter, and disoriented cytomegalic neurons were noted histopathologically. Focal cortical dysplasia was identified by immunohistochemistry with neurofilament protein (NF-M/H). Significantly strong NR1, NR2A/B immunoreactivities on cytomegalic and heterotopic neurons in NMD rats were demonstrated. **Conclusions:** The results of the present study indicate that epileptogenesis of NMD might be caused by upregulation of glutamate-receptor expression in dysplastic neurons of the rat cerebral cortex with NMDs. (Supported by Research Institute of Medical Sciences, Chonnam National University Medical School and Hospital.)

3.033
DIFFERENTIAL GENE EXPRESSION CORRELATED WITH REDUCED TEMPORAL LOBE VOLUME IN SEIZURE-PRONE VERSUS SEIZURE-RESISTANT RATS

Krista Gilby, Bruce Hutcheon, Khara Sauro, Sharon Sahota, Neera Malik, Michael O. Poulter, and Dan C. McIntyre (Institute for Neuroscience, Life Sciences Research, Ottawa, Ontario, Canada)

Rationale: Temporal lobe epilepsy has been linked to a loss in temporal lobe volume (Bothwell et al., 2001; Bertram et al., 1990). However, whether this loss of volume is a cause or consequence of seizures remains unknown. Seizure-prone and seizure-resistant rat strains have been developed through selective breeding of rats with fast and slow amygdala kindling rates, respectively. Interestingly, in addition to creating differences in seizure susceptibility, the natural breeding process also produced differences in limbic structure volume. Specifically, seizure-prone rats show reduced dorsal hippocampal and

temporal lobe volumes relative to seizure-resistant rats. This finding suggests that differences in temporal lobe volume are indeed heritable and are not merely a consequence of neuronal damage following repeated seizures. Accordingly, genetic factors that influence the formation of the hippocampus and its basal operation may predispose that structure to seizure. The identification of differences in constitutive gene expression within the naive hippocampi of seizure-prone and seizure-resistant rats may, therefore, reveal mechanisms underlying seizure susceptibility. **Methods:** To screen for differences in constitutive gene expression between the strains, we probed 1.7K microarrays with fluorescently labeled cDNAs derived from the hippocampi of naïve seizure-prone and seizure-resistant rats. Differential gene expression isolated using this screening technique was verified using several molecular biologic tools including QPCR and in situ hybridization. **Results:** A number of genes were found to be constitutively underexpressed in the hippocampi of naïve seizure-prone rats relative to naïve seizure-resistant rats. These genes included ubiquitin protein ligase, P53, mGluR4, and a number of genes involved in fatty acid synthesis and metabolism. Surprisingly, only one of the 1,700 genes probed on the microarray was found to be overexpressed in the hippocampi of seizure-prone animals: the thyroid hormone–binding protein transthyretin. **Conclusions:** The finding that the majority of genes differentially expressed between the strains are underexpressed in the seizure-prone hippocampus may suggest a loss of one or more cell populations that would normally contribute to seizure resistance. On the other hand, it may be that the selective downregulation of these genes throughout the hippocampus plays a crucial role in seizure susceptibility. Further understanding of a common thread between the genes identified may help to resolve this issue. (Supported by CIHR.)

3.034
WAVES OF AP1, NF-κB, AND STAT-1 TRANSCRIPTION FACTORS IN HIPPOCAMPUS DURING KAINATE-INDUCED EPILEPTOGENESIS

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Rationale: Experimentally induced epileptogenesis elicits profound changes in early response gene (ERG) expression in the brain. In these studies we describe in adult rat hippocampus, early (0–6 h), medium (1–7 day), and long-term (2–8 week) changes in the DNA-binding of transcription factors (TFs) AP1, AP2, Egr1, STAT1, NF-κB, NFIL-6, SP1, and TFIID to target DNA sequences found in the immediate promoters of the cFOS and cyclooxygenase-2 (COX-2) ERGs after a single kainic acid (KA) injection). Using LAU8080, a specific intracellular platelet-activating factor (PAF) antagonist, we provide evidence that during experimental epileptogenesis, this highly bioactive phospholipid is a key intermediate in triggering AP1-, NF-κB- and STAT1-DNA binding, elements known to drive the rapid induction of ERG expression. At the end of this activity participants should further understand the interrelationships between specific TF activation and cFOS and COX-2 gene expression. **Methods:** To trigger epileptogenesis, male albino Wistar rats were injected i.p. with 10mg/kg KA using saline as a vehicle. At indicated time points (0, 1, 3, 6 h; 1, 3, 7 days; and 2, 4, 8 weeks), rats were killed and hippocampal and cortical cellular and nuclear proteins and total RNA were co-isolated. TF-DNA binding was studied using gel shift and super-shift assay; RNA message levels were determined using RT-PCR, and cFOS and COX-2 protein levels were quantitated using Western immunochemistry. **Results:** AP1-, NF-κB-, and STAT1-DNA binding were found to display phasic profiles over the short, medium, and long term. AP1-DNA binding kinetics strongly correlated with COX-2 gene activation over the short term, while NF-κB-DNA binding paralleled COX-2 gene expression at longer times. Sustained increases in TFIID-DNA binding suggested prolonged de novo induction of transcription from TATA-containing brain genes. Both TF-DNA binding and cFOS and COX-2 ERG expression were significantly quenched using LAU8080 prior to epileptogenic stimuli. **Conclusions:** Taken together, these results suggest that induction of the proinflammatory TF triad AP1, NF-κB and STAT1, and their binding to specific target DNAs in ERG promoters drives proinflammatory gene expression in the short term and reprograms hippocampal gene expression patterns long after the triggering of a single epileptogenic event. (Supported in part by NIH NS23002 and AG18031.)

3.035
MITOCHONDRIAL OXIDATIVE STRESS IN MANGANESE SUPEROXIDE DISMUTASE–DEFICIENT MICE RESULTS IN INCREASED SEIZURE SUSCEPTIBILITY

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Rationale: Epileptic seizures are a prominent clinical feature of mitochondrial diseases. Mitochondria have vital functions such as energy generation, control of cell death, and free radical production. Which of these critical mitochondrial functions contributes to the seizures associated with mitochondrial diseases is unknown. Understanding the role of mitochondrial dysfunction in seizure susceptibility can provide insight into the mechanisms by which seizures are triggered in rare mitochondrial diseases as well as by common metabolic insults such as hypoxia or trauma. Manganese superoxide dismutase (MnSOD) heterozygous knockout (+/-) mice with chronically increased mitochondrial superoxide were used as a model to determine if mitochondrial oxidative stress and resultant dysfunction renders the brain vulnerable to increased seizure activity. **Methods:** Two strains of MnSOD (+/-) mice and their wild-type littermates were analyzed for spontaneous, handling-induced, and kainate-induced seizures. Spontaneous and handling-induced seizures were analyzed in three age groups of mice (4–5, 9–12, and >18 months old). Seizure severity and incidence was correlated with mitochondrial aconitase inactivation, an index of mitochondrial superoxide production and cell death. **Results:** MnSOD (+/-) mice had 50% brain MnSOD activity and 25–30% inactivation mitochondrial aconitase, an index of steady-state superoxide production. Spontaneous and handling-induced seizures were observed in a subset of 9- to 18-month-old MnSOD (+/-) mice. The subset of aged MnSOD (+/-) mice that developed spontaneous seizures also showed increased mitochondrial superoxide production and cell death compared to age-matched MnSOD (+/-) mice that did not develop seizures. Kainate-induced seizures, mitochondrial superoxide production, and apoptosis were exacerbated in young MnSOD (+/-) mice. **Conclusions:** These results suggest that mitochondrial oxidative stress may be an important biochemical mechanism that renders the brain vulnerable to epileptic seizures. Furthermore, mitochondrial dysfunction arising from oxidative stress may play a mechanistic role in seizure disorders associated with rare mitochondrial diseases as well as common age-related disorders that are known to increase mitochondrial oxidative stress. [Supported by NIH RO1NS39587 and Parents Against Childhood Epilepsy (P.A.C.E.).]

3.036
IDENTIFICATION OF QUANTITATIVE TRAIT LOCI CONTROLLING EXCITOTOXIN CELL-DEATH SUSCEPTIBILITY IN INBRED STRAINS OF MICE

Paula Elyse Schauwecker and Yan Bai (Cell and Neurobiology, University of Southern California, Los Angeles, CA)

Rationale: Mice from various inbred strains are resistant to excitotoxin-induced cell death at different strain-specific levels. In particular, C57Bl/6 mice exhibit resistance to kainate-induced cell death, while mice from the FVB/N strain exhibit susceptibility. Breeding studies have demonstrated that the kainate-induced cell death resistance phenotype is a monogenic and highly penetrant autosomal dominant trait. We now report an investigation of the genetic basis for excitotoxic cell death susceptibility using F1 X FVB/N backcrosses (N2) to establish chromosomal locations of genes controlling susceptibility to kainate-induced cell death. At ths end of this activity, participants should be able to assess the importance of genetic diversity in seizure-induced damage. **Methods:** To confirm the mode of inheritance and determine the genetic loci that confer resistance to excitotoxic cell death, (C57BL/6 X FVB/N)F1 mice were backcrossed in both direc-

tions to susceptible FVB/N mice to determine phenotypic differences in susceptibility to kainate-induced cell death in 400 progeny. Microsatellite mapping techniques were then used to isolate the chromosomal segments containing resistance or susceptibility loci in the N2 population by performing an initial genome screen with 87 polymorphic microsatellite primer pairs. Quantitative trait loci (QTL) mapping methods were used to identify regions of the genome that contribute to variation in susceptibility to kainate-induced cell death. **Results:** As reported previously, N2 mice displayed two predominant phenotypes responding either like resistant (C57BL/6) or susceptible (FVB/N) mice. Logistic regression analysis revealed significant or suggestive evidence for QTLs that influence susceptibility to kainate-induced cell death on chromosomes 15 and 4. We detected the locus of greatest effect on proximal Chr 15 (LOD = 2.2) between markers D15Mit174 and D15Mit156 (29 cM wide). We detected two other QTLs on Chr 4. Interestingly, the two QTLs on Chr 4 act in completely different ways, in that the locus on proximal Chr 4 is associated with C57BL/6-derived susceptibility while the locus on distal Chr 4 is associated with FVB/N-derived susceptibility. However, as expected for a monogenic trait, kainate-induced cell death susceptibility loci were primarily derived from 'susceptible' strains (FVB/N). **Conclusions:** This study represents the first analysis of differential inbred mouse strain susceptibility to kainate-induced cell death. While in the present experiment we found three QTLs that influence the severity of kainate-induced damage in C57BL/6 and FVB/N mice, future studies are aimed at confirming or eliminating candidate genes for kainate-induced cell death susceptibility using functional characterization and higher resolution mapping studies. We conclude that susceptibility to kainate-induced cell death is genetically controlled. Due to the high degree of similarity between the mouse and human genomes, identification of the location of specific genes modulating susceptibility to excitotoxin-induced cell death will provide important insights into the manner in which genetic predisposition affects the pathogenesis of human epilepsy. (Supported by The James D. and Delia B. Baxter Foundation and NIH grant NS38696-01.)

3.037
ACCUMULATION OF NESTIN IN CORTICAL CELLS IN RELATION TO ANATOMIC PATHOLOGY AND FOCAL EPILEPTIC ACTIVITY IN CHILDREN

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Rationale: The expression of developmentally regulated cytoskeletal proteins, such as the neural epithelial stem cell protein, nestin, downregulates during normal corticogenesis. However, in children with early-onset seizures, intracellular proteins accumulate, do not decrease with age, and may either contribute to or interfere with synaptic functions. We studied anomalous nestin densities to determine whether these protein accumulations were related to epileptic hyperexcitability. **Methods:** Specimens were analyzed from four patients aged 2, 7, 8, and 13 years at time of surgery, with seizure onset aged 3 months, 20 months, 7 years, and 2 days, respectively. Subdural EEG grid monitoring defined regions of onset, spiking rates, and relatively normal activity. The anatomic pathology was related to the EEG activity after the margins of the resection were defined. Nestin immunoreactivity was identified in four different cell types: pyramidal cells, "giant cells," and round cells with and without neuritic processes. Serial sections were stained with cresyl violet. Protein amounts were measured using Western blots, and relative cell densities for each cell type were noted and analyzed in relation to age at onset, EEG activity, and clinical history. **Results:** Two patients with clinical history of tuberous sclerosis complex (TSC; age at seizure onset, 3 months) and Parry–Romberg syndrome/Rasmussen encephalitis (age at seizure onset, 7 years) showed highest density of nestin immunoreactive cells of all four types, with almost equal distribution in EEG active, or "spiking," and EEG inactive, or "normal" cortex. In the other two patients, nestin-postive cells were highest in the spiking and onset cortex, compared to the relatively normal cortex. Round-type cells without processes were found almost exclusively in regions of seizure onset and frequent spiking in three of the patients. However, in the TSC patient, in which the surgery was designed to remove the tuberous cortex, nestin immunoreactivity was highest compared to the other patients, and round-type cells were abundant in all regions, while pyramidal cells were sparse. Giant cells were also found in both white and gray matter of the TSC patient. **Conclusions:** The presence of nestin immunoreactive cells in epileptic cortex represents another example of arrested cortical development characteristic of other protein changes found in receptors of brains with migration disorders. Nestin cell densities are highest in the regions of pathology and may contribute to focal neuronal loss, such as decreased pyramidal cells. Nestin-positive round cells were most abundant in regions of severe pathology, and high EEG spiking may indicate a failure to differentiate from a brain stem cell progenitor to a neuron or glial phenotype. If these immature cells remain throughout childhood, receptor protein configurations and synaptic activity may result in intractable epilepsy. (Supported by National Institutes of Health grant NS38150.)

3.038
EPILEPTIC HUMAN DENTATE GYRUS GRANULE CELLS EXPRESS HIGH LEVELS OF THE HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE–GATED CHANNEL MOLECULES

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Rationale: In the normal hippocampus, channels activated when neurons are hyperpolarized (HCNs), contribute to maintenance of cellular resting membrane potential and to synchronized activation of neuronal ensembles. Recent studies have suggested that *abnormal* expression of HCNs may occur in an animal model of prolonged febrile seizures and contribute to hippocampal hyperexcitability. However, whether these channel molecules are expressed in human epileptic hippocampus, and whether their expression correlates with clinical characteristics is unknown. **Methods:** Surgically resected hippocampi (n = 12) from patients with temporal lobe epilepsy (TLE), with (n = 9) or without HS (n = 3), were compared with autopsy cases (n = 8). HCN mRNA expression was determined by both semiquantitative and nonradioactive in situ hybridization. **Results:** HCN1 mRNA was highly expressed in dentate gyrus granule cells of hippocampi resected from patients with TLE, whereas autopsy cases had no or little HCN1 mRNA expression. Preliminary analyses suggest that HCN expression was particularly prominent when GC cell loss was severe, but did not correlate with duration of epilepsy. **Conclusions:** The novel and marked upregulation of HCN expression in human granule cells of TLE patients might signify an involvement of these channels in the epileptogenic process. Mechanisms for HCN upregulation may include the recurrent seizures (Brewster et al. *J Neurosci* 2002) or the increased activation of these channels by aberrant γ-aminobutyric acid (GABA)ergic innervation (sprouting), and might constitute a compensatory mechanism, in attempt to attenuate the impact of dendritic excitatory input on granule cell firing (Poolos and Johnston, 2001). The implications of these data for epileptogenesis are under investigation. [Supported by EFA (R.A.B.), NS02808 and NS38992 (G.W.M.), NS35439 and NS28912 (T.Z.B.).]

3.039
DOWNREGULATION OF GLUTAMINE SYNTHETASE IN THE HUMAN EPILEPTOGENIC HIPPOCAMPUS DESPITE GLIAL PROLIFERATION: A KEY TO SUSTAINED LEVELS OF GLUTAMATE DURING SEIZURES?

Tore Eid, Marion J. Thomas, Dennis D. Spencer, Ole P. Ottersen, and Nihal C. de Lanerolle (Department of Neurosurgery, Yale University School of Medicine, New Haven, CT; Department of Anatomy, University of Oslo, Oslo, Norway)

Rationale: Increased ictal concentrations of extracellular glutamate have been demonstrated by in vivo microdialysis in the epileptogenic

hippocampus compared to the nonepileptogenic hippocampus in patients with mesial temporal lobe epilepsy (MTLE). In the present study we explored the possibility that the elevated levels of glutamate in MTLE could be due to a downregulation of the glutamate-detoxifying enzyme, glutamine synthetase (GS) in astrocytes in the epileptogenic hippocampus. **Methods:** Sclerotic (MTLE) and nonsclerotic human hippocampi were obtained from neurosurgical treatment of drug-resistant TLE. After surgery, the tissue was immersion fixed, sectioned, and immunostained for GS. The pattern of immunostaining in sclerotic hippocampi (where the seizure focus resides in the hippocampus) were compared to that of nonsclerotic hippocampi (where the seizure focus is not in the hippocampus). **Results:** GS staining was found in astrocytes in both sclerotic and nonsclerotic hippocampi. In the sclerotic hippocampi the Ammon's horn was characterized by neuronal loss and glial proliferation, especially in area CA1. However, in the glia in the sclerotic area CA1 and to a lesser degree in the hilus, the expression of GS was markedly reduced. In contrast, in the nonsclerotic hippocampi, numerous GS-positive glial cells were present thoughout all hippocampal subfields. **Conclusions:** This observation supports the hypothesis that a deficiency of GS may underlie the ictal accumulation of glutamate in the epileptogenic hippocampus in MTLE. (Supported by NIH grant P01 NS39092-01.)

3.040

NEO-TIMM STAINING IN HUMAN HIPPOCAMPI FROM TEMPORAL LOBE EPILEPSY PATIENTS: IT IS ALWAYS ASSOCIATED WITH HIPPOCAMPAL SCLEROSIS AND PROGRESSIVELY INCREASES WITH LONGER SEIZURE DURATION

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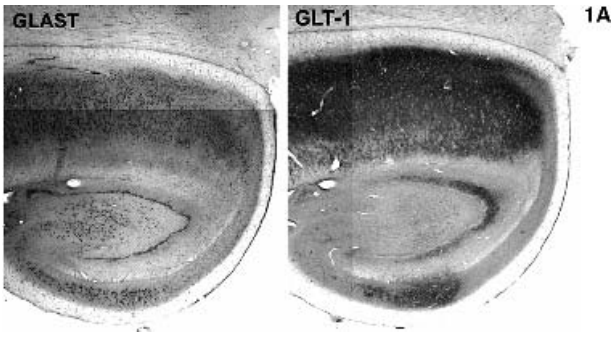
Rationale: Hippocampal fascia dentata aberrant mossy fiber sprouting is a frequent pathological finding in human temporal lobe epilepsy patients. Previously studies have reported hippocampal sclerosis (HS) patients without mossy fiber sprouting, but this was based on dynorphin immunostaining not neo-Timm staining, which is often more sensitive. It is therefore controversial whether aberrant sprouting is always associated with HS patients, and how often significant sprouting occurs in cases without sclerosis. **Methods:** Neo-Timm stain and cell counts were performed on 193 surgical and 10 autopsy cases. Supragranular neo-Timm staining was measured by image analysis as the gray value (GV) difference between the inner and outer molecular layer (IML-OML GV). Surgical cases were classified as cryptogenic ($n = 38$), HS ($n = 116$), lesion only ($n = 19$), or dual pathology ($n = 20$). Clinical variable included age at seizure onset, duration of seizures, etc. **Results:** All cases of hippocampal sclerosis (mean ± SD: 107 ± 25) demonstrated significant supragranular mossy fiber sprouting compared with autopsy cases (9.9 ± 8.3; $p < 0.0001$). Based on the IML-OML GVs, three ranges could be determined: GVs in the autopsy range (mean ± 2SD; no sprouting), GVs between autopsy and HS cases (indeterminate sprouting), and GVs in HS range (mean ± 2SD; significant sprouting). In cryptogenic cases, 69% were in the HS range, 24% were indeterminate, and 7% showed no sprouting. For lesions, 88% were in the HS range, 6% were indeterminate, and 6% showed no sprouting. In dual pathologies, 93% were in HS range, and 7% ($n = 1$) showed no sprouting. IML-OML GVs inversely correlated with hilar cell densities ($p < 0.0001$), and positively correlated with habitual seizure duration ($p = 0.002$). **Conclusions:** Significant supragranular mossy fiber sprouting is found in all cases of HS, indicating it is an important pathological marker of epileptogenesis. In addition, severe sprouting occurs in most surgical cases with cryptogenic, lesion, or dual pathologies despite less hippocampal cell loss, suggesting that synaptic reorganization is a common feature in human TLE. The increase in sprouting with longer seizure duration regardless of pathological substrate supports the notion that there is a slow progression of pathological changes in human TLE as a consequence of repeated seizures, similar to previous reports from our laboratory showing progressive hippocampal cell loss. (Supported by NIH P01 NS02802 and NS38992.)

3.041

ALTERATIONS IN GLIAL GLUTAMATE UPTAKE AND METABOLISM IN AREAS OF SCLEROSIS IN TEMPORAL LOBE EPILEPSY

Alexander A. Sosunov, Robert R. Goodman, and Guy M. McKhann II (Neurological Surgery, Columbia University, New York, NY)

Rationale: Astrocytes are critically important regulators of glutamate in the central nervous system, clearing neuronally released glutamate from the extracellular space and subsequently cycling glutamate to glutamine via the enzyme glutamine synthetase or converting glutamate for utilization in the TCA cycle via the enzyme glutamate dehydrogenase (GDH). To test the hypothesis that glutamate uptake and metabolism are impaired in areas of hippocampal sclerosis in human temporal lobe epilepsy, we carried out immunohistochemical analysis of glutamine synthetase (GS), GDH, and astrocytic glutamate transporter proteins in resected human hippocampi. **Methods:** Fifteen hippocampi obtained from temporal lobe epilepsy surgeries were studied. Double-labeling immunohistochemistry combined with confocal microscopy was used to evaluate the neuroglial capacity for uptake and metabolism of glutamate. **Results:** As detected by MAP-2 staining, all cases had hippocampal sclerosis, with marked neuronal loss in the CA1, CA3, and hilar regions. Astrocytes in these sclerotic areas had high levels of glial fibrillary acidic protein (GFAP) and S100b expression, in contrast to very weak immunoreactivity for GS. In contrast, in less sclerotic regions (subiculum, CA2, molecular layer of dentate gyrus), high levels of astrocytic GS immunoreactivity were detected, with lower expression of GFAP and S100b. Figure 1A demonstrates representative immunostaining of human epileptic hippocampus showing increased GFAP and decreased GS expression in areas of sclerosis. No difference was seen in GDH expression in sclerotic and nonsclerotic areas of hippocampus. Immunoreactivity for the astrocytic glutamate transporters GLAST and GLT-1 was visualized in nonsclerotic regions but markedly decreased in areas of sclerosis (Fig. 1B). Unlike astrocytes, oligodendrocytes displayed high levels of GS immunoreactivity in sclerotic areas but were GS negative in nonsclerotic regions. S100b expression was observed in oligodendrocytes only in nonsclerotic areas. **Conclusions:** In areas of hippocampal sclerosis, astrocytes express low levels of glutamate transporters and GS, suggesting that glutamate clearance and metabolism are impaired in these regions. There may be compensatory glutamine synthesis by oligodendrocytes in sclerotic tissue. [Supported by the Klingenstein Foundation, New York Academy of Medicine, and Parents Against Childhood Epilepsy (P.A.C.E) (G.M.).]



3.042
CORTICAL DYSPLASIA AND EPILEPSY: REPORT OF 15 CASES
Amel Mrabet, Mohamed Fredj, and Dalila El Bahri (Neurological Department, Charles Nicolle Hospital, Tunis, Tunisia)

Rationale: Cortical developmental malformations are a cause of refractory epilepsy and are best diagnosed by magnetic resonance imaging (MRI).We report 15 cases of cortical dysplasia (CD) referred to our neurological department for refractory epilepsy. **Methods:** Fifteen patients with CD were assessed for age at onset, seizures type, course of seizures, EEG, MRI, response to antiepileptic drugs (AEDs), and surgery. **Results:** MRI revealed agyria, pachygyria, with polymicrogyria in 10 cases, periventricular nodular heterotopia in two cases, bilateral band heterotopia associated with corpus callosum agenesis in two cases, and schizencephalia in one case. EEGs were abnormal at the site corresponding to CD. Epilepsy was refractory. One patient had surgery and vagal nerve stimulation with significant improvement. **Conclusions:** Classification of CD has an obvious attraction, but it is still insufficient to explain all cases. A careful clinical study combined with results of EEG, neuroimaging, and other investigations should increase our knowledge of these conditions. Surgey must be considered in cases with intractable epilepsies.

3.043
CELLULAR CHARACTERIZATION OF BALLOON CELLS IN HUMAN CORTICAL DYSPLASIAS
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Rationale: Focal cortical dysplasias (CDs) are frequent causes of medically intractable epilepsy. CDs are typically characterized by the presence of dysmorphic neurons and balloon cells (BCs) in the setting of neocortical architectural disorganization. The cellular characteristics and role of BCs in focal CDs remain unknown. **Methods:** Neocortical tissue resected from three patients who underwent focal cortical resection for the treatment of medically intractable epilepsy was used in this study. Neocortical areas containing BCs were identified using cresyl violet Nissl staining. Single- and double-labeling immunocytochemical staining using various neuronal (neuronal nuclear, NeuN; and microtubule-associated protein, MAP; and TUJ1) and glial (glial fibrillary acidic protein, GFAP; and vimentin) antibodies together with antibodies against stem cell–specific proteins nestin and CD 131. The immunocytochemical staining patterns of BCs were visually studied. **Results:** BCs were mainly found in the deeper layers of the neocortex and the subjacent white matter. BCs stained positive for mature and immature neuronal markers: TUJ1 and NeuN/MAP, respectively, and both mature and immature glial cells: GFAP and vimentin, respectively. BCs in the deeper parts of the resected cortex stained positive for nestin and CD131. **Conclusions:** BCs are a heterogeneous population of cells that show neuronal or glial characteristics in the setting of severe CD in patients with medically resistant focal epilepsy. Moreover, BCs show protein characteristics of immature neurons and glial cells and exhibit features of stem/progenitor cells. These results suggest that BCs may have a potential for cell division in a postnatal brain. (Supported by NIH grant to Imad Najm.)

3.044
CONTRIBUTION OF γ-AMINOBUTYRIC ACID TYPE A RECEPTOR–DEPENDENT MECHANISMS TO EPILEPTOGENICITY IN THE HUMAN DYSPLASTIC CORTEX
Massimo Avoli, Rudy Kohling, Jacques Louvel, Irene Kurcewicz, Margherita D'Antuono, Rene Pumain, Vincenzo Esposito, Andre Olivier, and J.G. Villemeure (Neurology & Neurosurgery, Montreal Neurological Institute/McGill University, Montreal, Quebec, Canada; IRCSS Neuromed, Pozzilli (Is), Italy; Institut für Physiologie, Westfälische Wilhelms Universität Münster, Münster, Germany; U 573 INSERM, Centre Paul Broca, Paris, France)

Rationale: Taylor-type focal cortical dysplasia (FCD) corresponds to a localized disruption of cortical lamination with large, aberrant neurons. FCD patients present with medically intractable epilepsy, and thus they become candidates for surgical treatment. Histochemical analysis of surgically resected, human FCD tissue has shown an abnormal distribution of *N*-methyl-D-aspartate (NMDA) receptors and a decrease of presumptive interneurons that can, however, provide an increased number of GABAergic terminals surrounding principal cells (Spreafico et al. *Neurology* 1998;50:27). We have also found that FCD tissue slices maintained in vitro respond to 4-aminopyridine (4-AP) application by generating NMDA receptor–mediated ictal discharges along with GABA receptor–mediated potentials (Avoli et al. *Ann Neurol* 1999;46:816). We tried to determine whether and how GABA receptor–mediated mechanisms lead to ictogenesis in FCD tissue. **Methods:** We used field potential and $[K^+]_o$ recordings in slices obtained from FCD and (for comparison) from temporal lobe epilepsy (TLE) patients. The latter tissue does not present any obvious structural abnormality. 4-AP (50–100 μ*M*), the $GABA_A$-receptor antagonist bicuculline methiodide (BMI, 10 μ*M*), and glutamatergic receptor antagonists were bath applied. **Results:** Ictal discharges (duration, >10 s) were readily induced by 4-AP (n = 12 slices), while BMI (n = 3) only disclosed brief (<3 s) epileptiform discharges. Moreover, during 4-AP application, ictal discharges were shortly preceded (and thus triggered) by presumptive GABA receptor–mediated synchronous potentials. Ictal discharges were never seen in TLE slices that, however, generated GABA receptor–mediated potentials. These events persisted during blockade of glutamatergic transmission in both FCD and TLE slices and were associated with elevations in $[K^+]_o$ ≤6.5 and 4.2 m*M,* respectively. **Conclusions:** Our findings suggest that epileptiform activity in FCD tissue is initiated by a rather novel synchronizing mechanism that paradoxically relies on the activation of GABA receptors and leads to increases in $[K^+]_o$ that are larger in FCD tissue. (Supported by Canadian Institutes of Health Research and Savoy Foundation.)

3.045
ENTORHINAL CORTEX INVOLVEMENT IN NEURAL NETWORKS UNDERLYING MESIAL AND MESIAL–LATERAL TEMPORAL LOBE SEIZURES
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Rationale: Temporal lobe seizures are the most frequent type of partial seizures, and they are often drug-resistant. The underlying mechanisms of seizure generation are unknown. An increasing number of experimental works have shown evidence for the involvement of the entorhinal cortex (EC) in TLE pathogenesis. However, the role of EC in TLEs genesis has been poorly directly documented in human TLEs. This study aimed at determining the respective role of the EC and other temporal lobe structures in the genesis of TLE seizures recorded by depth electrodes (stereoelectroencephalography, SEEG) in patients undergoing presurgical evaluation. **Methods:** Twenty-four seizures from 13 patients with TLEs affecting the medial structures were analyzed. In addition to visual analysis of SEEG recordings and according to our previous studies, a nonlinear measure (nonlinear correlation) of signal interdependencies was used to evaluate the degree and direction of functional couplings occurring between temporal lobe regions during seizures. **Results:** Three patterns of seizure onset were defined: (a) Pattern 1, in which a fast low-voltage discharge is preceded by a complex of slow waves, (b) Pattern 2, characterized by the occurrence of a periodic discharge of high-voltage spikes with a frequency < 2 Hz; and (c) Pattern 3, in which no prior change is observed before the emergence of the ictal discharge in the temporal structures. During the seizure initiation, the EC was the leader structures in seizures with

pattern 3 and in patients with lesions affecting this region (pattern 1). In contrast, amygdala and hippocampus were the most important structures eliciting ictal activity in pattern 2 seizures. **Conclusions:** The temporal lobe seizures can not be restricted to a single anatomophysiologic scheme but involve various types of interactions between the neural structures. The EC is involved in seizure generation in various ways. It appears to be the key structure in seizures starting with a rapid discharges arising from the medial structures. (Supported by INSERM.)

3.046
SIGNIFICANT ELECTROPHYSIOLOGIC ALTERATIONS IN DENTATE GYRUS GLIA BUT NOT IN CA1 GLIA FROM HUMANS WITH EPILEPSY WITH TEMPORAL LOBE SCLEROSIS

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Rationale: Glia have been implicated in regulating extracellular ions, in particular K^+ via gap junction coupling and inwardly rectifying K^+ channels. It has been speculated that epilepsy is associated with a defect in the ability of glia to properly buffer extracellular ionic changes. However, little is known about the biophysical properties of glia in sclerotic human hippocampi. **Methods:** Human glia were studied using whole-cell patch-clamp recordings in acute hippocampal slices from surgical patients with intractable temporal lobe epilepsy (TLE). Data were obtained from 12 cases: four cases of intractable temporal lobe epilepsy (TLE) with hippocampal sclerosis (named mesiotemporal sclerosis, MTS) and eight "control" cases composed of two TLE cases without neuronal loss and six cases of tumors associated with seizures. Glia cells were identified based on their characteristically hyperpolarized resting membrane potential, and the lack of spontaneous action potentials and synaptic currents. **Results:** It was first apparent that in control tissue, CA1 and dentate gyrus (DG) glia have distinct electrophysiologic characteristics. CA1 glia display prominent cell-to-cell dye coupling and therefore have significantly lower membrane resistances than DG glia (see Table 1) that are not dye coupled. This result could indicate differences in glial K^+ buffering in these two regions. In MTS patients, there is a significant decrease in inward K^+ current amplitudes in DG glia compared to control tissue, while no significant changes were observed in CA1 glia. These currents are carried by inwardly rectifying K^+ channels. There is also a significant increase in voltage-dependent Na^+ conductances in MTS glia in the dentate gyrus as compared to control tissue, while CA1 glia do not express detectable Na^+ conductances. The functional role of such an increase Na^+ conductances is still unknown. **Conclusions:** Overall, these data strongly suggest that K^+ buffering by glia is impaired in the DG but not in the CA1 region. This could lead to significant hyperexcitability originating or being amplified in this region. (Supported by NIH P01-NS39092-03.)

TABLE 1. *Electrophysiologic properties of glia (mean ± SD)*

	MTSn, four cases	Control, eight cases	p (Student's *t* test)
Dentate gyrus	N = 22 cells	N = 7 cells	
Resting potential (mV)	−80.2 ± 8.8	−84.8 ± 7.4	
Membrane resistance (MOhm)[a]	336 ± 239	171.9 ± 77.1	0.089
Inward K^+ currents (pA/pF)	−13.5 ± 5.7	−29.3 ± 9.9	0.0013
Na conductance (pS/pF)[b]	0.36 ± 0.22	0.15 ± 0.16 (4/4)	0.0021
CA1	N = 3	N = 9	
Resting potential (mV)	−84.0 ± 2.8	−85.0 ± 6.9	
Membrane resistance (MOhm)	34.3 ± 18.0	26.6 ± 8.8	0.83
Inward currents (pA/pF, at −160 mV)	−93.7 ± 44.7	−138.0 ± 35.1 (6/6)	0.32
GNa (pS/pF)	Undetectable	Undetectable	

[a] Rm, measured at −70 mV.
[b] GNa, peak Ina/(Vm − VNa); Ina, peak sodium currents measured at a membrane potential Vm, Vna = reversal potential of Na+ ions.

3.047
OLFACTORY SHORT-TERM MEMORY AND RELATED ELECTROPHYSIOLOGIC RESPONSES OF THE AMYGDALA IN TEMPORAL LOBE EPILEPSY

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Rationale: The importance of temporal lobe structures in human olfactory function has been early recognized since the nineteenth century with the observation that olfactory auras could precede paroxysmal seizures in epilepsy patients (Jackson and Stewart, 1899). Our study determined the influence of unilateral temporal lobe epilepsy (TLE) on olfactory short-term recognition memory and also examined the related electrophysiologic responses recorded in the amygdala. **Methods:** A delayed odor-matching task was performed in 36 right- and left-TLE patients that were entering a preoperative assessment program for possible surgical treatment, which included a stereotactic electroencephalography (SEEG) procedure. Taking advantage of this procedure, the SEEG activity associated with the odorant stimulations and collected from the amygdala of 18 patients was examined as a function of hemispheric side, matching condition (match vs. mismatch), and stimulus type (sample vs. target). **Results:** Behavioral results showed global impairments of the olfactory short-term recognition memory function, evaluated in terms of hit rate, false-alarm rate, discrimination measure, and bias measure. An epileptogenic locus side effect was found, with more prominent deficits in left than in right TLE patients. We additionally evidenced a gender effect with higher false-alarm scores in male than in female patients, regardless of the side of the epileptogenic focus. Electrophysiologic recordings collected from the amygdala demonstrated that odorant stimulations were associated with olfactory evoked potentials (OEPs) consisting of two main components: a positive peak (P1) occurring at 280 ms and a negative one (N2a) at 470 ms. OEPs obtained in response to target (repeated) odorants had reduced peak amplitudes and latencies when compared to OEPs obtained in response to sample (novel) odorants. **Conclusions:** The behavioral results are discussed in terms of psychosocial traits generally observed between the different groups of patients. The electrophysiologic data are explained with regard to electrophysiologic data obtain in animals and to concepts stemming from cognitive psychology. The reduced peak amplitudes may suggest a mechanism of repetition-suppression, a process assumed to reflect neural activity related to high cognitive processes, such as attention, memory, and decision making. Latency modulations, rather appear to be linked to early stages of information processing, and may therefore reflect a facilitation process due to selective attention. (Supported by The Region Rhône-Alpes; The Roudnitska Foundation; The Medical Research Foundation.)

3.048
ADAPTIVE SEIZURE-PREDICTION SYSTEM

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Rationale: Based on the analysis of EEG recordings from patients with temporal lobe epilepsy, we have shown that seizures occur in a deterministic fashion (Nonlinear dynamical analysis of the EEG. *World*

Sci 1993:30; *Epilepsy Res* 1994;17:81). More important, results from continuous epileptic EEG recordings indicate that, in a retrospective analysis, temporal lobe seizures are preceded by a preictal transition (*J Combin Optim* 2001;5:9). Obviously, a retrospective analysis (i.e., looking backward in time after a seizure's occurrence to try to detect a preictal transition) does not constitute seizure prediction. In the first prospective study reported (*Epilepsia* 2001;42:41), seizures could be predicted with sensitivity 86.5% and false-positive rate of 0.14 per hour about 75.4 min before their occurrence. This prediction scheme was based on the dynamics of preceding seizures. We herein report results from an improvement of that algorithm, that is, from an adaptive scheme for seizure prediction that does not depend on the occurrence and continuous detection of preceding seizures. **Methods:** The method was tested in continuous 0.76–5.84 days 28-channel intracranial EEG recordings from a group of five patients with refractory temporal lobe epilepsy. The adaptive seizure-prediction system involved the following steps: (a) translate the multichannel EEG recordings into multivariate Lyapunov (STLmax) time series, (b) select the groups of critical electrodes sites from a 10-min window before the first recorded seizure using integer quadratic optimization (training), (c) calculate the average T-index of the selected critical sites forward in time and issue a warning of an impending seizure when STLmax converge (dynamical entrainment transition), (d) reselect the critical sites using a 10-min window after the observed entrainment transition, (e) repeat steps c and d. The warning was considered to be true if a seizure occurred within 3 h after a transition was detected and false if it did not. **Results:** A fixed parameter setting (number of optimal groups and number of critical electrode sites per group selected) applied to all patients predicted 82% of seizures with a false prediction rate of 0.16/h. Seizure warnings occurred an average of 71.7 min before ictal onset. Optimizing the parameters for individual patients improved sensitivity (overall, 84%) and reduced false prediction rate (0.12 per hour). **Conclusions:** These findings suggest that this real-time seizure-prediction system, free from seizure-detection ambiguities, is capable of predicting an impending seizure with performance characteristics that could have practical clinical utility. Such a device could be incorporated in an on-line EEG monitoring system. In the future, implantable systems incorporating this type of algorithm could be used for timely activation of physiologicl or pharmacologic interventions aimed at aborting an impending seizure. [Supported by NIH/NINDS NS039687, ASU Whitaker Seed Grant, University of Florida Division of Sponsored Research, Children's Miracle Network, U.S. Veterans Affairs.]

3.049

CHARACTERIZATION OF NEURONAL ACTIVITY IN HUMAN NEOCORTICAL SLICE PREPARATIONS OBTAINED FROM THE SEIZURE FOCUS OF PEDIATRIC PATIENTS

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Rationale: The purpose of this study is to electrophysiologically characterize cortical neurons in brain slices taken from pediatric patients with focal epilepsy. Our intracellular characterization aims at identifying membrane properties that contribute to epileptic seizures pharmacologically and electrophysiologically characterized prior to the resection. **Methods:** Human neocortical tissue was removed from patients with medically intractable epilepsy. The sites selected for the slice studies were determined by source localization techniques and clinical relevance. Upon resection, the tissue was placed into artificial CSF (aCSF: 118 NaCl, 3 KCl, 1.5 $CaCl_2$, 1 $MgCl_2$, 25 $NaHCO_3$, 1 NaH_2PO_4, and 30 D-glucose, pH of 7.4) bubbled with carbogen (95% oxygen and 5 % CO_2). Slices (500 μm) were sectioned perpendicular to the gyri of the seizure focus with six layers of the cortex identifiable. The slices were immediately transferred to aCSF bubbled with carbogen and stored at room temperature. Experiments were conducted in a recording chamber at 29°C. After 30 min, the K^+ concentration was raised from 3 to 5 m*M*. Population recordings were obtained with suction electrodes positioned on the surface of the cortical layers. Intracellular whole-cell patch-clamp recordings were obtained from cortical neurons with the blind patch technique. To identify the cell layer and the cell type, cells were stained with biocytin. **Results:** Intra- and extracellular recordings were simultaneously obtained from cortical human slices. Slow oscillatory population activity was recorded in slices from several patients. In one of the slices obtained from the epileptic focus of a patient that was refractory to several anticonvulsants (AEDs), recurrent epileptiform population activity was induced by application of *N*-methyl-D-aspartate (NMDA). In the slice obtained from this patient, epileptiform activity was not blocked by any of the examined AEDs (lamotrigine, topiramate, zonisamide). At the cellular level, we identified several different types of spiking neurons: low-threshold spiking, regular spiking, and fast spiking, which had similar discharge properties as neurons previously described by Foehring et al. (*J Neurophysiol* 1991;66:1825–37). Unlike Foehring et al., we were able to identify an intrinsically bursting neuron type. Depolarizing current injection increased the frequency of bursting and bursting activity was abolished by hyperpolarizing current injections. **Conclusions:** The present study begins to characterize the activity of epileptic foci both in the pediatric patient and subsequently under in vitro conditions in a slice preparation. This approach enables us to directly compare data obtained at the cellular and network level in acute slice preparations with those obtained from clinical EEG. These observations may provide the basis for future investigations of oscillatory network behavior and mechanism specific pharmacotherapy involved in epilepsy. [Supported by Falk Foundation (W.vD., K.E.H., C.J.M.), PEW Fellowship (F.P.), Rett Syndrome Research Foundation (J.M.R.), NIH HL 60120 (J.M.R.).]

3.050

INTRACEREBRAL RECORDINGS OF THE THALAMIC PULVINAR NUCLEUS IN PHARMACORESISTANT TEMPORAL EPILEPSY

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Rationale: Few clinical works in the past and more recent studies in animals have focused on the possible participation of subcortical structures in epilepsy. Considering its widespread connectivity with medial limbic structures and temporal neocortical areas, the medial pulvinar nucleus (PuM) could be involved in epileptic activities originating in such structures. This study aims at evaluating this possibility by recording PuM activity in patients with pharmacoresistant temporal epilepsy. **Methods:** Using stereo-electroencephalographic recordings performed for presurgical examination, PuM and suspected epileptogenic zones activities were recorded in eight patients. Localization of recording sites was verified by superimposing postimplantation frontal x-ray on magnetic resonance imaging images. Signals were studied using spectral and time-frequency analysis. **Results:** During interictal period, fully awake patients presented with a peak of delta-theta activity in PuM. Avering PuM activity time-locked on cortical spikes showed that the latter were consistently followed by a potential transient in PuM. During ictal period, a clear propagation of ictal activity to the PuM was observed in seven patients who developed seizures. This thalamic activity was characterized either by the generation of rhythmic (5–12 Hz) spikes or by a recruiting low-voltage high (27–31 Hz) frequency discharge appearing 1–77 s after seizure beginning. The recruiting mode was observed only in association with neocortical discharges. In three patients, the onset of ictal activity in PuM correlated with a large seizure cortical diffusion suggesting an active participation of PuM to the seizure spread. **Conclusions:** These results demonstrate an involvement of PuM in epilepsy of temporal origin. The precise role of this thalamic nucleus in the maintenance and/or propagation of par-

oxysmal activities remains to be clarified. (Supported by Hospices Civils de Lyon.)

3.051
EFFECTS OF MAGNESIUM-FREE MEDIUM ON INTRINSIC PROPERTIES OF RAT AND HUMAN HIPPOCAMPAL CA1 NEURONS IN VITRO

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Rationale: *N*-methyl-D-aspartate (NMDA) glutamate receptors may contribute significantly to epileptiform activity induced by magnesium-free medium recognized in vitro model for the study of epilepsy. Electrophysiologic recordings from brain slices perfused with magnesium-free Ringer's solution show interictal and ictal-like seizure discharges. The aim of this study is to test the hypothesis that NMDA-receptors would alter eletrophysiologic properties of CA1 hippocampal neurons in both rats and human tissue. **Methods:** Hippocampal slices were prepared from adult male Wistar rats and surgical samples of human tissue. The rats were decapitated under deep ether anesthesia, the brains quickly removed, and 400-mm-thick slices were prepared. The hippocampal human tissues were cut into 500-μm-thick sections. The slices were kept in a prechamber at room temperature in Ringer, which was continuously bubbled with 95% O_2, 5% CO_2. The slices were then transferred into an interface recording chamber continuously perfused with an oxygenated Ringer solution. Intracellular recordings were obtained from CA1 pyramidal neurons of control adult Wistar rats, pilocarpine-induced epileptic rats, and human hipoccampal tissue. Ictal-like activity and interictal discharges were induced by perfusing the slice with oxygenated Mg^{2+}-free Ringers solution. Passive (membrane potential, input resistence, time constant) and firing properties (excitability, threshold, amplitude, and duration of the spikes) were analyzed before, during, and after perfusion with Mg^{2+}-free medium. **Results:** The control (40 cells) and epileptic (22 cells) rats show significant differences in some intrinsic electrophysiologic properties such as membrane potentials and excitability in every moment studied. The control rats show significant differences in the input resistence comparing the periods before, during, and after perfusion. These neurons displayed spontaneous single spike and/or bursts of action potentials. On the other hand, only 25% of human hippocampal neurons showed epíleptiform activity induced by the medium, and none of them had altered its electrophysiologic properties. **Conclusions:** Our data suggest that NMDA-receptor activation with Mg2+-free medium can induce electrophysiologic changes in hippocampal neurons but not in human ones. (Supported by CAPES, CNPq, FAPERGS, PUCRS, Secretaria de C&T do RS.)

3.052
MULLED WINE PREPARED WITH JAPANESE STAR ANISE INDUCED A TRANSITORY PHENOTYPE OF IDIOPATHIC GENERALIZED EPILEPSY

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Rationale: Anisatrin is a toxic sesquiterpene isolated from the seeds and carpels of the Japanese star anise (*Illicum anisatum* L.). It is a potent noncompetitive antagonist at γ-aminobutyric acid (GABA)-dependent neurons in mammals, where it possesses a picrotoxin-like mechanism of action. We report to our knowledge the first two patients with a transitory phenotype of idiopathic generalized epilepsy (IGE) related to anisatrin ingestion present in mulled wine prepared with Japanese star anise. **Methods:** Two patients aged 33 and 24 years, without personal and familial history of epilepsy, were admitted for a first generalized tonic–clonic seizure associated with vomiting in one case <24 h after mulled wine ingestion. Magnetic resonance imaging (MRI), biological screening, video-EEG were perform immediately and 1 month later. **Results:** MRI and biological screening were normal. Early EEG showed asymptomatic brief generalized spike–waves discharges mimicking IGE phenotype. Sleep and awakening EEG perform 1 month later without any treatment were normal. **Conclusions:** Following a generalized tonic–clonic seizure even with an EEG pattern of IGE, an intoxication with Japanese star anise should be suspected. Further animal studies are necessary to define the EEG phenotype of anisatrin intoxication (Kakemoto E, et al. *Biochem Pharmacol* 1999; 58:617–21).

3.053
REDUCTION OF GLUTAMATE TRANSPORTER FUNCTION IN DENTATE GYRUS GLIAL CELLS BUT NOT IN CA1 GLIAL CELLS FROM HUMANS WITH EPILEPSY AND TEMPORAL LOBE SCLEROSIS

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Rationale: Glutamate uptake is mediated by high-affinity glutamate transporters (GluTs) present in both neurons and astrocytes. Glutamate uptake into astrocytes is the most important uptake system in the central nervous system that prevents glutamate buildup and resultant excitotoxicity. Although a defect of glial glutamate uptake has been suggested, little is known about the function of glial GluTs in epileptic human tissue. **Methods:** Human glial cells were studied using whole-cell patch-clamp recordings in acute hippocampal slices from surgical patients with intractable temporal lobe epilepsy (TLE). Data were obtained four cases of intractable TLE with hippocampal sclerosis (mesiotemporal sclerosis, MTS), and eight control cases composed of two TLE cases without neuronal loss and six cases of tumors associated with seizures. To measure glutamate uptake currents, 1 m*M* D-aspartate was pressure applied on recorded glial cells. **Results:** Puff of D-aspartate induced small inward currents that were significantly reduced by 300 m*M* threo-β-hydroxyaspartate (THA), a substrate agonist of glial glutamate transporters (GluT), in all the tested glial cells. This identifies D-aspartate–induced currents as glutamate transport currents. In addition, D-asparate–induced currents were voltage dependent and strictly inwardly rectifying between –70 and +30 mV. In control tissue, CA1 and dentate gyrus glia express different levels of activity of GluTs based on their current amplitude (see Table 1). Because larger GluT currents are associated with a larger intracellular Na^+ accumulation, known to stimulate glycolysis and energy production in glia, CA1 and dentate gyrus glial cells may have some intrinsic difference in their handling of energy production in response to the neuronal demand. In MTS patients, there is a significant decrease of the GluT current amplitude in dentate gyrus glia. In addition, in nine of 18 cells tested, D-aspartate or THA did not induce any current. **Conclusions:** These data strongly suggest that glutamate uptake into dentate gyrus glia in MTS patients is impaired. This would lead to a significant increase of extracellular glutamate levels and could also result in a reduction in energy production in glia in these regions. (Supported by NIH P01-NS39092-03.)

TABLE 1. *Glutamate transporter current amplitude in glia (mean ± SD)*

	MTS	Control	p (Student's *t* test)
Dentate gyrus/hilus			
GluT currents (pA/pF)[a]	−0.28 ± 0.18 (9/18 cells)	−0.72 ± 0.09 (4/4)	0.0007
CA1			
GluT currents (pA/pF)[a]	−8.0 ± 1.0 (2/2)	−5.5 ± 1.0 (7/7)	0.014

[a] Measured at a holding potential of −70 mV.

3.054

ABNORMAL EXPRESSION OF *N*-METHYL-D-ASPARTATE RECEPTOR SUBUNITS IN DISSOCIATED CELLS FROM HUMAN PEDIATRIC CORTICAL DYSPLASIA USING SINGLE-CELL RT-PCR

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Rationale: Cortical dysplasia (CD) is the most common substrate leading to seizure surgery in children. Previous electrophysiologic studies reported that abnormal cytomegalic cells have altered *N*-methyl-D-aspartate (NMDA) currents. To determine if electrophysiological changes were related to alterations in gene expression, we studied NMDA-receptor subunits in normal and dysmorphic neurons from CD and non-CD patients. **Methods:** Neocortical samples from nine patients (six CD and three non-CD) were collected, and slices were prepared. Their ages ranged from 5 months to 8 years and were not significantly different (CD, 0.4–7.8 years; non-CD, 1.2–8 years; $p = 0.18$). For each dissociated cell, rt-PCR was performed using human primers to amplify the NMDA subunits NR1, NR2A, NR2B, and one housekeeping gene. Expression of amplified cDNA was visualized on ethidium-bromide gels. Depending on the expression pattern of the three NMDA subunits, cells were classified into four groups (presence of NR1 + NR2A + NR2B; presence of NR1 + 1 NR2, presence of NR1 only; presence of NR2(s) without NR1). **Results:** In the CD group, 51 cells were processed for PCR among which 12 (23%) were classified as abnormal-looking while 100% of the cells in the non-CD group ($n = 23$) were classified as normal-looking cells ($p = 0.01$). The distribution of NMDA subunits was significantly different comparing CD and non-CD cells ($p = 0.009$). In the non-CD group, 100% of the cells showed colocalization of NR1, NR2A, and NR2B mRNAs, whether the cell shape was pyramidal or not. In the CD group, only 63% of the cells showed the presence of the three subunits, while in 15%, NR1 and only one NR2 were expressed, in 10%, NR1 only was expressed, and 12% of the cells showed no NR1 but NR2(s). Moreover, in CD, abnormal shaped cells showed lack of NMDA subunit(s) compared with normal-shaped pyramidal neurons ($p = 0.01$). **Conclusions:** In this study, we demonstrated that the mRNA expression for NMDA subunits NR1, NR2A, and NR2B differed in CD and non-CD cells from pediatric surgical patients. In CD, some of the NMDA subunits are not expressed in all the cells. Since NMDA currents depend on subunit composition, the lack of NR2A/NR2B could induce different responses to glutamate and could be responsible for hyperexcitability and seizures. The lack of NR1, NR2A, and NR2B could also be indicative for abnormally developed or immature cells in CD. (Supported by NIH RO1 NS 38992.)

3.055

DIFFERENTIAL EXPRESSION OF SELECTED CANDIDATE GENES IN HEMIMEGALENCEPHALY

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Rationale: Human hemimegalencephaly (HMEG) is a cortical dysplasia syndrome characterized by unilateral enlargement of one cerebral hemisphere and cytoarchitectural abnormalities such as laminar disorganization, neuronal cytomegaly, and heterotopia. HMEG is highly associated with severe and intractable seizures. The molecular and developmental pathogenesis of HMEG is unknown. In view of the pervasive disruption of organized lamination in HMEG, we hypothesized that altered expression of select candidate genes may contribute to the formation of HMEG during brain development. **Methods:** We implemented cDNA array analysis as a strategy to evaluate the expression of select candidate genes in human HMEG specimens. We obtained eight HMEG surgical specimens from patients with intractable epilepsy. Poly (A) mRNA was amplified from whole HMEG sections (10 sections per case) or from tissue homogenates and after radiolabeling, was used to probe cDNA arrays containing >150 full-length cDNAs. Candidate cDNAs included neurotransmitter receptor subunits, uptake sites, growth factors, transcription factors, and cell-signaling molecules relevant to brain development. The relative expression of each mRNA was determined and compared to expression in postmortem control cortex (analysis of variance; $p < 0.05$). The expression of several of these mRNAs was corroborated at the protein level by Western analysis, ligand binding assays, or immunohistochemistry. **Results:** When compared with postmortem control brain samples ($n = 4$), we identified differential expression of >50 genes in all candidate gene families. For example, the expression of c-fos, OTX-1, and IGF-1 was significantly reduced in HMEG whereas angiopoietin-1, angiogenin, VEGF, CREB, aFGF, FGF receptor subunit, and HGF expression was significantly enhanced ($p < 0.05$). The expression of GluR1, 2, 4, and 5, as well as several γ-aminobutyric acid (GABA)A receptor subunits was reduced in HMEG. Significant reductions in NMDA-receptor subunit mRNAs were corroborated at the functional protein level as determined by ^{125}I-MK-801 binding assays. **Conclusions:** These results demonstrate new insights into candidate genes and proteins whose altered expression in HMEG may lead to abnormal cytoarchitecture and epileptogenesis. Select alterations in transcription factor gene expression may lead to aberrant expression of additional downstream mRNAs. Changes in growth and angiogenesis factor mRNA expression may lead to neural and vascular proliferation during brain development. Altered expression of neurotransmitter subunits may lead to changes in neural excitability leading to enhanced propensity for seizures in HMEG patients. [Supported by MH01658, NS39938, the Esther A. and Joseph Klingenstein Fund, and Parents Against Childhood Epilepsy (P.A.C.E.).]

3.056

HILAR SCLEROSIS IN INTRACTABLE TEMPORAL LOBE EPILEPSY

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Rationale: We have encountered a unique group of intractable temporal lobe epilepsy cases that show a significant decrease in neuronal density limited to the hippocampal CA4 and dentate fascia, which is designated as hilar sclerosis (HS). In endfolium sclerosis, the term originally defined by Margerison and Corsellis (*Brain* 1966;89:499), the dentate fascia is not included for consideration. Our aim is to find the possible clinical and other parameters that are different between conventional hippocampal sclerosis (CHS) and HS. **Methods:** We studied the hippocampal neuronal density in surgically resected hippocampi from 250 patients (median age, 30 years; M/F = 131:119), who underwent partial anterior temporal lobectomy for intractable temporal lobe epilepsy. Criteria for CHS were met when the neuronal density of CA1 was less than 60% of that of the nonepileptic postmortem hippocampal CA1. For HS, the combined average density of CA4 and dentate fascia should be <60% of that of nonepileptic hippocampi, while the CA1 neuronal density should be ≥60% compared with that of nonepileptic hippocampi. Nonparametric statistical analysis was utilized to evaluate the differences in clinical and historical parameters between CHS and HS. **Results:** The 172 of 250 cases showed a significant neuronal density decrease in either CA1 (CHS) ($n = 160$) or CA4 and dentate fascia (HS) ($n = 12$), as defined above, while the remainder (78 cases) failed to show a statistically significant decrease in the neuronal density of the fields designated. No statistically significant differences between CHS and HS were noted in age at the time of surgery (median years, 30 vs. 27.4), gender (M/F, 82:78 vs. 4:8), age at the time of the first nonfebrile seizures (median months, 23 vs. 78), or duration of nonfebrile seizure history (median years, 26.1 vs. 20.0). Other parameters that failed to show statistically significant differences include the family history of seizures, head trauma, infection, or various perinatal risk factors. However, a history of febrile seizures was shown in two of 12 HS cases (16.6%) , while it was positive in 104 of 160 CHS cases (65%) ($p = 0.0009$). Also noted were significant differences between the two conditions in the frequency of extrahippocampal pathology (eight of 160 in CHS vs. five of 12 in HS; $p < 0.0001$). Extrahippocampal pathology includes five tumors, one ab-

scess, and two ischemic disorders in CHS and five tumors in HS. **Conclusions:** In HS, as compared with CHS, cases with a history of febrile seizures are less frequent and extrahippocampal pathology is more commonly encountered, which may, in part, be responsible for the unique pattern of neuronal density decrease observed in HS. (Supported by NIH 5PO1 NS39092.)

3.057
EXPRESSION OF CYTOKINE AND CELL-DEATH PATHWAY MARKERS IN TUBEROUS SCLEROSIS

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Rationale: Tuberous sclerosis (TSC) is an autosomal dominant disorder highly associated with epilepsy that results from mutations in one of two genes. Cortical tubers in TSC are developmental malformations of the cerebral cortex characterized by disorganized lamination, disrupted radial organization of neurons, and the presence of dysplastic neurons (DNs) and giant cells (GCs) that exhibit abnormal dendritic arborization and cytomegaly. We have previously demonstrated increased expression of the cell-adhesion molecule ICAM-1 in tubers. We now investigate the expression of genes and proteins that modulate ICAM-1 expression and identify activation of a proinflammatory cytokine and cell death pathway in tubers. **Methods:** Tuber specimens were obtained intraoperatively or at postmortem examination from 15 TSC patients. Poly (A) mRNA was amplified from tuber sections and homogenates and used to probe cDNA arrays containing select candidate genes. Protein lysates from tubers were used for Western assay. Some tuber specimens were also fixed, paraffin embedded, and then sectioned for immunohistochemical analysis. The candidate genes and proteins analyzed included ICAM-1, tumor necrosis factor α (TNF-α), nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK/Erk1, Erk2), Fas, Fas ligand (Fas-L), caspase 8, and the macrophage marker CD 68. For comparison, expression of these genes and proteins was determined in perituberal cortex from TSC patients and control cortex obtained postmortem. **Results:** We confirmed the robust expression of ICAM-1 mRNA and proteins in tubers. The expression of TNF-α, NF-κB, and MAPK was increased in tuber protein lysates by Western assay compared with control cortex or perituberal cortex. TNF-α, NF-κB, and MAPK immunolabeling was increased in giant cells and dysplastic neurons. We hypothesized that an inflammatory pathway may be activated in tubers and to our surprise, numerous CD68 immunolabeled macrophages were detected in tubers, often clustered around giant cells. The expression of Fas was robust on numerous dysplastic neurons and giant cells and Fas-L was expressed by astrocytes in tubers. Caspase 8, but not caspase 2, expression was marked in numerous cell types within tubers suggesting activation of the extrinsic cell death pathway. **Conclusions:** We demonstrate the potential activation of a proinflammatory cytokine pathway as well as initiation of the extrinsic cell death cascade in tubers. The presence of numerous activated macrophages in tubers and the expression of select inflammatory markers such as ICAM-1, TNF-α, and MAPK suggest that activation of a proinflammatory cytokine signaling pathway may be a new and previously unappreciated feature of tubers. The selectivity of ICAM-1 expression may serve as an immunohistochemical marker to distinguish tubers from control cortex and non-TSC cortical dysplasia. These results suggest a possible relationship of tissue inflammation in tubers with epileptogenesis and may lend insights into understanding infantile spasms in TSC. Activation of the extrinisic cell death pathway suggests that a population of cell types may undergo apoptosis in tubers. [Supported by Tuberous Sclerosis Alliance and the Center Without Walls, MH01658, and the Esther A. and Joseph Klingenstein Fund (P.B.C.).]

3.058
EXTRATEMPORAL BRAIN LESIONS ASSOCIATED WITH IPSILATERAL TEMPORAL LOBE EPILEPSY

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Rationale: Dual pathology in temporal lobe epilepsy has been reported. Although extrahippocampal temporal brain lesions presenting with mesial temporal epilepsy are relatively common, brain lesions anatomically remote from the temporal lobe associated with mesial temporal epileptic foci are rare. The mechanism of secondary epileptogenesis in humans remains uncertain. **Methods:** Three patients, one with a parietal intraventricular meningioma and two with vascular malformations in the frontal and occipital regions associated with mesial temporal lobe epilepsy, are described. Patient 1, a 38-year-old woman, developed simple partial seizures shortly after undergoing a right parietal craniotomy to excise an intraventricular meningioma; 10 years later, she developed complex partial seizures. Treatment with >10 different anticonvulsants (AEDs) did not control these seizures. Nineteen years later, magnetic resonance imaging (MRI) of brain showed a small recurrent meningioma, right parietal encephalomalacia, and right hippocampal atrophy. EEG study with subdural electrodes recording revealed active epileptic discharges from the right parietal region and ictal discharges from the right mesial temporal region. Patient 2, a 30-year-old patient, who had a frontal arteriovenous malformation (AVM) with generalized seizures, presented with complex partial seizures within 1 year after undergoing an AVM excision; depth electrode recording disclosed an ipsilateral mesial temporal ictal discharges. This case was reported previously. Patient 3, a 41-year-old patient, had occipital vascular malformations. Ictal epileptic discharges from the ipsilateral mesial temporal region were confirmed by EEG. All three patients underwent anterior temporal lobectomy and hippocampectomy. Patient 3 did not undergo excision of the occipital vascular lesion because of the risk of contralateral hemianopsia. **Results:** Patient 1 became seizure free after the right anterior temporal lobectomy, right parietal cortical excision, and removal of the recurrent meningioma; pathology confirmed hippocampal sclerosis. Patient 2 had good improvement in seizure control after the right frontal AVM excision followed by the right anterior temporal lobectomy. Patient 3 remains seizure free after 10 years. **Conclusions:** Potential relevance of kindling and secondary epileptogenesis was observed in these three patients. At the end of the presentation, the participants may discuss the mechanism of possible secondary epileptogenesis in human.

3.059
ALTERATIONS IN TIMING OF SECRETION OF LUTEINIZING HORMONE AND INTERACTION WITH PROLACTIN IN TEMPORAL LOBE EPILEPSY IN MEN

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Rationale: To investigate chronic and postictal alterations in hormonal secretion and circadian timing in limbic epilepsy. Mesial temporal lobe epilepsy (MTLE) has been associated with abnormalities of reproductive physiology, but the mechanisms of hormonal dysregulation are not clear. The acute impact of seizures could alter hypothalamic function, represented by the downstream secretion of luteinizing hormone (LH) and its interaction with prolactin (PRL). Previous analyses revealed that postictal LH secretion is less orderly than baseline secretion patterns. The present study evaluates the interictal and postictal interaction of LH and PRL and the circadian timing of LH in MTLE. **Methods:** We characterized LH and PRL secretion in patients with MTLE during two 24-h epochs: a interictal baseline, and a postictal interval initiated by an electrographically confirmed spontaneous seizure. Males, rather than females, in these pilot studies studied to ensure that menstrual cycles could not account for differences between epochs. Serum LH and prolactin were measured every 10 min. Deconvolution analysis defined hormone secretion in terms of interpulse interval, amplitude, and mass. Cross approximate entropy (XApEn) of concentration–time data quantified the interaction of LH and PRL release. The time of day of maximum hormone secretion was calculated from the cosinor estimate of grouped data. Time estimates were compared to data from 10 healthy controls. **Results:** Ten men with epilepsy completed both inter- and postictal epochs. As reported previously, means of interpulse interval, mass, and amplitude did not differ sig-

nificantly between baseline and postictal epochs, although interpulse interval of LH tended to be increased postictally (75 vs. 81 m, paired *t* test, p = 0.40), and PRL interpulse interval decreased postictally (75 vs. 58 m, p = 0.06). The concentrations of LH and PRL showed no significant interactions in timing by XApEn analysis. However, seizures caused a phase advance of >8 h in the time of maximal secretion of LH (08:22 ± 45 min SD vs. 00:43 ± 53 min). Both baseline and postictal phase of LH secretion differed from that of healthy controls (03:11 ± 23 min). **Conclusions:** In men with intractable MTLE, the pulsatile secretion of LH and PRL have no clear correspondence either at baseline or postictally, suggesting that mechanisms of dysregulation for these two hormones are dissimilar. Seizures, however induce phase shifts in the daily secretion pattern of LH. Altered timing of neuroendocrine pulse patterns may underlie other disorders of homeostasis in MTLE. [Supported by General Clinical Research Center at the University of Virginia (NIH-M01RR00884, NINDSK08-02021 (M.Q.).]

3.060

SUBACUTE ELECTRICAL STIMULATION IN HIPPOCAMPUS OF PATIENTS WITH TEMPORAL LOBE EPILEPSY ENHANCES THE TISSUE LEVELS OF INHIBITORY AND EXCITATORY AMINOACIDS

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Rationale: Patients with temporal lobe epilepsy (TLE) present decreased γ-aminobutyric acid (GABA) content in the epileptic area (hippocampus). In contrast, subacute electrical stimulation of the hippocampus (SAHCS) in patients with TLE induces inhibitory effects. We suggest that the SAHCS in patients with TLE increases the content of inhibitory aminoacids. **Methods:** The tissue content of inhibitory and excitatory amino acids was determined by HPLC technique, in hippocampus and parahippocampus surgically resected from patients with TLE pharmacologically resistant and submitted to SAHCS (SAHCS group) (n = 4). SAHCS consisted on continuous stimulation with biphasic pulses (130/s in frequency, 0.45 s in duration with an amplitude of 0.2–0.4 mA, and delivered by a Medtronic DBS pulse generator. Control tissue was obtained from subjects dead by accident without neurologic damage (C group, n = 3) and patients with TLE without electrical stimulation (E group, n = 10). **Results:** When compared with the E group, the SAHCS group showed hippocampal increased levels of GABA (332%), taurine (126%), glycine (114%), glutamine (220%), and glutamate (296%), whereas in parahippocampus, there were high levels of taurine (156%), glutamine (181%), and aspartate (199%). In contrast with the C group, the E group did not show significant changes. **Conclusions:** These results suggest that the SACHS activates inhibitory and excitatory neurotransmitters in hippocampus and parahippocampus of patients with TLE. It is possible that the cerebral electrical stimulation with antiepileptic effects in the epileptic focus and its surrounding area, stimulates endogenous mechanisms that restrict or reduce the seizure activity. [Supported by CONACyT (grant 31702-M).]

3.061

DIFFERENTIAL PATTERNS OF MOSSY FIBER SPROUTING IN CHILDREN AND ADULTS WITH INTRACTABLE MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Patients with mesial temporal lobe epilepsy (MTLE) characteristically present a history of IPI and onset of complex partial seizures by the end of first or second decade of life. In the present study we evaluate if hippocampal structural changes in pediatric temporal lobe epilepsy (TLE) are progressive and differ from those in adult patients. Hippocampi from children and adolescents with intractable TLE were compared with those from adult patients for granule cell dispersion (GCD) and intensity of mossy fiber sprouting (MFS). **Methods:** Pediatric patients with <12 years of epilepsy were evaluated at Ribeirão Preto Epilepsy Surgery Program using protocols previously published and approved by Ethics Committee. Cases for this study were selected from temporal lobectomies between 1996 and 2000. Evaluation included a detailed history and neurologic examination, interictal/ictal video-EEG monitoring, neuropsychological test, magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT). Preoperative data localized the focus to the anterior temporal region and patients were referred for a standardized en bloc resection including 2–3 cm of the hippocampus. At surgery, hippocampi specimens were cut transverse to the long axis and processed for Nissl and neo-Timm stainings. Pediatric patients with short epilepsy duration (SD ≤10 years, n = 11) were compared to adults with long duration (LD ≥22 years, n = 10). Fascia dentata (FD) width and MFS gray values were measured on hippocampi slices using an Image Analysis System (NIH Image). **Results:** Hippocampi from pediatric group (n = 11) had less intense mossy fiber staining in the inner molecular layer (mean, 109.70; SEM ±8.17) than adults (mean, 140.56; SEM, ±9.96; p = 0.026). No differences in granular cell dispersion were found between groups. **Conclusions:** Our results suggest that GCD does not progress as a consequence of epilepsy duration but supragranular MFS increases with age. This finding supports the notion that there may exist some progressivity after intractability is established in children. [Supported by CNPq, PRONEX, and FAPESP (Proc. 99/11729-2, 00/01773-3); Brazil.]

Experimental Animal Models

3.062

IN VIVO RECORDINGS FROM KETOGENIC DIET–FED Kcna1-NULL MICE, LACKING THE Kv1.1 CHANNEL SUBUNIT

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Rationale: The Kcna1-null mouse presents with recurrent spontaneous seizures beginning during the second to third postnatal week, providing a clinically relevant model of developmental epilepsy. In vivo electrophysiological recordings were conducted in the dentate gyrus of Kcna1 wild-type (+/+), heterozygote (+/-), and knockout mice (-/-) to investigate potential genotypic differences in network excitability. We also examined the effects of a ketogenic diet (KD), a treatment for children with intractable epilepsy, on excitability in the Kcna1 -/- mouse. **Methods:** Postnatal day 37–47 animals (-/-, n = 14; +/-, n = 9; and +/+, n = 8) were anesthetized with urethane (1.5 g/kg) and electrodes were positioned ipsilaterally into the granule cell layer of the dentate gyrus (recording) and the angular bundle (stimulating). Paired pulses (0.1 Hz) were delivered to assess network inhibition/facilitation within the dentate gyrus, using interstimulus intervals (ISIs) of 30, 70, and 250 ms. In addition, stimulus trains (pulses of 0.3-ms duration, 20 Hz, 30-s train) of increasing intensities were administered until electrographic seizure (maximal dentate activation) threshold was determined. Half the mice in each genotypic group were fed either a normal diet (ND) (Rodent Chow, Purina) or a ketogenic diet (Bio-Serv, F-3666) beginning at age P18-21. Diets were maintained for >17 days and fed ad libitum. Plasma β-hydroxybutyrate (BHB) levels were assessed using a Keto-site reflectance meter. **Results:** For ND-fed mice, a greater paired-pulse population spike inhibition (in response to one-half maximal stimulation) was seen at the 30-ms ISI in the Kcna1 -/-

mice (n = 6), compared to the +/+ (n = 3, p < 0.001) and +/- (n = 4, p < 0.025) mice. Kcna1 -/- mice also showed a higher threshold to maximal dentate activation compared to +/+ or +/- ND-fed littermates. Preliminary observations comparing ND- and KD-fed animals indicate that ND-fed Kcna1 -/- mice showed more paired-pulse inhibition compared to KD-fed -/- animals at all intervals tested (30, 70, and 250 ms). There were no other diet-induced differences across genotypes. **Conclusions:** These data indicate that the spontaneously-epileptic Kcna1 -/- mice exhibit enhanced early inhibition to paired-pulse stimulation within the dentate gyrus and an elevated threshold to electrographic seizures at 5–6 weeks of age. This finding is consistent with previous work demonstrating augmented inhibition in other chronic seizure models. Preliminary results of ketogenic diet treatment do not indicate that KD further augments this inhibition. [Supported by the University of Washington Pediatric Epilepsy Research Center and the NIH-RO1 DC03805 (B.L.T.).]

3.063
STATE-SPECIFIC NONLINEAR NEURODYNAMIC FEATURES IN AN ANIMAL MODEL OF GENERALIZED EPILEPSY

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Rationale: Methods derived from the theory of nonlinear dynamics have allowed the identification of a preictal phase in a generalized animal model of epilepsy in which the H218/AGR16/edg-5/LPB2 sphingosine 1-phosphate gene has been disrupted (Carney et al., 2001). This study tests the hypothesis that specific neurodynamic changes are state specific and can be identified in the EEG signal using the short-term maximum Lyapunov exponent (STLmax) as a measure of stability. After reviewing this abstract, the participants should be able to distinguish state specific nonlinear neurodynamical features in an animal model of generalized epilepsy. **Methods:** Daily bifrontal and bilateral hippocampal intracranial video-EEG recordings were obtained in postnatal days (P) 18–25 H218 mice (n = 8) and in littermate controls (n = 2) to determine seizure periods, awake, and sleep states. Seizures were characterized by generalized spike-and-wave discharges (SWDs) with categorical behavioral changes. During wakefulness, EEG activity consisted of continuous, well-modulated and organized, 8- to 10-Hz activity. Sleep was identified by the presence of bifrontal 12- to 14-Hz spindles lasting between 2 and 5 s. STLmax values were estimated every 10.24 s for each electrode site in H218 mice (P18–25) and littermate controls. Random samples of STLmax from the left frontal electrode were selected from both awake and sleep states in the following three cases: (a) seizure period in H218 mice (n = 8), (b) seizure-free period in H218 mice (n = 8), and (c) littermate controls (n = 2). In each case, mean values of samples of the awake and sleep states were compared by employing the distribution free Wilcoxon rank-sum test. **Results:** Seizures were observed only during the awake state in P18–25 H218 mice (n = 8). During the SWD seizure period, STLmax mean values were 2.52 during the awake state and 2.77 during the sleep state (p value = 0.0213) in H218 mice (n = 8). During the seizure-free interval, STLmax mean values were 2.55 during the awake state and 3.08 during the sleep state (p value = 0.0003). STLmax mean values in littermate control mice were 2.16 during the awake state and 1.97 during the sleep state (p value = 0.4061; n = 2). **Conclusions:** Mean STLmax values were lower in the awake state than in sleep in H218 mice (P18–25). Mean STLmax values were lower in the sleep state than during the awake state in littermate controls. The results suggest that brain dynamics were more ordered (lower STLmax mean value) during the awake state in H218 seizure-prone mice. Although STLmax values were lower (more ordered state) during sleep than during wakefulness in littermate controls, the difference was not statistically significant. Thus, mean STLmax as a measure of brain dynamics may be a sensitive tool to determine arousal state specificity. These findings may help to distinguish arousal state changes from preictal dynamical transitions that have been observed to precede seizures. (Supported by NIH/NINDS NS039687, University of Florida Division of Sponsored Research, Children's Miracle Network, U.S. Veterans Affairs.]

3.064
CARBACHOL-INDUCED SEIZURE SUSCEPTIBILITY IN THE FRAGILE X MOUSE

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Rationale: Fragile X syndrome is a common inherited cause of mental retardation in children. A high prevalence of complex partial epileptic disorders is seen in these patients (20–30% of the cases). Here, we used brain slices obtained from wild type (WT) and Fragile X knockout (KO) mice to identify the cellular and pharmacologic mechanisms underlying the epileptiform activity induced by the cholinergic agent carbachol (CCh) in the subiculum. This limbic structure is involved in seizures recorded in patients presenting with partial seizures. **Methods:** We used field potential recordings from slices of the subiculum of WT and KO mice, during bath application of CCh. **Results:** Epileptiform discharges in WT animals were elicited only when concentrations of CCh >70 μM were used. These epileptiform events were characterized by series of oscillations at 5–15 Hz that rode a DC negative shift (1–4 mV in amplitude), occurred at intervals of 2–2.5 s, and lasted 0.2–8 s (n = 4). By contrast, similar epileptiform activity were induced in KO slices with CCh concentrations as low as 25 μM (n = 8). Next, we investigated which muscarinic receptor subtypes contribute to the generation of CCh-induced epileptiform activity. Similar antagonistic effects were induced on CCh-induced epileptiform discharges in both WT an KO slices with methoctramine (1μM, n = 3; an M2 antagonist), 4DAMP (1 μM; n = 3; an M3 antagonist). In contrast, pirenzepine (1 μM; n = 3; an M1 antagonist) made epileptiform activity disappear in WT slices only. **Conclusions:** Our findings demonstrate that subicular networks in Fragile X mice have an increased susceptibility to generate CCh-induced epileptiform discharges. These differences in muscarinic receptor mechanisms may underlie both learning and memory deficits and epileptic disorders in Fragile X patients. [Supported by Fragile X Research Foundation of Canada and Canadian Institutes of Health Research (CIHR).]

3.065
THE AMYGDALA IS A CRITICAL SITE IN THE NEURONAL NETWORK FOR BOTH BRAINSTEM- AND FOREBRAIN-DRIVEN COMPONENTS OF AUDIOGENIC SEIZURES

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Rationale: Considerable previous work has established that the network nuclei required for audiogenic seizures (AGSs) reside exclusively in the brainstem. The forms of AGSs that have led to this conclusion include the severe seizure strain of genetically epilepsy-prone rats (GEPR-9s) and the Wistar AGS-susceptible rats of Strasbourg, which both exhibit tonic seizures. Highly epileptogenic forebrain limbic structures, such as the amygdala (AMG) and perirhinal cortex (PRC), which are critical in producing the facial and forelimb (F&F) clonus characteristic of forebrain-driven seizures, are not requisite structures in the neuronal network in the well-studied forms of AGSs. However, the AMG becomes a critical component of the expanded seizure network in the Wistar and GEPR-9 forms of AGSs after repetitive induction of AGSs (AGS kindling). The less well-studied moderate seizure strain of genetically epilepsy-prone rats (GEPR-3s) exhibits running and bouncing (R&B) clonic (but not tonic) behaviors during AGSs. After AGS kindling in GEPR-3s, F&F clonus began to occur immediately follow-

ing the R&B clonic AGSs. Recent studies in GEPR-3s suggest that the neuronal network for AGSs involves the same brainstem sites that have previously been implicated in other forms of AGSs. However, the role of forebrain sites such as the AMG and PRC in the neuronal network for seizures has not been evaluated in GEPR-3s. **Methods:** Cannula guide tubes were stereotaxically implanted bilaterally over the lateral AMG or PRC in GEPR-3s in ketamine/xylazine-anesthetized rats. At least 7 days later focal microinjections (0.2 for 5 min or 0.25 μl/min/side for 2 min) of a NMDA-receptor antagonist (2-amino-7-phosphonoheptanoate, AP7) or saline vehicle were carried out in behaving GEPR-3s through cannulae inserted into AMG or PRC. Histologic verification of the microinjection sites was subsequently carried out. **Results:** Microinjection of AP7 (1 nmol/side) in AMG significantly decreased AGS severity at 30 min after infusion in both kindled and nonkindled GEPR-3s with recovery by 24 h. AP7 (7.5 nmol) in the AMG reversibly (by 24 h) blocked AGS and F&F clonus at 30 min after infusion in kindled GEPR-3s. The 0.2 nmol dose of AP7 in AMG significantly and reversibly (by 24 h) reduced the incidence of F&F clonus 30 min after infusion in AGS kindled GEPR-3s without affecting R&B clonic AGSs. Microinjection into PRC of AP7 (1 nmol) significantly and reversibly (by 24 h) reduced the incidence of F&F clonus 30 min after infusion of AGS kindled GEPR-3s but did not affect R&B clonic AGSs in kindled or non-kindled GEPR-3s. **Conclusions:** The ability of AP7 in the AMG to block AGSs completely indicates that the AMG plays a critical role in the network for AGSs in GEPR-3s, unlike the GEPR-9 and Wistar forms of AGSs. The finding that lower doses of AP7 in the AMG block F&F clonus with no effect on R&B clonic AGSs suggests that the AMG plays a critical role in the neuronal network for both R&B clonic AGSs and AGSs kindling-induced F&F clonus. The effects of PRC microinjections in GEPR-3s suggest that this site is only a critical component in the expanded seizure network induced by AGS kindling. (Supported by NIH AA 11628.)

3.066
SEIZURE SENSITIVITY IN INBRED MOUSE STRAINS: RELATIONSHIP TO KCNJ10 POLYMORPHISM

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Rationale: To identify seizure susceptibility genes in mice, we have used a strategy involving quantitative trait locus (QTL) mapping, congenic strain characterization and candidate gene analysis. Previous work from our laboratory documented a locus on distal chromosome 1 that mediates a large part of the dramatic difference in seizure sensitivity between C57BL/6 (B6) (resistant) and DBA/2J (D2) (sensitive) mice. Studies of genes in the critical interval identified a Thr/Ser (B6/D2) polymorphism (C785G) in a potassium ion channel gene (Kcnj10) which makes it a high-priority seizure susceptibility candidate. Our objectives were to reduce further the size of the critical interval using B6/D2 congenic strains and to correlate seizure sensitivity with Kcnj10 genotype in other common inbred mouse strains. **Methods:** A series of chromosome 1 interval specific B6.D2 ($n = 6$) and D2.B6 ($n = 3$) congenic strains and common inbred strains ($n = 15$) of mice ($n =$ 10-20/strain) were tested for maximal electroshock seizure threshold (MEST) using a single daily shock with a stepwise (1 mA/day) increment in current until a maximal seizure (tonic hindlimb extension) was elicited. Brain tissue was used for RNA isolation followed by RT-PCR for amplification of Kcnj10. An RFLP assay based on the C785G polymorphism was used to determine Kcnj10 genotype for each strain. **Results:** Results showed that all C57-related strains ($n = 5$) harbor the B6-like (Thr) Kcnj10 polymorphism, and this corresponds to a higher MEST. An exception is the C57BLKS strain which exhibits the B6 polymorphism but a D2-like MEST. All other strains ($n = 10$) exhibit the D2-like (Ser) Kcnj10 polymorphism and tend to have a lower MEST. Reciprocal B6/D2 congenic strains confirm the strong distal chromosome 1 influence on MEST and have allowed systematic reduction of the critical interval to ~3 cM. **Conclusions:** Strain survey results provide evidence for a close correspondence between MEST and a genetic variation in Kcnj10 but as well emphasize the multifactorial nature of seizure sensitivity in common strains of mice. Congenic strain studies document that the critical interval contains Kcnj10 and together with survey results support its continued evaluation as a seizure susceptibility gene. (Supported by NIH grants NS33243 and NS40554.)

3.067
THE FRINGS MONOGENIC AUDIOGENIC SEIZURE-SUSCEPTIBLE (*MASS1*) GENE MUTATION IS ASSOCIATED WITH A LOWER THRESHOLD FOR BRAINSTEM SEIZURES

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Rationale: The Frings audiogenic seizure-susceptible mouse is a genetic model for sensory-evoked reflex seizures. The audiogenic seizure phenotype in the Frings mouse is the result of a single spontaneous mutation producing a premature stop codon in *mass1*. Recently, longer isoforms encoded by alternate transcripts have been identified as a new member of the very large G protein–coupled receptor subfamily. The present study tests the hypothesis that the *mass1* mutation alters intrinsic neuroexcitability in Frings mice and in a congenic strain with the Frings *mass1* alleles placed on the C57BL/6 background. **Methods:** Regional neuroexcitability was assessed by determining transcorneal electroconvulsive thresholds for minimal clonic (60 Hz, 0.2 s), maximal tonic (60 Hz, 0.2 s), and psychomotor-partial (6 Hz, 3.0 s) seizures. The thresholds for each electroconvulsive seizure test were measured in both genders of Frings, SWR/J, C57BL/6 and congenic (Frings × C57BL/6) mice. Statistical significance between groups was determined using Probit analysis. **Results:** For each of the electroconvulsive seizure tests, results obtained from Frings mice were compared to those from SWR/J mice, and results from C57BL/6 mice were compared to those from congenic mice. In general, the C57BL/6 and congenic mice exhibited higher electroconvulsive thresholds than Frings and SWR/J mice, and male mice displayed higher thresholds than female mice within each strain. In the maximal electroconvulsive seizure test, the congenic mice exhibited a significantly lower seizure threshold compared to the C57BL/6 mice (females, $p < 0.05$; males, $p < 0.01$), and the Frings female mice were lower compared to the SWR/J female mice ($p < 0.01$). For the psychomotor–partial electroconvulsive seizure test, the congenic female mice displayed a lower threshold compared to C57BL/6 female mice ($p < 0.01$). The minimal electroconvulsive seizure test did not reveal a difference between any of the groups evaluated. A decrease in the ratio for maximal to minimal electroconvulsive seizure thresholds for Frings and congenic mice compared to SWR/J and C57BL/6 mice was also observed. **Conclusions:** The *mass1* mutation in the Frings and congenic mice lowered the threshold for maximal electroconvulsive seizures demonstrating an effect on neuroexcitablility within the brainstem. The only evidence for lowered thresholds in the forebrain was observed in the congenic female mice. These results are consistent with the observations that audiogenic seizures predominately involve brainstem structures. The decreased ratio for maximal to minimal electroconvulsive thresholds observed in the Frings and congenic mice suggests a lowered resistance to seizure spread. [Supported by NIH grant NS38616-01 (L.J.P., H.S.W.), HHMI (L.J.P.), NIH contract N01NS42311 NINDS (H.S.W., K.S.W.), AFPE (B.D.K.).]

3.068
THE VOLTAGE-DEPENDENT CALCIUM CHANNEL SUBUNIT GENES, CACNG2 AND 4, AND THEIR ROLE IN ABSENCE SEIZURES IN MICE

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Rationale: The stargazer and waggler mice have mutations in the voltage-dependent calcium channel gamma subunit gene, Cacng2. No-

ticeably these mice have absence seizures throughout their lives. There are many other related γ subunit genes, several of which are predominantly expressed in the brain. If these genes are disrupted, do they also cause absence epilepsy in mice? To pursue this question we have made a targeted disruption of the Cacng4 gene. **Methods:** The Cacng4 gene was disrupted by replacing exon 4 encoding the carboxy terminus of the protein with a DNA cassette including the lacZ gene. This disruption was introduced into mice using standard knockout technology, and homozygous mice for the targeted disruption were studied. EEGs were measured from bipolar electrodes implanted into each cortical hemisphere. Recordings were taken daily over a 3-h interval. **Results:** The homozygous mice carrying both targeted alleles of Cacng4 were overtly normal. EEG recordings from these mice reveal that they have no significant absence seizure activity. We have now set up crosses between these mice and wagglers to introduce the Cacng4 targeted disruption onto the Cacng2 mutant background. On measuring the absence seizure activity in the double homozygotes, we noticed that the activity was markedly enhanced in the double mutant compared to the waggler mutation alone. We have further crossed the γ4 targeted mutant to other mutants associated with voltage-dependent calcium channel mutations, including stargazer-3J (a new allele of stargazer), lethargic, and tottering mouse mutants. The same seizure phenotype was also observed in stargazer-3J γ4 double homozygotes although the stargazer 3J mutant itself shows no absence seizure activity. **Conclusions:** Both waggler and stargazer-3J have residual Cacng2 expression, and neither shows the marked absence seizure activity observed in the original stargazer mutant. By introducing the mutation of the Cacng4 allele onto these backgrounds, the absence phentoype becomes more pronounced. These results indicate that these two closely-related gamma subunits both have a role in absence seizure activity. The expression pattern of these two molecules shows some overlap, for instance in the granule cell layer of the cerebellum. However Cacng2 is predominantly expressed in dorsal regions of the brain, including the cortex, hippocampus and cerebellum, whereas Cacng4 shows higher expression levels in more ventral structures, the habenulae and caudate putamen. Thus, it is probable that these results are not due to an interaction between the Cacng2 and 4 molecules but rather, that an overall depletion of these two γ subunits confers a more severe absence phenotype. (Supported by NIH NS 32801.)

3.069
BOLD fMRI AND ELECTROPHYSIOLOGICAL RECORDINGS OF SPIKE–WAVE SEIZURES IN WAG/Rij RATS

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Rationale: Previous studies demonstrate that absence seizures are generated by enhanced burst firing in both cortical and thalamic neurons. However, fluorodeoxyglucose–positron emission tomography (FDG-PET) imaging studies during human absence seizures have provided contradictory results about whether or not cerebral activity increases during absence seizures. We have used blood oxygenation level–dependent (BOLD) fMRI in a rodent model of absence seizures to map cortical and subcortical activity during seizures, and we seek to relate these signals to neuronal firing recorded electrophysiologically. **Methods:** WAG/Rij rats under fentanyl/haloperidol anesthesia exhibit spontaneous spike–wave seizures. BOLD fMRI measurements were performed in a 7-T horizontal bore spectrometer and superimposed on high-resolution anatomic images in the coronal plane. EEG was recorded simultaneously using carbon filament electrodes. Single unit recordings were performed separately under stereotactic guidance. **Results:** Comparison of ictal and interictal epochs revealed a symmetrical increase of the BOLD fMRI signal in both cortical and subcortical regions during spike–wave discharges. Increased neuronal firing during spike–wave seizures was also seen in these regions with electrophysiological recordings. **Conclusions:** Spike–wave seizures are accompanied by an increase in neuronal firing and in fMRI BOLD signals in both cortical and subcortical structures, likely representing an increase in cerebral blood flow (CBF) during these seizures. This study represents the first reported use of BOLD fMRI to map ongoing seizure activity in a human or animal model. Further studies will quantify the relationship between neuronal firing, CBF and metabolism in this model. (Supported by NIH NS02060 and the Patterson Trust.)

3.070
EFFECTS OF LINOPIRDINE ON SEIZURE THRESHOLDS OF *Kcnq2* MUTANT MICE

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Rationale: Benign familial neonatal convulsions (BFNC) is caused by reduction-of-function mutations in the genes that encode the KCNQ2 or KCNQ3 subunits of the M-type K^+ channel, which underlies the M current. The objective of the present study was to characterize the effects of the M current–selective antagonist linopirdine (LPD) on electroconvulsive seizure thresholds (ECT) in mice heterozygous for a spontaneous deletion mutation (*Szt1,* seizure threshold 1), which deletes the C-terminal half of KCNQ2, as well as the *Chrna4* locus and at least one other known gene on mouse Chr 2, *Arfgap1* (ADP-ribosylation factor 1 GTPase activating). These mice, by virtue of lethal lung defects in the homozygotes and generally normal appearance in the heterozygotes, appear much like the published *Kcnq2* null mutants of Watanabe and colleagues (2001). **Methods:** Stimulus currents of differing intensities and frequencies were delivered through transcorneal electrodes to evoke three types of seizures: partial psychomotor, minimal clonic, and maximal tonic hindlimb extension (THE). Convulsive current (CC) curves for each seizure type were constructed using BALB/cByJ and BALB.B6-*Szt1*/+ mice to elicit baseline differences in seizure threshold between the strains. At the calculated CC_{25} values, both strains were then injected with LPD (10 mg/kg) or 0.5% methylcellulose (control) and tested for each seizure type to determine the effects of LPD on seizure thresholds. **Results:** Results obtained from this study demonstrate that the seizure threshold of BALB.B6-*Szt1*/+ mice is significantly lowered relative to BALB/cByJ mice in all seizure types tested. LPD treatment significantly lowers the seizure thresholds of both mouse strains in all seizure types tested. LPD does not appear to preferentially affect one strain more than the other in partial or maximal seizure testing. Interestingly, however, when tested for minimal clonic seizures, nine of nine LPD-treated BALB.B6-*Szt1*/+ mice had seizures, with six of these nine mice progressing to maximal THE seizures. **Conclusions:** Our results show that the spontaneous *Szt1* mutation in the *Kcnq2* gene decreases partial psychomotor, minimal clonic, and maximal THE seizure thresholds as determined by ECT testing. In addition, the M current antagonist LPD further decreases the seizure thresholds of both strains, indicating that both normal- and reduced-function M-type K^+ channels are sensitive to M current antagonists. The magnitude of shift induce by LPD in the minimal clonic seizure test in the BALB.B6-*Szt1*/+ strain suggests that the *Szt1* mutation confers increased sensitivity to the effects of LPD. [Supported by NIH 5-RO1-NS-40246 (W.N.F., H.S.W.).]

3.071
TOWARD THE IDENTIFICATION OF TEETERING *(tn):* A GENE UNDERLYING ABSENCE SEIZURES IN THE MOUSE

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Rationale: Teetering *(tn)* is an autosomal recessive mouse mutation first identified in the 1960s. The homozygous mutant mice are recognisable by their ataxic gait from ~2 weeks of age. In addition, pathological examination shows that they display selective dysgenesis of the hindbrain. More recently, teetering mice have also been shown

to exhibit bilaterally symmetrical, synchronous spike–wave discharges on cortical EEG (J. Noebels, personal communication), a pattern characteristic of mouse models of absence epilepsy. We set out to identify the gene underlying the teetering phenotype by a positional cloning strategy. The gene had previously been mapped to the distal end of mouse chromosome 11 in a region displaying conserved synteny with human chromosome 17q25.3. We have used an interspecific intercross to refine the location of the *tn* gene and are currently investigating candidate genes within this defined region. The eventual identification of this gene will shed further light on the molecular basis of seizure generation. **Methods:** An interspecific intercross has been established (B6C3Fe-*a/a/tn* × CAST/Ei) to produce recombinant meioses allowing the area containing the *tn* gene to be precisely delineated. Affected F2 progeny from this cross will each contain two recombinant chromosomes 11,and these are then typed for a number of markers which display polymorphisms between the two parental strains. Genomic DNA has been extracted from 250 offspring (i.e., 500 meioses) and genotyped using the polymerase chain reaction for a panel of seven simple sequence length polymorphic markers (SSLPs) spanning the most distal 10 cM of chromosome 11. **Results:** We have narrowed the *tn* region to a 1-cM interval on distal mouse chromosome 11 between the markers *D11Mit104* and *D11Mit69,*- representing a physical distance of ~2 Mb of DNA. To refine the gene location further, novel polymorphic markers (including microsatellites and single-nucleotide polymorphisms) are being developed within the intronic sequences and 3' untranslated regions of the many genes in this genomic region. Calcium channel subunit genes are obvious candidates for teetering as four other mouse models with a similar EEG phenotype (tottering, lethargic, stargazer and ducky) have been found to possess mutations in such genes. Several calcium channel subunits map to mouse chromosome 11 including the brain expressed *Cacng4* and *Cacna1g*. However, analysis of mouse draft genome assembly resources (http://genome.cse.ucsc.edu and http//www.ensembl.org/Mus_musculus) and comparison with the corresponding human genomic region suggest that both of these genes lie outside the current region of interest. **Conclusions:** Further analysis of this region is now being undertaken to identify candidate genes which will be evaluated using RT-PCR, DNA sequencing and northern analysis. It is anticipated that the identification of the teetering gene and knowledge of the role of the gene product will further inform the process of seizure generation in the mammalian brain and may lead to the development of novel AEDs. (Supported by The Medical Research Council of the United Kingdom.)

3.072
ANALYSIS OF HIPPOCAMPAL NEURONS AND GLIA IN THE EPILEPITIC EL MOUSE

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Rationale: The epileptic EL mouse is a genetic model for complex partial seizures with secondary generalization. There is controversy whether brief, recurrent seizures result in progressive neuronal loss and synaptic reorganization. In this study, we evaluated neuronal number, mossy fiber organization, and astrocytosis in the hippocampus of epileptic EL mice. **Methods:** Epileptic EL mice (n = 6 independent mice) were compared with nonepileptic DDY (n = 4) and B6 (n = 5) mice at adult (>1 year) ages. The EL mice experienced ~25–30 handling-induced seizures by this age. All analyses were performed on 30-μm cryostat sections. An optical fractionator method was used to count Nissl stained neurons in the hilus, CA1, and CA3 regions of the hippocampus. Infrapyramidal mossy fiber organization was analyzed using the Timm silver stain and was scored using a semiquantitative scale. The distribution of astrocytes was examined using an antibody specific for glial fibrillary acidic protein (GFAP). **Results:** Timm Scores in the CA3 hippocampal region of the B6, DDY, and EL mice were 0.8 ± 0.2, 0.1 ± 0.1, 0.2 ± 0.1, respectively; and in the CA1 region were 1.1 ± 0.1, 1.5 ± 0.7, 1.5 ± 0.3, respectively. The number of neurons in these strains was 166 ± 25, 152 ± 18, and 179 ± 11 for the hilus; 634 ± 41, 644 ± 80, 612 ± 33 for the CA1 region, and 548 ± 45, 761 ± 120, 645 ± 44 for the CA3 region, respectively. None of the observed differences was significant between the EL and nonepileptic control strains. However, the number of hippocampal GFAP-positive astrocytes was significantly higher ($p < 0.05$) in the EL than in the B6 and DDY mice. **Conclusions:** These results support previous studies indicating that seizure susceptibility and seizures in EL mice are not associated with hippocampal neuronal loss, despite the presence of a significant astrocytosis. These results also suggest that neuronal loss may be necessary for aberrant mossy fiber synaptic reorganization. The EL mouse is a good model of multifactorial idiopathic epilepsy. [Supported by NIH grants HD39722 (T.N.S.) and NS27984 (G.L.H.).]

3.073
SEIZURE SUSCEPTIBILITY OF NEUROPEPTIDE-Y (NPY) KNOCKOUT MICE IN ELECTRICAL KINDLING AND CHEMICALLY INDUCED SEIZURE MODELS

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Rationale: Previous studies have shown that neuropeptide Y (NPY) has anticonvulsant effects through presynaptic effects in hippocampus that depress excitatory synaptic events, without affecting inhibition. Seizures enhance NPY expression, particularly in the frontal pyriform and entorhinal cortices and in the amygdala and hippocampus. We tested the seizure susceptibility of NPY knockout (KO) mice in different seizure models. We compared 129S6/SvEv NPY(+/+) and NPY (-/-) mice in the kindling model and as well as the kainate and pilocarpine seizure models. In addition, we determined the anticonvolsant effects of carbamazepine (CBZ) and levetiracetam (LEV) in kindled NPY (+/+) and (-/-) mice. **Methods:** A bipolar electrode was stereotaxically implanted into the right amygdala of 129S6/SvEv NPY (+/+) and 129S6/SvEv NPY (-/-) mice. Mice were given daily stimulations (400 μA, 60 Hz, 1 s) until ≥10 stage-5 (Racine scale) seizures occurred; behavioral seizure scores and EEG afterdischarge (AD) durations were recorded throughout. Postkindling seizure thresholds and AD durations were determined weekly for 4 weeks. After thresholds stabilized, the anticonvulsant effects of CBZ (30 mg/kg, i.p.) and LEV (50 mg/kg, i.p.) were determined. In chemically induced seizure models, kainic acid (20 mg/kg, i.p.) or pilocarpine (100 mg/kg, i.p.) were injected every 20 min until the first limbic seizure. The number of doses and minutes to onset of limbic seizures were recorded. **Results:** During kindling development, the NPY (-/-) mice had more severe behavioral seizure scores and longer AD durations than the NPY (+/+) mice. However, the differences between the two groups was not large. Postkindling, the NPY (-/-) mice had markedly lower thresholds and longer AD durations than NPY (+/+) mice ($p < 0.0001$). CBZ and LEV increased the seizure thresholds of both NPY (-/-) and (+/+) mice. In addition, NPY KO mice required significantly fewer doses and less time to onset of limbic seizures after both kainic acid and pilocarpine. **Conclusions:** NPY (-/-) mice were more seizure prone than NPY (+/+) mice in all seizure models, in agreement with previous investigators. The present results in the kindling model suggest that NPY may play a role in the inhibition of epileptogenesis. In addition, the present results indicate that NPY likely plays a substantial role in the severity of seizures in that both electrically and chemically induced seizures were more severe in NPY(-/-) than in NPY(+/+) mice. On the other hand, a lack of NPY does not appear to make seizures drug resistant in that CBZ and LEV were anticonvulsant in both wild-type and NPY null mutant mice. (Supported by Eli Lilly and Company.) (Disclosure: Salary: Eli Lilly and Company; Equity: Eli Lilly and Company; Stock: Eli Lilly and Company.)

3.074
NONLINEAR APPROXIMATE ENTROPY ANALYSIS OF BRAIN ELECTRICAL ACTIVITY IN A GENERALIZED EPILEPSY ANIMAL MODEL

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Rationale: Approximate entropy (ApEn), a statistic for quantifying the system regularity/complexity of a time series, has been applied on medical data analysis, such as in heart rate analysis (*Proc Natl Acad Sci U S A* 1991;88:2297). This method allows distinguishing normal from abnormal data. In theory, the smaller the ApEn value, the less ordered is the system. In this study, we apply ApEn on continuous video-EEG recordings in an animal model of generalized epilepsy in which the H218/AGR16/edg-5/LPB2 sphingosine 1-phosphate gene has been disrupted and a littermate control mouse. The aim of this study was to test the hypothesis that H218 mice and littermate controls can be distinguished by both the mean values and the variability of ApEn. After reviewing this abstract, the participants should be able to distinguish an animal model of generalized epilepsy and control mice by the complexity (or the changes of complexity) of their EEG signals. **Methods:** Continuous daily bifrontal and bilateral hippocampal intracranial video-EEG recordings were obtained in postnatal days (P) 18–25 H218 mice (n = 8) and in littermate controls (n = 2). Seizures were characterized by generalized spike-and-wave discharges (SWDs) with categorical behavioral changes. ApEn were estimated in every 10-s nonoverlapping window of EEG signals for each electrode site in three postnatal age intervals of H218 mice (P18; seizure vulnerable period, P21 and P25; seizure-free periods) and one postnatal age interval in an age-matched P18 littermate control. At each age (P18, P21, and P25), mean value and the variance of ApEn were compared with a P18 control by employing the standard two-sample *t* test and *F* test for mean and variance equality, respectively. **Results:** Mean value and variance of ApEn were 1.582 and 0.016, respectively in littermate controls. Mean values were 1.418 at P18 during the seizure-vulnerable period, 1.372 at P21 and 1.328 at P25 in H218 mice. Variances were 0.042 at P18 during the seizure-vulnerable period, 0.035 at P21, and 0.043 at P25 in H218 mice. For mean values and variances for P18–25 H218 mice were significantly different (p value <0.0001) from age-matched littermate controls. **Conclusions:** Mean ApEn values were significantly lower in H218 mice than in littermate controls. Variances of ApEn values were significantly higher in H218 mice than in littermate control. These results suggest that brain dynamics is more ordered (or less complex) in H218 seizure-prone mice, and the complexity of the brain dynamics has less variability in littermate controls. These findings may help to develop a simple algorithm to distinguish the normal and abnormal states in epileptic patients. (Supported by NIH/NINDS NS 039687, Veterans Affairs, University of Florida Division of Sponsored Research, Children's Miracle Network.)

3.075
MODULATION OF FLUROTHYL-INDUCED SEIZURES BY NORADRENERGIC RECEPTOR AGONISTS/ANTAGONISTS

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Rationale: The ability of norepinephrine (NE) to modulate seizure activity is quite clear. However, it is unclear which adrenoreceptor (AR) is responsible for NEs inhibitory action since each of the four different ARs (α1, α2, β1, and β2) have demonstrated an anticonvulsant response in various paradigms. Genetically engineered mice that lack NE (dopamine β-hydroxylase knockout mice; *Dbh* -/-) were used to determine which AR subtype modulates seizures induced by the convulsant flurothyl. α2AR-subtype knockout mice were used to determine which of the α2AR subtypes mediates the effects of clonidine (α2 agonist). These studies will indicate which noradrenergic receptor modulates flurothyl-induced seizures in mice with normal NE levels and in mice that lack NE, indicating how endogenous NE inhibits seizure activity. **Methods:** Flurothyl seizure thresholds were determined in *Dbh* -/- and *Dbh* +/- mice (controls) 30 min after the administration of different AR agonists/antagonists. To determine which α2AR subtype mediates the action of clonidine, flurothyl seizures thresholds were measured in α2A, α2C, and α2AC knockout mice 30 min after clonidine or saline. To determine if the effects of clonidine were specific to mice, flurothyl-induced seizures were determined in rats at various ages after either saline, clonidine, or idazoxan (α2 antagonist). **Results:** Four important points were determined from these studies. (a) Stimulation of α2AR with clonidine is proconvulsant in *Dbh* +/- and *Dbh* -/- mice. This proconvulsant response of clonidine is mediated through the α2A-AR. The proconvulsant response of clonidine is also observed in rats; (b) Blockade of the α1AR is proconvulsant when endogenous NE is present, though stimulation of α1AR does not produce an anticonvulsant response in either *Dbh* -/- or *Dbh* +/- mice; (c) Administration of any single AR agonist does not produce an anticonvulsant response in *Dbh* -/- mice, but a combination of agonists does produce an anticonvulsant effect; (d) Further stimulation of ARs does not produce an anticonvulsant response in *Dbh* +/- mice. **Conclusions:** These data indicate the inhibitory action of the noradrenergic nervous system against flurothyl-induced seizures is complex. The α1AR is, in part, responsible for the anticonvulsant action of endogenous NE; while stimulation of the α2AR is proconvulsant in mice and rats with normal NE and in mice lacking NE. This proconvulsant response is due specifically to the α2A-AR, which is localized both pre- and post-synaptically. In mice which lack NE, no single AR agonist produced an anticonvulsant response. A combination (α2, β1, and β2) of AR agonists was required to produce an anticonvulsant response. This combination of AR agonists produced an anticonvulsant response only in mice lacking endogenous NE. (Supported by National Alliance for Research on Schizophrenia and Depression, Pediatric Epilepsy Research Center, Department of Veterans Affairs and Howard Hughes Medical Institute.)

3.076
THE M-CURRENT ANTAGONIST LINOPIRDINE LOWERS SEIZURE THRESHOLD IN WILD-TYPE AND GENETICALLY EPILEPSY-PRONE MICE

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Rationale: Benign familial neonatal convulsions, an inherited epilepsy, is caused by mutations in either the KCNQ2 or KCNQ3 subunit of the M-type K+ channel which underlies the M current. The M current regulates the subthreshold electrical excitability of most neurons. Linopirdine [DuP 996, 3,3-bis(4-pyridinylmethyl)-1-phenylindolin-2-one] enhances depolarization-induced release of several neurotransmitters in the central nervous system through inhibition of M current. This study was designed to evaluate the effects of linopirdine in seizure genesis in normal and epilepsy-prone mice. **Methods:** Experiments were performed on adult wild-type CF1, C57BL/6J and FVB/NJ mouse strains, the Frings audiogenic seizure-susceptible mouse strain, and the BALB.B6-*Szt1*/+ mouse strain known to have a spontaneous deletion which truncates the *Kcnq2* gene, causing a dominant susceptibility to electroshock and pentylenetetrazol (PTZ)-induced seizures. This study investigated the proconvulsive properties of linopirdine (10, 20, and 30 mg/kg, i.p.) administered alone and in combination with a convulsive dose of PTZ sufficient to produce a minimal clonic seizure in 25% (CD25) of the mice tested. For the combination study, the CD25 for PTZ was administered 15 min after linopirdine (20 mg/kg). Alterations in both behavior and EEG were monitored for 45 min after injection of linopirdine. EEG spectral analysis was performed. **Results:** By itself, linopirdine at 10, 20, and 30 mg/kg did not induce seizures in CF1 (n = 9), C57BL/6J (n = 10), or FVB/NJ (n = 3) mice. At 30 mg/kg, body tremors and limb shakes were observed. In Frings mice, 10 mg/kg linopirdine produced whole-body tremors; whereas 20 and 30 mg/kg linopirdine produced clonic seizure activity, followed by tonic extension and death at 30 mg/kg. In BALB.B6-*Szt1*/+ mice, 30 mg/kg linopirdine produced severe body tremors and limb shakes, although only two of the five mice tested displayed seizure activity. In the PTZ-linopirdine combination study, there was a significant increase in the number of animals exhibiting clonic seizures in the group that received 20 mg/kg linopirdine 15 min before CD25 PTZ injection, compared with animals that received only PTZ ($p < 0.01$ in all strains tested, binomial test). EEG spectral analysis confirmed that onset of seizure significantly increased the spectrum

power in the low frequency band (delta wave). However, it was interesting that this increase started earlier than the onset of behavioral seizure, and it took more time for the EEG to recover. **Conclusions:** These results suggest that linopirdine facilitates PTZ-induced seizures in wild-type CF1, C57BL/6J, and FVB/NJ mice, and Frings and BALB.B6-*Szt1*/+ mice, which are genetically epilepsy prone, are more sensitive to linopirdine than the CF1, C57BL/6J and FVB/NJ mice. These data suggest that the M current is involved in seizure susceptibility, and linopirdine decreases seizure threshold by modulating the function of these channels. [Supported by NIH 5-RO1-NS-40246 (W.N.F., H.S.W.).]

Human Genetics

3.077
APOE ε4 ALLELE INCREASES RISK OF LATE POSTTRAUMATIC SEIZURES

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Rationale: Posttraumatic epilepsy (PTE) is a common complication of moderate and severe traumatic brain injury (TBI). However, only a fraction of patients with TBI develop PTE, and it is likely that host genetic factors may influence the epileptogenic process. Inheritance of the *APOE* ε4 allele is associated with increased risk of Alzheimer disease, increased disability in patients with multiple sclerosis, and poor outcome after TBI. This study was undertaken to determine whether inheritance of *APOE* ε4 is associated with increased risk of developing late posttraumatic seizures. **Methods:** Patients admitted to the neurosurgical service with a diagnosis of moderate and severe TBI were enrolled in the study, and after informed consent obtained, a DNA sample was acquired. Patients with preexisting epilepsy, brain tumors, or other brain lesions likely to result in epilepsy were excluded. Six months after injury patients were administered a structured questionnaire to determine functional outcome (according to the Glasgow Outcome Scale-Expanded (GOSE) and the presence of late post-traumatic seizures. Genotype at the *APOE* locus was determined by restriction-fragment length polymorphism mapping of an amplified 244-mer oligonucleotide, using published techniques. Data was analyzed according to Fisher's Exact test. **Results:** DNA and outcome information was obtained from 90 subjects; 22 (24%) inherited at least one copy of *APOE* ε4. Six months after injury, 28 (31%) had a poor outcome (GOSE 1-4), 39 (43%) had an intermediate outcome (GOSE 5-6), and 23 (26%) had a favorable outcome (GOSE 7-8); 18 (20%) of cohort had experienced at least one late posttraumatic seizure. The relative risk (RR) of PTE for patients with the ε4 allele was 2.28 (95% CI, 1.14–4.60, $p = 0.036$). In this cohort inheritance of *APOE* ε4 was not associated with an unfavorable GOSE (RR, 1.36; 95% CI, 0.63–2.91, $p = 0.574$). **Conclusions:** We conclude that inheritance of the *APOE* ε4 allele is associated with increased risk of developing PTE. In this cohort, this risk appears to be independent of an effect of ε4 on functional outcome, as measured by the GOSE. *APOE* may influence the reaction of neural tissue to injury, or may affect regeneration and repair of injured neurons. A better understanding of the molecular role of *APOE]* in neurodegenerative diseases may be helpful in developing antiepileptogenic therapies. (Supported by RD-A NIH RO1 AG17861, RO3 MH64889, and R24 MH59656.)

3.078
FEBRILE SEIZURES: APOE HAPLOTYPE AND RISK OF EPILEPSY IN ADULTS

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Rationale: Between 2 and 5% of all children will experience a febrile seizure (FS) before the age of 5 years. In certain Pacific populations, this can be as high as 15%, making FSs the most common seizure disorder of childhood. Generally, a single FS or cluster of febrile events would have no long-term effect. A selected group of these individuals, however, go on to develop full-blown epilepsy. Our goal is to determine if the presence of an ApoE4 allele predicts future outcome. Identification of any genetic influence resulting in the remarkably different outcomes for these patients would be clinically significant. Investigations into the possible influences of ApoE haplotype on CNS injury have focused almost exclusively on the severely injured adult neurotrauma population, and the elderly. Clearly a significant percentage of moderate CNS trauma occurs in the pediatric population. Even short delays in recovery can exact a huge toll on the ultimate development and accomplishments of these children. There is no reliable assessment of what effect ApoE haplotype is having on recovery in the pediatric population. It is imperative that any noxious role the ApoE 4 allele may play in pediatric development and recovery from trauma be investigated. **Methods:** We hypothesize that if an individual with an Apo E4 allele is less able to repair any subtle neuronal damage that may follow a febrile seizure, there could be subsequent long-term ramifications from what in most of the population would be a benign event. We have studied 200+ samples with a detailed medical assessment of the initial febrile seizure profile and in the older family members at least, an evaluation of any seizures/epilepsy later in life. Assuming a normal allele frequency distribution, we expect to see perhaps 15–18% of patients with an expected Apo E4 allele. **Results:** There was a surprising trend toward a disassociation of seizure phenotype with the presence of an ApoE 4 allele, perhaps contraintuitive to what we would have expected based on the adult literature supporting a role for ApoE 4 in significant delay in recovery from neurotrauma. **Conclusions:** Efforts are under way to further subdivide the patient population into those who only had FSs as children and those that went on to develop seizure disorders or other neurologic issues as adults. Given that this population was not collected specifically to fit those criteria, efforts are being made to retrospectively contact patients when possible and to target future family collection with an eye toward this type of long-term follow-up data. (Supported by The Neurogenetics Laboratory would like to acknowledge the generous support of the Barrow Neurological Foundation Women's Board.)

3.079
ASSOCIATION ANALYSIS BETWEEN A FUNCTIONAL POLYMORPHISM IN THE PRODYNORPHIN GENE PROMOTER AND DIFFERENT TYPES OF SEIZURE DISORDERS

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Rationale: Several studies have established the prodynorphin gene (PDYN) as a prime candidate gene for increased seizure susceptibility. A common functional polymorphism has been identified in the PDYN gene promoter with "low-expression-alleles" (L) consisting of either one or two repetitive 68-bp elements, and "high-expression-alleles" (H) consisting of three or four repeat elements, respectively. Recently, L-alleles have been shown to be associated with an increased risk for temporal lobe epilepsy in patients with a family history for seizures (Stoegmann et al. *Ann Neurol* 2002;51:260–3). **Methods:** In our study we first attempted to confirm the latter findings by genotyping the PDYN polyorphism in 160 temporal lobe epilepsy (TLE) patients, of whom 43 patients reported a family history of seizures. Second, we extended our study sample by investigating 104 patients with febrile seizures (FSs) and 275 probands with idiopathic generalized epilepsy (IGE). In the FS group, a family history of seizures was reported in 45 cases and in 106 probands of the IGE group, respectively. **Results:** First, we found a trend toward the same allelic distribution as described by Stoegmann et al., although our results did not reach a significance level of $p < 0.05$. However, we found a significant association between

the L-alleles and an increased risk for FSs in patients with a family history of seizures. Within the IGE study sample, we detected only a trend toward a susceptibility effect of the L-alleles; however, when we split the entire IGE sample into the main diagnostic subgroups, we found a significant effect in patients with idiopathic absence epilepsy who were derived from families with at least one affected sibling. **Conclusions:** Our results show that the L-alleles of the PDYN gene promoter may probably be regarded as a general seizure susceptibilty factor for different types of seizure disorders. Further studies are required to confirm these findings and may thus open new research avenues for the development of target-directed antiepileptic compounds. [Supported by The Deutsche Forschungsgemeinschaft (D.F.G.).]

3.080
THE ROLE OF FAMILIAL HISTORY IN MALFORMATIONS OF CORTICAL DEVELOPMENT

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Rationale: Several studies have analyzed the importance of prenatal events in malformations of cortical development (MCD) in humans, since these disorders are believed to occur in the first half of pregnancy; however, there is growing evidence that genetic factors play an important role on the genesis of these disorders. We evaluated the family history of epilepsy in these patients, to investigate the pathogenetic role they play in distinct MCD. **Methods:** Seventy-two patients with MCD diagnosed by MRI were enrolled in a prospective protocol that analyzed the clinical evidence of possible genetic factors. The familial occurrence of epilepsy was identified by a systematic search of family history of seizures in patients with MCD followed up in the Hospital das Clinicas at the University of Sao Paulo, Brazil. Family history of developmental delay, motor deficits, and speech disorders were also taken into account and categorized in a distinct group. Prenatal events were analyzed, and those considered harmful were significant maternal physical trauma, ingestion of medications, exposure to roentgenograms, surgery, infections, uterine disorders (e.g., bleeding, contractions), and metabolic abnormalities. **Results:** A genetic predisposition (family history of epilepsy, speech disorder, mental retardation, or congenital malformations of the CNS) was detected in 30 (41.7%) of these families. Family history of epilepsy was reported by 26 patients (36.1%), and evidences of CNS abnormalities in other family members in six (8.3%). Miscarriages occurred in 16 families (22.2%) and stillbirths in five (6.9%). In four patients with MCD (polymicrogyria) with a family history of epilepsy and/or speech disorder a neuroimaging study disclosed a similar MCD in other family member. Prenatal events were reported in 32 patients (44.4%). There was an association of familial history and pregnancy events in 11 patients (15.3%). **Conclusions:** These findings suggest that prenatal potentially harmful environmental events play a central role in the pathogenesis of NMD in humans. Nonetheless, the presence of a prenatal history does not exclude a positive family history for epilepsy, which may show an interaction between genetic factor and prenatal injury in MCD, demonstrating a predisposition for cortical abnormalities in some of these patients. (Supported by University of Sao Paulo-Brazil.)

3.081
EPILEPSY ASSOCIATED WITH A LHON MITOCHONDRIAL DNA MUTATION: STUDIES ON BIOENERGETIC MECHANISMS

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Rationale: There is accumulating evidence that mitochondrial DNA mutations can play an important role in the generation of epileptic seizures, but the pathogenetic link between genotype and phenotype is not fully understood. **Methods:** To define the bioenergetic consequences of mitochondrial mutations in these disorders, we studied tissue preparations from muscle and brain from 6 patients carrying the three pathogenic homoplasmic Leber's hereditary optic neuropathy (LHON) mtDNA mutations C4640A/ND2 (a male with epilepsy and a female carrier), G11778A/ND4 (a male with blindness and a female carrier) and T14484C/ND6 (a male with blindness and a female carrier). Interestingly, on preoperative Wada testing (unilateral infusion of amytal to evaluate the prospective outcome of the hippocampectomy), the patient with epilepsy and the mitochondrial ND2 mutation developed severe reversible visual loss. From this patient also brain tissue was available for further studies. **Results:** All mutations led in patients and nonaffected carriers of the mutation to a similar decrease of citrate synthase-normalized activities of complex I being most severe for the ND6, less severe for ND4, and close to the detection limit for the ND2 mutation. This enzyme activity change was observed to be responsible for decreased respiration rates with NAD-dependent substrates detected in saponin-permeabilized muscle fibers, isolated skeletal muscle mitochondria, and digitonin-treated brain homogenates (for the ND2 mutation). In addition, titrations of the activity of NADH:CoQ oxidoreductase with the complex I inhibitors amytal, rotenone, and piericidin A revealed with all mutations no difference to controls indicating no alteration of kinetic properties of the CoQ reduction site by any of the investigated mutations. **Conclusions:** Since all mutations led to a considerable increase of amytal sensitivity of mitochondrial respiratory chain, our data are compatible with the concept that the investigated mutations lead to decreased quantities of the active NADH:CoQ oxidoreductase enzyme complex having in brain tissue more severe metabolic consequences.

3.082
FINE MAPPING OF A COMMON EPILEPSY-SUSCEPTIBILITY ALLELE AT THE HUMAN KCNJ10 LOCUS

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Rationale: Our objectives are to use genetic linkage and association techniques to identify human seizure-susceptibility genes. Mapping studies identified the potassium ion channel gene KCNJ10 as an excellent epilepsy candidate gene. KCNJ10 protein plays a critical role in regulating extracellular potassium ion concentration in the CNS. Previous work from our laboratories identified DNA variation in the mouse and human KCNJ10 gene implicating it as a putative seizure susceptibility gene for both focal and generalized epilepsy. To confirm and extend these earlier results we are fine mapping the genomic region surrounding the human KCNJ10 locus to systematically identify those DNA variations that are associated with common forms of epilepsy. **Methods:** We have identified several SNP variations in the human KCNJ10 gene using single stranded conformation electrophoresis and DNA sequencing and found others surrounding the gene locus via database searching (dbSNP at NCBI). We currently use restriction fragment length polymorphism analysis and Pyrosequencing to genotype single nucleotide polymorphisms (SNPs) in high priority genomic regions thought to contain seizure susceptibility genes such as KCNJ10. **Results:** One SNP (C1037T, based on NCBI NM002241) in the KCNJ10 coding region alters an amino acid (R271C) and shows a statistically significant association with common human seizure disorders such as mesial temporal lobe epilepsy ($n = 153$), childhood absence epilepsy ($n = 84$), juvenile myoclonic epilepsy ($n = 111$), and other forms of idiopathic generalized epilepsy ($n = 59$) ($\chi 2 = 5.65$, df $= 1$, $p = 0.017$, $n = 407$ epilepsy, 284 control individuals). The c allele is common (cc ~87%, ct ~12%, tt ~1% in controls) and the

conversion to a t allele occurs twice as often in controls compared to epilepsy patients. All genotypes are in Hardy Weinberg equilibrium. We are currently genotyping SNP markers at small intervals (2-5KB) both proximal and distal to the C1037T SNP to identify additional seizure susceptibility variations if they exist. Thus far no other SNP marker studied in this region shows a significant association with common human seizure disorder. **Conclusions:** In the absence of any other DNA variation in this region that is statistically associated with common forms of epilepsy, the C1037T SNP in KCNJ10 is likely to constitute the first gene variation discovered that affects risk for both generalized and focal epilepsy subtypes. The variation from a c to t allele seems to be protective as it is associated with a decreased risk for common forms of epielspy. Thus, KCNJ10 could be considered a *bona fide* seizure susceptibility gene. (Supported by NIH grants RO1NS40554 & RO1NS39516 to T.N.F. and RO1NS40396 to R.J.B. The University of PA Center for Neurobiology and Behavior. F.W. Lohoff was supported by a scholarship from University Hospital Charité, Humboldt University of Berlin, Germany.)

3.083

EVIDENCE SUGGESTING BRD2 IS THE EJM1 LOCUS FOR JUVENILE MYOCLONIC EPILEPSY

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Rationale: Several reports have demonstrated linkage of juvenile myoclonic epilepsy to the HLA region of chromosome 6. Our group found statistically significant evidence of association to alleles at the DQB1 and RING3 (BRD2) loci (*Am J Hum Genet* 2000;66:508–61). The objectives of the present study were to define the region of interest more precisely using densely spaced SNP markers and to identify possible causative mutations. **Methods:** Twenty JME probands, taken from families showing moderate to strong evidence for linkage (Iod >0.1) to the 6p locus, and 46 unlinked JME probands, were typed for 11 SNPs in the region between HLA-DP and HLA-DQ. SNPs were typed using the technique of fluorescent polarization. Haplotype frequencies were compared in a case–control design, and also using the program SNPHAP (www-gene.cimr.cam.ac.uk/clayton/software/snphap.txt). Additionally, all exons and splice sites in the region were tested for mutations in all four linked families. **Results:** One consistent haplotype was identified in linked JME probands, which was significantly more frequent than in comparison chromosomes (odds ratio, 5.8; 95% CI, 1.7–19.4; $p = 0.001$). This haplotype extended to the boundary of the BRD2 gene and contained the CA repeat allele with which we had originally demonstrated association. There was no significant evidence of linkage disequilibrium beyond the gene boundaries. Similar results were obtained through SNPHAP; the same consistent haplotype was predicted with highest probability in JME linked probands more than twice as often as in comparison chromosomes. Sequencing did not reveal any mutations that would lead to changes in amino acids. **Conclusions:** Other reports of loci in common disease also have failed to find consistent mutations in exons in loci which show association. While we cannot yet definitively exclude the rest of the DQ-DP HLA region, the presence of a SNP haplotype, together with our previous evidence of association with an allele of a microsatellite marker only in linked families, continues to suggest that BRD2 is EJM1. (Supported by NIH grants: DK31775, NS27941, MH48858, NS37466.)

3.084

LINKAGE ANALYSIS BETWEEN CHILDHOOD ABSENCE EPILEPSY AND *GABRA5*, *GABRB3*, AND *GABRG3* ON CHROMOSOME 15Q11-13

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Rationale: Evidence suggests that mutations in genes encoding γ-aminobutyric acid $(GABA)_A$ receptor subunits may underlie childhood absence epilepsy (CAE). Linkage analysis in 33 nuclear families found weak evidence of linkage to the $GABA_A$ receptor gene cluster on chromosome 15q11-13. The aim was to test this linkage in a larger collection of nuclear families each with two or more individuals with CAE. **Methods:** Seventy-four families were ascertained from European populations. Individuals were classified as affected using diagnostic criteria based on the ILAE classification. Linkage to *GABRB3, GABRA5,* and *GABRG3* on chromosome 15q11-13 was tested using three polymorphic microsatellite markers. Multipoint linkage analysis was carried out using GENEHUNTER. **Results:** Positive heterogeneity LOD scores were obtained for markers *GABRB3CA, 155CA2, A55CA1* that encompass the $GABA_A$ receptor subunit genes *GABRB3, GABRA5,* and *GABRG3.* Assuming a recessive mode of inheritance, the maximum HLOD was 1.8 ($\alpha = 0.37$) at *A55CA1,* which lies between *GABRA5* and *GABRG3* and is ~20 kb centromeric to *GABRG3.* Assuming a dominant mode of inheritance, the maximum HLOD was 0.9 ($\alpha = 0.29$) at *A55CA1.* The nonparametric linkage (NPL) score was 2.5 ($p = 0.004$). **Conclusions:** CAE shows a complex non-mendelian mode of inheritance. Both dominant and recessive susceptibility alleles may exist in several genes. These positive results are consistent with a contribution from *GABRB3, GABRA5,* or *GABRG3* in a subset of patients. Further investigation of these genes is planned using both intrafamilial and case-control association analyses with intragenic single nucleotide polymorphisms (SNPs) in a larger number of patients. (Supported by Action Research, The Epilepsy Research Foundation, The Medical Research Foundation, and The Wellcome Trust.)

3.085

MOLECULAR GENETIC ANALYSIS OF JUVENILE MYOCLONIC EPILEPSY IN CONSANGUINEOUS SAUDI ARABIAN FAMILIES

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Rationale: The aim is to map and identify the gene(s) responsible for autosomal recessive juvenile myoclonic epilepsy (JME) in consanguineous Saudi Arabian families. **Methods:** Three consanguineous Saudi Arabian families comprising a total of 13 individuals affected with JME have been ascertained. Inheritance of JME in all families is consistent with that of an autosomal recessive trait. To identify genomic regions harbouring potential susceptibility loci, a genome scan was conducted using polymorphic microsatellite markers spaced at ~10-cM intervals. Homozygosity mapping, in which affected individuals of consanguineous families are predicted to have inherited identical chromosomal regions surrounding the disease locus from both parents, was then used to identify candidate regions. **Results:** Initial results from the genome scan identified a region on chromosome 6q27 that was homozygous by descent in seven affected individuals of one large consanguineous family (*Epilepsia* 2000;41:72). Two-point linkage analysis assuming autosomal recessive inheritance and a penetrance of 0.9 revealed a maximum LOD score of 4.39 ($\theta = 0$) at *D6S281.* However, subsequent analysis of an additional affected individual of this family revealed that he was heterozygous at *D6S281* which resulted in a maximum LOD score of 1.44 ($\theta = 0$) at *D6S281.* Neither of the two remaining consanguineous Saudi Arabian families were consistent with linkage to this region. **Conclusions:** Despite initial indications that a JME susceptibility locus resides on chromosome 6q in a single, large consanguineous Saudi Arabian family, typing of an additional affected individual of that family has revealed that under an autosomal recessive model, genes in this region are unlikely to be responsible for JME in this family. Alternative regions of homozygosity on chromosomes 7p12.3 and 9p22.1 are currently under investigation. (Supported by The Wellcome Trust and The Medical Research Council.)

3.086

A POSSIBLE LINK BETWEEN CALVARIAL BONE DEFECTS AND DISORDERS OF CORTICAL DEVELOPMENT: FAMILIAL ALX4 HOMEOBOX GENE MUTATION

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Rationale: Calvarial bone defects such as parietal foramina (PF) have been found to be caused by mutations in the MSX2 homeobox gene located on Chr 5 (PFM1). Parietal foramina also occur as part of the Chr 11p11.2 deletion syndrome, where they are caused by haploinsufficiency of the ALX4 homeobox gene (PF2). The association of malformations of cortical development (MCD) and PF have been scattered reported, however no genetic defect was described. The aim of this study is to present the neurological, imaging and eletroclinical profile of a three generation family with an ALX4 point mutation. **Methods:** Calvarial bone defect were detected in four patients in a three-generation family. A detailed history was obtained of three patients of these (son, mother, and grandfather). The genetic profile of these patients was previously addressed by Mavrogiannis et al. (*Nat Genet* 2001;27:17–18) and showed an ALX4 point mutation. Neuroimaging studies consisted of evolutionary skull radiographs (PA and lateral), CT scan of the head without intravenous contrast, 3D CT bone reformatted images, and MRI. The MRI data include a structural protocol and complementary MR venography imaging performed to address the full spectrum of the brain anomalies associated with this calvarial defect previously considered of benign nature. A complete neurologic follow-up was performed, and EEG routine and a short-term V-EEG (4 h) was done. **Results:** The imaging studies of all three patients showed individual variations and expressions of the same abnormalities, which were (a) Bones: calvarial bone defect in the gross spectrum of the parietal foramina and cranium biffidum occultum, (b) Vascular: Persistent falcine venous sinus and an athretic straight sinus, (c) White matter: deep white matter signal changes in the periatrial region; and (d) Gyral and cortical pattern: Unusual variation of the paramedian occipital infolding surrounded by a polymicrogyric cortex, especially located on the mesial portion of occipital lobes. We also noticed a high tentorial incisura with an enlarged posterior fossa. Two of these patients (mother and son) presented a history of nonrefractory epilepsy characterized by sporadic seizures of occipital origin, starting in infancy in the son and childhood in the mother with remission during puberty. EEGs revealed frequent low-amplitude sharp waves over the posterior quadrant. **Conclusions:** Parietal foramina have been largely considered a benign calvarial bone defect. However, our three-generation family with PFM2 presented distinct morphostructural changes with an evolutionary aspect, involving not only the bone but also the cortical infolding, deep white matter, and cerebrovascular drainage system. The straight correlation between the topographic and electroclinical alterations associated with an ALX4 point mutation could light up a new direction for researchers and gene hunters. (Supported by University of Sao Paulo-Brazil.)

3.087
HUMAN CELLULAR PRION PROTEIN GENE VARIANT ALLELES ARE ASSOCIATED WITH INTRACTABLE SYMPTOMATIC EPILEPSIES

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Rationale: Most cases of medically intractable epilepsy are related to hippocampal sclerosis (HS) and malformations of cortical development (MCD). Molecular defects were mapped in single-gene epilepsies, but HS and most types of MCD have not been regarded as having a major genetic contribution. Deletion of the cellular prion gene (PrPc), enhances neuronal excitability and sensitivity to seizures in mice, indicating that PrPc gene might be related to epilepsy. **Methods:** The PrPc gene sequence of peripheral blood cells DNA of 102 patients (mean age, 36 years) treated surgically for epilepsy related to HS ($n = 80$) or MCD ($n = 22$) were compared with 172 healthy controls. Statistical analysis was done by Student's test for independent samples and Fisher's Exact test. The OR and respective 95% CI were also determined. **Results:** There were no differences in the sex and age of patients and controls. Association with epilepsy was observed for individuals carrying a valine at codon 117 (AlaVal) (OR = 13.7; CI, 5.0–37.3; $p < 0.000000001$) and a new polymorphism found at codon 110 (LysAsn) (OR = 8.4; CI, 3.0–23.4; $p < 0.00001$), as compared to controls. A mutation in codon 171 (AsnSer), not found in controls, observed in heterozygous was found in 26.5% of the patients ($p < 0.000000000001$) was an independent risk factor for epilepsy. The observed associations did not change when HS and ACD were analyzed separately. None of the patients or controls presented signals or symptoms suggestive of any type of spongiform encephalopathy. Histopathologic examinations of ressected tissue from none of the patients exhibited any spongiform degeneration. **Conclusions:** The present data indicates that PrPc gene sequences are risk factors for untreatable epilepsy related to distinct structural and physiopathologic subtracts (HS and MCD). PrPc is involved with several physiologic functions, including antioxidant properties, neuronal cell adhesion, neurite extension and maintenance, and signal transduction. The relevance of the PrPc gene polymorphisms and mutation, herein observed in patients with epilepsy, concerning PrPc function is still unknown. Evaluation of the PrPc gene coding sequence might be used to improve epilepsy diagnosis and treatment. [Supported by FAPESP (99/07124-8) and FAEPA-HC. RMRPS, P.C.M., and R.W. are fellows from CAPES, FAPESP and CNPq, respectively.]

3.088
KCNQ2 POLYMORPHISM ANALYSIS IN IDIOPATHIC GENERALIZED EPILEPSY SYNDROMES

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Rationale: To examine the relationship between KCNQ2 polymorphism and idiopathic generalized epilepsy syndromes. **Methods:** Four patients having idiopathic generalized epilepsy according to the ILAE-89 classification and with a positive family history followed up at the Marmara University Hospital epilepsy outpatient clinic are presented in this study. Detailed neurologic history, neurological examination, EEG and neuroradiological imaging in selected cases were performed. The phenotype of patients and their affected family members were determined according to the ILAE-89 classification. To examine the relationship between KCNQ2 polymorphism and idiopathic generalized epilepsy syndrome, DNA of all the participants were extracted from whole blood samples. **Results:** The genotype analysis in all four families affected with the idiopathic generalized epilepsy syndrome revealed a possible linkage of the disease to the KCNQ2 gene in only one family (Family I). The pattern of inheritance in all four families with idiopathic generalized epilepsy syndrome seems to be similar. It could either be inherited in recessive mode or a dominant mode with a low

penetrance. **Conclusions:** As a conclusion, in order to assess the KCNQ2 mutation profile of the Turkish population, a large study aimed at screening both idiopathic generalized epilepsy patients and healthy subjects seems necessary. (Supported by Marmara University Research Foundation, number: 49/060700.)

3.089

INTERICTAL AND ICTAL CHARACTERIZATION OF EPILEPSY PATIENTS WITH RING CHROMOSOME 20 MOSAICISM: A FRENCH AND SWISS SERIES OF 27 PATIENTS

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Rationale: Epilepsy associated with a ring chromosome 20 mosaicism (rCh20m) is considered as a rare condition and only short series have been reported in the literature yet, with a total of <50 cases. We present the clinical, interictal, and ictal features of a series of 27 patients. **Methods:** In every patient, cytogenetic analysis showed a pool of cells with a rCh20 associated with a variable proportion of normal cells. For every patients, detailed history, neurologic examination, MRI, video-EEG with seizure characterization were obtained. In most of the patients, neuropsychological assessment was performed. **Results:** The proportion of affected lymphocytes varied from 0.5 to 100% in our series. None of the patients had a familial history of epilepsy; none of the patients had any dysmorphism except in four cases, a microcephaly; they all had frequent episodes of nonconvulsive status epilepticus with a typical EEG pattern. Cognitive performances might be normal, and were very variable and not in relation with the proportion of affected cells in the karyotype, but seemed to be more correlated with the age at onset of the epilepsy. This age at onset is also very variable (from 0 to 17 years); in one case, epilepsy began a few hours after birth. In most cases, diagnosis was delayed because of the unusual seizures presentation and the frequent association with psychiatric behavior. **Conclusions:** This syndrome is more frequent and more heterogeneous than previously reported, the main characteristic is the ability to have long-lasting electroclinical status. A very low proportion of cells may be found on the karyotype, if the history, the electroclinical pattern is compatible, >100 mitoses must be studied.

3.090

MUTATION SCREENING OF THE HUMAN P/Q-TYPE CALCIUM CHANNEL GENE CACNA1A IN COMMON FORMS OF IDIOPATHIC GENERALIZED EPILEPSY

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Rationale: Several animal models with naturally occurring mutations of the CACNA1A gene exhibit a complex phenotype including spontanous seizures usually accompanied by ataxia. These findings emphasize the human CACNA1A gene as a prime candidate gene in human forms of epilepsy. However, the role of CACNA1A in common forms of idiopathic generalized epilepsy (IGE) remains elusive as no susceptibility mutations have been identified so far. **Methods:** In this study we searched for disease-causing mutations by following a large-scale sequencing approach. We initially included 35 IGE multiplex families with at least two affected siblings. After we excluded linkage to the CACNA1A locus on chromosome 19 in 15 of these families, DNA samples from 20 probands were subjected to automated direct sequencing. We amplified all 47 coding exons and adjacent splice sites. **Results:** We found several CACNA1A sequence variants, coding and noncoding, which are currently under investigation with respect to their potential role in the etiology of common IGE subtypes. **Conclusions:** We conclude that genetic variation in the CACNA1A gene may confer susceptibility to common forms of idiopathic epilepsies in some cases or families; however, the majority of IGE cases must be due to mutations or common sequence variation in genes others than CACNA1A. [Supported by Deutsche Volkswagenstiftung and Bundesministerium für Bildung und Forschung (BMBF, NGFN).]

3.091

PATTERN OF LD AND HAPLOTYPE DIVERSITY OF THE SCN1A GENE AS A BASIS FOR ASSOCIATION STUDIES IN EPILEPSY

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Rationale: To establish an efficient genotyping strategy for association studies of susceptibility genes in epilepsy, based on knowledge of the pattern of linkage disequilibrium (LD) and haplotype diversity of the gene of interest. **Methods:** The first gene selected for this project was the neuronal sodium channel gene SCN1A, as this is a fairly large gene with an established role in mendelian epilepsy and anti-epileptic drug responsiveness, and is thus considered a good candidate susceptibility gene for common epilepsy and/or drug sensitivity. To identify single nucleotide polymorphisms (SNPs) in a 1,700-kb genomic region around SCN1A, we sequenced 31 amplicons of 400–500 bp each. We subsequently typed all identified SNPs in 32 Chinese and 32 Malay trios (father, mother, child). Parental haplotypes were reconstructed from these data, and haplotype diversity established. The pattern of LD in the gene region was assessed by p values for Fisher's Exact test on pairwise allele combinations. Finally, a small number of haplotype tag SNPs (htSNPs) for further genotyping in association studies was selected using r^2-based criteria. **Results:** A total of 20 SNPs was identified, of which 14 were located within the SCN1A gene. Of these 20 SNPs, seven were published at the time. Of the 13 SNPs from the dbSNP database (dbSNPs) amplified, only six proved to be polymorphic in our population. The entire gene appeared to be contained in one single block of LD. For the 14 SNPs located within the gene, 13 different haplotypes were observed, of which seven were shared by both population groups. Five common haplotypes accounted for, respectively, 92 and 82% of all haplotypes in the Chinese and Malay groups. Based on this information, we selected five htSNPs to type the SCN1A gene in large association studies, estimated to cover ~99% of all haplotype diversity. **Conclusions:** The knowledge of the pattern of LD and haplotype diversity of the SCN1A gene validates and greatly simplifies genotyping in association studies in epilepsy and antiepileptic drug responsiveness. We suggest this strategy should be used for genotyping of any candidate gene in association studies in epilepsy or other diseases (Fig. 1). (Supported by National Neuroscience Institute Singapore, Genome Institute Singapore.)

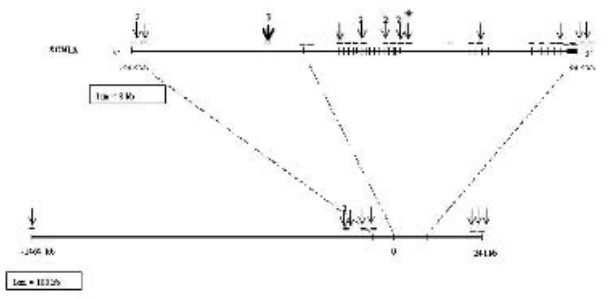

Figure representing the region of about 1700 kb of genomic DNA on chromosome 2q24 in which sequencing was undertaken. Base pair positions are relative to the first base of exon 1, which was designated the "zero" position. SCN1A is shown enlarged, with exons represented by vertical lines (Source). The approximate location of amplicons is shown by small horizontal lines (black = successful reactions, blue = weak, dot (grey) = no). Arrows show the approximate positions of SNPs, with numbers above arrows if more than one (black), typical SNP was detected in four amplicons. dbSNPs polymorphisms in our samples, green arrows; all SNPs not present prior to our samples, red arrows; newly identified SNPs). The red star indicates the SNP in a 5′ untranslated region (UTR).

3.092

A NEW FAMILY WITH AUTOSOMAL DOMINANT PARTIAL EPILEPSY WITH AUDITORY FEATURES

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Rationale: Autosomal dominant partial epilepsy with auditory features (ADPEAF) is a recently described idiopathic localization-related epilepsy syndrome characterized by auditory and visual ictal symptoms. ADPEAF is a rare syndrome, thus far described in fewer than a dozen families. ADPEAF was mapped to chromosome 10q24, and is caused by mutations in the leucine-rich, glioma-inactivated 1 (LGI1) gene. We describe the clinical characteristics and molecular studies in a new, large, multigenerational Italian-American family with partial epilepsy with auditory features. **Methods:** Clinical study: Our family consisted of 36 individuals in five generations. Nine had a history of partial epilepsy. Seven affected members agreed to participate after informed consent. They underwent a semistructured interview focusing on seizure semiology and seizure-precipitating factors, and neurologic examination. Their medical records were reviewed, including EEG records and brain-imaging studies when available. We collected eight blood samples, seven were from affected family members. Genetic studies: Exon spanning primers were designed for each of the eight exons of LGI1. Each exon was amplified by polymerase chain reaction using the genomic DNA of an affected individual. The product was purified and screened for mutations by automated cycle sequencing. **Results:** All seven affected individuals had an auditory aura. The mean age of onset was 25 years (range, 8–42). Two of the affected individuals reported visual auras. Complex partial seizures occurred in two subjects. All patients had generalized tonic–clonic seizures. All affected individuals had normal neurologic examinations. Neuroimaging was normal except magnetic resonance imaging in the proband showed symmetric, bilateral T2 and FLAIR signal abnormalities in the medial basal ganglia. EEGs in five affected individuals were normal, the proband's EEG showed left anterior temporal epileptiform features. Genetic studies: The partial epilepsy segregated as an autosomal dominant trait with reduced penetrance. LGI1 mutation screening is in progress. **Conclusions:** ADPEAF is a rare syndrome. As more families are described, the clinical, electrophysiological, and genetic characteristics will be better defined. ADPEAF can arise from haploinsufficiency of LGI1, a gene previously known to play a role in progression of glial tumors. However, mutations have been demonstrated thus far in 5 families. Whether ADPEAF is genetically heterogeneous is yet to be determined by further studies of large families with this epilepsy syndrome. [Supported by Paul Beeson Physician Faculty Award and the Hellman Family Foundation (F.M.H.).]

3.093

GENOTYPE IN THE 24-kDa SUBUNIT GENE (NDFUV2) OF MITOCHONDRIAL COMPLEX I AND SUSCEPTIBILITY TO NONLESIONAL TEMPORAL LOBE EPILEPSY

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Rationale: Deficiency of complex I of the mitochondrial respiratory chain has been implicated in the pathogenesis of temporal lobe epilepsy (TLE). Here we evaluated whether the novel polymorphism (Ala29Val) in the mitochondrial 24-kDa subunit gene (NDUFV2) is a risk factor for TLE. **Methods:** The study group consisted of 133 patients (74 women and 59 men) who had a diagnosis of nonlesional TLE, based on a comprehensive clinical, neuropsychological, electroencephalographic, and routine magnetic resonance (MR) evaluations. Based on the MR study, TLE was classified as nonlesional if no epileptogenic foreign-tissue lesion was detected. TLE patients with neuroimaging evidence of mesial temporal sclerosis were also included. At the time of the study, the age of the patients ranged from 14 to 87 years (mean, 50 years, SD, ±18). The molecular study was performed using standard methods. It was also performed in 126 age- and gender-matched normal individuals. **Results:** There were no differences between patients and controls in either allelic or genotypic frequencies of the NDUFV2. Moreover, no effect of NDUFV2 polymorphisms was found on the age at onset and severity of epilepsy. **Conclusions:** The results of our study indicate that, despite a biologic plausibility, the NDUFV2 polymorphisms are not a significant genetic risk factor for the occurrence of nonlesional TLE. Moreover, NDUFV2 genotypes do not seem to influence the age at onset and prognosis of this epileptic disorder.

3.094

EEG ABNORMALITIES AND EPILEPSY IN SMIT–MAGENIS SYNDROME AND IN A GENETIC MOUSE MODEL

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Rationale: Smith–Magenis syndrome (SMS) is a microdeletion syndrome of chr. 17p11.2. The neurologic phenotype in children includes self-injurious behaviors, sleep disturbance, speech delay, mental retardation, and EEG abnormalities. Seizures are present in ≤30%. We evaluated the epilepsy phenotype in SMS and a genetically engineered mouse model. **Methods:** Prolonged EEGs in SMS patients were obtained during an overnight sleep study. Intracranial EEG in freely moving animals with the deletion and wild-type littermates was recorded during both wake and sleep. **Results:** We examined a cohort of 60 SMS patients. Of the 60, 29 (48.3%) had abnormal EEGs, 27 were epileptiform in nature. Focal abnormalities were found in eight of 27 (29.6%), and 21 of 27 (77.8%) showed generalized epileptiform features, including various 2- to 4-cps spike and slow-wave patterns in single waveforms or bursts up to several seconds in duration. Seizures were reported by parents in 11 (18.3%), and included absence (seven of 11), generalized tonic–clonic (four of 11), and drop attacks (two of 11), but not febrile seizures. Half of these (54.5%) showed abnormal EEGs. When noted, seizures were reported to be infrequent. Human chr. 17p11.2 is syntenic to the 32- to 34-cM region of murine chr. 11. Utilizing chromosomal engineering, we deleted a region on mouse chr. 11 that spans the syntenic region for the most commonly deleted interval in humans to generate a mouse model for SMS. In the F1 background (50% C57BL/6-Tyr c-Brd/50% 129S5/SvEvBrd) eight of 27 deletion mutants had witnessed seizures. On a background of 75%/25% only three of 21 (14.3%) had seizures. Seizures occurred between the age of 4 weeks and 6 months and occurred infrequently. All witnessed seizures were generalized tonic–clonic. We studied the EEG in freely moving animals with the deletion ($n = 5$), and in wild-type littermates ($n = 3$). Waking and sleep background activity appeared normal in all animals. Of the five mice recorded, witnessed seizures had occurred in two prior to recording. Bilaterally synchronous spike and slow-wave activity occurred in four of five and generalized tonic–clonic seizures occurred in two of five. Of those with seizures, one had occasional myoclonic jerks without a clear EEG signature. Spike-and-wave activity occurred in singlets and occasional doublets; rare polyspikes were seen. In a recorded seizure, single spikes progressed to polyspike bursts of increasing duration, which coincided with tail extension. Subsequently, a generalized seizure ensued with continuous spike-and-wave activity lasting 23 s, followed by postictal depression. **Conclusions:** Epilepsy is a frequent component of SMS. In our study, nearly one-half of patients with SMS have abnormal EEGs, the majority of which show generalized spike and slow wave variants, however, the epileptiform EEG abnormalities do not correlate well with seizure history, which was positive in 11 of 60. We identified epilepsy in 14–29% (strain-dependent) of mice deleted for the syntenic region of SMS. Seizures were infrequent, but showed generalized features. Multiple genes are deleted in SMS. It is unclear which of these may underlie paroxysmal EEG activity and seizures. None of the genes identified within the commonly deleted region have a currently known role in epilepsy. This mouse model will be useful in characterizing the contribution of spe-

cific genes to the epilepsy of SMS. [Supported by NIH 1PO1CA75719 (J.R.L.), 29709 (J.L.N.), and T32-NS07399-04.]

Clinical Epilepsy—Adult

3.095
PROGNOSIS FOR SURVIVAL AND FUNCTIONAL OUTCOMES IN PATIENTS WITH MYOCLONIC STATUS EPILEPTICUS FOLLOWING CARDIOPULMONARY RESUSCITATION

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Rationale: Myoclonic status epilepticus is a characteristic form of status epilepticus commonly observed in comatose survivors of cardiopulmonary resuscitation. It is difficult to treat and has been associated with a poor prognosis for survival. Although some survivors have been reported, the prognosis for myoclonic status epilepticus has been described by some experts to be so poor that treatment is considered futile. This poses major problems for the clinician who must decide whether and how aggressively to treat myoclonic status epilepticus. We report our experience in a large series of patients with myoclonic status epilepticus following cardiopulmonary resuscitation. At the end of this activity the participants should be able to discuss the association of myoclonic status epilepticus with outcomes after cardiopulmonary resuscitation **Methods:** We reviewed our experience with all patients with myoclonic status epilepticus following cardiopulmonary arrest identified by our neurology services over a twenty-year period. Myoclonic status epilepticus was defined as spontaneous, repetitive, irregular, brief jerks of the axial or peripheral musculature lasting for ≥30 min and supported by EEG findings. All patients received antiepileptic drug (AED) therapy but no formal, standardized treatment protocol was utilized. Therapy was individualized by managing physicians based on their own concepts of optimal care. We assessed various outcomes including survival at discharge, recovery of consciousness, and functional status. For those individuals who survived to be discharged, we also determined their condition 6 months following discharge. **Results:** We evaluated a total of 52 patients with myoclonic status epilepticus following cardiopulmonary resuscitation. Of these 52 patients, seven (13%) survived to be discharged from the hospital, but of those seven, only three survived after 6 months. Of the three who survived >6 months, only one recovered to a good functional level, but she was able to resume her baseline functional activities for several years until she subsequently died of a new cardiac event. Of the two other 6-month survivors, one was severely disabled and unable to function independently, and the other remained in a persistent vegetative state. Only one of the 52 patients ever recovered consciousness to a good, independent functional level. **Conclusions:** We confirm the generally poor prognosis of myoclonic status epilepticus following cardiopulmonary resuscitation. Of 52 patients, only one (2%) made a good, functional neurological recovery. However, seven survived to be discharged from the hospital, and three were alive 6 months later. Although the likelihood of a 6-month survival was only 6%, recovery of some degree of conscious function was 4%, and good recovery of neurologic function was 2%, indicating that favorable outcomes are possible. Therefore, we emphasize the importance of individualized assessments considering multiple clinical and neurologic variables when determining treatment, prognosis, and potential withdrawal of life support in patients with myoclonic status epilepticus following cardiopulmonary resuscitation. (Supported by a grant from the Rosen Foundation.)

3.096
STATUS EPILEPTICUS IN AN OUTPATIENT EPILEPTIC POPULATION: A RETROSPECTIVE STUDY

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Rationale: We reviewed clinical records of 1,520 adults outpatients (800 female, 720 male patients; mean age, 40.6 years) to evaluate the prevalence of status epilepticus (SE) in a group of patients referred to a medical center for epilepsy. **Methods:** On the basis of clinical and EEG data, we divided SE into generalized convulsive (tonic–clonic, and myoclonic), generalized nonconvulsive, and partial (convulsive and nonconvulsive). **Results:** Eighty patients (5.3%) had one or more SE, with higher prevalence in males (44 pts., 6.1%) than in females (36 pts., 4.5%). The mean age at the appearance of the (first) SE was 28.8 years (range, 1 month to 67 years). Thirty-eight pts. (47.5%) have a generalized epilepsy [idiopathic (IGE) in 18, cryptogenetic or symptomatic (C/SGE) in 20], 42 pts. (52.5%) have a partial epilepsy [cryptogenetic (CPE) in 11, symptomatic (SPE) in 31]. The prevalence of SE was 5.3% in IGE (18 of 340 pts.), 15.3% in C/SGE (20 of 131 pts.), 2.2% in CPE (11 of 500 pts.), 6.2% in SPE (31 of 500 pts.). None of 49 pts. with idiopathic partial epilepsy had SE. SE was generalized convulsive in 38 pts. (47.5%; seven with IGE, 12 with C/SGE, 19 with partial epilepsy), generalized nonconvulsive in 14 pts. (17.5%; 10 with IGE, four with C/SGE), myoclonic in six pts. (7.5%; one with IGE, four with C/SGE, one with partial epilepsy), partial convulsive in five pts. (6.2%), partial nonconvulsive in 17 pts. (21.3%). A precipitating factor of SE is recognizable in 39 pts. (49%), often pharmacologic (36 pts.; fever in the three other): suspension or reduction in AED therapy in 17 pts (36.8% of generalized convulsive SE, 7.1% of other SE; by patient itself in 14 cases, iatrogenic in three); administration of a new AED in 18 pts. (64.3% of generalized nonconvulsive SE, 83.3% of myoclonic SE, 17.6% of partial nonconvulsive SE); estrogen at high doses in one pt. with generalized nonconvulsive SE. In detail: (a) nine pts. had a generalized nonconvulsive SE after administration of carbamazepine (CBZ), phenytoin (PHT), vigabatrin (VGB) or tiagabine (TGB); (b) lamotrigine (LTG) caused a myoclonic SE in four pts. (three pts. with severe myoclonic epilepsy and one pt. suffering from epilepsy with myoclonic absences); (c) three pts. had a partial nonconvulsive SE after add-on of TGB. Nineteen pts. (1.25% of total group) experienced SE as first sign of the epileptic syndrome; 15 of these have a symptomatic partial epilepsy. Other 19 pts. had multiple SE; six of these ≥10 episodes (two pts. with Lennox–Gastaut syndrome, three female pts. suffering from IGE with absences). **Conclusions:** Our data show that ~5% of patients with chronic epilepsy experienced at least an episode of SE, and that pharmacologic factors are relevant in 45% of these patients. (Supported by University of Turin.)

3.097
TOPIRAMATE IN STATUS EPILEPTICUS: REPORT OF THREE CASES

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Rationale: To report the effectiveness of topiramate (TPM) in treating complex partial status epilepticus (one patient) and refractory generalized status epilepticus (two patients). **Methods:** Two patients with refractory generalized status epilepticus and one patient with end-stage liver disease, hepatic encephalopathy, and complex partial status epilepticus were treated with TPM. The patients' clinical status and neurologic examinations were followed up. Two patients had continuous EEG whereas the third had intermittent prolonged EEG recordings. In all patients, TPM was initiated at 500 mg b.i.d. for 2–5 days and the dose gradually tapered thereafter to 200 mg, b.i.d. **Results:** Patient 1 was admitted for subacute encephalopathy of unclear etiology. Initial EEG showed generalized slow-wave activity, Two days after admission he developed recurrent partial seizures with secondary generalization that were resistant to repeated doses of lorazepam (LZP) and loading with fosphenytoin (FPHT). He was intubated, and pentobarbital (PTB) coma was induced. Over the next 8 days, continuous EEG showed recurrent ictal discharges with repeated attempts to taper PTB despite optimization of serum PHT level and the addition of intravenous valproate (VPA). TPM, 500 mg, b.i.d., was added and 2 days later PTB was again tapered with no recurrence of ictal discharges. The patient was eventually extubated and discharged on a combination of PHT and TPM (200 mg, b.i.d.). Patient 2 had end-stage liver disease, was hospitalized for peritonitis and his course was complicated by hepatic

encephalopathy and variceal bleeding. On day 16 of hospitalization, he had four complex partial seizures and encephalopathy worsened. Prolonged EEG showed recurrent ictal discharges arising from the left frontocentral region. TPM, 500 mg, b.i.d., was started. Two days later mental status improved and he became more responsive. A repeat EEG study showed improved background activity and no further ictal discharges although periodic epileptiform discharges were seen in the left centroparietal area. Two days later the patient died of recurrent variceal bleeding. Patient 3 suffered cardiopulmonary arrest after choking on food, and was treated for postanoxic seizures with LZP and FPHT. The following day EEG showed recurrent generalized ictal discharges, serum PHT level was optimized, and intravenous VPA was added. Continuous EEG showed recurrent generalized ictal discharges, propofol coma was induced, and TPM 500 mg, b.i.d., was started. Two days later, propofol was tapered and discontinued and EEG showed generalized slow-wave activity and no ictal discharges. TPM was mistakenly held for 2 days and EEG showed recurrence of frequent epileptiform discharges but these subsided after reinitiation of TPM 200 mg, b.i.d. The patient was discharged to another facility 2 days later. **Conclusions:** TPM was effective in treating two patients with refractory generalized status epilepticus and one with complex partial status epilpticus. It could therefore be considered as an option in treating refractory status epilepticus or when standard AEDs cannot be used.

3.098

ELECTROENCEPHALOGRAPHIC EFFECTS OF KETAMINE TREATMENT FOR REFRACTORY STATUS EPILEPTICUS

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Rationale: To understand the EEG changes associated with ketamine treatment for status epilepticus which was refractory to conventional anticonvulsants (AEDs). Experimental studies suggest that after an hour or more of seizure activity, γ-aminobutyric acid (GABA) agonists may lose efficacy while *N*-methyl-D-aspartate (NMDA)-receptor activation becomes more prominent. Ketamine is the only clinically useful NMDA antagonist. In anesthetic doses, ketamine alone produces enhanced β activity and some background slowing, but not suppression-burst (S-B) in normal humans. When added to GABAergic agents such as propofol, it may enhance the appearance of S-B in head-injured patients. The EEG effects of ketamine in refractory status epilepticus (RSE) patients have not been well described. **Methods:** After IRB approval, we searched for all cases of RSE treated with ketamine and reviewed the available EEG records. The response to ketamine with regard to seizures was judged by the available EEG records; other effects were extracted from the patients' medical records. **Results:** We obtained the records of seven patients treated with ketamine for RSE. In all cases, only segments of the continuous EEG records had been archived. In all cases, ketamine was introduced because other agents had failed or could not be tolerated hemodynamically. The average duration of seizures prior to ketamine therapy was 60 h (range, 5–192 h). All of the patients were critically ill before ketamine was introduced (mean APACHE II score, 23), and were receiving at least two other AEDs, one of which was usually propofol or pentobarbital (PTB). Most patients received a loading dose (range, 0.9–3.0 mg/kg); in two patients, the loading dose terminated RSE at least briefly. In the other five patients, infusion rates ranged from 0.3 to 5.8 mg/kg/h; seizures stopped in two of these patients. Adding ketamine to other AEDs induced a S-B pattern in three patients without a preexisting S-B pattern. All patients eventually died during the index hospitalization. Ketamine had minimal effects on blood pressure. **Conclusions:** Ketamine produced electrographic seizure control in over half of the RSE patients without inducing more hemodynamic instability. The response rate as judged by bedside clinicians was greater, but this was not the criterion used in this study. None of the deaths was unexpected or appeared related to the use of ketamine. The loading doses used were probably too small. We conclude that ketamine is a potentially important agent for the control of RSE and should be the subject of a prospective clinical trial. (Supported by University of Virginia Department of Neurology.)

3.099

STATUS EPILEPTICUS AT THE ONSET OF EPILEPSY

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Rationale: At the end of this activity, the participants should be able to discuss the incidence of status epilepticus as the initial presenting symptom of epilepsy. Status epilepticus (SE) may cause epilepsy since 40% of generalized convulsive status epilepticus (GCSE) patients later develop epilepsy and epilepsy can be induced by experimental SE; however, the frequency with which epilepsy presents with SE is not well studied. We hypothesized that SE is the initial presenting symptom of epilepsy in a substantial minority of patients. Since experimental SE can induce partial epilepsy, we hypothesized that partial epilepsy syndromes, especially temporal lobe epilepsy, are more likely to present with SE. **Methods:** Patients with definite epilepsy seen in the Epilepsy Clinic between 1/1/01 and 12/31/01 were identified from the University of Virginia Comprehensive Epilepsy Program patient database. Patients with only unclassified spells or only pseudoseizures were excluded. The database was queried to determine whether or not an episode of SE had been reported, and to determine demographic, seizure, and epilepsy syndrome characteristics. Phone contact or chart review was attempted to confirm the information contained in the database, including whether the recorded episode of SE occurred (defined as >30 min of seizure activity), clinical type of SE, SE duration, and whether the episode represented the patient's initial seizure. $\chi 2$ analysis was performed to determine whether there was a difference in the frequency of SE as the presenting seizure between patients with partial and generalized seizures and among specific epilepsy syndromes. **Results:** Of 786 patients derived from query of the database, we found 157 (20.0%) had a reported history of SE. The history of SE was confirmed in 107, unable to be confirmed (unreachable for confirmation) in 40, denied in eight, and unknown in two; 125 (15.9%) had at least one episode of GCSE, and 43 (5.5%) had at least one episode of nonconvulsive status epilepticus (NCSE). SE as first seizure was present in 26% of those with GCSE and 26% of those with NCSE. Average SE duration was longer for NCSE than GCSE (390 vs. 111 min, $p = 0.003$). SE was the first clinical seizure in 42 (5%) and was not different between seizure classes (partial only, generalized only, or both). Among well-represented epilepsy syndromes, SE was the initial presentation of epilepsy most frequently in TLE (7.3%) and least frequently in idiopathic generalized epilepsies (<3%). **Conclusions:** SE is frequently present at the onset of epilepsy. TLE is the syndrome most likely to present with SE, possibly because SE causes TLE. SE is rarely the first seizure in IGE, probably because it is the first manifestation of an already epileptic brain in these patients.

3.100

BOUNCING BACK AFTER STATUS EPILEPTICUS: FACTORS AFFECTING FUNCTIONAL OUTCOME

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Rationale: Status epilepticus (SE) is a medical emergency associated with significant mortality. This study examines morbidity in terms of functional outcome in pediatric, adult and elderly SE cases in a large population-based SE database. **Methods:** Data were obtained from the NIH Greater Richmond Metropolitan Area Status Epilepticus Database, a prospective population-based study. Morbidity was measured using the Glasgow Outcome Scale (GOS), scored as follows: 5, good recovery/normal (may have mild deficits), 4, moderate disability [disabled but independent, able to perform activities of daily living (ADLs)], 3, severe disability (conscious but disabled), dependent with ADLs, 2,

coma/persistent vegetative state, 1, dead. Scores were recorded to reflect functional status prior to SE, at discharge, and 30 days after SE for cases with long hospitalizations. Cases were divided into three groups: those who had the same score after SE as they had before SE (same), those who had a decrease in function after SE (worsened), and those who died. $\chi 2$ was used to test significance; very few cases showed an improvement after SE and were not included in statistical analysis. Cases were divided into three age categories: pediatric cases included 1 month of age up to 16 years, adult cases included those aged 16–60 years, and the elderly group consisted of those cases 60 years and older. **Results:** A total of 698 cases had GOS scores available for analysis. Of these, 264 (38%) were pediatric, 193 (28%) were adult, and 241 (34%) were elderly. Combined morbidity and mortality was highest in the elderly group (48%), compared with adult (35%) and pediatric groups (10%). Mortality was significantly higher in the elderly (36%) and lower in pediatric cases (5%) than in adult cases (26%), $p < 0.0001$ In the survivors there were also statistically significant changes in functional outcome by age group. Of the pediatric cases, 94% stayed the same and 6% worsened, while in adults 81% remained the same and 19% worsened, and in the elderly group, only 64% remained the same and 36% worsened ($p < 0.0001$). There were no statistically significant differences in outcome by gender or race in any of the age groups. In all age groups, there were statistically significant differences in outcome with relation to seizure history: fewer cases with a previous seizure history worsened ($p < 0.004$), and there were also similar findings in adult and elderly cases with a previous history of SE ($p < 0.004$). **Conclusions:** Following SE, children are likely to maintain functional abilities, while the elderly are likely to deteriorate. Patients with a previous history of seizures and/or SE are less likely to experience functional deterioration. These findings have important implications for prognosis and rehabilitation of patients with SE. (Supported by NIH P01 NS25630.)

3.101
A PHARMACOKINETIC/PHARMACODYNAMIC STUDY OF MIDAZOLAM NASAL SPRAY IN EPILEPSY PATIENTS USING ENZYME-INDUCING ANTICONVULSANTS

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Rationale: Diazepam (DZP) rectal solutions are widely used as treatment for early status epilepticus. An acute treatment with a benzodiazepine (BZD) can prevent evolution into refractory status epilepticus in most cases. However, application of a rectal solution is not always social acceptable, or may encounter physically insurmountable problems. A nasal spray may overcome some of these limitations. In a previous study in healthy volunteers we have proven that midazolam (MDL) nasal spray has high social acceptance and is absorbed fast with a bioavailability of 70% of intravenous administration. By using a concentrated nasal spray, the midazolam is absorbed topically, and no first-pass effect could be demonstrated. **Methods:** Twelve patients with medically refractory epilepsy using enzyme-inducing AEDs were randomly assigned to application of either 5 or 10 mg MDL nasal spray. A nasal spray was used which delivered 2.5 mg pro 0.09 ml pif, ~5 times as concentrated as the commercially available parenteral solution. The clinical effect and side effects were evaluated, including monitoring of oxygenation; EEG samples were taken at regular intervals during 2 h for analysis of the power spectra; an indwelling venous catheter was placed during 8 h for frequent blood sampling to calculate the AUC. **Results:** Twelve patients fulfilled inclusion criteria and gave informed consent. Application of the nasal spray was accompanied with nasal pain and watery eyes. These complaints subsided within a few minutes in all patients. After 5 min, the patients became sedated, especially when 10 mg was administrated. No other generalized side effects were noticed. We will present the results of plasma level monitoring and of EEG powerspectra. **Conclusions:** MDL concentrated nasal spray is well tolerated, has good social acceptance, and is rapidly absorbed also in persons using AEDs. MDL nasal spray may have potential for intervention in early status epilepticus. A study is in preparation to compare the efficacy and side effects of MDL nasal spray with those of DZP rectal solutions in beginning status epilepticus. (Supported by Dutch epilepsy fund NEF.)

3.102
STIMULUS-SENSITIVE STATUS EPILEPTICUS

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Rationale: The electroencephalographic (EEG) hallmark of status epilepticus (SE) is continuous spike and wave activity or electrographic seizures recurring at frequent intervals. External stimulation has not been reported to have an effect on this EEG activity. This study was done to describe patients in whom SE was triggered by external stimulation. At the end of this activity, participants should appreciate the presence of stimulus-sensitive SE. **Methods:** All patients undergoing prolonged EEG monitoring for SE by the Duke EEG Laboratory between July 1999 and May 2002 were reviewed. Patients were enrolled if external stimulation (i.e., pinching, suctioning) resulted in the EEG changing from a nonepileptic pattern to continuous spike-and-wave activity. The clinical characteristics of these patients were noted. **Results:** Three patients were identified who met criteria for enrollment. The mean age was 32.3 years; all were females. SE represented the first seizures for all. They were being treated for SE with multiple antiepileptic drugs (AEDs) and anesthetics. Prior to stimulation, the patients' EEG consisted of either a burst-suppression pattern or generalized periodic epileptiform discharges (GPEDs). With stimulation, the EEG evolved into rhythmic, continuous spike-and-wave activity that lasted from several seconds to minutes. Two patients survived, one was transferred to a rehabilitation facility. One patient died. **Conclusions:** Stimulus-sensitive SE may be seen in patients who appear to be in burst suppression with AEDs and anesthetic medications. Patients in induced burst suppression for SE should be tested with stimulation to confirm adequate treatment.

3.103
BEWARE THE SRPIDs: STIMULUS-RESPONSIVE PSEUDOICTAL DISCHARGES ARE A COMMON AND IMPORTANT EEG PATTERN IN CRITICALLY ILL PATIENTS

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Rationale: To describe an EEG pattern frequently encountered in intensive care unit (ICU) patients undergoing continuous EEG monitoring (cEEG). **Methods:** We reviewed clinical and EEG details of all patients with SRPIDs on cEEG between 7/1/2001 and 4/1/2002 (9 months). SRPIDs were defined as periodic, rhythmic or ictal-appearing discharges that were consistently induced or suppressed by alerting stimuli such as suctioning or sternal rub. **Results:** We identified 33 patients with SRPIDs (~20% of all patients undergoing cEEG). Digital video was recorded in addition to EEG in 24 patients. EEG features: specific patterns seen included periodic "epileptiform" discharges [$n = 21$ patients: nine lateralized (PLEDs), 11 generalized (GPEDs), three triphasic waves; some had more than one periodic pattern]; rhythmic patterns with evolution with or without intermixed spikes fulfilling criteria for ictal discharges ($n = 18$; 13 unilateral, seven bilateral; some with both); or high-voltage frontally dominant rhythmic delta (FIRDA; $n = 14$; seven with at least one other SRPID pattern as well). All 33 patients had SRPIDs induced by stimulation; two also showed suppression of SRPIDs by stimulation at other times. Clinical features: eight patients had prior epilepsy, and 24 had an acute brain injury (including eight SAH, four ICH, three trauma, two CNS infection, two infarct). Half (16 of 33) of the patients had definite seizures during the acute illness (in addition to SRPIDs), and half (17 of 33) did not. Ten patients had previous clinically obvious seizures. Eight patients had subclinical or very subtle seizures on video (unnoticed by staff/family); only one of these eight had clinical seizures as well. Status epilepticus had been present in 11 patients: nonconvulsive in three, convulsive in four, and both in four. **Conclusions:** Periodic or ictal-appearing EEG patterns are

commonly elicited by stimulation in critically ill ICU patients. Recording video, documenting patient stimulation on the EEG record, or repetitively examining patients during cEEG is necessary to recognize this pattern, avoid misinterpretation, and differentiate SRPIDs from spontaneous seizures. Further research is necessary to determine the pathophysiologic, prognostic, and therapeutic significance of SRPIDs.

3.104
HIGH-DOSE PHENYTOIN AND BENZODIAZEPINE DECREASE NEED FOR ANESTHESIA IN INTRACTABLE CONVULSIVE STATUS EPILEPTICUS

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Rationale: Anesthesia for intractable status epileticus is labor intensive, costly and carries an increased risk for iatrogenic complications. A previous report (*Epilepsia* 1989;30:464–71) suggested that i.v. phenytoin (PHT) doses >18mg/kg and diazepam (DZP) >10 mg/kg may control status epilepticus not responsive to conventional doses. This study expands on those observations. **Methods:** Fifty-one patients in convulsive status epilepticus were treated with conventional doses of PHT (18 mg/kg) and either DZP (10 mg) or lorazepam (LZP; 0.125 mg/kg), i.v. If there was no response (verified electrographically) the patients received an additional 12 mg/kg of PHT and DZP 10 mg or LZP 0.125 mg/kg, i.v. If at the end of the second infusion, there was no response (by EEG) and patients could safely receive i.v. pentobarbital (PTB) at that time, this therapy was begun. Otherwise, a third infusion of PHT 10 mg/kg and DZP, ≤10 mg and LZP ≤0.125 mg/kg were given, while preparations for anesthesia were being made. Response was measured via EEG. **Results:** Thirty-two (63%) patients responded to conventional treatment. Ten patients (20%) were controlled with a total PHT dose of 30 mg/kg and 20 mg of DZP or 0.250 mg/kg of LZP. Five patients who did not respond to high-dose therapy received PTB anesthesia. In four patients, for whom preparations for anesthesia had not been completed at the time the infusions of additional medications ended, received more PHT (total, 40 mg/kg) and DZP (≤30 mg) and LZP (≤0.375), status came under control. **Conclusions:** Very high doses of PHT and BZD may obviate the need for anesthesia in status epileticus, reducing the morbidity and high cost inherent to this form of therapy. The very high PHT dose finds support in animal data (*Epilepsy Res* 1994;19:99–110). (Supported by Alliance for Epilepsy Research.)

3.105
PILOT STUDY COMPARING INTRANASALLY ADMINISTERED DIAZEPAM AND MIDAZOLAM

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Rationale: Intranasal administration offers a potentially valuable means of treating seizure emergencies outside of the hospital. The ideal drug for this indication would be highly concentrated, rapidly and consistently absorbed with an extended duration of effect. The purpose of this study was to compare the pharmacokinetics and tolerability of intranasal diazepam (DZP) and midazolam (MDL). **Methods:** Two healthy volunteers completed a single-blind, four-way crossover study involving intravenous (i.v.) and intranasal (i.n.) administration of 5 mg DZP and MDL. Serial blood samples were collected over 48 h, and a questionnaire about nasal discomfort and level of alertness (sedation) was completed by the subjects. **Results:** The duration of nasal discomfort was brief with subjects returning to baseline in 60 min. Sedation was more prolonged, paralleling the time course of plasma concentrations, and was greater following MDL administration. Please refer to the Table 1 for results. **Conclusions:** Based on these preliminary results, DZP appears to have high bioavailability and an extended elimination half-life with a T_{max} comparable to MDL. These properties indicate that i.n. DZP may be preferable to i.n. MDL in treating seizure emergencies. (Supported by University of Minnesota Seed Grant.)

TABLE 1. *Comparison of intranasal diazepam and midazolam*

	Diazepam (subject 1, subject 2)	Midazolam (subject 1, subject 2)
IN Tmax (min)	15, 30	30, 10
Bioavailability (0–180 min)	84%, 110%	66%, 69%
Half life (h)	33, 26	2.1, 0.9
Maximal nasal discomfort (10, extremely uncomfortable)	5.5, 8	4, 8
Maximal degree of sedation (10, extremely drowsy)	4.5, 2	9, 1.5

3.106
STATUS EPILEPTICUS ASSOCIATED WITH INTRATHECAL BACLOFEN IN PATIENTS WITH MULTIPLE SCLEROSIS

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Rationale: Baclofen-induced status epilepticus has been reported in a small number of case reports. The goal of our study was to investigate the incidence of status epilepticus in a series of 81 patients with multiple sclerosis (MS) treated with intrathecal baclofen. **Methods:** Data were obtained from the Mellen Center Intrathecal Baclofen Therapy Registry. The registry contains records of all patients since 1990 with a definite clinical diagnosis of MS who had an intrathecal baclofen pump implanted. **Results:** Eighty-one patients underwent implantation of a baclofen pump between October 1990 and January 2002. At the time of surgery, mean age was 49.9 ± 7.4 years, and mean disease duration was 16.9 ± 8.4 years; 78% were nonambulatory. Mean baclofen rate on the most recent follow-up was 266.8 ± 239.8 μg/day. A total of 320 cumulative baclofen pump years was reviewed. Two of 81 patients (2.4%) went into status epilepticus. Both patients had no previous seizures. The first case was a 46-year-old woman with secondary progressive MS since 18 years. An intrathecal baclofen pump was implanted and started at a rate of 88 μg/day. Three months after implantation, she presented with a prolonged episode of confusion and hypothermia lasting 7 days. EEG showed continuous slow, generalized sharp waves as well as generalized clinical and subclinical seizure at a frequency of four to 10 per hour. The baclofen pump was discontinued temporarily without improvement. She was treated with intravenous phenytoin (PHT), phenobarbital (PB), and later valproic acid (VPA) with slow improvement over 3 weeks. Additionally, persistent high fever throughout the hospital stay was treated with i.v. antibiotics. MRI demonstrated MS-typical lesions and restricted cortical diffusion, which resolved on follow-up. The patient remained seizure free with VPA during the remainder of hospital stay and was continued on 50 μg/day intrathecal baclofen. The second case was a 51-year-old woman with secondary progressive MS for 26 years. She became unresponsive immediately after baclofen pump implantation. Evaluation of the pump reservoir revealed that she had accidentally received a 10-fold (2,050 μg) of the programmed initial bolus. EEG monitoring demonstrated subclinical generalized seizures which resolved within 24 h after discontinuation of the baclofen pump and treatment with i.v. fosphenytoin. On follow-up the patient remained seizure free on gabapentin (GBP) and on intrathecal baclofen 100 μg/day. **Conclusions:** Intrathecal baclofen application bears a low but definite risk of status epilepticus. Whereas one case immediately responded to lowering of the baclofen dose, a relationship between status epilepticus and intrathecal baclofen remains unclear in our second case. None of both patients had a preexisting epilepsy. In both cases, additional aggravating factors (coexisting fever and overdose) may have precipitated status epilepticus. [Supported by Innovative Medizinische Forschung, WWU Münster (FoeKz. LO 610101) and NRW-Nachwuchsgruppe Kn2000, Federal

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3.107
INCONSISTENCY OF MENTAL STATUS EXAMINATION WHEN DIAGNOSING NONCONVULSIVE STATUS EPILEPTICUS

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Rationale: Nonconvulsive status epilepticus (NCSE) is often difficult to diagnose, even with benzodiazepine (BZD) injection, because mental status improvement may be subtle and can be misinterpreted if systematic testing is not performed, or if different tasks are presented to the patient before and after administration of BZD. We hypothesized that consistent mental status (MS) testing is not performed systematically before and after BZD administration during EEG in patients who are suspected of having NCSE. **Methods:** We retrospectively reviewed EEG tracings in 14 patients who clinically and electrographically met the diagnosis of NCSE, who also received BZD to help establish the diagnosis. Clinical and EEG improvement were not required for this review. We collected the type of EEG discharge (spike–wave vs. non-spike–wave), location (generalized vs. lateralized or localized), type of BZD administered, clinical and EEG response (complete, partial, no response), and number of tasks that were presented to patients before and after BZD administration. **Results:** Of the 14 patients, 43% had spike–wave discharges on EEG and 78% had generalized discharges. BZDs administered included diazepam in 11, lorazepam in two, and midazolam in one; 50% had complete EEG response and 36% had partial response; 43% had complete clinical response and 28% had partial response. On average 2.7 (range, 0– 9) tasks were presented to patients prior to BZD administration, and 3.4 tasks (range, 0–9) after administration. On average, 55% of the tasks that were presented to patients prior to BZD administration were presented afterward. On one occasion, the person who presented the tasks prior to BZD administration was different from the person who did that after the administration. **Conclusions:** Casual MS testing in the evaluation of NCSE is often not consistent or systematic, which raises the possibility that "partial" improvement in MS may not be appreciated after BZD administration. MS testing during the evaluation of NCSE should be detailed and consistent before and after BZD administration, such as with a standardized examination.

3.108
WHEN SHOULD SURGERY BE PERFORMED FOR STATUS EPILEPTICUS?

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Rationale: The mortality of status epilepticus (SE) requiring anesthesia to stop it is ≤50%. We have recently managed four cases of SE in which surgery was considered. A fifth case was operated on after status. **Methods:** We prospectively and retrospectively gathered data from cases of SE at our institution for which surgical treatement was suggested. **Results:** Case 1: a 5-year-old with history of prenatal complications, developmental delay, uncontrolled tonic or atonic seizures since age 3. EEG showed left frontal SW, MRI normal, FDG-PET: L frontal hypometabolism. She developed SE, uncontrolled with three antiepileptic drugs (AEDs) and pentobarbital (PTB) coma. Viral, metabolic, and genetic tests were normal; brain biopsy was nondiagnostic. After 6 weeks, she underwent implantation of subdural electrodes over the left frontal and temporal regions. This confirmed an inferior frontal focus, and resection was performed with motor mapping. Recovery from high barbiturate levels was prolonged, but she regained milestones, and has had no seizures since, although frontal SW persists in sleep. Case 2: 6-month-old with onset of encephalitis (viral tests negative), and L occipital-temporal seizures which failed to respond to oral AEDs, and propofol/MDL. He was taken for implantation of subdural strips, with plans to resect if possible. Poor hemostasis prevented this. The seizures finally responded to 15 mg/kg topiramate (TPM). He awoke with a visual tracking defect and depressed milestones. Case 3: 18-year-old man with onset of encephalitis (viral tests negative), SE and PTB coma for 2 months. He finally awoke on three AEDs but continued to have 12 GTC/mo. After rehabilitation, motor functions were normal; IQ loss was 60 points with language at 1–3%. MRI showed diffuse volume loss; PET-L temporal hypometabolism. LTL resection decreased the seizures to 1 per month. Case 4: 22-year-old man with new-onset R focal leg seizures failed to respond to four AEDs, then MDL/propofol coma. Video-EEG showed a L dorsal frontal focus. MRI changed from normal to increased T2, L mesial frontal. Surgery with ECoG, motor mapping, and resection was recommended, but the family refused. The patient died of numerous medical complications. Autopsy revealed no pathology. Case 5: A 25-year-old man presented with new onset L facial seizures. These progressed and failed control with five AEDs and MDL/propofol. MRI was normal, video-EEG showed a R frontal focus, viral tests were negative. After 5 days of coma, seizures persisted so he underwent implantation of R fronto-parietal and temporal subdural electrodes. Ictal onsets were recorded in the postcentral gyrus and operculum. This area was resected and he was weaned off anesthesia on three AEDs. Pathology was negative. At 1 month postresection he has had one to two SPS per week, and shows some frontal disinhibition. **Conclusions:** In this series, two of two cases of SE undergoing surgery had good outcomes, whereas of those not operated on, one of three died, one of three had severe cognitive damage, and one of three is too young to tell. When status appears to originate from a focal or regional area, surgery should be considered before irreversible brain damage ensues, and prospective studies in different age groups should be considered. (Disclosure: Honoraria: Dr. Swartz is on speakers bureau for Pfizer, Ortho-McNeil, Abbott, UCB Pharma, Elan, and Glaxo.)

3.109
NEW-ONSET STATUS EPILEPTICUS IN HOSPITALIZED PATIENTS: A DISTINCT SUBSET OF STATUS PATIENTS

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Rationale: Status epilepticus (SE) commonly occurs in patients with a history of epilepsy. However, SE that occurs de novo, as a complication of acute medical and neurologic conditions, represents a distinct clinical scenario that may have different characteristics and prognosis. A recent retrospective study found a 61% mortality in this subset of patients (Delanty N, et al. *Seizure* 2001;10:116–9). **Methods:** Seven hundred seventy-five prospectively identified SE cases in the NIH Greater Richmond Metropolitan Area SE database were included, and were divided into four patient populations: (a) no history of seizures, and new onset of SE while hospitalized; (b) no history of seizures and new onset of SE outside the hospital; (c) history of seizures but not SE; and (d) history of SE and seizures. Parameters examined were age, mortality, race, etiology, SE type, and duration. **Results:** There were 158 patients in group 1, 250 in group 2, 190 in group 3, and 175 in group 4. The groups did not significantly differ with respect to gender. Inpatient de novo SE was significantly more likely to occur in the elderly and in whites. Group I patients were significantly more likely than other groups to have SE etiology of hypoxic/anoxic injury or acute CNS process. SE in group 1 patients, compared to other groups, was significantly more likely to be prolonged, to be nonconvulsive, and to result in death. The mortality rates were group 1, 53%, group 2, 22%; group 3, 17%; and group 4, 6%. **Conclusions:** Hospitalized patients with new-onset SE are a distinct subset of SE patients with characteristics associated with a significantly worse prognosis. These findings emphasize the need for clinical vigilance in this at-risk subset of hos-

pitalized patients, and have implications for therapeutic strategies. (Supported by NIH PO1 NS25630.)

3.110
STATUS EPILEPTICUS INCREASES THE RISK OF DEATH AMONG INPATIENTS WITH SUBARACHNOID HEMORRHAGE

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Rationale: Status epilepticus (SE) is a significant risk factor for death among inpatients with stroke; the increased risk of death among those with SE and stroke is independent of the size of the infarct (Waterhouse et al., 1998). Using data from the National Inpatient Sample of the Healthcare Cost and Utilization Project (NIS, HCUP-3), we recently reported that SE increases the odds of death among a sample of 161,524 inpatients, even after controlling for multiple confounding variables (Trevathan, 2002). In order to study the impact of early diagnosis and timely treatment of SE among inpatients, it is important to identify subpopulations of inpatients at increased risk of death from SE. **Methods:** We used NIS, HCUP-3 data from 1988 to 1997 to ascertain discharge records with a diagnosis of SAH (ICD-9, 430). Neonates were excluded. The NIS contains >65 million patient-discharge reports that represent a systematic 20% sample of United States hospital discharges. Descriptive analyses were performed, and unadjusted odds ratios were calculated using in-hospital death as the primary outcome variable and SE as the primary exposure variable. Multiple logistic regression models were developed using Stata 7.0, entering variables in a step-wise fashion that were both clinically relevant comorbid conditions and potential confounding variables based upon univariate analysis. **Results:** 44,914 discharge records (37.1% male) with a diagnosis of SAH were ascertained; 121 discharge records also had a diagnosis of SE; 62% of patients with SAH were between ages 26 and 65 years. The overall case fatality rate among those with SAH was 30.1%; those with SAH and SE had a case fatality rate of 40.7%. SE increased the odds of death among those with SAH (unadjusted OR, 1.64; 95% CI, 1.14–2.36). In the logistic regression model the most significant predictor of death was cerebral anoxia (adjusted OR, 9.7; 95% CI, 7.6–12.5). Respiratory failure, cerebral edema, intracerebral hemorrhage, ketoacidosis, and hypernatremia were also significant risk factors for death. After adjusting for comorbid conditions (39 variables in the final model), SE significantly increased the odds of death among those with SAH (adjusted OR, 1.69; 95% CI, 1.08–2.63). **Conclusions:** SE increases the risk of death among inpatients with SAH, after controlling simultaneously for multiple comorbid conditions. [Supported by 1 RO3 HS11453-01 (E.T.) from the Agency for Healthcare Research & Quality.]

3.111
HIGH-OUTPUT CURRENT/RAPID CYCLING VAGUS NERVE STIMULATION FOR REFRACTORY STATUS EPILEPTICUS: PRELIMINARY RESULTS

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Rationale: Refractory status epilepticus (RSE), defined as SE that fails to respond to second-line therapy,and its treatments are associated with high morbidity and mortality. Thus, new therapies are needed that are safe with no drug interactions. Vagus nerve stimulation (VNS) is a safe, minimally invasive therapy with no drug interactions. We investigated high-output current VNS with rapid cycling as adjunct therapy in refractory status epilepticus. Participants should be able to undertand the role VNS may have in management of RSE. **Methods:** Patients who had persistent RSE which had not responded to intravenous benzodiazepines (BZDs), phenytoin (PHT), phenobarbital (PB), and valproic acid (VPA) and did not have a deteriorating/progressive neurologic/systemic etiology of the RSE were considered for compassionate use of VNS from 2000 to current. RSE was confirmed by continuous EEG recording with impaired consciousness. Age, SE etiology, duration of SE prior to VNS,concomitant treatments and MRI results were reviewed and fully considered in the implantation decision. Time to RSE termination was confirmed by EEG and clinical outcome with 1-year follow-up was assessed by phone follow-up. Surgical complications, stimulation parameters including output current, signal frequency, on/off time and pulse width were registered. **Results:** Three patients (of 10 potential RSE cases) met criteria for compassionate use of VNS for RSE (two men, aged 20, 82; one woman, aged 64). All had EEG-confirmed persistent RSE and all were in a clinically subtle status with loss of consciousness. Each had a history of medication-refractory multifocal partial epilepsy, and the etiology of SE in each patient was antiepileptic drug (AED) withdrawal. All patients failed to respond to lorazepam (LZP), supratherapeutic levels of PHT (serum range, 25–27), VPA (serum range, 90–110), and PB (serum range, 50–65). Two patients failed trials of general anesthesia with periods of generalized EEG suppression. MRI of the brain showed no evidence of stroke or CNS tumor. Duration of SE prior to any treatment was 12–36 h, whereas duration of SE prior to VNS treatment was 1–5 weeks. All patients had VNS implanted under general anesthesia with no surgical complications. All patients had continuous EEG monitoring pre- and postoperatively. VNS was quickly ramped up to maximum output current of 3 mAmp at a signal frequency of 30 Hz, pulse width, 500, on time, 60 s, off time, 1 min. No pulmonary or cardiac problems were encountered. All patients remained on their concomitant PB and/or PHT, VPA. Time to RSE termination with EEG confirmation after VNS implantation was 3–5 days. All patients were subsequently discharged from the hospital. At 1 year follow-up, two patients remain with the VNS at lower stimulation parameters; one patient (aged 82 years) died 1 year later after full recovery from RSE from complications from a generalized tonic–clonic seizure. **Conclusions:** Adjunct high-output current VNS with rapid cycling is potentially useful in RSE cases that lack poor prognotic etiologies. VNS and other stimulation techniques should be investigated in RSE due to AED withdrawal and other RES etiologies with less dire prognosis. Further studies assessing RSE and its treatment are needed. (Disclosure: Grant: Dr. Sirven had a research grant with Cyberonics in 1999; Honoraria: Dr. Sirven has received honoraria for speaking.)

3.112
COMPARISON OF HEART MASS IN SEIZURE PATIENTS DYING OF SUDDEN UNEXPLAINED DEATH IN EPILEPSY TO SUDDEN DEATH DUE TO SOME OTHER CAUSE

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Rationale: We hypothesized that individuals dying of sudden unexplained death in epilepsy (SUDEP) would have abnormally enlarged hearts, increasing the risk of sudden cardiac death should the autonomic nervous system initiate a dysrhythmia. This study compares the mean heart mass of individuals who died of SUDEP to the mean heart mass of individuals with epilepsy who died suddenly due to some cause other than SUDEP. At the end of this activity participants should be able to discuss the relationship of SUDEP and heart mass and the diagnosis of SUDEP at autopsy in a medical examiner population. **Methods:** We conducted a retrospective review of 133 deaths investigated and autopsied by the Medical Examiner's office in decedents with a history of seizures. After reviewing each case, deaths were classified as SUDEP ($n = 57$) or non-SUDEP ($n = 76$, eight deaths due to accident, 26 deaths unrelated to seizure, 42 deaths indeterminate between SUDEP and a potential anatomic cause such as heart disease). Age, history of hypertension, and history of alcoholism were examined as possible confounding factors. Expected heart mass was calculated using the decedent's body mass and published formulae. **Results:** We found no significant difference in the mean heart mass between the SUDEP (mean heart mass, 358 g) and non-SUDEP (mean heart mass, 399 g) groups when analyzing the unadjusted data from this study of decedents with a history of seizures who died suddenly. Analysis of unadjusted data showed a decreased frequency for dying of SUDEP in

individuals with a heart mass ≥100 g greater than expected based on body mass compared to those without an enlarged heart (odds ratio, 0.30, 95% confidence interval, 0.12–0.72). In other words, individuals with seizures who had an enlarged heart were 70% less likely to die of SUDEP than individuals with seizures who did not have an enlarged heart. The decrease in SUDEP was especially pronounced in individuals 40 years or older compared to those younger than 40 years (See Table 1, Classification 1). This decrease disappeared when cases where the cause of death was indeterminate between SUDEP and heart disease were reclassified from non-SUDEP to SUDEP (see Table 1, Classification 2). **Conclusions:** Increased heart mass does not lead to an increased likelihood of dying of SUDEP. With increasing age the likelihood of finding a cause of death that competes with SUDEP increases, making SUDEP appear a phenomenon of the young. The inclusion of seizure deaths evaluated in a medical examiner office in studies of SUDEP would provide a more certain diagnosis in each given case. Moreover, the inclusion of cases from the medical examiner population would stem attrition in a study due to loss to follow-up.

TABLE 1. *Odds ratios for likelihood of SUDEP according to classification of cases where death could be due to either SUDEP or heart disease*

Classification	Age (yr)	Odds ratio (95% confidence interval)
1	<40	0.41 (0.12–1.34)
1	≥40	0.24 (0.06–0.95)
2	<40	0.58 (0.18–1.80)
2	≥40	0.74 (0.25–2.19)

Classification 1 with the 12 indeterminate cases classified as non-SUDEP. Classification 2 with the 12 cases reclassified as SUDEP.

3.113
MULTIVARIATE ANALYSIS OF RISK FACTORS FOR SEIZURE-RELATED INJURIES IN PATIENTS WITH EPILEPSY: A POPULATION-BASED STUDY

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Rationale: Previous studies of risk factors for seizure-related injuries in epilepsy patients have been biased toward refractory epilepsy. Multivariate study of risk factors is lacking in the literature. **Methods:** Subjects consist of 247 Rochester, MN, residents with epilepsy diagnosed between 1975 and 1984. Patients were followed up from time of diagnosis until death, migration out of Rochester, or until July 1, 1999. Seizure-related injuries were defined as any injury occurring directly as a result of a seizure, other than orolingual trauma, sufficient for patient to seek medical attention or for injury occurrence to be determined during the course of medical care. Characteristics of patients with injuries were compared to those without injury to identify risk factors for seizure-related injury. Kaplan–Meier life table methods were used to determine cumulative probabilities of having a seizure-related injury after first seizure. Cox proportional hazards regression models were utilized to assess the univariate associations between patient characteristics and occurrence of seizure-related injury. Stepwise multivariate Cox regression analysis was performed on factors that were significant on univariate analysis. **Results:** During a total follow-up of 2,714 patient-years, 62 seizure-related injuries were identified in 39 patients (16%; one injury every 44 patient-years). Most injuries were minor extracranial soft tissue contusion or laceration of the head (79%). After the initial seizure, the cumulative probability of having a seizure-related injury increased steadily to 13% in year 5 and then remained relatively stable through year 10. After year 10, it then increased steadily again until it reached 20% in year 15 and then remained stable. On univariate analysis, three factors were significant: seizure frequency score ($p < 0.0001$, Risk Ratio, 1.33); history of generalized seizures ($p < 0.0045$, Risk Ratio, 4.48); and number of antiepileptic drugs used ($p < 0.0191$, Risk Ratio, 1.94). Other factors of note not identified to be significant (i.e., $p > 0.05$) included gender, living environment, missing of antiepileptic drug dose, Rankin score, epilepsy cause (cryptogenic/idiopathic vs. symptomatic), and type of epilepsy. However, seizure frequency score was the only significant risk factor for seizure-related injury on multivariate analysis ($p < 0.0001$, Risk Ratio, 1.33). For every increment in the seizure frequency score, there was a 33% increase in the risk of seizure-related injuries. **Conclusions:** In this population-based study, the only independent determinant of seizure-related injuries was degree of seizure control. Effective treatment with complete elimination of seizures is the only reliable means to reduce the risk of seizure-related injuries. Our findings have implications for counseling patients regarding therapeutic goals and treatment options in epilepsy. (Supported by Mayo Foundation for Research and Education.)

3.114
A NATIONWIDE SURVEY OF CORONERS AND MEDICAL EXAMINERS ON DOCUMENTATION OF SUDDEN UNEXPLAINED DEATH IN EPILEPSY (SUDEP): PRELIMINARY RESULTS

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Rationale: A major limitation in the investigation of SUDEP is the lack of accurate data in the death certificates of persons with epilepsy. We designed a research survey to assess how coroners and medical examiners in the United States document causes of death in persons with epilepsy. Information gained from the study will be used to develop educational programs for coroners and medical examiners to improve the ascertainment of SUDEP occurrence and in the identification of its potential risk factors. **Methods:** A literature search identified historical and laboratory data that are required for the determination of SUDEP, but are frequently lacking in the examination and documentation of the death. A survey form was developed with the assistance of the Survey Research Center of the Mayo Clinic and sent to all 2,997 coroners and medical examiners on a mailing list obtained from the National Public Safety Information Bureau, Stevens Point, WI. **Results:** To date 338 responses have been analyzed with additional returns in process. Of these 338, 25% (84) came from medical examiners (MEs), 53% (178) from coroners, and 23% (76) from others (e.g., Justice of the Peace, Sheriff, Judge). Approximately one third (121) of responses reported never seeing a case of epilepsy. Forty-seven percent (160) of the responses to date, consisting of 87% of pathologists, 63.5% of nonpathologist physicians and 38% of nonphysicians, acknowledged SUDEP as a valid diagnosis. However, these percentages were much higher than the actual percentage of deaths attributed to SUDEP in autopsied cases performed by the same respondents where no cause of death was found. Autopsies on epilepsy cases were routinely performed by 41% of respondents (i.e., in >75% of cases) while 27% of respondents never performed autopsies on epilepsy patients. The medical examiners were most likely to perform such autopsies, while non-medical examiners were less likely to do so. **Conclusions:** These preliminary data indicate that MEs (mostly forensic pathologists) are more likely to consider SUDEP as a valid diagnosis. However both MEs and coroners do not use SUDEP as a common cause of death when signing off on autopsied cases that have no pathological explanation for the death. The autopsy rate in epilepsy cases is higher in urban/suburban jurisdictions compared to small cities, towns and rural areas. An educational effort is needed to improve coroner and medical examiner awareness of the importance of performing autopsies in epilepsy and using SUDEP as a final diagnosis. (Supported by the Albert Einstein Society and by Mayo Clinic.)

3.115
PULSE OXIMETRY CHANGES IN A PATIENT WITH SIMPLE PARTIAL SEIZURES: POSSIBLE CONTRIBUTING EVIDENCE TO THE EXPLANATION OF SUDEP

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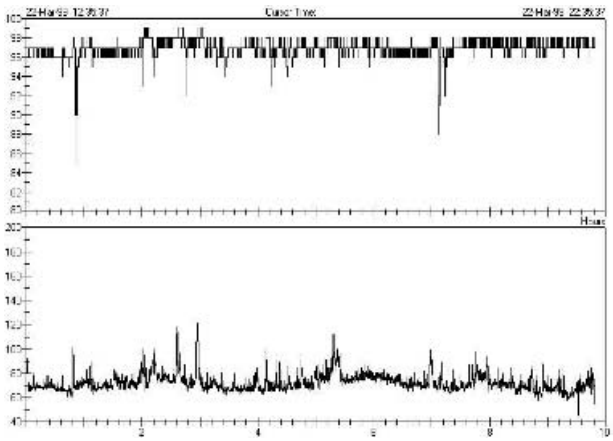
Rationale: Sudden death in epilepsy (SUDEP) is a fatal illness that may occur in patients with intractable seizure disorders. SUDEP is perhaps related to hemodynamic changes associated with the seizures themselves. The frequency of SUDEP is tenfold greater in patients with frequent seizures compared to 1 per 1,000 person-years for the whole population of patients with epilepsy. **Methods:** A 34-year old man with a diagnosis of medically refractory epilepsy was admitted for video-EEG telemetry at Aarhus University Hospital, Department of Neurology. Prior to admission the monthly seizure average was 10, consisting of both complex and simple partial seizures. MRI showed right hippocampal sclerosis. The routine video-EEG monitor was synchronized with pulse oximeter (disposable digital probes, Novametrix 511 M) and Holter monitors. After admission, all antiepileptic medications (AEDs) were slowly discontinued over a week. The data were then collected in the patient off AED therapy. **Results:** Seven simple partial seizures of 1.5–3 min duration were recorded. He was sitting in a chair watching TV, when he suddenly complained of an odd, light sensation in the head. Subsequently the head and the whole trunk was bent forward to 30 degrees, and a discrete left upper limb tremor was noticed. Afterward he felt tired for ~15 min. Obstructive sleep apnea was not observed. In four consecutive stereotype seizures, the recorded pulse oximetry signal was clear, and these data were used for subsequent analysis. Seizure number two arose from sleep. During the seizures, SO2 dropped ictally to 85, 91, 92, and 88. These changes lasted from 1.5 to 2 min. All seizures originated from the temporal lobe, but there were no overt differences between the onset of seizure activity in the right versus the left lobe. The maximal ictal heart rate ranged from 100 to 120 beats/min during the hypoxia. **Conclusions:** We are the first to document oxygen desaturation during simple seizure activity. We have recently demonstrated that ST-segment depression identical to that observed during cardiac ischemia follows epileptic seizures, especially when there is a sustained increase in heart rate. Oxygen desaturation may contribute to this phenomenon or exacerbate it further. Solitary reports have demonstrated oxygen desaturation following complex partial seizures without secondary generalization in medicated patients. The demonstration of the association between simple partial seizures and oxygen desaturation in seizures of a temporal site onset furthers the sparse information in this area. Due to the deep brain seizure discharges, it might be that the central cardiorespiratory reflex is early involved, thus initiating the further cascade of hemodynamic perturbations that might trigger ischemia and/or malignant arrhythmia and further explain the possible mechanism for SUDEP (Fig. 1).



3.116
ANTIEPILEPTIC DRUG MONITORING IN THE EPILEPSY MONITORING UNIT

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Rationale: This study examined the utility of therapeutic drug monitoring (TDM) in epilepsy patients with gradual reduction of antiepileptic drugs (AEDs) as part of presurgical evaluation in an epilepsy-monitoring unit (EMU). **Methods:** Thirty patients received a routine daily TDM while admitted to the hospital, whereas 14 patients received a single TDM on admission only. Data on the number of seizures experienced by the two patient groups were analyzed for the impact of the following independent variables on the precipitation of seizures in the EMU: (a) day of seizure occurrence in the EMU (day 1–2, day 3–4, day 5 and on); (b) day of last seizure occurrence before admission to the EMU (<7 days prior to admission, ≥7 days before admission). **Results:** Overall, single TDM resulted in a higher average of seizure frequency than serial TDM. Additionally, in the patients whose last preadmission seizure occurred <7 days prior to hospitalization, higher seizure occurrence was observed during the first 2 days after admission. However, this effect was only noted in patients with single TDM. **Conclusions:** This study demonstrated that routine daily TDM is unnecessary for AED withdrawal during presurgical evaluation of epilepsy patients in the EMU setting.

3.117
WHEN IS AMBULANCE TRANSPORT NECESSARY FOR PATIENTS WITH A SINGLE OUT-OF-HOSPITAL SEIZURE?

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Rationale: In the San Francisco Emergency Medical Services (SF-EMS) system, an ambulance is often dispatched for patients who have experienced a single out-of-hospital seizure. Most of these patients are transported to an emergency department for further evaluation. There is a need to develop evidence-based criteria for paramedic triage and transport of patients with a single out-of-hospital seizure. **Methods:** We retrospectively reviewed the SF-EMS paramedic patient care records and emergency department records of 215 patients who experienced a single, out-of-hospital seizure and were transported to an emergency department. Cases were evaluated for demographic information, clinical history, and management in the prehospital and in-hospital environments. **Results:** At the time of paramedic evaluation of these 215 patients, 27 patients (13%) had evidence of head trauma, 115 patients (54%) were confused (GCS, ≤14), and in 49 patients (23%), there was no indication that these patients had ever experienced a prior seizure in their lifetime. A total of 142 patients (66%) met at least one of these criteria. The remaining 73 patients were atraumatic, known to have a history of seizures, and were awake and alert at the time of ambulance transport. Of these latter patients, 68 patients (93%) were discharged directly to home from the emergency department. A complicating medical condition (other than seizure) was present in four of the five patients admitted to the hospital. Only four patients experienced a recurrent seizure in the emergency department and all of these patients were discharged directly to home. **Conclusions:** Patients with a single, out-of-hospital seizure are commonly encountered by paramedics. Many of these patients are atraumatic, known to have a history of seizures, and are fully conscious at the time of paramedic evaluation. These patients are unlikely to have recurrent seizures in the emergency department or to have a complicating medical condition that is unknown to the paramedics. Emergency medical services systems should

consider these findings in the development of triage and transport criteria for patients with out-of-hospital seizures. [Supported by a grant from the National Institutes of Health (RO1 31403).]

3.118
ANTERIOR TEMPORAL RESECTION IS INEFFECTIVE IN PATIENTS WITH INFEROMESIAL EEG FOCI BUT WHO HAVE POSTERIOR TEMPOROPARIETAL SYMPTOMS

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Rationale: The role of posterior lesions leading to inadequate results following inferomesial temporal resection is well recognized. Even in the absence of obvious structural lesions, posterior temporoparietal symptoms indicate poor surgical outcome following temporal resection despite well-defined focal inferomesial temporal epileptogenic discharges. **Methods:** We reviewed histories, video-stereo-EEGs and neuroimaging studies of five patients with temporal, posterior temporal, and parietal symptoms at seizure onset but who had anterior and inferomesial interictal epileptiform discharges on scalp EEG. **Results:** Including subpial transection, when posterior speech areas were involved the five patients had an average of 2.8 operations each. None had a structurally MRI-defined lesion. Because of electroclinical incongruity two patients had initial depth electrode studies. Ictal onsets were neocortical temporal, posterior temporal, or lower central. First surgery was anterior temporal resection in four and face area removal in one. After initial resection, three had further depth-electrode studies prior to reoperation. There was limited improvement as a result of surgery in this group of individuals. **Conclusions:** Anterior and inferomesial interictal temporal discharges or neocortical temporal seizure onset are misleading in suggesting anteromesial surgical resection in patients with clinical features suggesting posterior temporoparietal seizure symptoms.

3.119
CHOLESTEROL-LOWERING EFFECT OF DIVALPROEX SODIUM IS CONCENTRATION RELATED IN A MONOTHERAPY STUDY OF COMPLEX PARTIAL SEIZURES

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Rationale: Epidemiologic and clinical studies have demonstrated that serum lipids are closely related to the development of coronary artery disease, and every 1% increase in total cholesterol results in 2% increase in the risk of developing coronary artery disease (CAD). A number of studies have reported the evidence that long-term antiepileptic drug (AED) therapy influences total cholesterol. The effect of divalproex sodium (DVPX) dosing on total cholesterol has not been systematically studied in epilepsy. **Methods:** A retrospective analysis of a randomized, double-blind, parallel-group, monotherapy trial comparing two dosing regimens of DVPX in adult patients with complex partial seizures was conducted. Subjects were randomized to two groups: high-dose DVPX with target serum concentration of 80–150 μg/ml, and low-dose DVPX with target serum concentration of 25–50 μg/ml. A variety of metabolic parameters were analyzed. Concomitant AEDs were withdrawn after target concentrations were attained. **Results:** Data from all 265 subjects who received randomized study drug were included in this analysis: 134 of those subjects were treated with high-dose DVPX, and 131 subjects were treated with low-dose DVPX. The average daily dose of DVPX in the high-dose group was 3,370 (±1,053.0) mg/day. The average daily dose of DVPX in the low-dose group was 1,294 (±434.4) mg/day. The entry characteristics of the two groups, the history of AEDs use, and the use of concomitant medication with metabolic properties taken during the study were similar. Mean serum cholesterol levels decreased by 34.4 mg/dl in the high-dose group and by 19.7 mg/dl in the low-dose group ($p < 0.001$). Mean change in glucose levels was not significantly different between the two groups ($p = 0.122$). Changes from baseline to final evaluation in total protein, albumin, and SGOT were significantly different between the two treatment groups. Total protein was decreased by 0.49 mg/dl in high-dose DVPX group and by 0.21 mg/dl in low-dose DVPX group ($p < 0.001$). Albumin was decreased by 0.61 mg/dl in high-dose DVPX group and by 0.27 mg/dl in low-dose DVPX group ($p < 0.001$). SGOT was increased by 19.9 mg/dl in high-dose DVPX group and by 6.5 mg/dl in low-dose DVPX group ($p < 0.001$). None of these changes was clinically significant. Mean weight increased by 1.3 (±6.4) kg in the high-dose DVPX group and by 2.0 (±5.0) kg in the low-dose DVPX group ($p = 0.380$). **Conclusions:** DVPX significantly decreased total cholesterol and this decrease was dose related. This reduction in cholesterol was observed despite an increase in weight. Cholesterol-lowering effects of DVPX has also been reported from preliminary data in patients with bipolar disorder. (Supported by Abbott Laboratories. (Disclosure: Salary: Abbott Laboratories; Grant: Abbott Laboratories; Stock: Abbott Laboratories.)

3.120
NEUROLOGIC AND FETAL OUTCOMES OF PREGNANCIES OF MOTHERS WITH EPILEPSY

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Rationale: A higher incidence of adverse fetal outcomes has been reported in pregnancies of mothers with epilepsy (ME). Prior studies have minimized the impact of pregnancy on epilepsy control. There have been no recent large studies in the United States. We sought to review the neurologic and fetal outcomes of pregnancies of ME treated at a university medical center. **Methods:** At the University of Cincinnati Medical Center, 215 ME were evaluated during the period from 1991 to 2001. Of these, 25 were not taking any antiepileptic drug (AED), 129 were taking one AED, and 61 were taking more than one AED. Pregnancy outcomes were reviewed including birth weights, Apgar scores, and proportion of infants who were small for gestational age (SGA). Changes in seizure control and AED dosage were examined. Analysis of variance was used for continuous variables while categoric variables were analyzed by $\chi 2$. **Results:** No significant difference was seen across the three groups of infants of ME for gestational age, birth weight, Apgar scores, or parity. The proportion who were primigravida was greater for ME taking no AED. This may be related to their lower mean age. The use of tobacco ($p = 0.206$) and alcohol ($p = 0.555$) in pregnancy were not significantly different. First trimester seizures oc-

TABLE 1.

Variable	No AED	Monotherapy	Polytherapy	P Value
No.	25	129	61	
Maternal age (yr)	22.8 ± 5.7	25.8 ± 5.8	25.6 ± 4.3	0.048
Gravida I	13 (52%)	34 (28%)	14 (24%)	0.029
1st trimester Sz	1 (4%)	39 (30%)	26 (43%)	0.002
Hospitalized for Sz	1 (4%)	12 (9%)	13 (21%)	0.025
AED dose increased		46 (36%)	36 (59%)	0.002
Gestational age (wk)	38.4 ± 2.9	38.0 ± 2.7	38.0 ± 2.0	0.807
Birth weight (g)	3,267 ± 525	3,135 ± 679	3,131 ± 586	0.974
SGA	1 (4%)	4 (4%)	3 (7%)	0.780
5-min Apgar <7	0 (0)	2 (2%)	1 (3%)	0.725

curred significantly more often in the treated groups. Hospitalization for seizures in pregnancy was greater for ME on polytherapy compared to no AED. AED dose was increased more often in those on polytherapy than in those on monotherapy. In about half of ME taking AEDs, the dose was increased due to seizures. The occurrence of 5-min Apgar score <7 and SGA were not significantly different across these groups. **Conclusions:** Use of an AED in pregnancy does not significantly affect gestational age, birth weight, or neonatal compromise as measured by Apgar scores. ME taking AEDs are more likely to have seizures in the first trimester. ME receiving polytherapy are more likely to require adjustment of their AED doses and hospitalization for seizures. ME should be monitored closely during pregnancy to ensure optimal neurologic and fetal outcome.

3.121
TOOTH-BRUSHING EPILEPSY: A CASE SERIES DEMONSTRATING LESIONS INVOLVING THE POSTCENTRAL GYRUS SUGGESTING LIKELY SOMATOSENSORY INDUCTION FOR THIS REFLEX EPILEPSY

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Rationale: Although reflex epilepsies are a relatively rare group of seizure disorders, they may provide valuable insight into potential mechanisms of epileptogenesis and the organization of functional neuroanatomy. We were the first group to report a case of reflex tooth-brushing epilepsy and demonstrate a structural and functional lesion in the perirolandic region. Our objective is to describe a further three cases of reflex epilepsy, all consistently associated with tooth-brushing and demonstrable lesions on neuroimaging. **Methods:** Descriptive epidemiologic analysis of four cases of tooth-brushing epilepsy with structural and functional imaging and electrophysiology. **Results:** Magnetic resonance imaging brain scans (MRIBS) were performed in all four cases. In three cases, MRIBS demonstrated circumscribed lesions involving the postcentral gyrus. One case occurred as a posttraumatic event, while the other three were without a clear acquired risk factor. Seizure types included simple partial in four, complex partial seizures in one, and secondarily generalized seizures in three. Abnormal neurologic examination was noted in two cases with subtle but definite facial weakness of upper motor neuron type. In the three cases that underwent video-telemetry, lateralising epileptiform activity was seen during typically induced events in two cases. Ictal single-photon emission computed tomography (SPECT) scan showed an area of hyperperfusion that corresponded to the MRI lesion on coregistration with a surface-matching technique in one case. Subsequent coregistered interictal SPECT scan demonstrated hypoperfusion in the same region in this case. Surgical resection was performed in this case with pathology revealing cortical dysplasia. **Conclusions:** This series of four cases of tooth brushing epilepsy provides further valuable evidence for a structural focus involving the postcentral gyrus. This cerebral localization suggests somatosensory induction may be the likely trigger in this form of reflex epilepsy. [Supported (W.D'S.) in part by a Epilepsy-Neurophysiology Fellowship from Pzfier Pharmaceuticals. He is also the recipient of the 2002 Royal Australasian College of Physicians GlaxoSmithKline Fellowship in Neurology.] (Disclosure: Salary: Wendyl D'Souza is currently employed as an Epilepsy-Electrophysiology Fellow at the Alfred Hospital with part salary support by Pfizer Pharmaceuticals; Grant: Wendyl D'Souza has been awarded the 2002 Royal Austrlasian College of Physicians GlaxoSmithKline Fellowship in Neurology.)

3.122
EXERCISE DOES NOT EXACERBATE PARTIAL SEIZURES IN EPILEPSY MONITORING UNIT PATIENTS

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Rationale: Patients with epilepsy (PWE) are restricted in many aspects of their lives. PWE are often denied participation in exercise and sporting activities due to concerns of a theoretical risk of seizure exacerbation during such physical activity. Partaking in sporting activities and exercise may improve quality of life for patients with epilepsy. Additionally, exercise is commonly used in epilepsy monitoring units (EMUs) to exacerbate seizures. However, little information exists regarding the relationship of seizures to exercise. This study will allow the participant to understand how mild aerobic exercise impacts seizure exacerbation in patients with partial onset seizures. **Methods:** Detailed time records of 25 confirmed partial-seizure patients (ES) and 25 non-epileptic seizure patients (NES) who were admitted to the Mayo Clinic Arizona's EMU were analyzed. Patients were admitted for diagnostic or presurgical evaluation. All patients who were physically able to exercise, rode a stationary bike under supervision on a daily basis for 10-min sessions. All seizure patients included in this study had their antiseizure drugs (AEDs) discontinued after a brief taper. Events were recorded during continuous video-EEG and their temporal relation to the exercise sessions were noted in all patients. The number of events occuring within 2 and 6 h of the exercise session were evaluated. The number of exercise sessions, total events and the mean time to first event after each session were noted in each group were noted. $\chi 2$ analysis was utilized in comparing the number of events at 2 and 6 h. **Results:** The NES group had a total of 122 events occurring after a total of 138 exercise sessions. Measuring the time to first event revealed that that within this group, seven and 13 events occured within 2 and 6 h, respectivly. The mean times to onset of the first events were 28.5 min and 118.5 min, respectively. The epilepsy group was noted to have 172 exercise sessions and 100 total events. Eight and 12 seizures occurred within 2 and 6 h, respectively. The mean time to first event in this group was 26.5 and 105 min, respectively. These mean times to the first event were not sigificantly different compared between ES and NES groups ($p = 0.86$; $p = 0.72$ for 2 and 6 h, resp). $\chi 2$ Analysis between the NES and seizure group for the number of events number of events within the 2- and 6-h postexercise time frame showed no significant difference in the proportion of those that had events. ($p = 0.75$ and 0.77, resp). **Conclusions:** There is no difference between ES and NES patients regarding the number of events occuring shortly after mild aerobic exercise. The results suggest that mild exercise may be performed safely by some patients with partial epilepsy without exacerbating seizures. These data have implications for deciding whether to exercise patients in EMUs to provoke seizures. Further prospective studies are needed to clearly define the relationship between exercise and seizures so that PWE may be counseled appropriately to ensure patient safety and potentially allow for participation in more vigorous physical activity.

3.123
MEASUREMENT OF MARKERS FOR OXIDATIVE STRESS IN EPILEPSY

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Rationale: Seizures are known to lead to free radical generation in animal seizure models. Some studies of epilepsy patients have found that lipid peroxidation in patients with epilepsy was significantly higher and antioxidants may be lower. Antiepileptic drugs (AEDs) may also alter antioxidant capacity and increase lipid hydroperoxide. The aim of this study was to determine if epilepsy and/or the use of multiple AEDs were associated with altered blood lipid peroxidation and antioxidants. A review of this poster should enable the participant to be familar with epilepsy and reactive oxygen species and antioxidants. **Methods:** Blood samples for the measurement of free radicals were taken from 20 adult patients with epilepsy, excluding those taking antioxidant medications. These patients had controlled or uncontrolled epilepsy and were on one or several AEDs. Measurements of ROS included: thiobarbituric acid reactive species (TBARS) as an index for lipid peroxi-

dation, glutathione peroxidase (GPx) and catalase (CAT) and superoxide dismutase (SOD) as indices for antioxidants. **Results:** Seizure duration and polypharmacy did not correlate with the indices for lipid peroxidation. Serum GPx was significantly reduced in patients receiving polypharmacy, but RBC GPx was not different in patients receiving monotherapy or polytherapy. Lipid peroxidation was not significantly different in controlled or intractable epilepsy patients. **Conclusions:** Our study failed to show a significant correlation between lipid peroxidation or antioxidants and seizure control or seizure duration. Polypharmacy was associated with a reduction in serum GPx but not RBC GPx. These results suggest that there are minimal systemic alterations in ROS or antioxidants; therefore systemic ROS are unlikely to contribute significantly to brain changes in epilepsy. (Supported by Cultural and Educational Bureau, Egypt.)

3.124
EVALUATING THE SAFETY AND COMPLIANCE OF TIAGABINE USING TWO DIFFERENT TABLET STRENGTHS WITH DIFFERENT TITRATION SCHEDULES

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Rationale: Dosing guidelines for the selective γ-aminobutyric acid (GABA)-reuptake inhibitor (SGRI) tiagabine HCl (TGB; Gabitril) state that treatment should be initiated at 4 mg once daily and increased 4–8 mg weekly until clinical response is achieved. It has been theorized that a titration schedule of 2 mg every 3–4 days would allow a patient to achieve the desirable clinical response more rapidly, while being equally tolerable. The purpose of this study was to evaluate the safety and compliance of two dosage strengths of TGB with different titration schedules when used as add-on therapy. This presentation will inform participants about the usefulness and safety of the following dosing schedule for TGB,2 mg/3–4 days. **Methods:** A multicenter, randomized, parallel-group, open-label, 28-day trial enrolled subjects with partial seizures, with or without secondary generalization, who continued to receive stable doses of other anticonvulsants (AEDs). Subjects randomized to the standard regimen group received one 4-mg tablet of TGB during week 1 and then the dosage (given b.i.d.) was increased by 4 mg/week to reach the 16-mg target daily dose. Subjects randomized to the contrast regimen group received one 4-mg tablet of TGB on day 1 and one 2-mg tablet of TGB b.i.d. on days 2–7. The dosage (given b.i.d.) was increased by one 2-mg tablet every 3–4 days to reach 16 mg/day target daily dose. Pills dispensed to and returned by each patient were counted, and compliance was defined as taking ≥70% of the study medication. Adverse events (AEs) were collected throughout the study. **Results:** Of the 412 subjects randomized, 410 were evaluated for safety (222 subjects in the standard regimen group and 188 subjects in the contrast regimen group). Eighty-six percent (86%) of the 222 subjects in the standard regimen group and 84% of the 188 subjects in the contrast regimen group completed the 28-day study. Seventy-six percent (76%) of patients in the standard regimen group and 79% of patients in the contrast regimen group reached the target daily dose of 16 mg by day 28. Eighty-five percent (85%) of subjects in both groups were compliant to the treatment regimen. Similar percentages of subjects in the standard regimen and contrast regimen groups reported one or more AEs (49 vs. 45%, respectively). The most common, treatment-emergent AEs reported by subjects in the standard and contrast regimen groups were dizziness (13 and 11%, respectively), headache (7%, 6%), somnolence (7%, 5%), nausea (6%, 2%), and asthenia (5%, 7%); most AEs were mild to moderate in nature. Few subjects in either treatment groups discontinued due to AEs (10% of patients in the standard regimen group vs. 11% of patients in the contrast regimen group). **Conclusions:** In this large, clinical trial of the SGRI TGB, both dosage strengths with different titration schedules (2 mg/3–4 days and 4 mg/7 days) were well tolerated in a b.i.d. dosing regimen. Both doses and corresponding titration schedules were associated with high patient compliance (85%). Since the titration rate of 2-mg increase every 3–4 days is more flexible, patients may be able to achieve the desired clinical response earlier in the treatment course. (Supported by Cephalon, Inc., and Abbott Laboratories.) (Disclosure: Grant: Abbott, Cephalon; Honoraria: Speaker bureau, Abbott, Cephalon.)

3.125
SPECTRUM OF EPILEPSY SEVERITY IN A GENERAL NEUROLOGY COMMUNITY PRACTICE

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Rationale: At the end of this activity the participants should be able to discuss the types of epilepsies seen in a general neurology practice. Prior work has shown that <30% of patients seen in tertiary epilepsy centers are referred by neurologists (Gilliam et al. *Epilepsia* 2001;42(suppl 7):288). The type and severity of epilepsy seen by general neurologists in the United States is not known. **Methods:** Effective January 2001, one of Greater Cincinnati's largest managed care organizations dropped the region's largest private practice general neurology group. This group provides the majority of general neurologic care in Greater Cincinnati. Subsequently a large number of epilepsy patients were seen by epilepsy specialists at the University of Cincinnati Medical Center. All patients had their epilepsy care taken over by an epilepsy specialist and were not specifically referred for subspecialty care. We reviewed the charts for patients with a diagnosis of epilepsy who were seen by an epileptologist between January 1, 2001, and December 31, 2001. All patients had medical records available for review from their prior treating neurologist. Intractable epilepsy was defined as <1 year seizure free and failing three or more antiepileptic drugs (AEDs). **Results:** Fifty-six patients (39 females) were seen in 2001. Mean age was 39.2 years. Mean epilepsy duration was 14.4 years (standard deviation, 12.5); 48.2% were not seizure free for the prior year. Mean monthly seizure frequency was 4.9 seizures per month (SD, 14.8). Mean number of AED failures was 2.0 (SD, 1.7) and 25% of patients had intractable epilepsy. If the definition of intractable epilepsy was changed to having failed two or more AEDs, then 37.5% had intractable epilepsy; 10 patients had repeated MRI scans performed after being seen in the epilepsy center. Four of the 10 patients had discovery of previously undetected abnormality (hippocampal atrophy in three, focal encephalomalacia in one); 21 patients had a repeated EEG performed after seeing the epileptologist. Only two of 21 had an abnormality on EEG that was not previously seen on prior EEG. A change in treatment plan was instituted by the epileptologist in 37.5% of the 56 patients: 33.9% had their AED changed, 3.6% of patients underwent video/EEG recordings for diagnostic purposes, and 8.9% began an epilepsy surgery evaluation. Five patients (8.9%) had a change in their diagnosis after seen at the epilepsy center (four patients had their presumed epilepsy syndrome changed from partial to generalized, and one patient was subsequently diagnosed with psychogenic nonepileptic seizures); 43 patients were seen in follow-up (mean duration, 6.9 months); 44.2% of patients were not seizure free on follow-up. The mean seizure frequency after seeing an epileptologist was 2.0 seizures per month (SD, 6.6; $p = 0.04$, signed rank test). No patient had yet had epilepsy surgery. **Conclusions:** Roughly half of patients with epilepsy treated by general neurologists continue to have seizures; 25–37.5% have intractable epilepsy depending on the definition used. Although after evaluation and treatment at an epilepsy center, a similar percentage of patients continued to have seizures, there was a significant reduction in seizure frequency. (Supported by NINDS 5K23NS002170.)

3.126
TEMPORAL LOBE EPILEPSY AS UNIQUE MANIFESTATION OF BENIGN MULTIPLE SCLEROSIS

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Rationale: It is known that epileptic seizures may occur in multiple sclerosis (MS), but no previous study has addressed the issue of wheth-

er or not epilepsy constitutes the sole manifestation for many years. Here, we report on six patients with temporal lobe epilepsy (TLE) as the unique manifestation of benign MS. **Methods:** Six patients (five women, one man; mean age, 34.3 years; range, 31–39) with TLE and MS were identified among 16 of 350 (4.6%) consecutive patients with MS who also had epileptic seizures. All patients underwent a comprehensive clinical, EEG, and laboratory investigation. Repeated brain magnetic resonance imaging (MRI) were performed at baseline and after ~1 year. The mean follow-up period for all patients was 5 years (range, 3–10 years). **Results:** Neurologic examination was unremarkable in all patients and remained unchanged at follow-up. In all cases the habitual seizures started in the second or third decade, and consisted of simple or complex partial seizures of clear temporal lobe origin. Interictal EEG revealed temporal sharp-slow wave complexes occurring mainly during sleep. On brain MRI, all patients had at least one juxtacortical lesion in the temporal region, which always coincided with the epileptogenic region. Antiepileptic medication was effective in all treated patients. **Conclusions:** The present study provides the first evidence of a peculiar form of benign MS characterized by TLE as the unique manifestation of the disease with no disability or MS relapses at long-term follow-up.

3.127
EARLIER REFERRAL FOR SUBSPECIALTY EPILEPSY EVALUATION CORRELATES WITH PATIENTS' PERCEPTION OF BETTER PRIMARY NEUROLOGICAL CARE

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Rationale: Recent studies have reported mean durations of refractory epilepsy of ~20 years prior to epilepsy subspecialty or presurgical evaluations at tertiary care centers (Wiebe et al. *N Engl J Med* 2001; 345:311–8; Gilliam et al. *Neurology* 1999;53:687–94), but little information is available regarding patients' perception of this experience. **Methods:** This was a prospective, eight-center study of patients' perceptions of their medical care prior to evaluation in a university-based tertiary epilepsy center. We used the Epilepsy Specialty Clinic Referral Survey (22 items) to assess multiple aspects of previous epilepsy care, including patient-perceived need for earlier referral and satisfaction with neurological care. The study was approved by the IRB at each center, and all patients consented to participation in the study. **Results:** Two hundred eighty patients were enrolled from the eight epilepsy centers. The mean age was 36.8 (SD, 13.5; range, 13–72). One hundred sixty-eight patients were women (60%), and 122 (40%) were men. Sixty-five percent reported uncontrolled seizures for >1 year, with 42% for >4 years. One hundred fifty-eight (63% of the 250 responders to this question) patients reported that they wished that they had been referred earlier. Ninety-five (48% of the 250 responders) reported that they were less than very satisfied with their prior care. Preference for earlier referral was significantly associated with dissatisfaction with prior care (likelihood ratio, 29.6; $p = 0.003$). **Conclusions:** Based on results of this prospective study from eight epilepsy centers with a broad geographic distribution within the United States, most patients with recurrent seizures would prefer to be referred for tertiary evaluation earlier than the current standard of practice. Earlier referral is also significantly associated with greater patient-reported satisfaction with prior care. (Supported by NIH grants NS01794 and NS40808.)

3.128
TOPIRAMATE COULD AGGRAVATE COMPLEX PARTIAL SEIZURE IN THE ADVANCED SECONDARY EPILEPTOGENESIS

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Rationale: Topiramate (TPM) is frequently used for treatment of partial complex seizure with good response. However, in clinical practice, there is a group of patients in whom TPM aggravates the symptoms, although the numbers are small. Reason for seizure aggravation has not been studied. This is a pilot study to find out the likely correlation with EEG findings and adverse seizure control by TPM. **Methods:** Electroencephalogram (EEG) was reviewed for those whose seizure frequency increased after starting TPM. TPM was continued $\geq$1 month prior to discontinuation. Six patients were identified in consecutive 127 intractable complex partial seizure patients in epilepsy clinic. In all of the cases, EEG studies were done before TPM was introduced. **Results:** Common EEG feature of these six patients was bilateral neocortical epileptic activities. None of them had mesial temporal involvements at T1-T2 electrodes in sleep and awake EEGs. MRI findings are normal for all of these cases. Case 1: 37-year-old veteran presented episodic macropsia with spatial distortion. EEG showed frequent epileptiform discharges in bilateral posterior synchrony in parietal head region. TPM aggravated symptoms. Gabapentin (GBP) eliminated the recurrence. Case 2: 45-year-old woman having frequent IID and electrographic seizure pattern in bilateral temporal neocortex, with bilateral synchronous seizure onset at T3 and T4 in EEG. Felbamate (FBM) had no benefit. TPM worsened seizure frequency, but GBP decreased frequency of seizures. Case 3: 42-year-old woman with intractable complex partial seizures (CPSs). EEG showed bilateral frontal IID. TPM aggravated symptoms, but they were alleviated by GBP. Case 4: 42-year-old woman with frequent CPSs due to head injury. EEG showed bilateral independent multifocal IID. Symptoms were aggravated by TPM but alleviated by GBP. Case 5: 10-year-old girl with intractable frontal lobe epilepsy. EEG showed frequent bifrontal synchrous IID with left side preponderence. TPM and FBM increased seizure frequency, but it was improved by GBP. Case 6: 35-year-old man. EEG showed 4-Hz bilateral frontal spike-and-wave discharges with left temporal neocortical IID. TPM increased seizure frequency by 50% in 1 month. Subsequently he was treated with GBP with moderate improve in seizure control. **Conclusions:** These observations suggest that bihemispheric epileptiform activities are a common denominator in those patients whose symptoms were aggravated by TPM. Neocortical bilateral synchrony is the advanced stage of the secondary epileptogenesis according to the classification by Morrell (Morrell, 1985). Unlike hippocampal seizures, neocortical bilateral synchrony primarily involves synaptic connection via corpus callosum. However, the mechanism of TPM aggravation is unknown, the clinical correlations suggest that TPM may not decrease the contralateral synaptic transmissions but rather enhance them in bilateral synchrony. It seems worth trying GBP if TPM or FBM fails or aggravates the symptoms for patients who have bilateral neocortical epileptogenicity. Further studies will be planned.

3.129
CHOLESTEROL-LOWERING EFFECTS OF DIVALPROEX SODIUM IN ADULT PATIENTS WITH COMPLEX PARTIAL SEIZURE (M88-194)

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Rationale: Epidemiologic and clinical studies have demonstrated that serum lipids are closely related to the development of coronary artery disease (CAD), and every 1% increase in total cholesterol results in 2% increase in the risk of developing CAD. A number of studies have reported the evidence that long-term antiepileptic drug (AED) therapy influences total cholesterol. There are conflicting reports on the effect of divalproex sodium (DVPX) on total cholesterol. **Methods:** A retrospective analysis of a randomized, double-blind, placebo-controlled, and add-on trial of DVPX in adult patients with complex partial seizure was conducted. Other AEDs were allowed. A variety of metabolic parameters were analyzed. **Results:** Data from all 147 subjects who received randomized study drug were included in this analysis; 77 of those subjects were treated with DVPX, and 70 subjects were treated with placebo (PBO). The mean concentration of DVPX was 62.8 (±22.81) during the experimental phase of 16 weeks. Mean serum cholesterol levels decreased by 11.6 mg/dl in the DVPX group and

increased by 2.1 mg/dl in the PBO group ($p = 0.011$). Changes from baseline to final evaluation in total protein, SGOT, and SGPT were significantly different between the two treatment groups. Mean albumin levels decreased by 0.28 (±0.33) in the DVPX group and by 0.03 (±0.26) in the PBO group ($p < 0.001$). Mean glucose levels decreased by 7.7 mg/dl in the DVPX group and decreased by 12.1 mg/dl in the PBO group ($p = 0.407$). Mean weight increased by 0.7 (±5.1) kg in the DVPX group and by 1.4 (±3.8) kg in the PBO group ($p = 0.281$). **Conclusions:** Compared with PBO, total cholesterol reduction by DVPX was statistically and clinically significant. The 6% decrease in total cholesterol by DVPX may potentially result in less risk of developing CAD. Cholesterol-lowering effects of DVPX have also been reported in recent preliminary reports in patients with bipolar disorder.

3.130
WORSENING OF SEIZURES WITH LEVETIRACETAM

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Rationale: In late 1999, levetiracetam (LEV) was approved by the Food and Drug Administration for the treatment of partial seizures in adults. Recent studies have indicated that it is effective in other seizures types as well. In addition, it may reduce the number of interictal epileptiform discharges when given as a single dose. However, there are no reports of seizure worsening during treatment with LEV. We present a small population of patients with refractory epilepsy whose seizures either increased in frequency or who experienced a new seizure type while receiving LEV. **Methods:** We conducted a retrospective chart review. Patients had received LEV for ≥1 month, were on polytherapy, and carried the diagnosis of either localization-related epilepsy or generalized epilepsy. **Results:** We identified eight patients whose refractory seizures increased in frequency or who began experiencing a new seizure type while receiving LEV; five of eight were women. Their ages ranged from 16 to 41 years (average, 25). The duration of their epilepsy was 2–41 years (average, 14 years). They had tried between two and 10 antiepileptic medications (AEDs) before starting LEV, and were taking one to four AEDs at the time that LEV was started. Two had also been implanted with the vagus nerve stimulator (VNS). Seven of eight were diagnosed with symptomatic localization-related epilepsy, and one had idiopathic generalized epilepsy (juvenile myoclonic epilepsy). Of the seven who had partial seizures, two had undergone previous epilepsy surgery, and two had abnormalities on MRI (one with heterotopia and one with mesial temporal sclerosis). All eight experienced an increase in the frequency of seizures. In addition, two of eight developed a new type of seizure. **Conclusions:** LEV is an effective treatment of both partial and generalized seizures. In this series, there were eight patients with refractory epilepsy whose seizures worsened during treatment with LEV: it caused an increase in seizure frequency in eight, and the appearance of a new seizure type in two of the patients. The exacerbation occurred in persons with localization-related epilepsy (seven of eight) and generalized (one of eight) epilepsy. Although this is a small series, these results suggest that LEV may cause a worsening of seizures or the emergence of a new seizure type in patients with refractory epilepsy.

3.131
IMPROVEMENT IN FOCAL DISCHARGES WITH OXCARBAZEPINE

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Rationale: The objective of this study was to evaluate any EEG changes that would occur once patients are changed from their baseline antiepileptic medications (AEDs) to oxcarbazepine (OCBZ). Specifically, the changes in the number of sharp waves and spike waves as well as clinical seizure episodes were measured. **Methods:** Thirty-one patients (male, 15; age range, 17–54 years) with known partial seizures were admitted to Robert Wood Johnson Hospital to undergo evaluation for either continued breakthrough seizures and/or excessive medication-related side effects from May 2000 to April 2002. The patients underwent video-EEG monitering study for 48–72 h while they were taken off their baseline AED or had the dose reduced while OCBZ was either started or its dose increased. The baseline AEDs included carbamazepine (CBZ, dose range, 400–1,800 mg/day), phenytoin (PHT, 300–600 mg/day), phenobarbital (PB, 90–370 mg/day), and valproic acid (VPA, 1,500–3,000 mg/day). The dose range for OCBZ was 450 to 3,000 mg/day. The video- EEG study was evaluated each day to appreciate any changes in the number of focal spikes or sharp waves. **Results:** There were 20 patients that had focal sharp waves and nine patients with focal spikes. Two patients had a mixture of sharp and spike waves on the EEG. Of these findings, 19 EEG studies had sharps or spikes localizing to the left frontal and/or temporal head region. Five of the patterns showed the abnormality in the right frontal and/or temporal head region. There was one patient with slowing in the right frontal area followed by generalized spikes with subsequent clinical seizure. Four patients had bifrontal and/or bitemporal sharps and spikes. One patient had multifocal spikes localizing to the right hemisphere, and one other patient had bitemporal and bicentral abnormality. Twenty-two (71%) of the patients had an improvement of their focal pathology on the EEG. Of these, 13 patterns (59%) involved improvement in the sharp waves and nine (41%) improved in their spikes. One patient had the slowing followed by generalized discharges and a seizure; however, after the switch to OCBZ, there were no further clinical episodes. A total of seven patients (22%) showed no improvement on the EEG. One patient's EEG worsened in the number of spikes since the total number went from 61 to 77 after the switch. The most dramatic change was seen in a patient who had 1,017 spike waves on CBZ and VPA. This patient's CBZ was discontinued on admission, and VPA was reduced by 60%. The OCBZ dose by discharge was 2,700 mg/day. By discharge, the number of spikes lessened to 625. **Conclusions:** Although the goal in treating our patients with epilepsy is to have them seizure free with a good quality of life, we believe that the improvement in the EEG pattern is also importat since it can guide treatment. In our retrospective analysis, we found that the EEG does indeed improve when patients change from the most commonly used AEDs to OCBZ. This is a positive improvement which can actually have a positive impact on their lifestyle and ultimately seizure control.

3.132
THE SIGNIFICANCE OF HOMOCYSTEINE IN EPILEPSY PATIENTS

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Rationale: Elevated homocyteine level (hyperhomocysteinemia) was observed in epilepsy patients receiving anticonvulsants (AEDs), especially with methylenetetrahydrofolate reductase (MTHFR) 677 TT genotype. Hyperhomocysteinemia induces atherosclerosis, fetal anticonvulsant syndrome, etc. We examined any other factors affecting the level of homocyteine in epilepsy patients. **Methods:** We investigated the plasma total homocysteine level in 145 patients with epilepsy. We analyzed various factors (clinical findings, neuroimaging findings, drugs, MTHFR gene, serum folate, and vitamin B_{12} level) affecting the level of homocysteine. **Results:** Among various factors, being male, having neurologic deficits, frequent seizure attacks, MTHFR 677 TT genotype, polypharmacy, and more conventional drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, benzodiazpines) than new drugs (lamotrigine, vigabatrin, topiramate, oxcarbazepine) were related to elevated homocysteine level. **Conclusions:** We recommend monotherapy with new drugs and higher vitamin requirement in the male epilepsy patients of MTHFR TT genotype with neurologic deficits and frequent seizure attacks. (Supported by Ok Joon Kim.)

3.133
PREGNANCY OUTCOMES OF MOTHERS WITH EPILEPSY COMPARED TO MATCHED CONTROLS

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Rationale: A higher incidence of intrauterine growth restriction and fetal distress has been reported in infants of mothers with epilepsy (ME). There have been no recent large studies using matched controls. We sought to compare the outcomes of pregnancies of ME at a university center to matched controls delivered at the same hospital. **Methods:** During the period of 1992 through 2001, there were 100 ME who delivered at the University of Cincinnati Medical Center. Of these, 25 were not taking any antiepileptic drug (AED), 52 were receiving monotherapy, and 23 were taking more than one AED. Control infants were identified from birth logs and were matched by date of delivery, gestational age, maternal age, method of delivery, gravidity, and presence of major maternal medical complications such as hypertension or diabetes. Analysis of variance was used for analysis of continuous variables while categorical variables were analyzed by $\chi 2$. **Results:** The average gestational age at the time of birth in infants of ME was 37.8 weeks. No significant difference was seen across the three groups of infants of ME and controls for birth weight, Apgar scores, or parity. The proportion of prima gravida mothers was significantly greater in ME taking no AED compared to the other groups. The presence of 5-min Apgar score <7 and being small for gestational age were not significantly different across these groups. The use of induction of labor was significantly lower in control mothers than in ME. **Conclusions:** When matched for gestational age, infants of ME with or without AED exposure during pregnancy do not show significant growth restriction when compared to the control infants. Mean Apgar scores and the proportion with 5-min Apgar scores <7 as measures of neonatal compromise are not significantly different. While the use of induction was greater in ME, the study suggests that infants of ME are likely to have good outcomes based on parameters typically measured at the time of birth.

TABLE 1. *Pregnancy outcomes of ME versus controls*

Variable	No AED	Monotherapy	Polytherapy	Controls	P Value
No.	25	52	23	100	
Maternal age (yr)	22.8 ± 5.7	24.7 ± 5.2	25.6 ± 4.9	24.3 ± 5.4	0.294
Gravida 1	13 (52%)	11 (21%)	3 (13%)	30 (30%)	0.012
Induction	10 (40%)	16 (31%)	11 (48%)	21 (21%)	0.035
Gestational age (wk)	38.4 ± 2.9	37.8 ± 2.9	37.3 ± 2.0	38.1 ± 2.6	0.420
Birth weight (g)	3,267 ± 525	3,088 ± 729	2,900 ± 535	3,147 ± 633	0.232
SGA	1 (4%)	2 (4%)	3 (13%)	9 (9%)	0.708
5-in Apgar <7	0 (0%)	2 (4%)	1 (4%)	3 (3%)	0.790

3.134
INFLUENCES OF HIPPOCAMPAL SCLEROSIS ON DRUG RESPONSE AND CLINICAL ASPECTS IN TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy is often refractory to medical treatment. Long-term remission has been reported in only one-third to one-half of the patients with temporal lobe epilepsy. Hippocampal sclerosis is the most common pathology in temporal lobe epilepsy. The presence of hippocampal sclerosis on MRI is known to correlate with medical intractability, however many cases of epileptics with hippocampal sclerosis on MRI have been well controlled by medical treatment. Thus, there is still a debate about the influence of hippocampal sclerosis on the response to medial treatment of temporal lobe epilepsy. The purpose of this study is to test whether the presence of hippocampal sclerosis has an influence on drug response and other clinical features of temporal lobe epilepsy. **Methods:** Forty-nine epilepsy patients with complex partial seizures were enrolled. Their follow-up periods with antiepileptic medication (AEDs) were >2 years. To exclude the complex partial seizures confined to frontal lobe, the patients having brief seizure duration and no postictal confusion were excluded. MRI examinations were performed at 1.5 Tesla with axial T1- and T2-weighted images and coronal T2-weighted oblique thin-section images. Two neurologists and one radiologist independently determined the presence of hippocampal sclerosis on MRI by visual evaluation, and then the patients were divided into hippocampal sclerosis group and non–hippocampal sclerosis group. We compared drug response, seizure frequency, sex, seizure onset, disease duration, secondary generalization, electroencephalographic abnormality, previous medical insult, and polytherapy between the two groups. The patients with seizure free for >1 year were considered those with tractable epilepsy. **Results:** Fifteen patients were in hippocampal sclerosis group and 34 patients were in non–hippocampal sclerosis group. Ten of 15 (66.7%) in hippocampal sclerosis group and 11 of 34 (32.4%) in non–hippocampal sclerosis group were intractable, and the difference of intractability between the two groups was significant ($p < 0.05$). Eleven of 15 (73.3%) in hippocampal sclerosis group and eight of 34 (23.5%) in non–hippocampal sclerosis group had seizures more than 4 times per year, and the difference was significant ($p < 0.01$). Other clinical features were not different between the two groups ($p > 0.05$). **Conclusions:** Our results showed that medical intractability in temporal lobe epilepsy was significantly associated with hippocampal sclerosis. Hippocampal sclerosis itself may be a crucial factor determining drug response of temporal lobe epilepsy.

3.135
A VERY NOVEL CASE OF NEW-ONSET NARCOLEPSY, CATAPLEXY, AND EPILEPSY IN A 40-YEAR-OLD BUSINESS PROFESSOR

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Rationale: Case description of new-onset narcolepsy and epilepsy with pathology suggestive of a Rasmussen syndrome variant to illustrate the possible autoimmune basis of these disorders. **Methods:** Case report. **Results:** A 40-year-old man with no medical history developed excessive daytime somnolence (EDS) over 2 months. He shortly developed cataplexy, hypnopompic hallucinations, and sleep paralysis. Narcolepsy was confirmed with a mean sleep latency of <2 min and 5/5 sleep-onset REMs, but no evidence of sleep-disordered breathing. Brain MRI done at onset of EDS was normal. There were no other constitutional or neurologic symptoms. He denied history of EDS, snoring, or parasomnias. He had recently traveled to Cambodia, and his EDS began while in New Zealand. One year later, he developed left temporal lobe seizures. A brain MRI showed an indistinct area of increased T2 signal with minimal contrast enhancement in the left temporal area extending into the inferior frontal and insular regions, believed initially to be an unresectable tumor. Three months later, he was hospitalized in complex partial status epilepticus. Biopsy and subsequent palliative partial resection of the anterior left temporal lobe excluded a brain tumor and was most consistent with an encephalitic process, similar to Rasmussen syndrome. There were microglial nodules, acute and chronic lesions with interspersed patches of normal brain tissue, and perivascular leukocytes without vessel necrosis. The

involved areas also showed disorganization of normal cortical lamination. An extensive search for infectious, autoimmune, neoplastic and paraneoplastic causes was negative. Four years later, his stereotyped events continue. They begin with an indescribable feeling followed by a sense of tightness in his right foot, then right shoulder, then hand, sometimes associated with flexion of that hand. The feeling moves to his right face and he develops hypersalivation, left eyelid twitching, dilation of the left pupil, and hears a voice speaking to him in Cambodian. He can speak but has altered responsiveness and no recall of a phrase or pinch given during the event. MRIs are stable since the temporal lobectomy. EEG monitoring and ictal SPECT showed the seizure onset in the left anterior insula and mesial temporal lobe. A further surgical resection is planned this summer. A recent lumbar puncture showed no oligoclonal bands or elevated leukocytes. He is positive for HLA-DQB1*0602, and CSF analysis found no detectable hypocretin, consistent with narcolepsy. Repeated sleep studies have shown decreased mean sleep latency and sleep-onset REM periods. **Conclusions:** This case is novel because of the association of narcolepsy and Rasmussen syndrome, which has not been previously described. Both disorders are postulated to have an autoimmune basis (Rogers et al. *Science* 1994;265:648–51; Lin et al. *J Neuroimmunol* 2001;117:9–20). Because our patient developed both disorders within a year, our case supports the autoimmune etiology of these disorders. The inciting trigger, viral or otherwise, of these two disorders in this patient awaits further study.

3.136
LEVETIRACETAM: A HELPFUL NEW DRUG

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Rationale: Levetiracetam (LEV) is a single enantiomer. It is clinically unrelated to existing antiepileptic drugs (AEDs). Its use in epilepsy centers and neurology practices is presently being evaluated. **Methods:** 124 patients at our epilepsy center have been started on LEV since August of 1999. Demographic data have been obtained. Seizure freedom and efficacy numbers have been recorded. LEV serum levels have been obtained. **Results:** 109 of the 124 patients (88%) were diagnosed with partial and /or partial with secondary generalized seizures; 15 of the 124 patients (12%) were diagnosed with primary generalized seizures. The patients ranged in age from 12 to 67 years, with 70 female and 54 male patients. Patients were treated with LEV from 3 to 30 months; 28 of the 124 patients (23%) were seizure free; 15 of the 124 patients (12%) were removed from drug. Full data as to 50 and 75% responder rates and relationships to levels are pending. Dosages of LEV ranged from 500 to 5,500 mg/day. LEV serum levels ranged from 5.6 to 69 μg/ml. **Conclusions:** LEV has been an easy drug to add on to intractable epilepsy patients. A significant number of patients have become seizure free. Discontinuation rates have been low. (Supported by UCB Pharma.) (Disclosure: Grant: UCB Pharma.)

3.137
CHOREA-ACANTHOCYTOSIS PRESENTING AS INTRACTABLE FAMILIAL TEMPORAL LOBE EPILEPSY

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Rationale: Chorea-acanthocytosis (CHAC) is an autosomal recessive neurodegenrative disorder characterized by the gradual onset of involuntary movements and the presence of acanthocytes in the peripheral blood smear. Neurologic features include chorea, orofaciolingual dyskinesia, dysarthriae, areflexia, seizures, and dementia. We present a family with affected members presented with temporal lobe epilepsy. **Methods:** Detailed medical and family histories, as well as medical records, were obtained on affected family members. Four patients were examined, investigated and monitored in detail. Blood smears on these four patients were obtained searching for acanthocytosis. **Results:** Four patients (three siblings, offspring of a consanguineous marriage, and their maternal first cousin) presented initially with familial temporal lobe epilepsy for years before developing involuntary movements including chorea, low amplitude myoclonic jerks, dysarthria, orofacial dyskinesia, and unusual tics. Their aura consisted of a sensation of deja vu, fear, palpitation and vertigo. In addition, the cousin saw a devil making fun of him during the aura always followed by generalisation. Epilepsy was intractable in all. Lamotrigine (LTG) and carbamazepine (CBZ) worsened the involuntary movements. Phenytoin (PHT) did not worsen the involuntary movements but was not effective in controlling seizures. The patients had mood disorder and slowly progressive cognitive dysfunction. MRI of the brain showed various degrees of caudate atrophy and abnormal signal in the basal ganglia. EEG and video telemetry confirmed ictal and interictal temporal epileptic abnormalities. Peripheral blood smear showed acanthocytosis. Eighteen individuals in this family (three generations) had various neurological and psychiatric disorders including epilepsy, chorea, orofacial and vocal tics, cognitive dysfunction, bipolar disorder and dysphagia. Inheritance of the disorder in this family seems to be either autosomal dominant or pseudo-dominant due to founder effect. Molecular studies to identify mutations in the CHAC gene are underway. **Conclusions:** The patients had an unusual presentation suggestive familial temporal lobe epilepsy which made the diagnosis of CHAC difficult. Epilepsy was intractable in all. LTG and CBZ increased the chorea and articulation disorder. PHT, while not controlling the attacks, did not worsen the movement disorder. Because of the underlying neurodegenerative disorder, surgical treatment of the epilepsy was not considered further.

3.138
COMORBIDITY OF ICTAL FEAR AND PANIC DISORDER

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Rationale: Psychiatric disorders are common in epilepsy, but associations may be limited to particular subgroups of patients, since epilepsy is a heterogeneous disease. We sought to determine the prevalence of psychiatric conditions, particularly panic disorder, in focal epilepsy patients with a fear aura. **Methods:** A consecutive series of 12 patients with ictal fear underwent psychiatric evaluation, either via formal consultation with a psychiatrist, or via standardized interview using the Mini International Neuropsychiatric Interview (MINI), an instrument which allows rapid diagnosis of Axis I disorders according to strict DSM-IV criteria. An addendum was made to the MINI to create an instrument specifically for use in epilepsy patients (MINI-Epi) by adding questions to clarify areas of potential diagnostic confusion in this population (e.g., schizophrenia vs. postictal psychosis, panic attack vs. partial seizure). **Results:** Four of the 12 patients (33%) with ictal fear had a comorbid diagnosis of panic disorder. One of these developed panic attacks only after epilepsy surgery, and another worsened after surgery, while in the other two panic attacks were not related to any surgical procedure. Two patients had other anxiety disorders. Eight patients (67%) had current or past depression; this did not appear to be related to the presence of panic disorder. All patients were able to clearly distinguish subjectively between their seizures and their panic attacks. **Conclusions:** A specific comorbidity exists between focal epilepsy with ictal fear and panic disorder. The prevalence of panic disorder in this group is far higher than the 3.5% lifetime prevalence seen in the general population (1) or the 5–10% prevalence seen in unselected epilepsy patients (2,3). The predisposition to panic disorder in these patients may be exacerbated by anterior temporal lobectomy. Involvement of the amygdala in both temporal lobe epilepsy and panic disorder may underlie the association between these two conditions. Physicians should be aware of the common co-occurrence of these disorders so as to avoid diagnostic confusion and provide appropriate treatment for each. [Supported by both the Merritt-Putnam award of the Epilepsy Foundation (sponsored by Parke-Davis) and the National Epifellows Foundation (S.M.).]

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3.139
ELECTROCLINICAL FEATURES OF SEIZURES IN MULTIPLE SCLEROSIS

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Rationale: Patients with multiple sclerosis (MS) can have a variety of symptoms that are manifestations of their disease. Seizures are thought to occur more frequently in patients with MS than in the general population, with estimated incidences ranging from 1 to 10%. Seizures in these patients are thought to result from plaques that abut the cortex and often enhance on gadolinium MRI scans. Some patients who present with a history of seizures can be found to have nonepileptic events. It is not clear how frequently nonepileptic events occur in patients with MS. **Methods:** This is a retrospective chart review that included patients with a diagnosis of MS and a history of seizures who had defined electroclinical syndromes based on routine EEG, prolonged EEG, and or video-EEG monitoring. **Results:** We identified 36 patients (27 females) with a diagnosis of MS and a history of seizures; 21 patients (15 females) were found to have epileptic seizures. The remaining 15 (12 females) had nonepileptic events. Among the 21 patients with epileptic seizures, seven had generalized epilepsy, one had right frontal lobe epilepsy, four had right or left temporal lobe epilepsy, and two had bilateral temporal lobe epilepsy. Among the two patients with parietooccipital lobe epilesy, one patient had no prior history of seizures and was found to have an abnormal EEG prior to entering a drug study. One patient had multifocal epilepsy and the remaining four patients had focal epilepsy not further definable. We also observed PLEDS in two patients, both of whom had end-stage MS with other complicating factors. Nonepileptic events were the presenting symptom in two patients with MS. Almost all of our patients with focal epileptic seizures had other symptoms of MS prior to the onset of their seizures. However, five of seven patients with generalized epilepsy developed seizures prior to developing other symptoms of MS. MRI enhancing lesions were seen in eight of 21 patients with epileptic seizures and only one of 15 patients with nonepileptic events. **Conclusions:** Epileptic and nonepileptic seizures contribute to the clinical manifestations of MS. This study describes a variety of epileptic syndromes that can be seen in patients with MS including nonepileptic events. Nonepileptic events should also be considered in the differential diagnosis in patients who have MS and seizures. Previous studies may have overestimated the incidence of seizures in MS by including patients with nonepileptic events as well as generalized epilepsy whose etiology may be genetic and unrelated to MS. The presence of MRI enhancing lesions appear to occur more frequently in patients with epileptic seizures than those who had nonepileptic events. Whether MRI enhancement can be used as a crude measure to help differentiate these two groups of patients would require further studies.

3.140
SERUM CALCIUM IN WOMEN WITH EPILEPSY RECEIVING ANTIEPILEPTIC DRUG MONOTHERAPY

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Rationale: Decreased bone mineral density and disorders of bone mineral metabolism have been reported in persons receiving antiepileptic drugs (AEDs). We previously reported significant reductions in vitamin D in women with epilepsy (WWE) on enzyme inducing AEDs compared to those on AEDs with no effect on the cytochrome P450 enzyme system. The vitamin D endocrine system plays a critical role in calcium homeostasis, and calcium homeostasis is an essential component of bone metabolism. **Methods:** Serum calcium levels were assessed in WWE receiving AED monotherapy. WWE on lamotrigine (LTG), phenytoin (PHT), carbamazepine (CBZ), and valproate (VPA) were enrolled. Each subject was required to have been taking the studied AED for a minimum of 6 months. All enrolled subjects ranged in age between 18 and 40 years, and had either primary generalized epilepsy or localization-related epilepsy. Subjects with impaired motor function, taking medications that may affect bone mineral status (e.g., glucocorticoids), or with a severe medical systemic illness likely to effect bone health were excluded. **Results:** Data were obtained from 90 WWE. There were 34 receiving CBZ, 22 receiving LTG, 14 taking PHT, and 20 taking VPA. All calcium serum levels were within the normal range. Significant reductions were found when comparing calcium levels of WWE taking CBZ and PHT (inducers of the cytochrome P450 enzyme system) to WWE taking LTG (no effect on cytochrome P450 enzyme system) ($p < 0.0001$, 0.0005, respectively). A significant reduction in serum calcium was also found when WWE receiving VPA (an inhibitor of the cytochrome P450 enzyme system) were compared to WWE on LTG ($p = 0.0023$). **Conclusions:** WWE on AED monotherapy had significant reductions in serum calcium according to specific AED. Significant reductions were found in WWE receiving CBZ and PHT when compared to LTG. In addition, a significant reduction was found in WWE on VPA when compared to WWE on LTG. The decreased serum calcium and previously reported decreased vitamin D in WWE on PHT and CBZ is consistent with increased catabolism of vitamin D to inactive metabolites and subsequent hypocalcemia as a possible mechanism of AED associated bone disease. The finding of decreased calcium in WWE on VPA suggests possible bone mineral biochemical abnormalities in WWE on VPA. (Supported by GlaxoSmithKline.) (Disclosure: Grant: GlaxoSmithKline, Novartis, Elan, Pfizer, Cyberonics, Abbott; Consulting: GlaxoSmithKline, Abbott, Elan, Pfizer, RW Johnson, Shire; Honoraria: GlaxoSmithKline, Novartis, Elan, Pfizer, Ortho McNeil, Abbott, Cyberonics.)

3.141
RASMUSSEN SYNDROME IN ADULTS: REPORT OF TWO CASES

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Rationale: Rasmussen syndrome (RS) is a progressive neurological disorder characterized by intractable focal seizures, hemiparesis, cognitive decline, and progressive unihemispheric atrophy on MRI. RS is regarded as an autoimmune disorder. Usually, it concerns children; some cases have been described in adulthood. We reported two new cases, each one with a different clinical course and response to treatment, underlying the likely heterogeneity of etiologic factors of RS. **Methods:** Patient 1 had her first nocturnal generalized tonic–clonic seizures at the age of 17. Nine years later, multifocal seizures within the left hemisphere occured; on average 10 seizures per year persisted despite treatment. CT was normal. After 30 years of relative stability of the disease, an aggravation with several partial motor epilepticus status and then an epilepsia partialis continua arose. At the same time, right hemiparesis and cognitive decline appeared. Progressive atrophy and hypoperfusion of the left hemisphere were observed on MRI and SPECT. CSF examination revealed normal protein and cells; no oligoclonal bands. There were no anti-GluR3 antibodies detected in serum but other autoantibodies (indeterminate nature) were present. Immunoglobulin (Ig) therapy was performed (7 years after the onset of aggravation) with efficacy: control of seizures and no worsening of neurologic deterioration were obtained during 2 years of follow-up.

Results: Patient 2 had her first left-side motor seizure at the age of 27. Right from the beginning, seizures were intractable and several partial epilepticus status occurred. MRI showed right progressive parietal atrophy. Parietotemporal cortectomy was performed 11 years later. Unfortunatly, pathologic examination was not informative. No seizures occured during 2 months. Then they reappeared and implied several different areas on the perimeter of cortectomy, they became intractable with several partial motor epilepticus status. Cognitive decline and worsening of postoperative hemiparesis progressively developped. Progressive atrophy and hypoperfusion on the perimeter of cortectomy were observed on MRI and SPECT. CSF examination revealed no abnormality. There were no autoantibodies detected in serum. Ig therapy was ineffective. Currently, she continues to worsen (8 years after cortectomy). **Conclusions:** Clinical and MRI presentation of these two cases are suggestive of RS. However clinical course and response to Ig therapy are quite different. In the first case, RS seems to occur a second time after a long period (30 years) of the evolution of a multifocal regional epilepsy, Ig therapy is effective; this suggests the appearance of a secondary immunologic disorder. In the second one, RS evolves in one piece (exepted transitory improvement after cortectomy) with a progressive and inexorable worsening during a period of 20 years without any arguments in favor of an immunologic disorder. RS is a clinical and radiologic syndrome that probably has various etiologic factors.

3.142
DISTRIBUTION AND COMORBIDITY OF OBSTRUCTIVE SLEEP APNEA AND PERIODIC LIMB MOVEMENTS DISORDER OF SLEEP AMONG PATIENTS WITH EPILEPSY

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Rationale: Shouse found distorted sleep in feline kindled epilepsy. However, no studies prove that seizure escalations result. In contrast, epilepsy is negatively affected by obstructive sleep apnea (OSA). To date, the associated sleep disruption has not been correlated to seizure severity or epilepsy type. Further, periodic limb movements disorder of sleep (PLMS) has not been adequately studied in epilepsy. **Methods:** We reviewed polysomnograms (PSGs) on 233 epilepsy patients with abnormal sleep histories seen from 1990 to 1999. Apnea/Hypopnea Index (AHI) and Periodic Limb Movements Index (PLMI), defined three study groups: OSA (19 patients, 15 men), PLMS (22 patients, eight men) and Combined Sleep Disorders (CSD): OSA/PLMS (six patients, five men). Controls were defined as those with normal values for AHI and PLMI. They were age-/sex-matched to each study group, then compared for PSG findings, epilepsy type, number of seizures during the preceding year, and number of antiepileptic drugs (AEDs). **Results:** The prevalence of OSA among men with epilepsy was 17%, >4 times the rate found in general population studies. The rate for women was 4%, >2 times the population rate. The prevalence of PLMS was 11% in men and 13% in women. Total Sleep Time, Sleep Efficiency, REM Sleep and Stages 3-4 were decreased in patients with OSA ($p < 0.04$, 0.01, 0.001, 0.04) and PLMS ($p < 0.004$, 0.003, 0.02, 0.01). Stage I and Total Arousal Index were increased in patients with OSA ($p = 0.007$, 0.0001) and PLMS ($p = 0.045$, 0.0001). The percentage of partial seizure patients was significantly higher in OSA (85%), PLMS (70%), and CSD (100%) than controls (56, 48, and 50%; $p < 0.05$ for all). Nocturnal seizures were overrepresented in OSA patients ($p < 0.025$), but not in PLMS patients. The number of seizures during the preceding year (21.6 vs. 5.5) and the number of AEDs used (2.1 vs. 1.3) were significantly greater than controls in the OSA group ($p < 0.05$, 0.02). **Conclusions:** There is a high prevalence of OSA in men with epilepsy, especially partial epilepsy. OSA is strongly deleterious to sleep, which in turn worsens seizure control, possibly playing a major role in the intractability usually found in partial epilepsy. PLMS, slightly more prevalent among women than men, has a milder exacerbating effect on seizure control.

3.143
ELECTIVE REIMPLANTATION OF THE VAGAS NERVE STIMULATOR

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Rationale: The vagal nerve stimulator (VNS) is an efficacious therapy that was approved in 1997 for intractable partial and secondarily generalized seizure disorders. Fifty-six patients have been newly implanted at our center since February 1998. Due to the high parameters that were set, the generators lasted an average of 2–3 years. The patients were then given the option at the end of service to have the device replaced. **Methods:** At our center we evaluated the VNS device at each office visit. We considered replacement when there was high lead impedance with a DC-DC code of 7 on the normal mode diagnostics or when the divice would not interrogate or showed high lead impedance on lead diagnostic testing. The decision for replacement was based on seizure reduction, seizure intensity, and efficacy of magnet. **Results:** Twenty-two (78.5%) of 28 patients elected to have their stimulators replaced. Twenty patients elected to have their device reimplanted due to end of service. Two patients were reimplanted because of lead dysfunction. Three (14%) of the patients who were reimplanted reported an overall >75% reduction in seizures, and five (28%) of the patients had a >50% reduction in the number of seizures reported. Nine (40%) reported that the intensity of their seizures was lighter. Five (22%) of the patients reported that the magnet either decreased the intensity or aborted the episodes. Two patients reported that the postictal phase was not as intense. Four (18%) of the patients had sufficient improvement to warrant reimplantation. One adolescent became more verbal. **Conclusions:** Twenty-two (78.5%) of 28 patients elected to have their stimulator reimplanted for various reasons including seizure reduction, lessening of seizure intensity, decreasing postictal phase and/or magnet efficacy. (Supported by The Comprehensive Epilepsy Care Center for Children and Adults, St. Louis, Missouri.)

3.144
USE OF LEVETIRACETAM IN PATIENTS WITH BRAIN TUMORS

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Rationale: Seizures are common in brain tumor patients, and traditional antiepileptic drugs (AEDs) pose problems, including interactions with chemotherapeutic agents and cognitive side effects. Levetiracetam (LEV) is generally well tolerated and has few drug interactions, and its usefulness in this poupulation is studied. **Methods:** We reviewed all patients with brain tumors seen in our department between 1/2000 and 3/2002. Forty-nine patients had taken LEV; 41 took it for ≥6 months, while two died in <6 months, two were lost to follow-up, and four started too recently. Of 41 analyzed patients (18 M, 23 F; age range, 24–78), 18 had glioblastoma multiforme, five anaplastic astrocytoma, eight mixed glioma, six oligodendroglioma, two meningioma, and two metastases. Twenty-three of 41 (57%) had seizures at presentation, 32 (78%) had seizures after surgery, and two (4%) had no seizures. **Results:** LEV was initiated because of (a) chemotherapy protocol (no enzyme-inducing drugs allowed), eight of 41; (b) neutropenia on prior AEDs, eight of 41; (c) sedation and fatigue on prior AED, nine of 41; (d) poor seizure control, 13 of 41; (e) seizure prophylaxis, two of 14. Sixteen patients were taking LEV monotherapy, and 25 receiving polytherapy. LEV dose was 1,000–3,000 mg/day. Adverse effects included mood disturbances, five of 41 (requiring discontinuation in one); fatigue or sedation, two of 41; other, one; 41 of 42 have continued the drug for 6–18 months; 21 of 41 had no seizures with LEV, 11 of 41 patients had moderate seizure reduction, and two of 41 had no improvement. Two patients taking LEV for prophylaxis had no seizures. **Conclusions:** LEV appears to be effective and well tolerated in patients with brain tumors.

3.145

SEIZURE OCCURRENCE IN RELATION TO THE 9/11 TERRORIST ATTACK AMONG PATIENTS WITH EPILEPSY IN THE WASHINGTON, D.C., AREA

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Rationale: Stress is commonly perceived by patients with epilepsy as a trigger of seizures. To further elucidate the relationship between stress and seizures, we compared seizure frequency among patients with epilepsy in the Washington, D.C., area before and after the 9/11 terrorist attack. **Methods:** 46 patients with epilepsy and reliable documentation of seizure frequency were selected randomly out of the database of the epilepsy clinic of Georgetown University Hospital. Patients' seizure diaries were reviewed retrospectively for 3 months before and 2–3 months after the 9/11 attack for seizure frequency. Patients were interviewed and completed questionnaires concerning their activities during the day of the attack and the ensuing month, the effect of the attack on their own lives and on the lives of their family members and of friends, their perceived level of stress, and medication changes, compliance, sleep deprivation, alcohol and other drug use before the attack and for the month after the attack. Patients' mood and arousal were assessed with the Beck Depression Inventory and the Hamilton Anxiety Scale. All evaluations were performed within 3 months of the 9/11/01 attack. Patients absent from the Washington, D.C., area during the attack, patients with moderate or severe cognitive impairment, and patients whose awareness of the 9/11 events was in doubt were excluded from the study. **Results:** 46 patients completed the survey; 19 (41%) patients did not perceive the 9/11 attack as stressful; 50% of patients experienced a mild or moderate degree of stress in association with the 9/11 events; 9% patients experienced a high degree of stress. Five (11%) of patients experienced both an increase in stress level and an increase in seizure frequency during the 6 weeks following 9/11 compared with the 6 weeks before 9/11. In two of these patients, increase in seizure frequency after the attack coincided with antiepileptic drug (AED) change. A second patient experienced her first seizure in three months 15 min after watching the attack on TV but had been AED noncompliant for 2 weeks previously. Two subjects experienced an increase in seizure frequency during the 6 weeks starting with 9/11/01 events that was not associated with any other confounding factors such as AED noncompliance, sleep deprivation, or alcohol use. By contrast, 25 patients (57% of all patients) stated that their seizures were triggered by stress, without showing a change in seizure frequency in their seizure diaries. **Conclusions:** Stress is commonly perceived as a seizure trigger among patients with epilepsy. In this retrospective study, only two of 44 (5%) of all patients with epilepsy who were present in the area of a major environmental stress during the stressful events, and two of 26 (8%) of patients affected by this stress experienced an otherwise unexplained increase in seizure frequency. The study higlights the difference in the frequency of subjectively perceived influence of stress level on seizure occurrence with objectively documented influence of environmental stress on seizure occurrence.

3.146

INFLUENCE ON ICTAL SEIZURE SEMIOLOGY OF RAPID WITHDRAWAL OF LAMOTRIGINE AND CARBAMAZEPINE

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Rationale: Quantitatively evaluating the rapid withdrawal effects of lamotrigine (LTG) and carbamazepine (CBZ) on ictal seizures during presurgical evaluation in patients with pharmacoresistant partial epilepsy. **Methods:** The duration, intensity and frequency of ictal seizure phenomena of 41 patients totally withdrawing from CBZ monotherapy ($n = 20$), LTG monotherapy ($n = 10$), and CBZ and LTG combined therapy ($n = 11$) were intensively studied by TISA (therapeutic intensive seizure analysis) method. Study phases ran from the baseline phase to the AED withdrawal phase until the AED-free phase, 3 days for each phase. **Results:** Seizure duration and frequency obviously increased during the withdrawal process in each group ($p < 0.05$). No change of seizure intensity was observed. Prolongation in duration of ictal signs like hypermotoric, oroalimentary automatisms, fumbling, and ictal speech were significant in each group ($p < 0.05$), especially during the AED-free phase. The duration and intensity of secondarily generalized clonic signs markedly increased with the tapering of each drug; tonic signs, however, only in the AED-free phase ($p < 0.05$). The frequency of all ictal signs only increased in the CBZ and CBZ+LTG group. Intergroup comparisons of all variables were insignificant ($p > 0.05$). There was no change of ictal EEG localization during each withdrawal protocol. **Conclusions:** All patients experienced increased duration and frequency during the withdrawal processes without an obvious change of seizure intensity. Prolonged duration and frequency of ictal automatisms, ictal speech, and hypermotoric signs were mostly observed during the AED-free phase. A discrepancy exists in the later part of the seizure structure during the secondary generalization. Tonic signs increased more in the AED-free phase, whereas clonic signs already began from the AED-withdrawal phase. Difference between the withdrawal effects of LTG monotherapy and CBZ monotherapy and polytherapy is mainly in the frequency change of ictal signs.

3.146A

DOES EARLY TREATMENT FOR SINGLE SEIZURES AND EARLY EPILESPY ALTER LONG-TERM PROGNOSIS? RESULTS FROM THE MULTICENTRE STUDY OF EARLY EPILEPSY AND SINGLE SEIZURES ON BEHALF OF THE MESS STUDY GROUP

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Rationale: At the end of this activity the participants should understand the effect of early treatment for single seizures and early epilepsy upon longer-term prognosis. The fact that antiepileptic drugs (AEDs) reduce the likelihood of seizures for people with epilepsy is undisputed. Whether they influence the natural history of the condition (epileptogenesis) is uncertain. We report the largest completed epilepsy randomized controlled trial. In this trial, antiepileptogenic effects were investigated for people with single seizures and early epilepsy. **Methods:** We undertook a pragmatic unblinded multicentre randomized controlled trial. We recruited people (adults or children) following a single seizure or with early epilepsy for whom both clinician and patient were uncertain as to whether AED treatment was required. Participants were randomized to either a policy of delayed treatment or a policy of immediate treatment. For those allocated immediate treatment, the choice of treatment was made by the treating clinician. For those allocated to delayed treatment, where necessary, treatment could be initiated at any time after randomization. Outcomes were time to first seizure after randomization and time to 24-month remission. Recruitment started in 1993 and ended in December 2000, and participants were followed up to the end of 2001. **Results:** The 1,443 participants were randomized, 833 following a single seizure and 610 following two or more seizures; 722 were allocated to immediate and 721 to delayed treatment. The median follow-up was 4.3 years; 717 were from the UK, 624 from other European companies, 34 from India, and 68 from South America. The age of participants ranged from 5 months to 92 years; mean, 30 years; 826 (62%) were male. Results for time to first seizure and 24-month remission will be presented. **Conclusions:** The influence of results upon future treatment policies will be outlined. (Supported by Medical Research Council UK.)

Human Imaging—Adult

3.147
COMPUTER-AIDED DETECTION OF FOCAL CORTICAL DYSPLASIA ON HIGH-RESOLUTION MRI

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Rationale: High-resolution magnetic resonance imaging (MRI) of the brain has made it possible to identify focal cortical dysplasia (FCD) in an increasing number of patients. However, in many of them, FCD lesions are characterized by minor structural abnormalities that often go unrecognized or are too subtle to be detected by standard radiological analysis. We previously developed a voxel-based image processing method including first-order texture and morphological analysis using features that were chosen to model in vivo the MRI characteristics of FCD (Bernasconi A, et al. *Ann Neurol* 2001;49:770–5). However, the visual assessment of these maps can be a subjective process. The purpose of this study was to implement an objective method of detection of FCD lesions by developing a fully automated classifier. We hypothesized that FCD lesions could be detected automatically by combining the models described above with second-order texture analysis, which has the ability to quantify spatial patterns of gray-level intensities within an MRI that may reflect tissue organization. **Methods:** We selected 18 patients with histologically proven FCD and 20 neurologically normal controls. FCD lesions were visually identified and manually segmented on T1-weighted 3D MRI prior to the automatic classification for later use in validation. Two sets of feature maps were calculated over the 3D T1-weighted MRI. The first set of maps was based on the characteristics of FCD as seen on T1-weighted MRI: gray matter thickness to model cortical thickening; gradient magnitude to model blurring of the GM–WM junction; relative intensity to model hyperintense signal within the FCD lesion. The next set of feature maps was generated by a series of second-order texture operators. Both sets of feature maps were used to train a bayesian classifier to identify FCD lesions. **Results:** FCD lesions were correctly detected by the classifier in 16 of 18 patients, as indicated by agreement with the location of the manually segmented lesion on the T1-weighted 3D MRI. The classifier did not detect any lesions in the control group. **Conclusions:** We demonstrate the ability of a novel and objective computer-aided method to automatically detect FCD on high-resolution T1-weighted MRI. In addition to the use of discernable MRI characteristics of FCD, our method is based upon the analysis of spatial patterns of gray-level intensities, which are more difficult to appreciate visually. Therefore, this technique has the potential for detecting abnormalities in patients with "nonlesional" partial epilepsy. (Supported by Canadian Institutes of Health Research and Savoy Foundation.)

3.148
MRI EVIDENCE FOR PROGRESSIVE STRUCTURAL DAMAGE IN THE HIPPOCAMPUS, AMYGDALA, AND ENTORHINAL CORTEX IN TEMPORAL LOBE EPILEPSY

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Rationale: In temporal lobe epilepsy (TLE), there is increasing evidence for the involvement of the parahippocampal region structures in seizure generation and propagation. Using high-resolution MRI, we previously demonstrated a decrease in volume of the parahippocampal region structures in intractable TLE (Bernasconi N, et al. *Neurology* 1999;52:1870–6; Bernasconi N, et al. *Ann N Y Acad Sci* 2000;911:495–500). The purpose of this study was determine whether there is an association between disease duration, presence of prolonged febrile convulsions and secondarily generalized seizures, and the amount of atrophy in the hippocampus, amygdala, and entorhinal cortex in intractable TLE. **Methods:** We studied 82 consecutive patients (mean age, 36 years) with intractable, non–foreign-tissue TLE, and 48 neurologically normal controls (mean age, 32 years) in whom we performed volumetric measurements of the hippocampus, amygdala, and entorhinal cortex on high-resolution MRI. Volumes were categorized as ipsilateral or contralateral to the predominant EEG focus. Association between ipsilateral and contralateral volumes and duration of epilepsy was assessed using Pearson's correlation. Simple linear regression was used to assess the slope (rate of volume change across time) and the intercept (volumes at the onset of recurrent seizures). Differences in volumes and presence of secondary generalized seizures and history of febrile convulsions was assessed using Student's *t* test. **Results:** There was no correlation between age and mesial temporal volumes in control subjects and patients. Volumes of the hippocampus ($p = 0.0001$), the amygdala ($p = 0.0002$), and the entorhinal cortex ($p = 0.03$) ipsilateral to the seizure focus were negatively correlated with duration of epilepsy. Regression analysis showed that at the onset of recurrent seizures, volumes of both the entorhinal cortex ($p < 0.00001$) and the hippocampus ($p = 0.0003$) were abnormally low ipsilateral to the focus, and that amygdalar volumes were normal. Patients with a history of febrile convulsions had significantly lower hippocampal volumes ipsilateral to the focus ($p < 0.0001$). No relationship was found between febrile convulsions and entorhinal cortex or amygdalar volumes. Comparing patients with and without secondarily generalized seizures, we found no difference in the volume of hippocampus, amygdala, and entorhinal cortex. **Conclusions:** Negative correlation between the volumes of the hippocampus, the amygdala, and entorhinal cortex and duration of epilepsy indicates that progressive and widespread damage occurs in TLE. Furthermore, the presence of hippocampal and entorhinal cortex atrophy at the onset of epilepsy suggest that both these structures play a critical role in the pathogenesis of intractable TLE. [Supported by Canadian Institutes for Health Research (CIHR) and Savoy Foundation.]

3.149
HIPPOCAMPAL TEXTURE ANALYSES AND VOLUMETRY IN PATIENTS WITH BENIGN MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Hippocampal atrophy (HA) in mesial temporal lobe epilepsy (MTLE) is frequently associated with refractory seizures and excellent postoperative prognosis. There are some reports of HA in patients with MTLE and good outcome, but it is not known if the hippocampal abnormalities in this group is different from that observed in refractory patients. The objective of this study is to describe hippocampal texture (Txt) analyses and volumetry in patients with MTLE and benign clinical course. **Methods:** We identified patients with MTLE that had a benign clinical course, defined as a maximum of one complex partial seizure per year. All patients underwent high-resolution magnetic resonance imaging (MRI) with T1 and T2-WI in

three orthogonal planes. Coronal T1-IR 3-mm slices were used for Txt analyses, using the software MAZDA, that generates 250 parameters. Region of interest was defined as the hippocampal head, and data were compared to values obtained in a group of healthy adult volunteers. In addition we performed hippocampal volumetric studies in all patients and in a group of normal controls. For statistical analyses we selected those parameters that better discriminated normal hippocampi from pathologically proven mesial temporal sclerosis in a previous study. All data were analyzed using SYSTAT9. We performed analysis of variance (ANOVA) and regression analyses between hippocampal volumes and Txt values. **Results:** A total of 22 patients (16 women) were studied, with mean present age of 42 years (18–68). Control group was composed by 20 adults (15 men), with mean age of 30 years (21–62). There were 16 patients with HA determined by volumetry: seven right, three left, six bilateral. ANOVA showed a significant difference among Txt values from hippocampi of controls, patients' normal-volume hippocampi, and patients' atrophic hippocampi. Post hoc comparisons showed a significant difference between controls' versus patients' normal-volume hippocampi ($p = 0.03$ to 0.001), as well as controls' versus patients' atrophic hippocampi ($p = 0.004$ to 0.00006). However, the difference between patients' normal-volume hippocampi and atrophic hippocampi did not reach statistical significance. Regression analysis showed no association between volumes and Txt values. **Conclusions:** Txt analysis is a new postprocessing technique that allows quantification of digital imaging characteristics, invisible to human eye. In our series of well-controlled patients with MTLE, Txt parameters that could best differentiate atrophic from controls hippocampi were the histogram-based parameters. These are correlated to the grey tone dispersion that may be correlated to structural complexity. In these patients, the reduction of these parameters indicates a simplification in hippocampal head formation. The significant difference between controls and patients' normal volume hippocampi is indicative that texture analysis may be of potential use for detection of subtle abnormalities, not necessarily associated with reduction of hippocampal volumes. (Supported by FAPESP, São Paulo, Brazil.)

3.150
ENTORHINAL AND PERIRHINAL CORTICES ARE OFTEN DAMAGED IN MESIAL TEMPORAL LOBE EPILEPSY BUT SPARED IN PRIMARY GENERALIZED EPILEPSY

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Rationale: Volumetric magnetic resonance imaging (MRI) has been successfully applied to evaluate the damage of the hippocampus and the amygdala in patients with temporal lobe epilepsy (TLE). A large network connects the cortical and subcortical structures of the mesial portion of the temporal lobe. The extent of damage beyond the hippocampus in patients with TLE is not yet fully defined. The objective of this study is to quantitatively assess the mesial temporal lobe structures using high-resolution MRI in patients with chronic refractory TLE and primary generalized epilepsy. **Methods:** We studied 30 healthy subjects, 20 patients with unilateral drug-refractory TLE and 10 patients with primary generalized epilepsy. All subjects were scanned in a 2T system (Elscint Prestige) with a T1 volumetric gradient echo sequence yielding a 1-mm isotropic voxel (TR = 22 ms, TE = 9 ms, matrix = 256 × 220, field of view = 25 × 25 cm). Images underwent field nonhomogeneity correction and linear stereotaxic transformation into a standard space. Structures of interest comprised of entorhinal cortex, perirhinal cortex, hippocampus, and the amygdala. Segmentation was performed with simultaneous assessment of the structure in the coronal, sagittal, and axial planes using anatomic landmarks based upon previous studies on histologic architecture and MRI of the temporal lobe. Statistical significance was set at $p < 0.05$. **Results:** There was no difference between the volumes of the mesial temporal lobe of the patients with primary generalized epilepsy and the control subjects. Patients with right TLE showed reduction of the right hippocampus ($p < 0.001$), the right entorhinal cortex ($p < 0.001$), and the right perirhinal cortex ($p < 0.001$). Patients with left TLE showed significant reduction in the volume of the left hippocampus volume ($p < 0.001$), the left entorhinal cortex ($p < 0.05$), left perirhinal cortex ($p < 0.001$), right perirhinal cortex ($p < 0.05$), and left amygdala ($p < 0.05$). **Conclusions:** These findings show evidence of damage that extends beyond the hippocampus in patients with temporal lobe epilepsy. This damage is greater in the regions with closer anatomic and functional connection to the hippocampus, and is restricted to patients with TLE (i.e., it is not observed in patients with primary generalized epilepsy). (Supported by FAPESP, São Paulo, Brazil.)

3.151
UTILITY OF REPEAT MRI IN EVALUATION OF PATIENTS FOR EPILEPSY SURGERY

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Rationale: Repeated magnetic resonance imaging (MRI) may give useful information in individuals undergoing evaluation for epilepsy surgery. Most patients with intractable partial epilepsy referred to an epilepsy surgery centre will already have had a brain MRI, some of whose scans will have been reported as normal. Prior studies have shown that detection of a focal lesion by MRI is a favourable prognostic variable in the evaluation of patients with intractable partial epilepsy when concordant with clinical, EEG, and neuropsychological information. **Methods:** The Epilepsy Surgery Unit at Beaumont Hospital, Dublin, is the national referral centre for patients with intractable partial epilepsy undergoing presurgical assessment in Ireland. We retrospectively evaluated whether repeat brain MRI provided useful additional information in the cohort of patients monitored with video EEG as part of a standard non-invasive evaluation for possible surgery at Beaumont Hospital from July 1999 to June 2001. **Results:** In total, 54 patients underwent a presurgical evaluation with video-EEG monitoring over this time. Of these 54, 23 (43%) had had more than one MRI. In these 23 patients, new information was obtained from the later scan in 11 (48%) patients. This new information subsequently influenced the surgical decision-making process in 10 patients. Many patients who were originally reported to have had a normal initial scan were found to have a focal abnormality (including mesial temporal sclerosis) on subsequent imaging. Possible reasons for discrepancy between initial and subsequent scans include progression of disease, failure to acquire appropriate imaging sequences in the initial scan, and intra- and interobserver variability. **Conclusions:** Repeated imaging with a tailored epilepsy-protocol MRI frequently reveals structural abnormalities associated with intractable epilepsy which are often not appreciated on initial imaging. Repeated MRI should be considered in some patients with previously reported normal scans who otherwise appear to be good surgical candidates.

3.152
MAGNETIC RESONANCE VOLUMETRIC ANALYSIS OF THE PIRIFORM CORTEX AND CORTICAL AMYGDALA IN CHRONIC TEMPORAL LOBE EPILEPSY

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Rationale: The piriform cortex (PC) is one of the most sensitive brain areas to become damaged by prolonged seizure activity in experimental models. Little is, however, known about the appearance and severity of the PC damage in humans with TLE. Here we investigated the occurrence of the PC damage and its coappearance with the hippocampal damage in patients with chronic TLE by using quantitative MR volumetry. **Methods:** The 38 adults (21 females, 17 males) with

chronic TLE and 23 age-matched controls (12 females, 11 males) were included in the study. All underwent a high-resolution MR imaging at 1.5 T, including a tilted T1-weighted 3D-dataset subsequently reformatted to the bicomissural line. A method to assess the volume of the region including the piriform cortex and the cortical amygdaloid nuclei (PCA) with a standard work console was designed by using landmarks defined by the analysis of Nissl-stained histologic sections from 23 age- and sex-matched autopsy controls. Ten controls were used to assess the intra- and interobserver variability (6% and 8%, respectively). Differences in the normalized PCA volumes and asymmetry ratios between the study groups (controls, TLE patients with focus on the left or right) were determined with nonparametric tests using Bonferroni adjustment. **Results:** Normalized control volumes were 530 ± 59 mm^3 (422–644) [mean ± SD (range)] for the right and 512 ± 60 mm^3 (406–610) for the left PCA. In controls, there was no right–left asymmetry. In right TLE patients, the mean right PCA volume was 15% smaller than in left TLE patients ($p < 0.005$) and 18% smaller than in controls ($p < 0.0005$). In left TLE patients, the mean left PCA volume was 16% smaller than in the right TLE patients ($p < 0.0005$) and 17% smaller than in controls ($p < 0.0005$). In both TLE patient groups, the asymmetry ratio of the PCA was significantly different compared to controls indicating that PCA volumes were smaller ipsilaterally than contralaterally. Patients with hippocampal volumes at least 2 standard deviations below the control mean had a mean ipsilateral PCA volume that was 18% smaller than in patients without hippocampal damage ($p < 0.005$). **Conclusions:** The results indicate that the PCA is an area extensively damaged in chronic TLE patients, particularly in those with hippocampal atrophy. [Supported by Portuguese Science and Technology Foundation (BD 18498/98), Kuopio University Hospital EVO Grant, The Vaajasalo Foundation, The Sigrid Juselius Foundation, and Academy of Finland.]

3.153
HIPPOCAMPAL ATROPHY IN PATIENTS WITH GENERALIZED TONIC–CLONIC SEIZURES DURING SLEEP

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Rationale: Patients with seizures exclusively during sleep are frequently well controlled, and are not routinely scanned. Mesial temporal lobe epilepsy (MTLE) can have a benign clinical course and may present with seizures exclusively during sleep. The frequence of hippocampal abnormalities in patients with nocturnal seizures is most likely underestimated. The objective of this study is to evaluate hippocampal volumes in patients with epilepsy presenting exclusively with generalized tonic–clonic seizures (GTCSs) during sleep. **Methods:** We evaluated 900 consecutive patients from UNICAMP epilepsy clinic and identified patients with seizures during sleep time only. We excluded those patients with abnormal neurologic examination or with clear-cut lesions on CT scan. All patients underwent high-resolution MRI in a 2-T scanner, with acquisitions in three orthogonal planes, including a 3-mm coronal T1-IR protocol for volumetric studies. A control group composed of 20 healthy volunteers was used to determine normal parameters. Absolute volumes corrected for variation in total brain volume, as well as asymmetry index were determined for each subject. Values below 2 standard deviations from the mean of control group were considered abnormal. **Results:** We identified 18 patients (eight women) with seizures exclusivelly during sleep time: eight with witnessed onset, semiologically compatible with complex partial seizures (CPSs) with secondary generalization. All had well-controlled seizures, and the majority are seizure free for ≥2 years. HA was identified in 14 of 18 (78%) patients: seven unilateral (all left) and seven bilateral (two asymmetrical). None of these patients had T2 hyperintense hippocampal signal on MRI. Only one of the patients with normal hippocampal volumes had partial onset identified by clinical history and EEG epileptiform discharges in the temporal lobe. Although the other three patients with normal volumes had no clinical evidence of partial seizure, their interictal EEGs showed temporal slow waves. **Conclusions:** Although we did not observe hyperintense T2 signal, HA determined by volumetry was found in a large proportion of patients with GTCSs during sleep. MRI is important for syndromic diagnosis of patients with nocturnal seizures. (Supported by FAPESP, São Paulo, Brazil.)

3.154
THE NEURODEVELOPMENTAL IMPACT OF EARLY-ONSET PARTIAL EPILEPSY ON THE CORPUS CALLOSUM

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Rationale: Higher cognitive functioning relies on the coordinated activity of distributed neuronal networks linked by projection, association and commissural white-matter fiber tracks. We previously reported that childhood onset temporal lobe epilepsy (TLE) was associated with reduction in the total volume of normal appearing cerebral white matter suggesting an adverse neurodevelopmental impact of early epilepsy onset. This study investigated (a) the volume of the corpus callosum as a function of the age of onset of recurrent temporal lobe seizures controlling for duration of epilepsy, and (b) the clinical neuropsychological significance of identified anomalies in brain connectivity. **Methods:** Subjects were 32 patients with TLE (16 with childhood onset and 16 with adult onset, matched for duration of epilepsy) and 15 healthy controls. Patients were 14–60 years of age with no MRI evidence of neocortical lesions or other developmental or neurologic disorders. Controls were healthy friends or family members of the patients. Using three coregistered image sets, manual trace of the corpus callosum was performed in the midsagittal and parasagittal planes. Total volume measures were based on traces spanning five sagittal slices (midsagittal plus the two adjacent bilateral slices). In addition, each trace was divided into the seven subregions by applying a BRAINS2 software utility modeled according to the Witelson partitioning method. Patients and controls were administered a battery of cognitive tests including measures of intelligence (WAIS-3), memory (WMS-3), speeded psychomotor processing (Trails A and B), and speeded fine motor dexterity (Grooved Pegboard). **Results:** Total corpus callosum volume (ANCOVA with age, gender, and height as covariates) differed among groups ($p = 0.004$) and post hoc comparisons showed childhood-onset patients to have significantly smaller corpus callosum volume compared to healthy controls ($p = 0.003$) and late-onset patients ($p = 0.006$), with no difference between the late-onset patients and controls ($p = 0.994$). Volume for the childhood-onset patients was reduced 15% compared to both healthy controls and late-onset patients. Examination of Witelson regions showed significant ($p < 0.05$) reductions in childhood compared to late-onset patients in the posterior half of the corpus callosum (areas 5, 6, and 7) and area 2. Partial correlations between total corpus callosum volume and neuropsychological measures (total ICV as covariate) showed reduced corpus callosum volume to be associated with significantly lower Performance IQ, immediate but not delayed memory, complex psychomotor processing and speeded fine motor dexterity with both hands. **Conclusions:** Childhood onset temporal lobe epilepsy is associated with a significant reduction in corpus callosum volume (–15%) compared to healthy controls and late-onset patients matched for duration of epilepsy. Volumetric reductions in childhood-onset patients are most prominent in posterior corpus callosum. This reduction in brain connectivity appears to be of clinical consequence in that volumetric reductions were associated with poorer performance on measures of nonverbal intelligence, immediate memory, and speeded motor and psychomotor processing. (Supported by NIH NS RO1 37738.)

3.155
MRI DEFORMATION-BASED SERIAL HIPPOCAMPAL MEASUREMENTS IN INTRACTABLE TEMPORAL LOBE EPILEPSY

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Rationale: Intractable temporal lobe epilepsy (TLE) may cause progressive neuronal injury, marked by progressive hippocampal volume loss. Using hippocampal deformation mapping, which can detect subtle hippocampal changes, we assessed for progressive hippocampal volume loss and shape change in a series of patients with intractable TLE and sequential volumetric MRI scans. **Methods:** Twenty-two patients undergoing epilepsy surgery for TLE had volumetric MRI scans at initial clinical presentation to our epilepsy center, and at the time of epilepsy surgery. In retrospective review of epilepsy surgery cases, we noted age, sex, duration of epilepsy, frequency of seizures between MRI scans, and dates of sequential MRI scans. We performed hippocampal deformation segmentations of the sequential MRI scans in all patients. Deformation images were grouped into composite images for the initial MRI group and surgical MRI group. Using deformation-based hippocampal shape analysis, we calculated volume differences and changes in three-dimensional surface structure in the initial composite and surgical composite MRI images. **Results:** The patient group consisted of 10 men and 12 women. Mean age at seizure onset: 10.7 years (range, 1–26 years). Mean duration from seizure onset to first MRI: 21.3 years (range, 3–45 years). Mean duration between first and second MRI: 7.6 months (range, 2–21 months). Mean seizure frequency between first and second MR: 2.8 per week (range, 1–10 per week). Table 1 summarizes volume changes between composite initial and composite surgical MRI scans. Three-dimensional shape analysis, comparing initial and surgical composite hippocampal images, showed accentuated volume loss in the mesial part of the hippocampal head, in the region of the uncinate gyrus for both the right and left composite hippocampi. **Conclusions:** Our series showed significant total hippocampal volume changes in the right hippocampus, and non-significant volume changes in the left hippocampus. Variability in measurements of abnormal hippocampi (*Radiology* 2000;216:291–7), changes of normal aging, and as well as ongoing epileptic seizures may be responsible for the volume changes. Three-dimensional deformation-based hippocampal shape analysis showed changes of accentuated volume loss in the medial hippocampal head region in both the right and left hippocampi, which may be a region of accentuated involvement from sequelae of ongoing epileptic seizures.

TABLE 1. *Volume changes (in mm^3)*

	Initial MRI (mean ± SD)	Surgical MRI (mean ± SD)	Volume change, 95% CI
Right hippocampus	2,549 ± 499	2,391 ± 458	158 [53.1–205] p = 0.005
Left hippocampus	2,206 ± 563	2,173 ± 556	32.8 [−104–170] p = 0.62

3.156
REGIONAL VOLUME CHANGES OF BRAIN IN JUVENILE MYOCLONIC EPILPESY

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Rationale: Magnetic resonance imaging (MRI) scans of patients with idiopathic generalized epilepsy are normal on visual assessment. Only one study showed an increase in cortical gray matter in the mesial frontal lobes of patients with juvenile myoclonic epilepsy (JME). We investigated regional volume changes of brain in JME patients. At the end of this presentation, participants should be able to discuss structural abnormalities of JME. **Methods:** Nineteen JME patients (22.6 ± 5.2 years old, six males, 13 females) and 19 normal controls (23.0 ± 7.3 years old, six males, 13 females) underwent 1.6-mm thickness whole-brain SPGR MRI. Exact midsagittal image was obtained with image reconstruction and geometric correction. According to the Witelson's work, the midsagittal area of corpus callosum was divided into seven subregions (a1 to a7 from anterior to posterior) and their areas were measured. Volumes of hippocampus, frontal lobe, and whole cerebrum were measured with a semiautomated method. The difference of each measurement between JME and normal groups were tested by *t* test and ANCOVA (adjusted by age and cerebral volume). **Results:** There was no significant difference of cerebral volume between groups (JME: 1,113 ± 123 cc, Normal: 1,093 ± 60 cc, p = 0.52, *t* test). Left hippocampus was smaller in JME (JME: 2.62 ± 0.26 cc, Normal: 2.78 ± 0.24 cc, p = 0.032, ANCOVA), whereas left frontal lobe was significantly larger in JME (JME: 213.9 ± 30.4 cc, Normal: 191.3 ± 15.1 cc, p = 0.004, ANCOVA). The areas of rostrum (p < 0.0001, ANCOVA) and rostral body (p = 0.044, ANCOVA) in corpus callosum were significantly smaller in JME. **Conclusions:** Rostrum and rostral body of corpus callosum, and left hippocampus were smaller in JME while left frontal lobe was larger in JME. These findings suggest a structural abnormality of left frontal lobe in JME, which may be related to microdysgenesis. Volume reduction of portions in corpus callosum could be related with axonal agenesis caused by microdysgenesis or recurrent seizures. [Supported by the Korean Ministry of Science and Technology under the National Research Laboratory (NRL) program (2000-N-NL-01-C-157).]

3.157
CONTRALATERAL LEFT HEMISPHERE STRUCTURE AND FUNCTION IN RIGHT TEMPORAL LOBE EPILEPSY

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Rationale: Although ictal EEG monitoring in temporal lobe epilepsy (TLE) patients typically identifies a unilateral seizure focus, recent research suggests that brain abnormalities in this population extend beyond this unilateral epileptogenic region. However, no study to date has comprehensively evaluated the integrity of the hemisphere contralateral to the seizure focus. In addition, the etiology of these extratemporal, contralateral abnormalities is unknown. Therefore, through utilization of quantitative MRI volumetrics and neuropsychological measures of left hemisphere (LH) functions, the purpose of the present study is twofold: to comprehensively evaluate the structural and functional integrity of the LH in RTLE patients in comparison to healthy controls, and to examine the relationship between these abnormalities and clinical variables for the purpose of elucidating the etiology of these abnormalities. **Methods:** Subjects included (a) 20 LH language-dominant, ictal EEG-monitored, RTLE patients with no other neurologic conditions or mental retardation; and (b) 20 right-handed healthy controls matched for age, gender, height, and Beck Depression Inventory (BDI) total. All subjects underwent a brain MRI and completed a neuropsychological evaluation of LH functions including right-hand dexterity, verbal memory, and language. LH regions of interest (ROIs) included the hippocampus, four lobes, gray matter, white matter, and total LH. Clinical variables included number if medications and epilepsy duration. **Results:** Relative to healthy controls, RTLE patients performed significantly worse on measures of letter fluency [t(32) = 0.276, p = 0.025], semantic fluency [t(32) = 3.216, p = 0.003], and right-hand dexterity (Grooved Pegboard: [t(32) = –2.308, p = 0.028]. A trend toward significantly poorer performance (p < 0.01) in RTLE patients relative to controls was found on a measure of naming and verbal delayed memory. Measures of verbal intelligence and immediate verbal memory did not yield significant group differences. MRI volumes did not differ significantly between the groups; however, multiple significant correlations were found between MRI volumes and neuropsychological measures. Epilepsy duration was not found to correlate significantly with any of the measures. Number of medications correlated only with letter fluency (p = 0.442, p = 0.016). **Conclusions:** Deficits on multiple measures of LH functions suggest that RTLE patients may present with abnormalities in the contralateral LH. Significant relationships between these functional measures and regions of the LH suggest LH brain dysfunction underlies observed functional deficits; however, group differences in LH regional brain volumes, if present, were not significant. Number of antiepileptic drugs potentially play a minor role in the etiology of extratemporal abnormalities. (Supported by Epilepsy Foundation Behavioral Science Summer Grant 2001, NIH grants NS R0137738 and RR-03186.)

3.158

HIPPOCAMPAL TEXTURE ANALYSIS IN PATIENTS WITH MESIAL TEMPORAL SCLEROSIS

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Rationale: Mesial temporal lobe epilepsy (MTLE) is frequently associated with refractory seizures and pathological features of mesial temporal sclerosis (MTS). New quantitative MRI techniques can improve the detection and quantification of hippocampal abnormalities. Texture (Txt) analysis has been successfully used in cerebral pathologies and can be used for evaluation of mesial temporal lobe structures. The objective of this study is to evaluate Txt analysis in patients with pathologically proven MTS and refractory MTLE. **Methods:** We selected 20 consecutive patients with refractory MTLE who underwent surgical treatment and had pathological findings consistent with MTS. We performed Txt analysis in 3-mm coronal T1-IR MRIs, using the software MAZDA, focusing on operated-on hippocampal head. Txt parameters that were highly influenced by the size of the region of interest (ROI) were excluded, as well those related only to brightness and contrast. Data were compared to a group of 20 healthy adult volunteers. For statistical analyses, we determined most significant parameters, through ANOVA and MANOVA. **Results:** We studied 20 operated-on patients (12 women and eight men) with MTS (12 right and eight left). MAZDA generates data on 250 parameters. We selected 44 parameters that showed the highest mean difference between patients and controls. The MANOVA showed that parameters that best differentiated normal from abnormal hippocampus in operated-on patients were histogram and absolute gradient (p from 0.009 to 0.00003); both were consistently abnormally low in the operated-on hippocampi, as compared to the control group. **Conclusions:** Txt analyses is promissing in the assessment of hippocampal abnormalities in patients with MTS. These abnormal findings show a straight correlation with the pathological neuronal loss that occurs in MTS. The abnormal Txt analyses in these resected hippocampi indicate a structural simplification of the hippocampal head, which correlates with the MRI observation of a flattened hippocampus, with hypo intense and abnormal internal structure. (Supported by FAPESP, São Paulo, Brazil.)

3.159

MESIAL TEMPORAL LOBE EPILEPSY PATIENTS WITH GOOD AND POOR SEIZURE CONTROL DO NOT DIFFER IN THE INTENSITY OF HIPPOCAMPAL ATROPHY

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Rationale: Several studies have shown an association between hippocampal atrophy and signal changes with intractable mesial temporal lobe epilepsy (MTLE). Such relationship has been usually established by tertiary centers. Therefore, a bias may play a role in sampling more severe epilepsy cases. In the present study we evaluate, in patients with MTLE, the imaging and clinical variables that may have a relevance on seizure control. **Methods:** MTLE patients from both general and intractable outpatient clinic of the Clinical Hospital of the University of São Paulo School of Medicine–Ribeirão Preto were evaluated with protocols for the temporal lobe. Patients were considered with good seizure control (GC) if they had fewer than four seizures per year independently on the antiepileptic regimen. Patients with one or more seizures/month were considered with poor control (PC). Forty-two GC patients and 44 PC were analyzed. Groups were compared for clinical parameters and hippocampal volume and FLAIR signal. **Results:** No statistical differences were observed between the GC and PC groups in the following parameters: age of the patient at the time of study, age of the patient at the time of the initial precipitating injury (IPI) or first epileptic seizure, duration of epilepsy and follow-up, and family history of epilepsy. The frequency of IPI was higher in the PC (75.0% vs. 54.8%; $p < 0.05$, Student's t test). No differences in hippocampal volumes between GC and PC were found. Nevertheless, we found a significant increase in FLAIR signal in the atrophic hippocampus of PC when compared with GC (ANOVA, $p < 0.001$). **Conclusions:** These findings suggest that hippocampal atrophy probably does not have influence on seizure outcome whereas the higher intensity of FLAIR signal is correlated with clinical intractability. [Supported by CNPq, PRONEX, and FAPESP (Proc. 99/11729-2, 00/12376-5); Brazil.]

3.160

PARTIAL VOLUME EFFECT CAUSES OVERESTIMATION OF THE ENTORHINAL CORTEX VOLUME IN QUANTITATIVE MRI STUDIES

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Rationale: Volumetric studies of the entorhinal cortex (ERC) depend upon the correct visualization of the anatomic landmarks. **Methods:** We studied 16 healthy subjects who underwent our MRI protocol. Images were acquired in a 2T scanner. We used coronal slices oriented perpendicularly to hippocampal long axis for manual delineation of regions of interest. We used the same anatomic protocol for the segmentation of all subjects either for the single plane–based analysis or for the three-dimensional analysis. This protocol was based on previously described methods for the entorhinal segmentation (Insausti et al. *Am J Neuroradiol* 1998;19:659–71). A T1-IR 3-mm single-plane acquisition was used for quantification of ERC volumes by NIH Image program, using TIFF format. A T1 gradient-echo three-dimensional sagittal acquisition was used for multiplanar reconstruction of 1-, 2-, and 3-mm-thick slices volumetric converted into MINC format and were analyzed using the software DISPLAY. For statistical analysis we used Student's t test and ANOVA. **Results:** We studied 16 healthy subjects (three men) with mean age of 31 years (ranging from 21 to 53). The 1-mm three-dimensional DISPLAY analysis (TDISPLAY) showed mean volumes of 895 ± 143 mm^3 (703–1,098) for the right ERC and 968 ± 186 mm^3 (673–1,317) for the left ERC. The 2-mm TDISPLAY showed a mean volume of $1,299 \pm 182$ mm^3 (943–1,686) for the right ERC and a mean volume of $1,317 \pm 151$ mm^3 (1,105–1,592) for the left ERC. The 3-mm TDISPLAY reconstructed images showed a mean volume of $1,609 \pm 187$ mm^3 (1,259–1,896) for the right ERC and a mean volume of $1,722 \pm 179$ mm^3 (1,463–2,016) for the left ERC. The 3-mm NIH analysis showed a mean volume of $1,905 \pm 264$ mm^3 (1,602–2,439) on the right and $1,903 \pm 226$ mm^3 (1,530–2,339) on the left. There was no influence of age, gender, or side on the volumes observed in TDISPLAY segmentation. Female subjects exhibited a larger entorhinal cortex, when the analysis was performed on NIH ($p < 0.05$). ANOVA revealed difference between the volumes obtained from the three-dimensional analysis with 1-mm, 2-mm, and 3-mm, and the coronal-based 3-mm analysis ($p < 0.001$). Tukey post hoc comparison revealed differences between all groups ($p < 0.001$) **Conclusions:** Morphometric analysis of the ERC performed with different slice thickness yield different results. Thick slices are sometimes used because it is time saving, but volumes obtained are linearly incremented according to increased slice thickness, and false estimates may then supervene. (Supported by FAPESP, São Paulo, Brazil.)

3.161

SPECIFICITY OF THALAMIC ATROPHY IN TEMPORAL LOBE EPILEPSY ON VOLUMETRIC MRI: COMPARISON WITH EXTRATEMPORAL AND IDIOPATHIC GENERALIZED EPILEPSY

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Rationale: As part of the limbic system, the thalamus has reciprocal anatomic connections with the hippocampus, entorhinal cortex, and

amygdala. The thalamus has been proposed to be involved in the regulation of cortical excitability and seizure propagation in temporal lobe epilepsy (TLE). Previous quantitative MRI studies have shown a decrease in volume of the thalamus in TLE patients. However, the specificity of these findings for TLE has not been established. To determine if thalamic volume changes are specific to TLE, we measured the thalamic volumes on high-resolution MRI in groups of patients with TLE, extratemporal lobe epilepsy (ETE), and idiopathic generalized epilepsy (IGE). We also determined correlation of thalamic volumes with volumes of mesial temporal structures in TLE. **Methods:** Thalamic volume measurements were carried out using T1-weighted 3D gradient-echo sequence magnetic resonance imaging (MRI) in 40 patients with TLE (20 with hippocampal atrophy and 20 without hippocampal atrophy), 16 patients with ETE, and 17 with IGE. Each individual's volume measurement was standardized relative to the volume of normal controls using a z-score transformation. Thalamic volumes in patients were compared to those in 21 neurologically normal controls. The correlation among volumes of thalamus, hippocampus, amygdala, and entorhinal cortex was also determined in TLE patients and normal controls. **Results:** In TLE patients, thalamic volumes ipsilateral to the seizure focus in patients with hippocampal atrophy (mean ± SD, –0.95 ± 1.25) and without hippocampal atrophy (–0.88 ± 0.92) were smaller than the volume in normal controls ($p < 0.05$). There was no significant difference in thalamic volume between patients with HA and without HA. Thalamic volumes contralateral to seizure focus in TLE groups were not significantly different from those in normal controls. Thalamic volumes in patients with ETE and IGE were not significantly different from those of normal controls. There was no correlation of thalamic volumes with the volumes of hippocampus, amygdala, and entorhinal cortex in TLE patients or in normal controls. **Conclusions:** Atrophy of the thalamus is present only in patients with TLE and is not found in patients with ETE or IGE. Thalamic atrophy ipsilateral to the seizure focus exists even in TLE patients who do not demonstrate hippocampal atrophy on MRI. Thalamic atrophy appears to be specific to TLE, probably as a part of the limbic system disorder, and may contribute to the diagnosis and lateralization of the seizure focus in TLE. (Supported by Canadian Institutes of Health Research.)

3.162
STRIKING PARALLEL ONSET OF SEIZURE MANIFESTATION IN IDENTICAL TWINS WITH SUBEPENDYMAL HETEROTOPIA

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Rationale: With the advent of sophisticated new imaging techniques, in particular high-resolution MRI, there is an increasing number of patients with newly diagnosed epilepsy in whom even subtle causes for their seizure disorder are detected. Heterotopias are a typical example of this progress. The current classification distinguishes between subependymal heterotopia (SEH), subcortical heterotopia (SCH), and band heterotopia or double cortex syndrome (DCS). Seizure manifestation may be the only clinical symptom in patients with SEH and SCH. **Methods:** We report on the course of two 17-year old identical twin sisters. We came to know the index patient (IP) at age 15 years when she presented with partial motor seizures of her right side for the first time. The clinical examination was normal, and there was no family history of epilepsy. The mother, though, reported several spontaneous abortions. The identical twin sister (ITS) had no seizures at that time and was without any clinical pathology. **Results:** Interictal EEG monitoring in the IP showed no focal abnormality. High-resolution MRI detected significant, widespread, symmetrical distributed SEH and right frontoparietal tissue density suggestive of cortical dysplasia. A very similar pattern was then found in both the patient's mother and her ITS. The IP remained seizure free under lamotrigine (LTG) monotherapy. Within 1 year, the ITS also presented in our clinic with her first generalized tonic–clonic seizure. She was also started on AED treatment and has been seizure free since. **Conclusions:** The heterogeneity of neuroradiologically proven cases of heterotopia was recently emphasized (Gleeson et al. *Neurology* 2000;47:265–9). The most probable genetic mutation underlying the SEH in both these patients and their mother would be a mutation of the filamin gene. However, ongoing molecular genetic analyses have not yet uncovered any abnormalities in the first eight exons studied. Our observation suggests that genetic factors in epilepsy may direct not only very similar epileptogenic tissue changes in first-degree relatives but may also play a significant role in the timing of first seizure manifestation.

3.163
T2-MAPPING OF THE NEOCORTEX IN LOCALISATION-RELATED EPILEPSY

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Rationale: Conventional MRI sequences exploit differences in the proton density, T1- and T2-relaxation times to provide tissue contrast and lesion conspicuity. Of these, T2-weighted imaging is the most sensitive in identifying cerebral pathology, which is often characterised by a change in either total tissue water or altered compartmentalisation of water within the tissue. Quantitative assessment of T2 signal intensity (T2-mapping) is more sensitive than qualitative evaluation in, for example, hippocampal sclerosis and multiple sclerosis. T2 mapping in the neocortex may be confounded by partial volume effects of cerebrospinal fluid. This is resolved by using a fast fluid attenuated inversion recovery (FLAIR) sequence. Our objective was to assess whether T2 mapping, analysed using statistical parametric mapping (SPM) would identify areas of abnormal T2 signal in patients with localisation-related epilepsy. **Methods:** Thirty healthy volunteers and 73 patients with partial seizures were scanned with conventional MRI and T2 mapping. The patient group comprised acquired lesions ($n = 11$), malformations of cortical development ($n = 18$), normal conventional MRI ($n = 44$). T2 mapping was performed using FLAIR imaging (TR/TI/TE = 5,000/1,638/15, 120 ms) with a resolution of 0.94 × 0.94 × 5 mm. T2 maps were calculated and normalised to Talairach space using SPM99. The patients' maps were then compared to the 30 control subjects' maps and significant differences were detected at a threshold of $p < 0.001$ (multiple comparisons: $p < 0.05$). **Results:** In all 11 patients with acquired lesions, and in 16 of 18 patients with MCD, SPM detected areas of increased T2. In five of 11 patients with acquired lesions and in six of 18 patients with MCD, areas of abnormal T2 signal were also detected in regions previously reported as normal. Twenty of 44 MRI-negative patients had areas of increased T2, of which 15 were concordant with the localisation of EEG abnormality. **Conclusions:** T2-mapping was sensitive in patients with acquired lesions and MCD. In these patients, abnormalities were also detected in normal appearing brain suggesting occult injury or more widespread MCD than apparent on visual inspection of conventional MRI. A clinically concordant abnormality of T2 signal was identified in 34% of MRI-negative patients. This could be due to either aetiological factors, such as occult dysgenesis, or as a result of chronic seizures, such as atrophy and neuronal loss. This technique, along with other new methods, increases the yield of identifying potentially curable aetiologies of epilepsy. (Supported by Action Research and The Gwyneth Forrester Trust.)

3.164
ASSOCIATION OF IMAGING FINDINGS WITH CLINICAL OUTCOME

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Rationale: Intractable temporal lobe epilepsy with hippocampal damage is often linked to a precipitating insult during childhood. The data available suggests that once epilepsy has emerged recurrent seizures may cause further structural and functional changes. However, longitudinal follow-up studies are needed to determine the course of epileptic process and to identify surrogate markers for disease modification. **Methods:** We designed a prospective follow-up study of 112 patients with newly diagnosed partial epilepsy who were allocated to treatment with either carbamazepine (CBZ; n = 54) or with tiagabine/vigabatrin (TGB/VGB; n = 40/18). The aim of the study was to investigate the occurrence of hippocampal damage and to assess whether the changes progress in the long-term follow-up. Specifically, we wanted to compare the hippocampal volumes in patients treated with either standard sodium-blocking agent or with newer γ-aminobutyric acid (GABA)ergic agents, and to examine whether volumetric measures correlate with clinical outcome. The initial magnetic resonance imaging (MRI) was performed before the antiepileptic medication (AED) was started, and later, after 1 year, 2–3 years, and 5 years of follow-up. We used Cavalieri method of modern design stereology for volume estimations of the hippocampus. A group of 20 healthy subjects served as control population for MRI. The clinical outcome of the patients was determined by assessing the efficacy and retention rate of the initial treatment. **Results:** The mean left and right hippocampal volumes did not differ between controls and patients studied at baseline, 1 year, 2–3 years, and 5 years of follow-up. At least a 2 SD reduction in the volume of the hippocampus was observed in altogether six patients. In the general linear model of repeated measures there was a trend of volume decrease when left and right hippocampal volumes of each patient were compared during 2–3 years of follow-up, but the change was not significant. When patients were divided into two groups according to the treatment (CBZ vs. TGB/VGB) or seizure control (seizure-free vs. seizures), no difference was observed in the serial hippocampal volumes. Accordingly, the efficacy of treatment in intial treatment groups was similar. Comparing the overall effectiveness of the treatments, CBZ proved to be more effective than TGB/VGB. **Conclusions:** This is first prospective quantitative MRI study that systematically follows up large number of newly diagnosed partial epilepsy patients. The study shows that hippocampal damage at the time of diagnosis is rare. No significant progressive change in the hippocampal volume was observed during follow-up. In the future most useful way for evaluating the course of epileptic process and effects of therapy might be combining several measures of outcome such as seizure-control, imaging data, and cognitive data. (Supported by Kuopio University Hospital EVO grant.)

3.165
MAGNETIC RESONANCE IMAGING SIGNAL INTENSITY AND HIPPOCAMPAL MOSSY FIBER SPROUTING IN TEMPORAL LOBE EPILEPSY

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Rationale: Hippocampal sclerosis is the most frequent pathologic finding in temporal lobe epilepsy (TLE) and is characterized by cell loss, gliosis, and supragranular mossy fiber sprouting. Such abnormal axonal reorganization present high amounts of zinc in their glutamatergic nerve terminals. Typical MRI findings of mesial TLE are atrophy of mesial temporal lobe structures, mainly the hippocampal formation, and high signal on T2-weighted sequences. The histologic basis of this hyperintensity is not completely understood. Some authors have interpreted the T2 high signal as a result of both gliosis and changes in the water tissue content. The objective of the present study was to determinate the relationship between mossy fibers sprouting and the high signal on T2 fluid-attenuated inversion recovery (FLAIR) sequence. **Methods:** Twenty-seven TLE patients with hippocampal sclerosis were submitted to surgical resection of mesial structures and had their hippocampi processed the neo-Timm histochemistry, which typically marks the zinc content of nerve terminals. Mossy fiber sprouting was quantified by a semiquantitative approach using a image analysis software (NIH Image) in specific areas, such as molecular layer and the hilar region. Data were expressed as gray value intensity (gvi, ranging from 0 to 255) and correlated with hippocampal intensity on FLAIR sequence. FLAIR images were analyzed with a semiquantitative approach based on the index beween the mean value of gray-level intensity on the hippocampus over the frontal cortex (I-H/F). Control groups were used to investigate MRI features (normal subjects, n = 18) and histological aspects (necropsy subjects without cerebral disease, n = 16). **Results:** Patients with TLE had an increase in the I-H/F when compared to controls (49 ± 10% and 19 ± 6%, respectively; $p < 0.0001$, Student's *t* test). We found a linear indirect relationship between the MRI FLAIR signal and the gray-value intensity on the inner molecular layer ($p = 0.0053$ and $r2 = 0.3$). **Conclusions:** This evidence suggests that, in addition to gliosis and water tissue content, the zinc present in the nerve terminals of mossy fibers interferes on the FLAIR signal observed during the MRI investigation of epilepsy subjects. [Supported by CNPq, PRONEX and FAPESP (Proc. 99/11729-2, 00/12951-0); Brazil.]

3.166
EARLY DEVELOPMENTAL DESTRUCTIVE BRAIN LESIONS AND THEIR RELATIONSHIP TO EPILEPSY AND HIPPOCAMPAL DAMAGE

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Rationale: To analyze the extended hippocampal damage and clinical features in patients with epilepsy and destructive brain lesions of early development. **Methods:** Fifty-one adult patients were divided into three main groups according to the topographic distribution of the lesion on the magnetic resonance imaging (MRI): hemispheric (H) (n = 9); main arterial territory (AT) (n = 25); arterial borderzone (Bdz) (n = 17). The mean areas of each hippocampal slice of the different groups were compared to the mean area of a control group in order to evaluate the changes in volume distribution along the hippocampal axis. **Results:** Visual analysis showed hippocampal atrophy (HA) in 74.5% of the patients and volumetric study in 92%. The HA was bilateral in six patients and it was more severe ipsilateral to the main lesion. The HA was unilateral in 41 patients and at the same side of the main lesion, except in two. The frequency of unilateral or bilateral HA was not different among groups ($p > 0.05$). Volume loss was diffuse but more concentrated on the anterior section of the hippocampus in patients of all groups. There was a shortening of the long axis of the hippocampus in patients of group H which was not present in the other groups. Duration of epilepsy correlated weakly with the volume of the hippocampus ipsilateral to the main lesion ($r = –0.29$, $p = 0.046$). Extratemporal ictal semiology was the most common presentation (66%), although EEG epileptiform discharges were more common over the temporal lobes (64%). The patients without HA had seizures with extratemporal semiology and interictal epileptiform activity localized outside the temporal lobes. **Conclusions:** The HA in these patients with large destructive lesions of early development seems to be related to the insult that caused the main lesion. The role of long term repetitive seizures appear to have minor additional effect in HA. Although the majority of patients in this series have extratemporal epilepsy, the high frequency of HA and epileptiform activity over the temporal lobe suggests that their epileptic syndrome is related to a more diffuse epileptogenic area, also involving the mesial temporal structures. These findings may have major importance in surgical planning of patients with destructive brain insults of early development who present intractable seizures. (Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP; São Paulo, SP, Brazil.)

3.167

HIPPOCAMPAL SCLEROSIS IS A PROGRESSIVE DISORDER: A LONGITUDINAL VOLUMETRIC MRI STUDY

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Rationale: Recent studies raise concerns that certain forms of partial epilepsy may be associated with progressive damage to medial temporal lobe structures. These studies, employing a variety of experimental and clinical methods, suggest that continuing seizures over time may result in progressive changes in hippocampal structure and function. To date, clinical studies have utilized a cross-sectional study design. Using a longitudinal study design, we studied patients with medically refractory temporal lobe epilepsy (TLE) due to unilateral hippocampal sclerosis (HS) to determine if progressive hippocampal atrophy was observed. At the end of this activity, the participants should understand that patients with HS who continue to have seizures are at risk for progressive hippocampal damage. **Methods:** From a cohort of 67 consecutive patients with medically refractory TLE and with volumetric MRI evidence of unilateral HS, 47 underwent anterior temporal lobectomy (ATL), five were lost to follow-up, one died during a seizure, and 14 were recommended to have surgery by our epilepsy team but refused. Of the 14 patients refusing surgery, three became seizure free on medication, and 11 continued to have seizures. These 14 patients underwent a repeated MRI scan after 2.5–5.2 years. Measures included the interval between the two MRI scans, hippocampal volumes ipsilateral (IHV), and contralateral (CHV) to the side of seizure onset, and seizure status during the interval (seizure-free vs continuing seizures). Reliable change indices (RCI) for HV were calculated using CHV test–retest correlations as the basis for SEM. **Results:** The mean interval between MRI scans was 3.4 (SD, 0.70) years. A significant decline occurred in mean IHV from first ($M = 2{,}676$) to second MRI [$M = 2{,}476$; $t(11) = 4.34$, $p < 0.01$]. Mean CHV did not change. There was a significant interaction between mean IHV change and seizure status [$F(1, 10) = 17.4$, $p < 0.01$], with seizure-free patients showing no change in mean IHV, and patients with continuing seizures showing a decline in mean IHV. Regarding individual change, all of the 11 patients with continuing seizures showed declines in IHV in excess of the RCI, and the three seizure-free patients did not, indicating a relationship between seizure status and decline in IHV ($\chi 2$ lr(1) = 13.5, $p < 0.01$). One patient who continued to have seizures showed a CHV decline greater than RCI. No correlations were found between the interval between MRI scans and changes in IHV or CHV. **Conclusions:** These results demonstrate that patients with medically refractory TLE due to unilateral HS develop progressive hippocampal atrophy over time. This suggests that HS is a progressive disorder that should be treated aggressively.

3.168

BIOENERGETIC IMPAIRMENT IN THE THALAMUS OF PATIENTS WITH INTRACTABLE TEMPORAL LOBE EPILEPSY

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Rationale: Although previous reports have shown that bioenergetics in the hippocampus in patients with temporal lobe epilepsy (TLE) is significantly impaired, little is known about the energetic state of other structures involved in the propagation of seizures. Recently both animal and human studies have shown that the thalamus may have a significant role in the propagation of seizures in TLE. Although FDG-PET studies have shown decreases in thalamic glucose uptake, it is unclear if this reflects a decrease in activity or damage of the thalamus. Therefore, the goal of this study was to map the energetic changes in the hippocampal formation and thalamus. At the end of this activity the participants should be able to discuss the relationship between energetic impairment in the thalamus and hippocampus in TLE. **Methods:** ^{31}P MRSI were acquired with a 4T Varian MR system in 12 patients with intractable TLE and 10 controls using 12-cc voxels and an acquisition time of 46 min. For anatomic visualization, 3D T1 images were acquired with an isotropic resolution of 1.5 mm. For analysis, 23 regions of interest were selected. Bilaterally, the amygdala, head of the hippocampus (pes), body of the hippocampus, anterior and posterior temporal lobe, thalamus, basal ganglia, parietal and frontal white matter were analyzed. Midline volumes were also selected for prefrontal gray matter, anterior, medial and posterior cingulate, and occipital gray matter. The degree of bioenergetic impairment was calculated from the PCr/ATP ratio. **Results:** PCr/ATP was reduced to the greatest extent the ipsilateral amygdala, followed by the ipsilateral pes, hippocampus, and thalamus with decreasing severity. A similar pattern was seen in the contralateral hemisphere, albeit to a lesser extent. The ipsilateral amygdala and pes were significantly reduced in comparison to controls, while the ipsilateral hippocampal body and thalamus were significantly reduced in comparison to the contralateral volumes ($p < 0.02$ and 0.03, paired two-tailed *t* tests) but not control values. The pes was also reduced ipsilaterally relative to the contralateral lobe ($p < 0.05$). No significant changes were detected from the other volumes. **Conclusions:** The data demonstrate that bioenergetic impairment in temporal lobe epilepsy extends beyond the hippocampal formation and includes the thalamus. The involvement of the thalamus is consistent with PET data which reported nearly identical frequencies of hypometabolism in the thalamus (63%) and hippocampus (70%) in TLE patients. However, if the decrease in FDG uptake solely reflected decreased neuronal glucose consumption in the absence of damage, no change in bioenergetics would be anticipated. The presence of bioenergetic impairment in the thalamus suggests that the thalamus's ability to meet its energetic needs has been compromised. Since the thalamus may function as a critical propagation point in TLE, the observed energetic impairment in the thalamus may be a contributing factor to the poor seizure control in these patients. (Supported by Charles A. Dana Foundation and the National Institutes of Health P01-NS39092, R01-NS40550.)

3.169

EVIDENCE OF THALAMIC DYSFUNCTION IN JUVENILE MYOCLONIC EPILEPSY: A PROTON MRS STUDY

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Rationale: To investigate neuronal dysfunction in the thalami of patients with juvenile myoclonic epilepsy (JME) using proton magnetic resonance spectroscopy (MRS). **Methods:** We studied 10 consecutive patients (five women) with JME with mean age of 31.6 years (ranging from 17 to 44 years). All patients had seizure onset in late childhood–teenage years, normal neurologic examination, typical EEG of JME, and normal high-resolution MRI. MRI and MRS examinations were performed on an Elscint 2T scanner (Prestige, Haifa, Israel). We performed single-voxel proton MRS using PRESS sequence (TR = 1,500 ms, TE = 135 ms, NEX = 200) over the right and the left thalami of patients and 10 healthy volunteers (five men) with mean age of 30.3 (range, 22–36 years). After the acquisition of scout anatomical images in axial planes for localization of thalami, one single-voxel ($2 \times 2 \times 2$ cm) was placed over the region of interest (ROI). Each subject underwent two single-voxel MRS, one for right and one for left thalamus. Prior to the acquisition, a localized shimming at ROI was performed to ensure adequate field homogeneity, followed by water suppression adjustment. Spectra were postprocessed and resonance intensities were determined from peak areas by integration using software supplied by the machine manufacturer. We measured signals 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-containing compounds (Cr) at 3.0 ppm. Spectra with broad peaks and poor separation of individual peaks were excluded from analysis. Values <2 SD from controls were considered abnormal. We performed Student's *t* test to evaluate group differences. **Results:** Thalami NAA/Cr ratios were significantly decreased in JME patients (left side, 1.58 ± 0.26; right side ,1.5 ± 0.15) as compared to controls

(left side, 1.98 ± 0.18, right side, 1.88 ± 0.15) ($p = 0.0001$ and $p = 0.007$, respectively). In addition, nine of the 10 patients had abnormal NAA/Cr values in at least one of the thalami (<2 SD from the mean of controls). **Conclusions:** This study shows evidence of neuronal dysfunction in the thalami of patients with JME supporting the theory of abnormal thalamocortical circuitry as an underlying mechanism for seizure generation in this form of generalized epilepsy. (Supported by Fundação de Amparo 'a Pesquisa do Estado de Sao Paulo - FAPESP, Brazil.)

3.170
IDENTIFICATION OF EXTRAHIPPOCAMPAL AND EXTRATEMPORAL METABOLICALLY ABNORMAL BRAIN REGIONS IN MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Structural and metabolic abnormalities in the hippocampal region in mesial temporal lobe epilepsy (mTLE) are well described. However, epileptogenic activity often spreads to other brain regions. Neuropsychological, volumetric, and metabolic abnormalities beyond the hippocampus have been reported. The aim of this study was to identify extrahippocampal and extratemporal brain regions with reduced NAA/(Cr+Cho) in individual patients with mTLE with (TLE-MTS) and without (TLE-no) MRI evidence for mesial temporal sclerosis using ^{1}H multislice magnetic resonance spectroscopic imaging (MRSI). **Methods:** MRSI in combination with tissue segmentation was performed on 21 patients with mTLE and 12 age-matched healthy volunteers. In controls, the metabolite ratios (NAA/Cr+Cho) of all voxels of a given lobe (frontal, parietal, etc.) were expressed as a function of white matter content using a linear regression analysis to determine the 95% prediction interval for any additional voxel of a given tissue composition. Voxels with metabolite ratios below the lower limit of the 95% prediction interval were defined as "pathological" in patients and controls. The localization of voxels defined as "pathological" was indicated on the corresponding MRI slice for anatomic reference. Z-scores were used to identify brain regions of mTLE subjects with a percentage of pathologic voxels greater than in controls. **Results:** In mTLE patients, extrahippocampal and extratemporal brain regions with (NAA/Cr+Cho) lower than in controls could be identified in the ipsi- and contralateral insula and frontal lobes and in the ipsilateral temporal and parietal lobes (cf. Table 1). The frontal limbic and prefrontal regions were more often affected than the lateral frontal regions. There was no difference between the ipsi- and contralateral hemispheres. There were no differences of extent and distribution of extrahippocampal NAA reductions between TLE-MTS and TLE-no. **Conclusions:** In mTLE extrahippocampal and extratemporal reductions of NAA/(Cr+Cho) were found in the frontal lobes, insula and ipsilateral temporal and parietal lobes; but there were no differences between ipsilateral and contralateral sides. The preferential involvement of brain areas directly and indirectly synaptically connected to the medial temporal structures may indicate that the abnormal extrahippocampal regions represent brain regions involved in seizure spread. (Supported by NIH grant R01-NS31966. S.G.M. was supported by a grant from the Swiss National Science Foundation.)

TABLE 1. *Mean and (interquartile range) of percentage of "pathologic voxels" in lobes*

Lobe	Frontal	Temporal	Insula	Parietal	Occipital
Controls	0.51 (0.5)	2.09 (3.3)	0.82 (0.0)	0.71 (0.1)	1.3 (0.32)
Ipsilateral	6.03 (6.2)[a]	11.40 (11.15)[a]	27.92 (42.6)[a]	7.37 (6.8)[a]	3.75 (4.0)
Contralateral	4.76 (7.6)[a]	3.43 (4.7)	14.01 (23.5)[a]	3.27 (4.6)	1.93 (1.4)

[a] $p < 0.05$ with Wilcoxon signed-rank test compared with controls.

3.171
^{13}C-MRS MEASUREMENT OF CEREBRAL GLUTAMATE METABOLISM IN EPILEPSY PATIENTS BY ORAL ADMINISTRATION OF ^{13}C-GLUCOSE

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Rationale: We report a study on cerebral glutamate metabolism by oral administration of ^{13}C-glucose in intractable occipital lobe epilepsy patients ($n = 5$) compared with young healthy controls ($n = 8$). **Methods:** The written consent was obtained after being informed about the procedure. A ^{13}C-MRS system based on a 2T TOSHIBA ^{13}C-MRS research system was used. ^{13}C spectra were simultaneously obtained from two voxels on bilateral occipital lobes after oral administration of 99% enriched [$^{1\text{-}13}$C] glucose (Glc-1; 0.75 g per 1 kg body weight) in a 30% weight/volume water solution. Each voxel size is 48 ml or 64 ml, and acquisition time is 5 min. ^{13}C-MRS spectra were acquired for 2–3.5 h to obtain time courses for ^{13}C-incorporated glutamate and glutamine. Blood samples were taken from the antecubital vein and analyzed to measure the blood sugar level, the insulin level, and ^{13}C fractional enrichment (F.E.) of Glc-1. Rate of TCA cycle (Vtca) and glutamate–glutamine cycle (Vgln) of each individual was computed based on the previously proposed mathematical model (Mason et al., 1992). **Results:** A mean value of Vtca was slightly decreased in epilepsy patients [control: 0.372 μmol/g/min (SD, 0.191), epilepsy: 0.276 μmol/g/min (SD, 0.115)], whereas Vgln was significantly increased in epilepsy patients [control: 0.027 μmol/g/min (SD, 0.010), epilepsy: 0.276 μmol/g/min (SD, 0.115)] ($p < 0.005$)]. **Conclusions:** Synthesis of glutamine from glutamate in glial cells is considered to be increased in epileptic brains. (Supported by Health Science Research Grants; Research on Brain Science Project, and National Research and Development Program for Medical and Welfare Apparatus under entrustment by NEDO, Japan.)

3.172
A STUDY OF METABOLITE CONCENTRATIONS IN IDIOPATHIC GENERALISED EPILEPSY USING PROTON MAGNETIC RESONANCE SPECTROSCOPY

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Rationale: Cortical hyperexcitability may be important in the pathophysiology of idiopathic generalised epilepsy (IGE). γ-Aminobutyric acid (GABA) and glutamate are respectively the principal inhibitory and excitatory neurochemicals in the brain. We have implemented methods for reliably measuring GABA plus homocarnosine (GABA+) and the glutamate plus glutamine signal complex (GLX) in vivo using proton magnetic resonance spectroscopy (MRS). We report on measurement of these metabolites in patients with IGE. The objective of this study was to determine whether IGE is associated with observable abnormalities in inhibitory (GABA+) or excitatory (GLX) neurochemical concentrations. **Methods:** Twenty-six patients with IGE and normal MR imaging and 20 normal control subjects were studied on a 1.5-T 5x GE Signa scanner. One voxel was prescribed (~35 cc) in each frontal lobe for each subject. *N*-acetyl aspartate plus *N*-acetyl aspartyl glutamate (NAA) and GLX were measured by performing short echo time PRESS localised MRS (TE/TR = 30 /3000 ms) whilst GABA+ measurement was via our double quantum GABA filter. **Results:** Comparison was made between IGE and control groups. The right (R) and left (L) voxels were considered separately. The main findings were low NAA (R: $p < 0.05$, L: $p = 0.08$) and high GLX (R: $p < 0.05$, L: $p <$

0.05) in the IGE group. No group differences were observed for GABA+. **Conclusions:** IGE is associated with frontal lobe metabolite changes that imply increased excitability or proportion of glutamatergic neurons (elevated GLX) and reduced NAA implying reduced neuronal numbers or neuronal dysfunction. Normal GABA+ measures imply that GABA+ concentrations may not be abnormal in patients with IGE who are taking antiepileptic drugs (Fig. 1). (Supported by Medical Research Council, Brain Research Trust, The National Society for Epilepsy.)

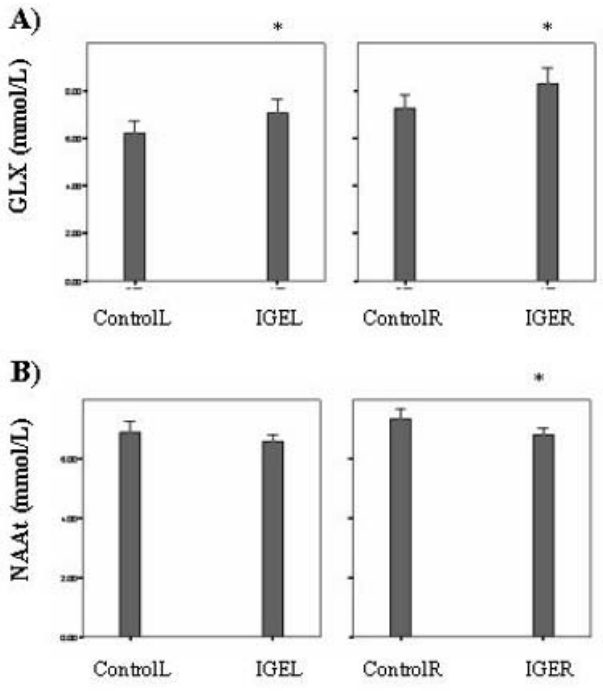

Figure: Bar plots of mean and 95% confidence intervals for: **(A)** glutamate plus glutamine (GLX); **(B)** N-acetyl aspartate plus N-acetyl aspartyl-glutamate (NAA) in the prescribed frontal region. The healthy volunteer group is designated Control. IGE = idiopathic generalised epilepsy group. R = right sided and L = left side. Significant variation ($p \leq 0.05$) between IGE and Control is indicated by *.

3.173
RELEVANCE OF THE RESECTION OF ^{18}FDG-PET HYPOMETABOLIC ZONES FOR THE SEIZURES OUTCOME IN PATIENTS WITH FOCAL CORTICAL DYSPLASIA AND INTRACTABLE MEDICALLY REFRACTORY EPILEPSY

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Rationale: The postoperative outcome of the refractory epilepsy associated with focal cortical dysplasia (FCD) is very unsatisfactorily. The morphologic demarcation of FCD remains problematic despite of the advances in the sensitivity of imaging studies. ^{18}FDG-PET shows hypometabolic zones with high sensitivity, which are often not restricted on the epileptogenic lesion or on the zone of the seizures pacemaker. Furthermore, operative electrocorticography studies have found epileptic activity in areas shown to be hypometabolic on ^{18}FDG-PET scans. In the present study, we evaluated whether the extension of the hypometabolic zone beyond or farther than the resection area has an influence on the postoperative seizures outcome. **Methods:** Preoperative ^{18}FDG-PET of 14 patients with refractory epilepsy and MRI and/or histologically confirmed FCD were evaluated by means of SPM99 regarding statistical significant hypometabolic zones. Hypometabolic zones were merged with postoperative 3D-MRI (MPRAGE) data. The distribution of hypometabolic zones was classified as (1) absent, (2) restricted to the lobe of the dysplasia, (3) involving other lobes of the ipsilateral hemisphere, and (4) involving also the contralateral hemisphere. We have correlated these findings with the postoperative seizure outcome (seizure free vs. not seizure free) and the extension of the resection with a follow-up period of 6–21 months (mean, 9 months). **Results:** From 14 patients, nine had a hypometabolic zone on the area of the dysplastic lesion detected with high-resolution MRI. In one of nine patients, the hypometabolic area was restricted to the MRI lesion; in eight patients, the hypometabolism were restricted to the same lobe but was more extended than the morphologic lesion. Four patients had an additional ipsilateral hypometabolism involving other lobes, and seven patients had hypometabolic zones in the contralateral hemisphere. One patient had no statistically significant hypometabolic zones. The presence of hypometabolism in the same lobe of the lesion showed a tendency to better postoperative seizure outcome ($p = 0.07$). In five of nine patients, the hypometabolic zone within the lobe of dysplasia was resected completely. They all became seizure free irrespective of additional hypometabolic zones in other ipsilateral or contralateral lobes. In six patients, the hypometabolic zone within the lobe of dysplasia was resected incompletely. Only two of these six patients became seizure free. This difference was statistically significant ($p = 0.04$). **Conclusions:** A significant hypometabolic zone in the same lobe of the FCD can influence the postoperative seizure outcome negatively if it is not resected. The ^{18}FDG-PET should be consequently taken into consideration when planning the extension of the resection. Additional hypometabolic areas outside the lobe of the lesion seem to have no relevance for the postoperative seizure outcome. (Supported by DAAD.)

3.174
THE CAUSE OF EXTRATEMPORAL HYPOMETABOLISM IN MESIAL TEMPORAL LOBE EPILEPSY: ATROPHY AND HYPOMETABOLISM OF HIPPOCAMPUS

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Rationale: The mechanism of extratemporal positron emission tomography (PET) hypometabolism in mesial temporal lobe epilepsy (mTLE) is still controversial. We performed this study to find whether the degrees of hippocampal atrophy and hypometabolism are related to the presence of extratemporal hypometabolism. **Methods:** Sixteen unilateral mTLE patients (22.6 ± 5.2 years) underwent ^{18}F-FDG PET and volumetric SPGR MRI with 1.6-mm thickness. Subjects were divided into two groups: PET hypometabolism in only temporal lobe (TH, temporal hypometabolism; age: 28.28 ± 10.41 years, seizure history: 14.71 ± 8.59 years); and hypometabolism in both temporal lobe and extratemporal region (ETH: temporal and extratemporal hypometabolism; age, 21.66 ± 6.65 years; seizure history: 8.77 ± 4.08 years) by visual inspection. The volumes of hippocampus (HV) and whole cerebrum (WCV) were measured by a semiautomated and manual drawing method. Mean PET metabolism of hippocampus (PET-hipp) was measured by PET-MRI co-registration and adjusting the ROI of hippocampus from SPGR MRI. HV was normalized with being divided by WCV of each patient, and PET-hipp was normalized with being divided by the mean PET metabolism of the nonepileptic hemisphere of each patient. Then asymmetry indices of HV and PET-hipp were calculated by the value of epileptic hippocampus/the value of nonepileptic hippocampus. Statistical analysis was performed with the Mann–Whitney *U* test. **Results:** There were no significant differences in WCV (TH:

1,030.3 ± 66.8 cc; ETH: 1,004.3 ± 61.9 cc; p = 0.491) and normalized HV of nonepileptic side (TH: 2.92 ± 0.43 cc; ETH: 2.86 ± 0.55 cc; p = 0.958) between TH and ETH groups. Normalized HV (TH: 2.07 ± 0.77 cc; ETH: 1.48 ± 0.34 cc; p = 0.062) of epileptic side and the asymmetry index of HV (TH: 0.71 ± 0.38; ETH: 0.46 ± 0.11; p = 0.063) appeared to be smaller in ETH. The asymmetry index (TH: 0.86 ± 0.24; ETH: 0.68 ± 0.098; p = 0.0195) and the normalized value of PET-hipp (TH: 15.2 ± 2.07; ETH: 12.6 ± 2.72; p = 0.025) were significantly lower in ETH. **Conclusions:** Epileptic hippocampus of patients with ETH showed significantly lower glucose metabolism and appeared more atrophic than that of patients with TH. This result indicates that extratemporal hypometabolism in mTLE is related to a greater degree of hippocampal damage. [Supported by the Korean Ministry of Science and Technology under the National Research Laboratory (NRL) program (2000-N-NL-01-C-157).]

3.175
HIPPOCAMPUS ATROPHY VERSUS HYPOMETABOLISM OF LATERAL TEMPORAL CORTEX IN MESIAL TEMPORAL LOBE EPILEPSY

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Rationale: Hippocampal sclerosis is frequently accompanied by positron emission tomography (PET) hypometabolism (PET-Hypo) of lateral temporal cortex, but its mechanism remains unclear. We investigated whether the PET-Hypo of lateral temporal cortex is related to the atrophy and PET-Hypo of hippocampus. **Methods:** Fifteen patients with mesial temporal lobe epilepsy (TLE) underwent ^{18}F-FDG PET and volumetric MRI with 1.6-mm thickness. Hippocampus was divided into head, body, and tail while lateral temporal cortex was divided into anterior, mid-, and posterior third. Hippocampal volume and PET metabolism of each region were measured by a semiautomated method and PET-MRI co-registration with adjusting PET ROI from SPGR MRI. Asymmetry indices of hippocampal volume (Vol-asym) and PET metabolism (PET-asym) in each region were calculated by the formula of the value of epileptic side/the value of nonepileptic side. The correlation coefficient was tested among Vol-asym of regional hippocampus, PET-asym of regional hippocampus, and lateral temporal cortex. **Results:** There were nine left TLE and six right TLE. There were significant correlations between Vol-asym and PET-asym in head (r = 0.705), body (r = 0.56) and tail (r = 0.59) of the hippocampus (p < 0.05). The PET-asym of anterior 1/3 of lateral temporal cortex was significantly correlated with Vol-asym of hippocampal head (r = 0.662, p = 0.01) and had a weak correlation with PET-asym of hippocampal head (r = 0.424, p = 0.065). But there was no correlation of body and tail of hippocampus with mid- and posterior 1/3 of lateral temporal cortex. **Conclusions:** The degree of hippocampal atrophy was correlated with not only PET-Hypo of hippocampus but also PET-Hypo of anterior lateral temporal cortex. This result suggests that PET-Hypo of lateral temporal cortex is partly due to decreased fiber connections from atrophic hippocampus. [Supported by a grant (No. HMP-01-PJ8-PG3-21301-0009) of the Good Health R&D Project, Ministry of Health & Welfare, Republic of Korea.]

3.176
SEIZURE-RELATED SHORT-TERM PLASTICITY OF BENZODIAZEPINE RECEPTORS IN PARTIAL EPILEPSY

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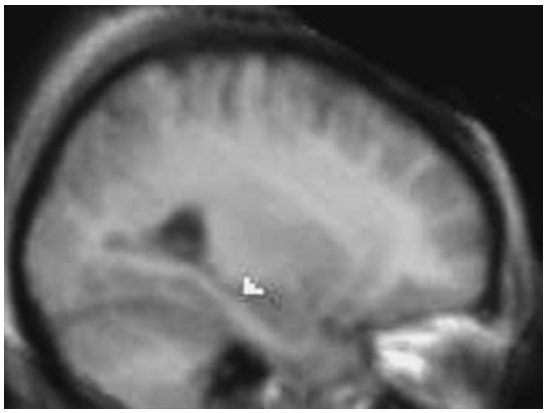
Rationale: We have previously reported that patients with temporal lobe epilepsy (TLE) undergoing repeated ^{11}C-flumazenil positron emission tomography (FMZ-PET) could demonstrate focal test–retest variatons of FMZ binding (Ryvlin et al. *Neurology* 1999;53:1882–5), and benzodiazepine (BZD) receptor Bmax (Bouvard et al. *Epilepsia* 1999;40:250). We have now extended our study to evaluate the relationship of such focal variations to the epileptic activity. **Methods:** Six TLE patients underwent a test–retest ^{11}C-FMZ study at 1-week interval, while undergoing a long-term video-EEG monitoring. The latter started 1 week prior to the first PET study, allowing precise counting of the number of seizures occuring during the week preceding each of the two PET studies, and defining which of the two was the closest to the last previously occurring seizure. FMZ-PET was performed using a validated partial-saturation protocol which allowed the calculation of Bmax (receptor density) parametric images. MRI-based regions of interest (ROIs) were placed over the hippocampus and transfered to the PET images, to look for the test–retest hippocampal Bmax variation as a function of seizure occurence (paired *t* test). In addition, we performed a SPM analysis, where the dummy covariate represented the delay between PET studies and the last previously occuring seizure. **Results:** Hippocampal Bmax significantly differed between the two PET studies. This difference pointed to more severe decreased Bmax in the epileptogenic hippocampus for PET studies associated with the shortest delay from the last previously occurring seizure (p = 0.005). This result was confirmed by the SPM analysis as illustrated. **Conclusions:** BZD receptor Bmax, as quantified through ^{11}C-FMZ-PET imaging, proved to significantly vary during a 1-week period in patients with TLE, in particular over the epileptogenic hippocampus. This variation appears to be partly related to seizure occurrence, with the closest the last seizure in the PET study, the greater the decreased hippocampal Bmax. This phenomenom might reflect a seizure-related release of bendozepines, and should be taken into account when using FMZ-PET in a clinical setting (Fig. 1). (Supported by Université Claude Bernard Lyon I.)



3.177
IN VIVO PET STUDY OF 5-HTA1 RECEPTORS IN MALFORMATIONS OF CORTICAL DEVELOPMENT

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Rationale: Increased serotonin (5-HT) innervation and synthesis have been demonstrated in human epileptogenic malformations of cortical development (MCD), using immunocytochemistry study of surgically resected tissue (Trottier et al., 1996), and more recently, in vivo positron emission tomography (PET) study of α[^{11}C]methyl-L-tryptophan (AMT) brain distribution (Chugani et al., 1998). In patients with tuberous sclerosis and multiple brain lesions, AMT captation appears to be specifically increased in the epileptogenic tuber (Chugani et al., 1998). In experimental models of epilepsy, serotonin receptors, and

in particular 5-HT1A receptors, are modulated in various ways, depending on the model considered. Based on these data, we have hypothetized that 5-HT1A receptors changes might also occurred in human epileptogenic MCD. **Methods:** Five patients were selected for this study, including two with bilateral nodular periventricular heterotopia, and three with a localized malformation of cortical organization. One of the latter patients also had a single nodular periventricular heterotopia contralateral to its cortical malformation. All patients, as well as 24 control subjects, underwent a 3D-mpr MRI and a 70-min duration dynamic [^{18}F]-MPPF PET study. [^{18}F]-MPPF (2'-methoxyphenyl-(*N*-2''-pyridinyl)-*p*-fluoro-benzamido-ethyl-piperazine) is a validated selective antagonist of 5-HT1A receptors. PET images were coregistrated with MRI, and quantified using the model of Gunn et al. (*Neuroimage* 1998), considering the cerebellum as a reference for nonspecific binding. We obtained binding potential (BP) parametric images which were then processed to perform a comparison between each individual patients and their respective sex- and age-matched control group, using the ANCOVA function of SPM 99. We also traced regions of interest (ROIs) over all MCD, as well as over various ipsilateral and contralateral cortical areas. **Results:** All five patients demonstrated significant focal 5-HT1A changes. Some, but not all heterotopias, were associated with an increased BP, which remained however lower than that of adjacent cortical structures. Within the same patient, major BP differences were observed between the multiple heterotopic nodules. Malformations of cortical organization could be associated with a significant increased ($n = 2$), or decreased ($n = 1$) BP. Other distant cortical and subcortical areas, which appeared normal on MRI, also demonstrated significant increased or decreased BP. Among the latter, the raphe nuclei of the mesencephalon and/or of the medulla, showed an increased BP in all five patients. **Conclusions:** Our preliminary data suggest that epilepsy patients with MCD have significant 5-HT1A receptor changes. The latter involve the MCD as well as other cortical and subcortical regions, including the raphe nuclei. The major 5-HT1A BP differences observed between the various MCD, both among and within individuals, raise the issue of the relation between 5-HT1A BP changes and the epileptogenicity of the MCD. This issue will need to be further addressed. Finally, the very consistent increased BP observed within the raphe nuclei suggests a general modulation of the serotoninergic system in epileptic patients with MCD , and might represent a potential therapeutic target. (Supported by Claude Bernard Lyon 1 University, Hospices Civils de Lyon.)

3.178
ABNORMALITIES IN BRAIN 5-HT1A RECEPTOR BINDING IN TEMPORAL LOBE EPILEPSY PATIENTS: AN [^{18}F]MPPF-PET STUDY

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Rationale: The objective of our study was to assess abnormalities in 5-HT1A receptors density in epileptic patients with refractory temporal lobe epilepsy (TLE). Experimental data in animals show that 5-HT1A receptors are mainly located in limbic areas and that serotonin, via 5-HT1A receptors, mediates an antiepileptic and anticonvulsant effect. In TLE patients, we quantified 5-HT1A receptor density in epileptogenic and nonepileptogenic areas, as defined by intracranial recordings with stereoelectroencephalography (SEEG). **Methods:** Five patients and 24 control subjects (four groups of six controls sex and age matched with patients) were studied by PET using a 5-HT1A receptor antagonist ([^{18}F]-pMPPF). Dynamic PET data were acquired during 70 min. PET and MRI data were coregistered for anatomic identification. A series of 34 anatomic regions of interest (ROIs) were drawn on patient and control MRIs. PET data were quantified using a simplified model (Gunn et al. *Neuroimage* 1998;8:426–40) to assess binding potential (BP) values in each ROI with cerebellum as a reference. For each patient, a normalized percentage of BP change was calculated as the relative variation of BP in each ROI compared to the corresponding ROI in control subjects (% = (BP patients – BPcontrols)/BP control). In patients, ROIs explored by SEEG, were categorized as showing (a) Ictal dischages and interictal spikes, (b) only interictal spikes, and (c) no epileptic activity activity. Percentage of BP change were then averaged over patients within each of these three ROI groups. **Results:** Compared to control values, BPs were on average decreased by 35 ± 19% in ROIs showing discharges and spikes, by 16 ± 32% in ROIs only showing spikes, and by 8 ± 20% in ROIs showing no epileptic activity. ANOVA performed on these three groups revealed that 5-HT1A binding was significantly more decreased in ROIs in which discharges and spikes were recorded compared to (a) ROIs showing no epileptic activity ($p < 0.003$) and (b) ROIs in which only interictal spikes were recorded ($p < 0.03$). No significant difference in BP change was found between regions in which only spikes were recorded and regions with no epileptic activity. **Conclusions:** This study shows that in vivo disponibility of 5-HT1A receptors is decreased in epilepsy patients as compared to normal subjects. This decrease is highly correlated to the degree of epileptogenicity of cortical areas explored by intracerebral recordings. Our data suggest that the serotonin neurotransmission might be more impaired in regions involved in epileptic discharges than in regions only generating interictal paroxysms. This study raises the question of the potential use of [^{18}F]-pMPPF-PET in the presurgical evaluation of refractory partial epilepsies. [Supported by Claude Bernard University Lyon1. Hospices Civils of Lyon (HCL). National Center for Sientific Research (CNRS).]

3.179
IMAGING CORTICAL AND SUBCORTICAL NETWORKS IN HUMAN TEMPORAL LOBE SEIZURES

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Rationale: The major behavioral manifestations of temporal lobe seizures include decreased responsiveness, contralateral dystonia, and amnesia. Previous studies have suggested that the dystonia and amnesia, respectively, may be caused by involvement of the basal ganglia and temporal lobe structures during seizures. Based on single-photon computed tomography (SPECT) perfusion imaging of individual patients during seizures, we have recently hypothesized that impaired consciousness may be related to seizure spread to the upper brainstem and diencephalic activating systems. Studies on individual patients are subject to noise and intersubject variability. Here, we use Statistical Parametric Mapping (SPM99) to examine cortical and subcortical activity in a homogeneous group of patients during temporal lobe seizures to locate areas which lie outside of expected variation of local brain function. **Methods:** Patients had mesial temporal onset confirmed by convergent diagnostic studies, as well as by pathological demonstration of hippocampal sclerosis, and seizure-free outcome for 1 year after surgery. We analyzed 11 seizures in 10 patients injected with Tc-99m HMPAO from 60 to 90 s after seizure onset, representing the middle to late portion of the seizures. A paired *t* test model was used in SPM99 comparing ictal and interictal SPECT scans for the group with an extent threshold of 125 voxels (1 cc) and a height threshold p of 0.01 (Z-score >2). **Results:** Voxel clusters demonstrating significant increases in ictal CBF were found in the temporal lobe, ventral basal ganglia, medial thalamus, and upper brainstem. Significant decreases were present in the frontal and parietal association cortex. **Conclusions:** The network of anatomic regions showing increased and decreased activity during temporal lobe seizures may explain ictal behavioral phenomena. Significant increases in activity in the medial thalamus and upper brainstem, may disrupt the normal activation of the cerebral cortex, resulting in decreased activity in the frontoparietal association cortex, and consequently, in loss of consciousness during temporal lobe seizures. (Supported by Dana Foundation.)

3.180

AN OUTCOMES-BASED ASSESSMENT OF THE PREDICTIVE VALUE OF ICTAL SPECT SCANNING IN PATIENTS WITH EPILEPSY NOT LOCALIZED BY OTHER NONINVASIVE METHODS

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Rationale: For localization of epileptic foci in evaluation for surgical resection, ictal single-photon emission computed tomography (SPECT) is an established tool and is one of the few noninvasive studies able to localize the ictal onset zone, which has a higher correlation to the epileptogenic region. Intracranial EEG recording, the gold standard in seizure localization, is associated with high rates of morbidity and mortality. Therefore, our objective is to determine if ictal SPECT scanning may provide sufficient localizing value to allow patients to avoid the risks of intracranial EEG and proceed directly to resective surgery. After reviewing this presentation, meeting attendees should have a better understanding of the role of ictal SPECT scans in the epilepsy localization process. **Methods:** Ictal SPECT scanning was performed utilizing a standard protocol with injection of 20 mCi of ^{99m}Tc-HMPA tracer immediately after seizure onset noted clinically or by EEG monitoring. We performed a retrospective review of patients' results from their ictal SPECT scans, and where applicable, their intracranial EEG recording, as well as the operative records for those patients who have undergone resective surgery. Postsurgical outcomes after surgery were directly verified by clinic visits and telephone interviews. Our population of 138 patients who were insufficiently localized (by video-telemetry, magnetic resonance imaging, FDG-PET scanning, and neurocognitive testing) and were still considered to be surgical candidates underwent ictal SPECT scanning. Of these, 86 had seizures during the recording period, and 79 of these yielded focal results. Twenty-five patients have undergone intracranial EEG monitoring, and results are available for 23. **Results:** Lateralization by ictal SPECT correlated with that of intracranial EEG in 17 (74%). Twenty-seven patients have gone on to resective surgery, of which outcomes are known in 22. The lateralization of the SPECT focus and the site resected correlated in 19. Follow-up information is available for 15 of those patients. Ten are seizure free (Engel class I), and three have had a significant reduction in their seizure frequency (Engel class II and III), yielding a sensitivity of 77% and a specificity of 60%. Conversely, results are available for 22 of the 24 patients who underwent both ictal SPECT and intracranial EEG. Surgical outcomes are available for 10 of those patients who underwent resection based on the results of intracranial EEG; six are seizure free, and one is class II/III (sensitivity 79%, specificity 70%). Finally, six patients proceeded to surgery without intracranial monitoring; in five of the patients, the SPECT localization was that of resection. Of those five patients, four (80%) are seizure free, and the fifth has noted a marked reduction in the frequency of her seizures. **Conclusions:** Ictal SPECT displays comparable sensitivity and specificity to intracranial EEG and can accurately predict the ictal onset zone in some patients and may have obviated intracranial EEG. Further studies are necessary to determine which subsets of patients can proceed to surgery based on ictal SPECT findings.

3.181

DIFFUSE CHANGES IN CEREBRAL BLOOD FLOW OUTSIDE TEMPORAL EPILEPTOGENIC FOCUS IN TEMPORAL LOBE EPILEPSY

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Rationale: Positive and negative subtraction SISCOM images have the ability to demonstrate the regional cerebral blood flow (CBF) changes in partial epilepsy. During the interpretation of subtracted SPECT, we frequently find widespread areas of CBF changes beyond the epileptogenic focus. Only a few reports pinpoint the presence of such changes. Most of them documented the changes of CBF in the frontal lobe during complex partial seizures of temporal lobe in origin. Regional blood flow changes in other areas have not been systematically studied. We assess the pattern of widespread CBF changes, using both positive and negative subtraction SISCOM, in temporal lobe epilepsy (TLE) patients. **Methods:** We retrospectively reviewed the video recordings, ictal–interictal SPECT scans, and brain MR images of 20 intractable TLE patients. The positive (ictal minus interictal), and negative (interictal minus ictal) subtraction SPECT coregistered with MRI were obtained using ANALYZE AVW 3.1. The positive subtraction SISCOM images (segmented to show voxels of 2 SD from the mean subtraction) demonstrating hyperperfusion areas, and the negative subtraction SISCOM images (segmented to show voxels of 1 SD from the mean subtraction) demonstrating hypoperfusion areas were reviewed simultaneously. The presence of ictal hyper or hypoperfusion in frontal, temporal, occipital, cerebellar, and basal ganglia were determined in reference to epileptogenic areas, which were determined by standard methods of seizure localization. **Results:** The mean age was 32.7 years (range, 12–48 years). The mean seizure duration was 78.3 s (range, 23–144 s). The mean latency of radioisotope injection after seizure onset was 34.6 s (range, 12–86 s). All radioisotope injections were performed during the clinical seizure. Fifteen patients (75%) showed ictal hyperperfusion in the temporal lobe of seizure origin, three patients (15%) had bitemporal hyperperfusion but more prominence on one side, one patient demonstrated temporal hyperperfusion on the contralateral side of seizure onset, and one patient showed no temporal hyperperfusion. Frontal hyperperfusion was found in nine patients (45%), basal ganglia hyperperfusion in five patients (25%), and cerebellar hyperperfusion in six patients (30%). For the negative subtraction SISCOM images, there were two patients who demonstrated temporal hypoperfusion (one on the contralateral side of epileptogenic focus). Seventeen patients (85%) had frontal hypoperfusion (ipsilateral in six, contralateral in seven, and bilateral in four). No basal ganglia hypoperfusion was observed. Cerebellar hypoperfusion was found in 11 patients (55%) (ipsilateral in five, contralateral in five, and bilateral in one). Occipital hypoperfusion was shown in seventeen patients (85%) (ipsilateral in nine and contralateral in eight patients). **Conclusions:** During temporal lobe epileptic seizures, there are diffuse changes of CBF beyond the epileptogenic focus. Although there is no specific pattern, the frontal and occipital hypoperfusion are the common findings. Our data support the importance of modifications in the synaptic network and interconnection between the temporal and extratemporal regions, and also provide further insight of the complex pathophysiology underlying TLE.

3.182

ASSOCIATION BETWEEN BASAL GANGLIA HYPERPERFUSION AND CONTRALATERAL TONIC LIMB POSTURE DURING SEIZURES: ASSESSMENT USING SISCOM TECHNIQUE

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Rationale: Detailed analysis of ictal semiology provides important insights into the localization or lateralization of seizure focus and seizure-propagation pathways. Our study was designed to identify subcortical distribution of SPECT hyperperfusion during seizures for correlation with clinical semiology. The SISCOM (Subtraction Ictal SPECT Co-registered on MRI) technique has the advantage of accurate delineation of subcortical structures for the localization of ictal SPECT hyperperfusion abnormalities (*Neurology* 1999;52;157–66). **Methods:** The study cohort consisted of patients with intractable partial epilepsy evaluated between July 1993 and July 1997. Patients were included in the study if they had ictal and interictal SPECT scans, and the video recording of the index seizure (i.e., during which either ^{99m}Tc-HMPAO or ^{99m}Tc-ECD was injected) was sufficient for assessment of seizure semiology. Blinded reviews of SISCOM images were conducted without knowledge of the clinical history, MRI imaging, or video-EEG

results. Video-EEG recording of the index seizure was reviewed to determine time of seizure onset and termination, duration of the seizure, and the presence of tonic limb posturing during the seizure. **Results:** Of the 68 subjects, 39 (57.4%) were males and 29 (42.6%) were females. The average age at time of study was 31.4 years (range, 1.5–61), and the average duration of epilepsy was 19 years. Right basal ganglia hyperperfusion was significantly associated with left tonic limb posturing; 54.6% (six of 11) of the patients with right basal ganglia hyperperfusion had left tonic posturing during the seizure, versus only 21.1% (12 of 57) of those without right basal ganglia hyperperfusion ($p = 0.021$). However, left basal ganglia hyperperfusion was not associated with right tonic posturing ($p > 0.05$). There is a tendency for right basal ganglia hyperperfusion to be associated with longer latency from seizure onset to appearance of contralateral tonic limb posture ($p = 0.07$). Unilateral basal ganglia hyperperfusion on either side was not significantly associated with ipsilateral tonic posturing ($p > 0.05$). **Conclusions:** Using SISCOM image analysis, our finding of association between ictal basal ganglia hyperperfusion and contralateral tonic limb posture is similar to that previously reported for dystonic limb posture using visual inspection of SPECT scans. (*Neurology* 1992;42:371–7). However, the ability to detect the association between basal ganglia hyperperfusion and tonic limb posture may potentially be influenced by factors such as the timing of the posturing. (Supported by Mayo Foundation for Research and Education.)

3.183
FOCAL COGNITIVE AND NEUROIMAGING CHANGES ASSOCIATED WITH PROPAGATION OF GENERALIZED TONIC–CLONIC SEIZURES IN ELECTROCONVULSIVE THERAPY

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Rationale: Generalized tonic–clonic seizures are often considered to involve the whole brain homogeneously. However, partial seizures with secondary generalization may involve specific brain networks more intensely than others leading to selective deficits. To investigate this phenomenon, we performed single-photon emission computed tomography (SPECT) perfusion imaging and neuropsychology testing in relation to electroconvulsive therapy (ECT)-induced seizures. **Methods:** We performed Tc-99m HMPAO SPECT injections at specific times relative to seizure initiation in patients receiving either bilateral or right unilateral ECT treatment for depression. Interictal injections were performed under the same anesthesia used in ECT. A two-sample *t* test model was used in SPM99 comparing ictal and interictal SPECT scans. Patients were grouped according to ECT type (bilateral or right unilateral) and time of injection relative to ECT stimulus (0 s, +30 s, or +60 s). To test retrograde memory, specific items were presented to each patient immediately before ECT. Three objects were presented verbally, and four faces were presented visually. Patients were tested for recall of these items 4 h after ECT. **Results:** Both bilateral and right unilateral ECT produced generalized tonic–clonic seizures. Analysis of CBF changes at consecutive time points showed evidence of early maximal activity at the region of seizure onset in the anterior frontal and temporal lobes followed by later activity in regions of seizure propagation such as the parietal lobes. Bilateral ECT produced symmetric CBF increases in the frontal and temporal lobes as well as the parietal cortex and the cerebellum. However, in right unilateral ECT, a greater activation of the right frontal lobe and a relative sparing of the left temporal lobe were observed. Interestingly, we found that verbal retrograde memory was significantly impaired in bilateral ECT patients, but not in unilateral ECT patients. **Conclusions:** Although generalized tonic–clonic seizures involve widespread regions of the brain, our results suggest that focal regions are activated sequentially, reflecting seizure propagation. Additionally, the activation of frontal and parietal association cortex may explain the profound loss of consciousness seen in generalized tonic–clonic seizures while the sparing of the left temporal lobe seen in right unilateral patients could explain the less severe impairments in verbal retrograde memory we observed in this group. (Supported by Dana Foundation Clinical Hypotheses in Neuroscience Award.)

3.184
VALUE OF SISCOM (SUBTRACTION ICTAL SPECT CO-REGISTERED TO MRI) IN PRESURGICAL EVALUATION OF EPILEPSY: A PROSPECTIVE STUDY

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Rationale: In presurgical evaluation of patients with epilepsy-discordant results or nonlesional MRI might complicate diagnostic workup. Ictal SPECT especially when postprocessed with interictal SPECT and MRI (SISCOM) might be an additional useful diagnostic tool. We examined the prospective value of SISCOM in presurgical evaluation with either nonlesional MRI or discordant results in semiology, EEG recordings, MRI, and/or neuropsychological testing. **Methods:** 55 patients with medically intractable epilepsy undergoing presurgical evaluation were included. 26 patients showed no abnormalities in MRI, five patients showed a doubtful lesion only, 18 patients showed lesional MRI, and six underwent an epilepsy surgical intervention before with unsatisfying outcome, but postoperative MRI showed no abnormalities besides the postoperative defect. At least in those patients with lesional MRI, results of EEG, MRI, semiology, and/or neuropsychological testing were discordant. SPECT imaging was performed with a CERASPECT (Digital Scintigraphics, Inc., Waltham, MA) with a FWHM of 6–8 mm. The field of view diameter was 214 mm and the matrix size was 128 × 128 resulting in 64 images with cubic voxel dimensions of 1.67 mm. A 3D-T1-weighted MRI dataset was performed on a 1.5 T ACS-NT system (Philips, Best, The Netherlands). SISCOM was claculated with ANALYZE PC 3.0 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). **Results:** 64% showed a focal hyperperfusion, 24% a multifocal hyperperfusion, and 13% could not be calculated because of insufficient quality of ictal SPECT (e.g., due to movement artifacts); 25% of the results with focal hyperperfusion were localized in the insular, 34% were localized in the temporal lobe, and 20% were localized in the frontal lobe. In 11 patients, intracranial electrodes were implanted according to the SISCOM results, nine ECoG results were concordant to the SISCOM localization, and two were discordant to SISCOM. In three patients with concordant and one with discordant ECoG/SISCOM results, surgery could not be performed due to high risk or a too widespread seizure-onset area. In 13 patients who underwent surgery so far, SISCOM was concordant/discordant to site of surgery in 10 of 11 patients. In two patients who underwent surgery, SISCOM could not be calculated. **Conclusions:** In presurgical epilepsy evaluation of difficult cases, SISCOM can provide helpful additional information to create a successful hypothesis for intracranial electrode placement. Furthermore, as SISCOM localized in about 1/4 of cases with focal hyperperfusion to eloquent areas, it might also identify patients who are inoperable. However, as SISCOM is a very time- and manpower-consuming diagnostic tool, it can be offered to a restricted number of patients only. Further investigations are necessary to evaluate the value of the variables as, for example, significance of multifocal results, injection latency, duration of seizure, type of seizure, or test–retest reliability.

3.185
SUBTRACTION ICTAL SPECT IN NEOCORTICAL EPILEPSY: THE ANALYSIS OF CLINICAL USEFULNESS AND FACTORS AFFECTING THE RESULTS

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Rationale: To demonstrate the role of subtraction ictal SPECT coregistered with MRI (SISCOM) in surgically treated neocortical epilepsies, authors investigated the localizing value and the related clinical factors affecting the results of SISCOM. **Methods:** Interictal/ictal SPECT and SISCOM images were retrospectively analyzed in 56 patients with neocortical epilepsy, who had undergone resective surgery with documented outcomes (Engel class I, II, III with follow-up duration >2 years). SISCOM images and side-by-side ictal–interictal SPECT evaluation were classified by two blinded reviewers as localizing or nonlocalizing. The results of SISCOM were analyzed according to the related clinical factors (seizure-originating lobe, MRI finding, ictal surface and invasive EEG pattern, radiotracer injection time, and presence or absence of generalized tonic–clonic seizure at the time of radiotracer injection). **Results:** SISCOM images were more often localizing than traditional side-by-side SPECT evaluation with marginal significance (27 of 56 vs. 18 of 56; 48.2% vs. 32.1%; $p = 0.08$). Logistic regression analysis showed rapid radiotracer injection obviously increased the likelihood of localized hyperperfusion ($p < 0.05$). Nineteen of 32 patients (59.4%) without generalized seizure at the time of injection had localizing SISCOM, but eight of 24 (33.3%) with generalization ($p = 0.05$). Intracranial initial ictal rhythm involving more than four of recorded electrodes during invasive monitoring tended to increase the yield of SISCOM ($p = 0.06$). Different ictal-onset lobe, absence or presence of lesion in MRI, and ictal surface EEG pattern did not affect SISCOM results. **Conclusions:** The localization of neocortical seizure foci may be powered by using SISCOM images. The usefulness of SISCOM is affected by radiotracer injection time, supported by the relationship between the absence of generalized seizure at the injection time and SISCOM localization. Sufficient ictal-onset areas may facilitate the visualization of localized hyperperfusion. (Supported by Seoul National University Hospital.)

3.186
MAGNETOENCEPHALOGRAPHY IN TEMPORAL LOBE EPILEPSY: SOURCE CHARACTERISTICS, LOCALIZATION, AND SURGICAL OUTCOME

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Rationale: EEG and magnetoencephalography (MEG) source imaging techniques provide noninvasive localization of the seizure focus. We sought to evaluate the characteristics, localization, and outcome predictive value of interictal and ictal magnetic sources in a series of temporal lobe epilepsy (TLE) patients evaluated for epilepsy surgery. **Methods:** We performed simultaneous scalp EEG/MEG recordings on a consecutive series of 26 TLE patients being evaluated for epilepsy surgery at the Northern California Comprehensive Epilepsy center at the University of California, San Francisco, between 1996 and 1997. Scalp EEG was obtained from 21 channels (10-20 international system), whereas MEG was recorded from two 37-channel sensors. Subsequently, we performed source analysis of the spike magnetic fields and early magnetic seizure discharges by using a single equivalent dipole model and coregistered modeling dipoles to the brain MRI. We assessed spike and seizure magnetic field evolution as well as the modeling dipole location and orientation and correlated these findings with intracranial EEG, neuroimaging and 2-year postoperative outcome. **Results:** Twelve patients had predominantly basal vertical or anteromesial oblique dipoles underlying early MEG spike activity. Mesial temporal onset was recorded in two of 12 patients during invasive EEG monitoring. All 10 of 12 patients who underwent surgery had successful outcome after selective amygdalohippocampectomy (AHC) or standard anteromedial temporal lobectomy (AMTL). Eleven patients demonstrated anterior horizontal or tangential dipoles to the anterolateral inferior temporal tip modeling early spike activity. Temporal mesial or entorhinal onset was recorded in two of 11 patients on intracranial EEG. In those 10 patients undergoing surgery, successful outcome was observed in nine patients after AMTL. The other patient failed selective AHC, but became seizure free after AML as well. Three TLE patients demonstrated predominantly lateral vertical tangential dipoles. Intracranial EEG onset in all three patients was localized to the temporal neocortex, and all patients had successful outcome after temporal neocortical lesional or nonlesional resection. We recorded ictal MEG in two of 26 patients and this included 12–32 s of the ictal onset. Ictal MEG lateralized the seizure onset and source analysis was concordant with interictal MEG localization in both patients. In one patient who underwent invasive EEG recording, ictal MEG source localization concorded with intracranial EEG localization to the entorhinal cortex. **Conclusions:** Early spike and seizure MEG source modeling reveals specific dipole patterns that provide clinically useful information in TLE. Interictal as well as ictal MEG source localization predicts intracranial EEG onset and can optimize surgical outcome after epilepsy surgery for intractable TLE. MEG is a useful functional and noninvasive technique in localizing the seizure onset particularly in complex intractable TLE or when planning more restricted resections for controlling temporal lobe seizures. (Supported by NIH-ROI-NS31966-01.)

3.187
LOCALIZING VALUE OF ICTAL MEG IN NEOCORTICAL EPILEPSY

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Rationale: To investigate the localizing value of ictal MEG recordings in patients with neocortical epilepsy. **Methods:** As part of the presurgical evaluation of patients with intractable localization-related epilepsy of neocortical origin, MEG recordings lasting ≥30 min were recorded using a 148-magnetometer whole-head MEG in a magnetically shielded room. Thirty-two channel digital EEG recordings were simultaneously collected. Seizures and interictal spikes on MEG were analyzed using single equivalent current dipole modeling and mapped onto the patient's coregistered MRI. MEG localization was compared to other presurgical diagnostic testing and postsurgical outcome in those who have had surgical resections. **Results:** We have recorded seizures in six patients, 8–31 years old, with neocortical epilepsy. Three of them have had resective surgery. On neuroimaging, two of the patients had a focal area of cortical dysplasia and one had generalized atrophy, worse in the hemisphere of ictal onset. Ictal MEG localizations were confirmed by subsequent intracranial EEG monitoring. One patient had a left frontotemporal lobe resection, one had a left temporoparietal resection sparing part of the epileptic focus, which extended into language cortex, and one had a left paracentral lobule resection. Prior to surgery each of the three patients was averaging 10–40 seizures per day. All three have had a dramatic improvement in seizures with simple partial seizures but no complex partial or secondarily generalized seizures in two and only two seizures in the past year in the third. Two of the three other patients are scheduled for intracranial monitoring, and the third has declined surgery. **Conclusions:** Ictal MEG has been useful in determining the site of implantation of intracranial electrodes and has accurately predicted the site of ictal onset in those who have had intracranial monitoring. Resection of the MEG ictal zone has been associated with good surgical outcome. Ictal MEG and concordant noninvasive diagnostic studies may some day replace intracranial EEG monitoring in selective patients with neocortical lesions. (Disclosure: Grant: Norman Tepley: 4D Neuroimaging.)

3.188

SAM COMPARED WITH ECoG IN CHILDREN WITH FOCAL CORTICAL DYSPLASIA

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Rationale: Accurate localization of the epileptic zone is important for a successful outcome from epilepsy surgery. Patients with focal cortical dysplasia (FCD) had clusters of magnetoencephalography (MEG) spike sources within and extending from the lesion on magnetic source imaging (MSI). Synthetic aperture magnetometry (SAM) is a spatially constrained minimum-variance beamformer for MEG and provides three-dimensional images of cortical power changes within specific frequency bands. The purpose of this study was to compare the localization of certain frequencies in the interictal discharges detected by SAM with the location of ictal rhythmic discharges identified by electrocorticography (ECoG) in children with intractable partial seizures secondary to FCD. **Methods:** MEG data were obtained using a whole-head helmet-shaped 151-channel SQUID sensor array (Omega 151, CTF Systems Inc.) in a magnetically shielded room. We recorded MEG for 30 min in three children with intractable partial seizures secondary to FCD and analyzed interictal discharges by using SAM. The first step was to compute the covariance of the data, with bandpass filter of delta (1–4 Hz), theta (4–8 Hz), α (8–15 Hz), β (15–30 Hz), and γ (30–60 Hz) bands. At each bands SAM weights were computed at 5-mm intervals throughout the entire MR images. We recorded subdural EEG with split screen video monitoring to localize the seizure-onset zone. We analyzed ictal subdural EEG data at same frequency bands using gaussian wavelet frequency analysis at the most active subdural electrodes in the FCD. **Results:** The wavelet frequency analysis revealed various frequencies in ictal stages, but accumulated beta band in two patients, gamma band in one at the time of seizure onset. The interictal SAM analysis demonstrated high z value in alpha (two patients), beta (three patients), and gamma (one patient) frequency bands. SAM delineated the anatomic location of those frequencies corresponding to the seizure-onset zone defined by subdural EEG. **Conclusions:** SAM analysis of interictal MEG discharges and ictal recordings on subdural EEG in patients with FCD agree in frequency and extent of epileptogenesis. SAM data from interictal MEG discharges may delineate the intrinsically epileptogenic FCD at the specific frequency band.

3.189

CORRELATION-BASED ALIGNMENT OF MULTICHANNEL MEG SIGNALS AND APPLICATION TO CLUSTERING OF PAROXYSMAL EVENTS

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Rationale: One of the common features of physiologic time-series is the abundance of noise that can mask or distort events such as interictal spikes and epileptic seizure onsets. This can hinder the automatic classification of epileptiform events. One way to reduce the influence of noise is to extract the essential information from a given type of events by recording a large series of those events and subsequently clustering them according to some distance measure. Such a procedure is meaningful only when the signals are defined in the same measurement frame where they can be compared and where those belonging to the same clusters can be averaged. **Methods:** We propose a new approach to the problem of classification of time events in multichannel signal recordings. An essential phase of such a classification is the alignment of the different events, or in more general terms, the transformation of the data to a common reference time frame. The common reference frame was reconstructed applying time-translation based on delayed mutual correlation functions of the individual events. The proposed method is applicable to more complicated cases such as seizure onsets. To validate our technique and to compare it with the standard clustering techniques we used a signal-to-noise measure defined in each time point as the ratio between the channel-averaged standard deviation between the members of a given cluster and the interchannel standard deviation of the cluster-averaged signal. In addition, we used a single moving dipole localization method to compare the results. The method is applied to 151-channel magnetoencephalograph (MEG) data sets recorded from four epilepsy patients showing epileptiform discharges: two patients had focal epilepsies, and another two had photosensitive epilepsy. One patient of the latter group had photically induced absences. **Results:** We were able to find three clusters of 19, 14, and 12 of total of 50 frontal spikes, two clusters of eight and nine of 18 temporal spikes, one cluster of six of nine photoinduced occipital spike and waves discharges (SWD) and a cluster of six of 11 onsets of photoinduced 3-Hz spike and wave absence seizure. In all cases, the merits of the proposed signal-alignment paradigm were quantified by the signal-to-noise ratio of the corresponding clusters. In the case of the photically induced SWD, the traditional method failed to cluster simultaneously the spike and the slow-wave components of the signal while the new technique succeeded. In the case of absence-seizure onsets, the alignment and clustering technique showed a common onset template. This last result was only possible to achieve with the new technique as the traditional, feature-based alignment could not be applied for complex events. **Conclusions:** Our method represents an improvement relative to the usual clustering methods where signal alignment is based on the identification of some local feature. The quality of the classification is validated by the signal-to-noise ratio analysis. Dipole localization solutions can be positively affected by our method for cases with plausible single-dipole source. (Supported by SEIN, Scientific Research, Heemstede, The Netherlands.)

3.190

COMPARISON OF CLONIDINE TO SLEEP DEPRIVATION IN THEIR POTENTIAL ABILITY TO INDUCE SPIKE OR SHARP-WAVE ACTIVITY

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Rationale: The aim of the study was to investigate previously observed side effects (i.e., increased spike or sharp-wave activity in epileptic patients during clonidine medication). This study aims to reproduce this effect in a larger number of epilepsy patients and to test safety and effectiveness of clonidine as spike inducing premedication compared to sleep deprivation. **Methods:** Recording was done using a magnetoencephalographic (MEG) system; 22 patients took part in three sessions. Sessions were either performed after sleep deprivation or after medication with clonidine. For baseline one session was recorded without any of the two activating measures. Target parameter was the number of spikes or sharp-waves during a 30-min data-acquisition period. **Results:** 67% of the patients showed an increase in spike activity after clonidine medication. After sleep deprivation, the number of spikes increased in 33% of the patients. 29% did not show any activation at all. Clonidine was more effective in patients with an epileptic focus in the right hemisphere compared to patients with a focus in the left hemisphere. Serum concentrations ranging between 0.6 and 1.0 ng/ml were most effective. **Conclusions:** Clonidine can be considered as a safe and effective spike or sharp-wave–inducing drug that is superior to the spike-inducing potency of sleep deprivation. (Supported by the ELAN grant from the University of Erlangen-Nuremberg.)

3.191
CORRELATION OF ICTAL MAGNETOENCEPHALOGRAPHY WITH ICTAL ELECTROENCEPHALOGRAPHIC RECORDINGS
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Rationale: MEG may have several advantages over EEG in determining epileptogenic focus. It is less influenced by differences in conductivities of various types of brain tissues. **Methods:** 480 patients underwent MEG testing at Memorial Hermann Hospital between July 1997 until April 2002. In >95% of patients, MEG study was performed as a part of presurgical evaluation for epilepsy. During routine preoperative interictal MEG evaluation in these patients, ictal MEG was fortuitously recorded in 11 patients. In all patients, interictal MEG evaluation was performed using 148-channel whole-head magnetometer with simultaneous EEG recording. Ictal MEG studies were compared to scalp ictal EEG recordings. **Results:** Of the 11 ictal MEG studies reviewed, only five showed reliable recordings adequate for interpretation. All patients also had scalp ictal EEG recordings. Three of five patients with reliable ictal MEG recordings also underwent intracranial electrode evaluation for further delineation of the epileptogenic focus. One of these patients had mesial temporal lobe epilepsy (MTLE) confirmed by intracranial recording. Ictal scalp EEG lateralized to the same hemisphere, but was not well localized at onset. Ictal MEG dipoles in this patient showed a focal temporal onset. The other four had extratemporal onset of seizures. In three of four patients with extratemporal epilepsy, ictal MEG localization was similar to scalp ictal EEG recordings. In the fourth patient, ictal MEG spikes were localized to the left mesial frontal region. However, scalp and intracranial electrode evaluation revealed an indistinct, diffuse EEG onset. **Conclusions:** These results suggest that ictal MEG studies may confirm scalp ictal EEG recordings, further define the epileptogenic zone, reveal a focal onset not seen with scalp EEG.

3.192
MEG SPIKE DIPOLE CLUSTERS HAVE DIFFERENT STATISTICS IN DIFFERENT EPILEPSIES
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Rationale: Knowledge of spike characteristics in frontal and temporal epilepsies are important in presurgical evaluation of epilepsy. **Methods:** We analyzed >300 spikes from >20 patients. Localizations were confirmed by standard protocol in more than half the patients. All had medically intractable partial epilepsy undergoing presurgical evaluation: There were more temporal than frontal. We recorded all spikes using a 100-SQUID, whole-head neuromagnetometer (CTF, VSM, Vancouver) in a magnetically shielded chamber (Vacuum Schmelze, BTI, 4D-Imaging, San Diego). We used the moving single equivalent current dipole model in a sphere to reconstruct the location and orientation of dipoles. All patients had at least five spikes recorded on magnetoencephalography (MEG) to allow calculation of population characteristics for each patient. Results were analyzed using SPSS for standard deviation of spatial location, residual variance, amplitude, and orientation. **Results:** There was a higher standard deviation of localization (larger spatial spread of the cluster) for frontal versus temporal patients ($p = 0.04$). **Conclusions:** The standard deviation of spatial spread of spike dipole clusters may be a promising statistical parameter to help distinguish temporal versus frontal lobe patients. Other statistical parameters also merit further evaluation. (Supported by NIH grant NS20806.)

3.193
MAGNETOENCEPHALOGRAPHIC LOCALIZATION IN NEOCORTICAL EPILEPSY
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Rationale: Our aim was to clarify the utilities and the limitations of recent whole-head magnetoencephalography (MEG) for presurgical seizure localization in neocortical epilepsy. **Methods:** Twenty epileptic foci in 19 patients with intractable neocortical epilepsy were preoperatively examined using whole-head MEG (Neuromag204) system. Data were analyzed using the equivalent current dipole (ECD) method. ECDs were superimposed onto individual sectional and three-dimensional MR images. Seizure localization on MEG was determined by the cluster of interictal spike sources (>10 ECDs) or ictal onset sources, and compared with electrocorticography (ECoG) using chronically implanted electrodes in 18 foci and intraoperative ECoG in two. We evaluated (a) reliability of interictal and ictal MEG, and (b) localization accuracy in the cerebral lateral, medial, and basal surfaces. **Results:** In this consecutive series, MEG determined 18 (90%) of 20 foci from ictal and interictal data. Sixteen (80%) were perfectly concordant with the epileptogenic zone determined by ECoG. MEG obtained 18 interictal spike zones. Those were strictly concordant with the interictal spike zone on ECoG in 17 (94%), and concordant with epileptogenic zone in 15 (83%). Ictal MEG data were obtained in five and identified four foci (80%) except one lateral frontal focus manifesting sudden clinical onset with large movement. Of 14 lateral, three medial, and three basal foci, MEG accurately or nearly identified 14 (100%), one (33%), and three foci (100%), respectively. Two (66%) in the medial surface were failed. **Conclusions:** Recent whole-head MEG is the sensitive examination as the presurgical seizure localization method in neocortical epilepsy. However, there are some limitations in appropriately interpreting interictal or ictal data of some patients, and in localizing the deeply underlying spike sources such in the cerebral medial surface.

3.194
AREAS OF INTERICTAL SPIKING ARE ASSOCIATED WITH METABOLIC DYSFUNCTION
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Rationale: Metabolic dysfunction correlates with frequency of spiking. **Methods:** We performed magnetoencephalography (MEG) and proton magnetic resonance spectroscopy (1H-MRS) on 20 subjects with nonlesional temporal lobe epilepsy. MEG was used to localize the source area of interictal spikes. 1H-MRS measured integrated peak areas for *N*-acetyl compounds (NAA) and choline-containing compounds (Cho) in both hippocampi, the MEG spike zone, and the region contralateral to the MEG spike zone in all subjects. 1H-MRS was also performed in seven controls. **Results:** Fifteen of 20 subjects had a lower NAA/Cho ratio in the MEG spike zone compared to the contralateral homologous region. NAA/Cho was significantly decreased in the MEG spike zone ($p < 0.01$). NAA/Cho ratios were not significantly different between the hippocampus ipsilateral and contralateral to the spike activity. NAA/Cho ratios did not correlate with spike frequency. **Conclusions:** Metabolic dysfunction is present in focal areas of interictal spiking in nonlesional temporal lobe epilepsy. These findings confirm functional abnormalities can be detected in vivo in structurally

normal cortex exhibiting abnormal excitability. At the end of this activity, participants should be able to discuss possible metabolic changes associated with areas of interictal spiking. (Supported by NIH NCRR M01 RR00997-25S3.) (Disclosure: Honoraria: 4-D Neuroimaging.)

3.195
MAGNETOENCEPHALOGRAPHY IN EPILEPTIC PATIENTS WITH WIDESPREAD SPIKE OR SLOW-WAVE ACTIVITY

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Rationale: Epilepsy can manifest itself as a focal or diffuse discharge. Traditionally, epileptic discharges are modeled as single equivalent current dipole (ECD) with EEG or magnetoencephalography (MEG). This model, however, fails to characterize diffuse discharges. We examined whether widespread iterictal discharges (IIDs) of epilepsy patients can be adequately mapped using a new analysis technique, dynamic statistical parametric mapping (dSPM), from MEG recordings, thereby extending the applicability of MEG to a larger population of epilepsy patients. **Methods:** MEG was collected with a 204-channel helmet-shaped system (Vectorwiew system; 4-D Neuroimaging Inc., San Diego, CA) with simultaneous EEG. We made dynamic statistical parametric maps to estimate the cortical distribution of IIDs (*Neuron* 2000;26:55–67). We also underwent single-photon emission CT (SPECT) in interictal period using ^{99m}Tc-HMPAO with a triple detector gamma camera (GCA-9300; Toshiba Medical Inc., Tokyo, Japan). **Results:** We studied two pediatric patients with symptomatic localization-related epilepsy. One patient had widespread spikes at Fp1, F3, C3, F8, Fz, and Cz as IIDs in EEG with complex gestural automatism seizure with a postoperative scar from a resection of a brain tumor in the left frontal lobe. The other had widespread left hemispheric slow-wave activity as IIDs in EEG with complex partial seizure accompanied by sensory auras in right arm and leg. In the patient with widespread spikes, the major activity at the peak of the spikes occurred at the vicinity of the postoperative scar in the left frontal lobe on dSPM. In the patient with hemispheric slow waves, the most active area was located in the left parietal lobe and additional activity was seen in the ipsilateral temporal and frontal lobes. The source estimates correlated well with the ictal clinical manifestation and interictal SPECT findings for this patient. **Conclusions:** We suggest that by means of dSPM, MEG is useful as a diagnostic tool, not only for patients with localized epileptiform activity, but also for patients with widespread spikes or slow waves. (Supported by The MIND Institute.)

3.196
MAGNETOENCEPHALOGRAPHIC LOCALIZATION OF SEIZURES ARISING FROM THE OPERCULUM

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Rationale: To analyze the value of magnetoencephalography (MEG) in patients with seizures of opercular origin in comparison to other noninvasive studies. **Methods:** A review of all surgical cases completed at Henry Ford Hospital since 1993 was performed to identify patients with seizures of presumed opercular origin. Patients who had completed intracranial implantation with recording of typical ictal events, a MEG study, and subsequent focal resection were included. Data obtained from MEG was compared to localizing data obtained from MRI, interictal/ictal SPECT, and scalp EEG (interictal and ictal). **Results:** Two patients were identified (ages 7, 39) with intracranial interictal/ictal patterns suggesting opercular onset (patient 1, right frontoparietal; patient 2, left parietal). Both patients were seizure free at the last follow-up visit (3 months , and 5 years). Noninvasive studies revealed normal MRI, and nonlocalizing interictal SPECT in both patients. Ictal SPECT was only completed in patient 1, but no significant asymmetry in perfusion was evident. Interictal EEG revealed generalized 1.5- to 2.5-Hz spike and slow waves, independent right > left temporal spikes, right frontotemporal slow waves, occasional SP1, F4, and F8 sharps, and right temporal PPDA (patient 1); rare T3 sharps (patient 2). Ictal EEG pattern consisted of a 1.5- to 2.5-Hz generalized spike and slow waves with an initial lead in consistently recorded over the right frontotemporal region in patient 1. No discernible ictal pattern was evident with recorded seizures in patient 2. MEG studies revealed high-amplitude discharges localizing to a large area of the right hemisphere with greatest density in the frontoparietal operculum (patient 1), and a strong concentration of discharges emanating from the posterior left perisylvian region (patient 2). **Conclusions:** Magnetoencephalography may provide key localizing data compared to other noninvasive studies in the presurgical evaluation of patients with partial epilepsy of opercular origin.

Treatment—Surgical (Adult and Pediatric)

3.197
SEIZURE FREEDOM OFF ANTIEPILEPTIC DRUGS AFTER TEMPORAL LOBE SURGERY

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Rationale: Limited data is available on persistence of seizure freedom off antiepileptic drugs (AEDs) after epilepsy surgery. **Methods:** We reviewed seizure outcome in patients who came off AEDs after being seizure free for 2 years after temporal lobe epilepsy surgery. **Results:** Follow-up was available in 45 patients who discontinued their AEDs following epilepsy surgery; 28 (62%) patients successfully discontinued their AEDs with no seizure recurrence; 17 (28%) had seizure recurrence requiring reinstitution of AEDs. **Conclusions:** The majority of patients who are seizure free after temporal lobe epilepsy surgery can successfully discontinue their AEDs.

3.198
THE AMYGDALA AND SEXUAL OUTCOME AFTER EPILEPSY SURGERY: DOES SIZE MATTER?

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Rationale: Previous animal and human studies have shown a specific role in the mediation of sexual function for the temporal lobe, a structure commonly resected for the treatment of intractable epilepsy. Postoperative sexual changes may have important psychosocial consequences, but despite its clinical significance, there has been little research on such changes and the potential underlying mechanisms. We compared the postoperative sexual outcome of patients undergoing temporal lobe resection (TLR) and extratemporal lobe resection (ELR) and examined the relationship between amygdalar volume and postoperative sexual change. **Methods:** Forty-five TLR and 15 ELR patients who underwent surgery at the A&RMC completed a semistructured interview and questionnaire at 1 month to 5 years after surgery. Manual segmentation of both amygdalae was performed on the preoperative MRI scans of patients and 46 neurologically normal volunteers following image registration into stereotaxic coordinate space. **Results:** Postoperative sexual change was significantly more likely in TLR patients (69%) than ELR patients (27%, $p = 0.01$). The amygdalar volume contralateral to the side of resection was larger in TLR patients who reported a sexual increase compared with those who reported a decrease or no change and controls (see Table 1). Analysis of variance

(ANOVA) showed significant differences in right amygdalar volumes between patients with different sexual outcomes who underwent left TLR and controls ($p = 0.00$). Post hoc comparisons revealed that left TLR patients reporting a sexual increase had significantly larger right amygdalar volumes than patients reporting a decrease ($p = 0.01$), or no change ($p = 0.01$) and controls ($p = 0.00$). Similarly, ANOVA showed significant differences in left amygdalar volumes between patients with different sexual outcomes who underwent right TLR and controls ($p = 0.00$). Right TLR patients reporting a sexual increase had significantly larger left amygdalar volumes than controls ($p = 0.00$). Comparisons with patients reporting a sexual decrease or no change did not reach statistical significance ($p = 0.07$ and $p = 0.28$, respectively). **Conclusions:** The findings show that postoperative sexual change is more common after TLR than ELR. They provide support for a specific role of the temporal lobe, specifically the amygdala, in the mediation of sexual function. (Supported by NH&MRC Australia.)

TABLE 1. *Mean amygdalar volumes by sexual outcome in TLR patients*

Sexual outcome	Left TLR (n = 27)	Right TLR (n = 18)	Controls (n = 46)
Left amygdala [mean cc (SD)]			2.59 (0.34)
Sexual increase	2.77 (0.48)	3.23 (0.69)	—
No change	2.62 (0.49)	2.73 (0.50)	—
Sexual decrease	2.87 (0.61)	2.66 (0.36)	—
Right amygdala [mean cc (SD)]			2.47 (0.32)
Sexual increase	3.02 (0.37)	2.96 (0.56)	—
No change	2.53 (0.31)	2.75 (0.28)	—
Sexual decrease	2.43 (0.48)	2.88 (0.40)	—

3.199

MRI-NEGATIVE TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy (TLE) due to mesial temporal sclerosis (MTS) is a well-defined clinical syndrome with recognized clinical, physiological, and neuroimaging features. MTS is the most common pathologic finding in patients undergoing temporal lobectomy for refractory TLE, and such patients have an excellent chance for seizure freedom after surgery. In patients with a normal MRI, the clinical syndrome is less well defined, and the chances of successful surgery are reported to be lower. **Methods:** Twenty-seven consecutive patients with normal MRI scans (MRI-NEG) who underwent temporal lobectomy for refractory TLE were retrospectively identified. Their clinical, electrophysiologic, neuropsychological, neuroradiological, and neuropathological characteristics were compared with patients having MRI evidence of MTS (MRI-MTS) matched for age, sex, and side of surgery. All patients had ≥1 year of postoperative follow-up, with outcomes defined using Engel's classification. **Results:** MRI-NEG patients had later seizure onsets (19.3 vs. 11.1 years) and shorter duration of seizures prior to surgery (13.2 vs. 21.7 years) than MRI-MTS patients. MRI-NEG patients were more likely to be employed than MRI-MTS patients. There were no differences in epilepsy risk factors, seizure semiologies, electrophysiological findings or ancillary neuroimaging data between the groups. MRI-NEG patients were more likely to have pathologic diagnoses other than gliosis or MTS, or to have multiple pathologies, than MRI-MTS patients. 63.0% of MRI-NEG patients and 74.1% of MRI-MTS patients were seizure free after surgery (Engel class 1). **Conclusions:** MRI-negative TLE is distinguished from TLE with MRI evidence of MTS by later seizure onset, shorter duration of epilepsy prior to surgery, and more diverse pathological findings at the time of surgery. Temporal lobectomy should still be considered in these patients, even though the chance of a good surgical outcome may be lower than in patients with MRI evidence of MTS. (Supported by NIH grant RO1-NS31966.)

3.200

LONG-TERM OUTCOME AND QUALITY OF LIFE IN PATIENTS UNDERGOING SURGERY FOR LOW-GRADE TUMOR-RELATED EPILEPSY

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Rationale: Low-grade neoplasms are responsible for ≤20% of cases of medically refractory epilepsy in some series. Tumor resection is known to improve seizure activity and quality of life in the short term. In this study, the reader will learn the long-term outcome of surgery for tumor-related medically refractory epilepsy with respect to seizure control and quality of life. **Methods:** The clinical records of all patients presenting with medically refractory seizures and low-grade gliomas who underwent evaluation at the Mayo Clinic between 1984 and 1990 were reviewed. Medically refractory seizures were defined as disabling seizures that continued despite trials of at least two antiepileptic drugs (AEDs) at therapeutic levels. Patients who underwent a presurgical epilepsy evaluation and tumor resection for the primary purpose of seizure control were included. Of 184 patients with tumor-related epilepsy, 42 met these criteria. Follow-up information was collected by questionnaire, which assessed several factors related to quality of life, tumor management, and seizure outcome. Categoric variables related to pre- and postoperative quality of life were analyzed with $\chi 2$ analysis, and Student's t test was used to compare mean values related to pre- and postoperative seizure frequency and AED use. An "excellent" outcome was defined as a postsurgical score of 4 or less on the modified Engel Classification Scale. **Results:** 31 of 42 patients returned a completed survey, three had died, one refused to participate, three did not return a survey or follow-up phone calls, and four were lost to follow-up. The mean follow-up was 14 years (range, 12–17). The mean monthly seizure frequency preoperatively was 21, the postoperative mean was 1.2 ($p < 0.001$). The mean number of daily AEDs decreased from 1.71 to 0.68 following surgery ($p < 0.001$); 19 of 31 (61%) respondents were seizure-free, and 25 of 31 (81%) had an excellent outcome; eight of 31 (26%) underwent additional surgery for either tumor or seizure recurrence. Nine of 22 (41%) patients old enough to drive prior to surgery did so, compared to 21 of 22 (95%) at present ($p < 0.0002$). Significant numbers of patients reported improvements in cognitive ability, and in the ability to work and socialize following surgery ($p < 0.01$). Emotional well-being and general quality of life were also significantly improved ($p < 0.0001$)' 27 of 29 (93%) respondents expressed general satisfaction with their decision to undergo epilepsy surgery, and 25 of 30 (83%) reported no or mild morbidity related to surgery. **Conclusions:** In this select group of patients who underwent resective surgery for low-grade tumor-related refractory epilepsy, 81% of respondents experienced an excellent outcome with a minimum of 10 years' follow-up. This reduction in seizure frequency correlated with a significant improvement in quality of life. This study may prove useful in counseling patients with low-grade brain tumors and partial epilepsy who are being considered for surgical treatment. (Supported by Department of Neurology Discretionary fund.)

3.201

EPILEPSY SURGERY IN CHILDREN AND ADULTS IN NEW SOUTH WALES, AUSTRALIA

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Rationale: While epilepsy surgery is a successful treatment for intractable partial seizures, many adults undergoing epilepsy surgery have onset in childhood with over a decade of uncontrolled seizures. The objectives of this study are to review the clinical characteristics of children (0–18 years) and adults undergoing epilepsy surgery in a single population and to compare the clinical syndromes, duration of epilepsy, surgical pathology, and outcome between children and adults. **Methods:** A retrospective review of the medical records of children and adults who underwent epilepsy surgery from January 1996 to June 2001 was performed among the five epilepsy surgery centers in New South Wales. Age at surgery, age at seizure onset, duration of epilepsy, surgical pathology, and outcome in terms of seizure freedom were compared between children and adults. Multivariate logistic regression analysis was performed to identify predictors of outcome. **Results:** Thirty one children (3 months–12 years old at time of surgery) and 21 adolescents (13–18 years) were compared with 156 adults (19 years and older). Postoperative follow-up ranged from 6 months to 4.5 years. Mean age at surgery for children was 7.8 years, adolescents 15.8 years, and adults 34 years. Mean duration of epilepsy prior to surgery for children was 5 years, adolescents 8 years, and adults 22 years. Although temporal lobe resections were the most common surgery across the groups (children and adolescents 52%, adults 77%), extratemporal lobe resections were more commonly seen in children and adolescents (19% and 33%, respectively) than in adults (12%). Temporal lobe resections in adults resulted in class I (seizure free) outcome in 63%, and in children and adolescents class I outcome was 78%. Mesial temporal sclerosis was the most common temporal lobe pathology in adults whereas in children, tumors (dysembryoplastic neuroepithelial tumor, ganglioglioma, low-grade astrocytoma), were the most common. Extratemporal resections in adults resulted in class I outcome in 47% whereas in children, class I outcome was 62%. Tumor was the most common extratemporal lobe pathology, followed by cortical dysplasia in both children and adults. There was no statistical difference between children and adults in terms of age at surgery, age at seizure onset, duration of epilepsy, pathology, and outcome. The only independent predictor of good outcome identified by logistic regression in both groups was surgery type. In particular, the odds of a good outcome after temporal lobe surgery were significantly better than after extratemporal lobe surgery. **Conclusions:** Despite the larger number of extratemporal resections and more varied pathology in children, the results of epilepsy surgery are very good. The frequency of seizure-free outcome after epilepsy surgery was similar for children and adolescents and comparable to outcome in adults. A long duration of seizures prior to surgery did not adversely affect outcome in terms of seizure freedom.

3.202
INDICES OF RESECTIVE SURGERY EFFECTIVENESS FOR INTRACTABLE NONLESIONAL FOCAL EPILEPSY

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Rationale: Patients undergoing epilepsy surgery without demonstrable specific lesions have mediocre results. Are there indices distinguishing patients with good results from those with bad? We present an enlarged series compared to a 1997 abstract with longer follow-up. **Methods:** Of 685 patients undergoing focal resection from 1989 to 1999, 70 (10%) had normal or nonspecific histology. These were followed up from 2 to 8.5 years (mean, 3.75 years). All 70 patients had normal neuroimaging and normal or nonspecific histological abnormalities as mild gliosis. **Results:** Among 70 patients with intractable focal epilepsy and no specific lesion, outcome after resective surgery was polarised: 26 (37%) became seizure free (SF), and 27 (39%) were not helped. Eighteen (42%) of standard temporal resections rendered patients SF, somewhat more than eight (30%) of 27 other procedures. To seek reliable prognostic factors the subsequent correlative data compared features of the 26 SF patients with the 27 unhelped. Although ictal semiology helped localize epileptogenesis, it and other aspects of seizure and neurological history failed to predict surgical outcome. However, two aspects of preoperative scalp EEGs correlated with SF outcomes: (a) among 25 patients in whom >50% of clinical seizures arose from the later resected lobe and no other origins, 18 (72%) became SF compared to seven (28%) of 25 with other ictal profiles, and (b) 15 (88%) of 17 patients whose interictal and ictal EEGs lacked features indicative of multifocal epileptogenesis became SF compared to 10 (29%) with such components. The considered need for subdural (SD) EEG lowered SF outcome from 18 (90%) of 20 patients without SD to eight (24%) of 33 with SD; this likely reflected an insufficient congruity of ictal semiology and interictal and ictal scalp EEG for localizing epileptogenesis. Within this SD group, ictal origin from the later resected lobe, determined by two measures of such congruency, increased SF outcome from 12–14% to 40–46%. **Conclusions:** Scalp EEG may help determine which nonlesional patients will benefit from resective surgery. (Supported by Dr. Warren Thomas Blume.)

3.203
SURGICAL TREATMENT OF INDEPENDENT BITEMPORAL LOBE EPILEPSY DEFINED BY INVASIVE RECORDINGS

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Rationale: To further define the role of surgery in patients with intractable bitemporal lobe epilepsy, we studied outcomes and prognostic factors in 12 patients who underwent resective temporal lobe surgery. **Methods:** Patients with intractable temporal lobe epilepsy who had a symmetric bitemporal lobe implantation at the Montreal Neurological Hospital between 1990 and 2000 and a subsequent temporal lobe resection were reviewed. All had at least one seizure recorded independently from both temporal lobes. Patients with extratemporal MRI abnormalities or extratemporal seizure generators were excluded. **Results:** Twelve patients (five male patients) with 236 clinical and over 300 electrographic seizures in video-stereo-EEGs were reviewed. Their mean age at surgery was 34 years (20–57), and mean age at seizure onset was 16.3 years (3–37). Nine underwent a selective amygdalohippocampectomy, and three had an anterior neocortical temporal resection in addition to an amygdalohippocampectomy. Two patients with <1-year follow-up were excluded. Of the remaining 10 patients, with mean 4.5 years' follow-up, three had excellent (class I*) and one had good (class II*) surgical outcome. Of six patients who continue to have seizures (one class III* and five class IV*), three subjectively reported >75% improvement in quality of their life after surgery due to reduced seizure frequency and severity and reduced medications. The only significant differences between patients with excellent and good outcome compared to those with class III and IV outcomes were mean seizure laterality of 91 versus 67.6% and unilateral mesial temporal atrophy versus bilateral atrophy, respectively. No statistically significant difference was seen in age at seizure onset, duration of epilepsy, and precipitating factors. **Conclusions:** We conclude that surgical resection is an option for the treatment of intractable bitemporal epilepsy. The goals of surgery, that is palliation by reducing seizure frequency or, more rarely, seizure freedom, should be made clear prior to surgery. Both outcomes have the potential for improving quality of life for the patient. *Class I: Seizure freedom, Class II: Rare seizure (1–3/year), Class III: >90% seizure reduction, Class IV: <90% seizure reduction.

3.204
SURGICAL TREATMENT OF REFRACTORY EPILEPSY ASSOCIATED WITH SUPRATENTORIAL CAVERNOMA

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Rationale: Cavernomas (CVs) have been increasingly diagnosed as a cause of refractory epilepsy after the extensive use of MRI. Patients

may bear single or multiple lesions. **Methods:** Eighteen patients with supratentorial CVs were studied. Sixteen had single, and two had two CVs. Age ranged from 26 to 52 years, and mean follow-up time was 1.9 years. Eight patients had temporal lobe CV (three lateral and five mesial), and four of these patients (two with lateral and two with mesial lesions) also had mesial temporal sclerosis (MTS). Four patients had parietal, three had frontal, two had occipital, and three had insular lesions. Mean seizure frequency was 2.2 per month. All patients with extratemporal CVs were given lesionectomy including the hemosiderotic periphery of the lesion. Three patients with temporal lobe cavernomas (one mesial, two lateral) have been previously submitted to lesionectomy without amygdalohippocampectomy (AH) in other centers; all patients with temporal lobe CVs were given lesionectomy and AH, except for those previously operated on, who were given AH only. AH was total in patients with MTS and composed the anterior 2.0 cm of the hippocampus in patients with apparently normal mesial structures on MRI. **Results:** All patients except one with a parietal lesion have been rendered seizure free after surgery. This patient with parietal CV had sporadic (one every 2 months) seizures over the first 6 months postoperatively, and then seizures disappeared. Transient (≤3 weeks) dysphasia was noted in two patients: one with a left posterior temporal and one with a large inferior left parietal lesion. **Conclusions:** Lesionectomy and resection of the hemosiderotic periphery are enough to abolish seizures in patients with extratemporal CVs. In patients with temporal lobe CV, the response to such approach seems to yield poorer results, and additional AH is recommended even in patients without associated MTS. Patients with nondominant lesions have no major risk for memory decline. The 2.0-cm AH performed in this series in patients with dominant temporal lobe lesions and no MTS did not aggregate new verbal memory deficits. (Supported by Sao Paulo Secretary of Health.)

3.205
FORNIX ATROPHY AND SEIZURE OUTCOME AFTER TEMPORAL LOBE EPILEPSY SURGERY

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Rationale: Previous studies suggest that 60–80% of patients fulfilling MRI criteria of mesial temporal sclerosis (MTS) can expect a good seizure outcome after temporal lobe surgery. Reasons for surgical failure in those satisfying the MRI criteria are poorly understood. Possibilities include presence of more widespread mesial temporal structural damage, bilateral MTS, and conservative amygdalohippocampal resection. Previous studies done by our group have found concurrent fornix atrophy in 86% with ipsilateral hippocampal atrophy. This reflects analogous pathologic changes to limbic circuit interconnected structures. The contribution of the fornix as an independent preoperative determinant of surgical outcome remains to be validated. This study evaluates the contribution of the fornix as a determinant of seizure outcome in patients with preoperatively detected hippocampal atrophy. **Methods:** We selected patients who had undergone standard anterior temporal lobectomy for intractable temporal lobe epilepsy at the UAB Epilepsy Center between 1994 and 1995 and who had a final diagnosis of mesial temporal lobe epilepsy. Patients with foreign tissue lesions and MRI showing no evidence of hippocampal atrophy were excluded. Using criteria and technique previously published by Kuzniecky et al., 1.5-T MRI study was performed in each patient as part of the presurgical evaluation. Subpial aspiration technique was used for temporal resections. Patients were assessed regularly for postoperative seizure control. All had ≥3 years of follow-up. Outcome was evaluated using Engel's classification. Fisher's Exact test was used to compare categorical data. **Results:** Seventy-three patients (45 women, 28 men; mean age, 32; range, 13–58) were studied. Mean age of seizure onset was 9.7 years, and mean duration of epilepsy was 21.3 years. Eight patients were excluded because of lack of follow-up. Thirty-five (47.9%) patients had hippocampal atrophy on MRI volumetry, and 30 had hippocampal and fornix atrophy. Eighty percent in the hippocampal atrophy group were seizure free (Engel's I) at last follow-up, compared with 73% in the fornix and hippocampal atrophy group ($p = 0.5668$, Fisher's Exact test) **Conclusions:** The existence of fornix atrophy may be secondary to wallerian degeneration from hippocampal cell damage, or as a result of abnormal excitotoxic damage to axonal flow. These findings suggest that identification of fornix atrophy on MRI is not an important preoperative determinant of surgical outcome. To our knowledge, this finding has not been previously reported.

3.206
SEIZURE OUTCOME AFTER EPILEPSY SURGERY IN PATIENTS WITH NORMAL PREOPERATIVE MRI

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Rationale: Patients with normal preoperative MRI have been suggested to have a less favorable prognosis for seizure-free outcome after epilepsy surgery compared to patients with a focal lesion such as hippocampal sclerosis, low-grade tumor, or malformation of cortical development. The results from previous series have been variable.The goal of this study is to determine seizure outcome after epilepsy surgery in pediatric and adult patients with normal preoperative MRI. **Methods:** We retrospectively reviewed patients with normal preoperative MRI who underwent cortical resection for refractory epilepsy at The Cleveland Clinic Foundation between 1994 and 2001. MRIs were assessed as normal by a neuroradiologist prior to surgery, and then reviewed for this study by two blinded epileptologists with a blinded neuroradiologist further reviewing any questionable scans. Clinical, laboratory, and outcome data were collected from medical records. The duration of postoperative follow-up was 1–5 years (mean, 28 months). **Results:** The 23 patients were 3–46 (mean, 20) years of age at the time of surgery. Preoperative seizure frequencies tended to be high: 61% of patients had daily seizures (30% with more than five seizures per day), while remaining patients had weekly seizures. An average of six antiepileptic drugs (AEDs) failed before surgery. Resections were frontal ($n = 19$), temporal ($n = 12$), central ($n = 1$), or multilobar ($n = 1$). Histopathologic analysis of resected tissue revealed cortical dysplasia [$n = 23$; seven (78%) of frontal cases] or nonspecific findings such as mild subpial gliosis [$n = 13$; nine (75%) of temporal cases]. Seizure outcome was similar at 1 year and at latest follow-up; 43% of patients were free of seizures at latest follow-up ($n = 10$), and another 22%($n = 5$) had >90% improvement with one seizure per month to 2 seizures per week. Seizure freedom was achieved for five patients (50%) after frontal lobe resections and for five patients (42%) after temporal lobe resection; 50% of patients with cortical dysplasia on histopathology were seizure free, compared to 38% of patients with nonspecific histopathology. More localized focal abnormalities on scalp EEG, subdural EEG, PET, and SPECT did not further improve, in this highly selected patient population, the likelihood of becoming seizure free (41, 40, 37, and 50%, respectively) **Conclusions:** All of these patients with normal preoperative MRI were selected for surgery based on strong features from other presurgical tests suggesting a focal epileptogenic zone, in the setting of a high seizure burden and medical intractability. Within this highly selected group, seizure outcome was favorable for the majority of patients, although the percentage of seizure-free patients was lower than that typically seen in the setting of some focal MRI lesions such as low-grade tumor or hippocampal sclerosis.

3.207
PARIETAL LOBE EPILEPSY: SURGICAL OUTCOME

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Rationale: Parietal lobe epilepsy is not common, comprising <10% of large surgical series. To elucidate its characteristics and surgical outcome, the authors reviewed their surgical experience. **Methods:** Between September 1994 and August 2001, 36 patients with parietal lobe epilepsy received surgical treatment at Seoul National University Hospital. All the patients underwent resection involving the parietal lobe. Male-to-female ratio was 21:15. Ages ranged from 4 to 38 years (mean, 23 years). Preoperative evaluation included video-EEG monitoring, MR imaging, PET, SPECT, and Wada test. Preoperative diagnosis was variable; parietal lobe epilepsy was the most common (12 of 36, 33.3%), followed by lateral temporal lobe epilepsy (eight of 36, 22.2%), frontal lobe epilepsy (six of 36, 16.7%) in decreasing frequency. Most common seizure type was complex partial seizure (24 of 36, 66.7%), followed by simple partial seizure (seven of 36, 19.4%). MR imaging revealed focal abnormality in the parietal lobe in eight of 36 (22.2%). Postoperative follow-up duration ranged from 9 months to 66 months (mean, 41 months). **Results:** Invasive study was performed in 32 cases, among whom 10 cases received the second invasive study. There was no mortality. Transient neurologic abnormality was observed in five of 36 (13.9%). However, it was recovered in 1 month postoperatively. Postoperative seizure outcome was as follows: 16 seizure-free, one rare seizure, 13 worthwhile improvement, and six no worthwhile improvement. Pathology was diverse, but the most common pathology was cortical dysplasia (28 of 36, 77.8 %). **Conclusions:** Parietal lobe epilepsy is difficult to diagnose preoperatively. However, once diagnosed, it could be surgically treatable with reasonable risk. (Supported by Seoul National University Hospital.)

3.208
CHILDHOOD-ONSET EPILEPSY DUE TO FOCAL CORTICAL DYSPLASIA: WHY OPERATE EARLY?

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Rationale: Focal cortical dysplasia (FCD) is increasingly recognized as a cause of medically intractable epilepsy and often becomes symptomatic early in life. We conducted a retrospective study to compare seizure outcome after epilepsy surgery in patients with FCD operated on within 3 years of seizure onset versus patients operated on after 3 years of seizure onset to address the hypothesis that outcome following surgical intervention in FCD is related to duration of epilepsy before surgical intervention occurs. **Methods:** Pediatric patients were identified from a neuropathology database and included if they had cortical resection for intractable epilepsy at Children's Hospital Boston between January 1990 and June 2000, with at least 1-year postoperative follow-up. Adult patients were identified from the epilepsy surgery database of Brigham and Women's Hospital (January 1990–June 2000) and included in the series if they had neuropathologically proven FCD and a 1-year minimum follow-up. FCD was characterized by loss of usual laminar architecture with large pyramidal neurons scattered through all layers. On the basis of the presence or absence of ballooned cells, we differentiated FCD type I (lack of balloon cells) from FCD type II. Outcomes with respect to epileptic seizures were classified according to the system proposed by Engel and collaborators (1993). **Results:** Thirty patients were divided into two groups based on the duration of epilepsy before surgery; 11 patients had intractable seizures for <3 years (range, 9–29 months; mean, 15 months), and 19 patients had a history of intractable epilepsy >3 years (range, 38 months to 4 years; mean, 19 years). Four patients were excluded because of insufficient follow-up data. Age at onset of epilepsy was slightly lower in patients with FCD type II (median, 2 years 8 months; mean, 4 years 5 months) compared with patients with FCD type I (median, 3 years; mean, 6 years). Localization of dysplastic lesion was temporal in 11 of 26 patients (42%), frontal in seven of 26 (27%), multilobar/frontal (including central region) in four of 26 (15%), posterior multilobar in two patients (8%), parietal in one patient (4%) and occipital in one patient (4%). Patients who had early surgical intervention (group 1) had a frequency of class IA of 88% (eight of nine) at 1 year and 77% (seven of nine) at the last visit. Patients who were referred for epilepsy surgery late in their course (group 2) were seizure free in 47% (eight of 17) of cases at 1 year after surgery and in 41% (seven of 17) of cases at the last visit. The two groups did not differ significantly in type of FCD. In group 1, FCD type I was diagnosed in six of nine (66.6%) and FCD type II in three of nine patients (33.3%), where among the 17 patients of group II, 12 (70.5%) had FCD type I and five (29.5%) had FCD type II. **Conclusions:** We demonstrated that surgery resulted in good seizure control in 14 of 26 (54%) of patients with intractable epilepsy due to FCD. Outcome was most favorable in patients with surgical resection of the FCD within 3 years of onset of seizures. Our data support the strategy of performing early surgery in children with intractable epilepsy secondary to FCD. Delaying surgery reduces the likelihood of eliminating disabling seizures. [Supported by a grant from the National EpiFellows Foundation to MRC, the Lombroso Foundation for Epilepsy Research, and a grant from the NINDS (NS27984) to GLH.]

3.209
FUNCTIONAL HEMISPHERECTOMY IN CATASTROPHIC EPILEPSIES: ROLE OF ETIOLOGY AND EEG ON PROGNOSIS FOR SEIZURE CONTROL

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Rationale: Early consideration of functional hemispherectomy is gaining acceptance in children and adolescents with catastrophic epilepsies associated with predominantly unilateral hemispheral epileptogenic lesions. The role of the specific etiology and of the preoperative EEG findings in anticipating prognosis is, however, still debatable. We wanted to analyze seizure and global outcomes in general and in relation to etiologic diagnoses and preoperative EEG findings in a consecutive series of patients undergoing functional hemispherectomy for hemispheral catastrophic epilepsies. **Methods:** Medical records and surgical outlines were reviewed, and personal or structured telephonic interviews were performed to evaluate etiologic diagnosis, clinical and electrographic variables, and surgical outcome. Four patients had, respectively, nonhemimegalencephalic hemispheral malformations of cortical development (NHMCD), encephalomalacia (EMC), and Rasmussen encephalitis (Ras), while there were three with hemimegalencephaly (HMG) and three with Sturge–Weber disease (SWD). **Results:** Overall, 10 of 15 (66%) and five of eight (63%) patients were seizure free (Engel's class I) at years 1 and 2 after operation, respectively. At year 1, first of three (33%) patients with NHMCD, one of two (50%) with HMG, one of two (50%) with SWD, three of four (75%) with EMC, and four of four (100%) with Ras were seizure free. In the latest analysis, 13 of 15 patients (86%) were considered as globally improved by their parents and teachers. Contralateral EEG epileptogenic discharges were present in six of nine (66%) of those patients who were seizure free at year 1, and in three of four (75%) of those who had persistent attacks (difference not statistically significant). **Conclusions:** Hemispherectomy for hemispheral catastrophic childhood epilepsies can bring forth significantly favorable results, irrespective of the presence of bilateral EEG abnormalities. Favorable results can be achieved in all etiologic groups, although Ras and EMC are more frequently associated with seizure freedom. (Supported by FAPERGS.)

3.210
EVOLVING PRESURGICAL EVALUATION PROTOCALS: TRENDS DERIVED FROM A SERIES OF 600 PATIENTS SUBMITTED TO SURGERY

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Rationale: Epilepsy surgery has undergone major changes over the last 20 years. We report a series of 600 epilepsy patients submitted to surgery trying to stress the trends in dealing with them. **Methods:** Six hundred patients submitted to surgery for refractory epilepsy were studied. Age ranged from 1.5 to 57 years; mean follow-up time was 3.4 years. Five hundreds and thirty-five were submitted to corticectomies; 63 to frontal, 352 to temporal, 19 to posterior quadrant, 36 to rolandic, 20 to multilobar, and 21 to hemispherectomy. Sixty-five patients were submitted to callosal sections. **Results:** Overall, seizure-free rates were 89% for temporal, 86% for frontal, 91% for posterior quadrant, 85% for rolandic, and 71% for multilobar resections. Eighty-nine percent of the patients submitted to hemispherectomy have been rendered seizure free by surgery. The mean reduction of generalized seizures' frequency after callosal section was 80%. Within the temporal lobe series, a marked reduction in the use of electrocorticography, Wada test and seizure's recording was seen over time, and none are considered presently as essential items of the basic workup in patients with MRI-defined mesial temporal sclerosis or other lesions. Within the extratemporal (ExT) series, a marked decrease in the complexity of the preoperative workup in patients with positive MRI findings was also seen; on the other hand, in those patients with negative MRI, who are almost always submitted to invasive recordings, an increase in the number of implanted electrodes was seen, paralleling the need for extensive cortical coverage. The number of patients with ExT epilepsy and normal MRI decreased substantially (presently ~15–20%). **Conclusions:** There is a trend toward simplification of the preoperative workup in patients with positive MRI findings. On the other hand, there remains a pool of patients with normal imaging in whom preoperative evaluation is time and resource consuming, who often have ExT or secondary generalized epilepsy and would generally need invasive recordings. (Supported by Sao Paulo Secretary of Health.)

3.211
SURGERY FOR MALFORMATIONS OF CORTICAL DEVELOPMENT: STRATEGY AND OUTCOME

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Rationale: Malformations of cortical development (MCD) are frequently associated with severe partial epilepsy. Unfavorable outcome after surgical resection has been reported in patients with Taylor-type focal cortical dysplasia (FCD). In other types of MCD, surgical results are difficult to analyze because of unresolved classification issues. **Methods:** Over a 5-year period, a MCD was found in 20 of 130 patients (15.4%) operated for intractable partial epilepsy: Taylor-type FCD in nine, other type of FCD in six, heterotopia in four and schizencephaly in one. Hippocampal sclerosis was associated with the MCD in three cases. Mean age at surgery was 28 years (range, 17–40). Taylor-type FCD was extratemporal in eight cases of nine (frontal in seven, parietal in one, temporal in one), while other types of MCD involved the temporal lobe in eight cases of 11 (pure temporal in six, frontal in two, occipital in one, and occipitotemporal in two). MRI was considered as normal in six cases (30%); however, PET-scan imaging demonstrated a focal hypometabolic area in 18 cases (90%). All patients underwent invasive monitoring using depth electrodes: in all patients with Taylor-type FCD interictal rhythmic spiking activity was recorded from electrodes implanted within the dysplastic tissue. Less typical patterns were observed in other types of MCD. **Results:** Surgical resection of the dysplastic cortex was based on both imaging and invasive monitoring data. Follow-up data of $\geq$1 year were available in 15 patients: all six Taylor-type FCD patients were in Engel's class IA, while only three of the nine patients with other types of MCD were in class I (two were in class IA). Other patients had less-favorable outcome: three in class II, one in class III, and two in class IV. Favorable seizure outcome in Taylor-type FCD was observed in all extratemporal cases with limited resections including the whole dysplastic cortex. In the temporal Taylor-type FCD, a large lobectomy was considered necessary. Less favorable or poor outcome in other types of MCD could be related to limited resection in functional cortex in three patients with occipital or occipitotemporal MCD. In addition, large epileptogenic networks as demonstrated by intracranial recordings could explain surgical failures. **Conclusions:** Taylor-type FCD represent a specific group among the MCD with particular electrophysiologic patterns that help in planning surgical resection. In this group, a complete seizure relief may be expected. Less favorable results on seizure outcome are observed in other types of MCD. [Supported by Public hospital global funding (no specific funding).]

3.212
A SIMPLIFIED METHOD FOR THE PREDICTION OF VERBAL MEMORY CHANGE AFTER RESECTION SURGERY FOR EPILEPSY

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Rationale: Prediction of changes in verbal memory after epilepsy surgery is important, but prediction formulas are not commonly used because of the complexities which are typically involved. The objective of this paper is to present an easily useable method for predicting memory change after epilepsy surgery. **Methods:** Patients were 48 adults (27 women, 21 men) with intractible partial seizures all of whom received resection surgery for their seizures which involved either the left temporal lobe (n = 29) or the right temporal lobe (n = 19). Variables considered as predictors of memory loss included age (mean, 31.96; SD, 11.07), age at onset of epilepsy (mean, 14.90; SD, 12.02), level of preoperative verbal memory (sum of WMS Form 1 Logical Memory immediate and delayed, Paired Associates easy and hard immediate and delayed plus Rey AVLT sum of nine trials; median split into HIGH and LOW groups), mesial temporal sclerosis (PRESENT vs. ABSENT by high-resolution MRI), surgery side vs. side of speech as shown by the Wada or intracarotid amobarbital test (SAME vs. DIFFERENT), Wada memory (three memory-assessment techniques considered as detailed in *Brain Cogn* 1997;33:210–33), and extent of resection (lateral, mesial, hippocampal). All patients received postoperative memory evaluations 11–53 months after surgery (mean, 21.85; SD, 8.40) and the percentage of change in the overall verbal memory score was calculated. Predictive variables were examined individually, and those which made a significant contribution to prediction of memory change after surgery were placed in a stepwise multiple regression paradigm. The results of these variables were then presented in a simplified flow diagram to show memory change. **Results:** Variables demonstrating statistically significant independent relationships with verbal memory change after surgery were as follows (in order of most to least potent): preoperative verbal memory level (HIGH level predicted loss); side of surgery versus side of speech (SAME side predicted loss); hippocampal sclerosis on MRI (ABSENT predicted loss). The other variables did not predict memory change after surgery although Wada memory (Seattle procedure) would have been a significant predictor had not the side of surgery versus side of speech variable been included. Percentage changes in verbal memory were as follows for each combination of the three predictors, respectively: LOW, OPPOSITE, PRESENT +32%; LOW, OPPOSITE, ABSENT, +14%; LOW, SAME, PRESENT –9%; LOW, SAME, ABSENT –7%; HIGH, OPPOSITE, PRESENT +1%; HIGH, OPPOSITE, ABSENT –12%; HIGH, SAME, PRESENT –11%; HIGH, SAME, ABSENT –31%. **Conclusions:** Preoperative verbal memory level, whether or not surgery was on the same side as speech, and presence or absence of mesial temporal sclerosis were the most potent variables in predicting changes in verbal memory after surgery. These variables are easily obtained and when they are considered in a dichotomous fashion, they predict changes in verbal memory with a considerable degree of accuracy.

3.213
CONTEMPORARY EPILEPSY SURGERY EXPERIENCE: 1,425 CASES REVIEWED AT ONE CENTER

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Rationale: Detailed retrospective review of a large series of epilepsy surgical cases for medically refractory epilepsy by one surgeon at one center is reported. To our knowledge, there is no large contemporary epilepsy surgery review from one modern epilepsy surgical team using uniform standards that can be used by another center as a guideline to compare their own outcome with. This report may serve as such a standard. **Methods:** This modern series spans 8 years beginning in 1994. Demographics, outcome, efficacy, complications, surgical indications, classification criteria, and surgical philosophy are discussed. Information presented covers 933 craniotomies, 88 bilateral invasive surveys, 69 single-stage resections, 369 two-stage procedures, 42 three-stage procedures, 305 vagal nerve stimulator operations, and 38 stereotactic procedures. There are 682 unique patients, of which 480 underwent craniotomy. The average age for patients who had craniotomy was 31 ± 12 years ranging from 0.3 to 75 years old; 47% were female. **Results:** Outcome is reported using a slightly modified Engle score. Single-stage resections (primarily anterior medial temporal lobectomy with hippocampectomy) had 91/6/4/0% respectively for Engle 1/2/3/4 outcome with a 76% follow-up. Two-stage procedures involved a period of invasive monitoring prior to resection and yielded an outcome of 64/14/14/8% with a follow-up of 81%. Three-stage procedures yielded outcomes of 50/19/28/3% with 76% follow-up. One-, two-, and three-stage operations produced a decrease in three Engle grades from preop to postsurgical state in 83, 53, and 41% of their associated patients, respectively. The majority of the presented efficacy data has >2-years follow-up. There was no mortality in this entire series, and important morbidity or complications were infrequent. For all of the cranial procedures, there were 15 infections and nine hemorrhages, representing a per craniotomy/per patient relative risk of 1%/1.8% for hemorrhage and 1.6%/3.1% risk for infection. Other noted morbidities are subdural hygromas, hydrocephalus, severe memory deficits, and cranial nerve III injury, respectively, in 0.4/0.8%, 0.1/0.2%, 0.5%/1.0%, and >0.1/0.1% risk. Bone resorption requiring cranioplasty occurred in three patients. No vascular injury, such as damage to the anterior choroidal artery or vein of Labbe, occurred. **Conclusions:** Surgical philosophy was to tailor each case specifically to its unique circumstances, using in-house surgical planning and navigation computer equipment, using custom-designed electrodes to fit smaller cranial exposures, with liberal use of invasive monitoring for EEG characterization of the epileptogenic network and for extraoperative functional mapping, and compulsive techniques to eliminate CSF leaking during invasive monitoring. More detailed and specific information of the demographics, surgical methods, and of the outcome data will be presented. Literature review reveals that our outcome is equal to or above all recently published reports.

3.214
RELATIONSHIP BETWEEN EXTENT OF TEMPORAL RESECTION AND NAMING OUTCOME IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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Rationale: Circumscribed lesions of the language-dominant temporal lobe may lead to significant selective naming dysfunction. Surgery for medically intractable dominant temporal lobe epilepsy (TLE) aims to remove the epileptogenic focus but may lead to naming difficulties. Our objective was to correlate the extent of anatomic resection with naming outcome following temporal lobe resection in patients with a history of drug-resistant TLE. At the end of this activity the participants should be able to discuss the relationship between temporal lobectomy and naming outcome. **Methods:** We retrospectively reviewed the postoperative MRI scans of 163 patients who underwent temporal lobe resection for medically intractable TLE (between 1990 and 2000). The linear extent of resection of the superior (T1), middle (T2), and inferior (T3) temporal gyri, the fusiform gyrus (FUS), parahippocampal gyrus (PHG), hippocampus (HIP) and amygdala (AMG) was measured. All patients were left hemisphere language-dominant as determined by amobarbital testing (WADA). The extent of resection of each region was correlated with the postoperative Boston Naming Test (BNT) outcome. Z-scores were calculated based on the expected changes due to practice effects in a group of normal controls. **Results:** Seventy-three patients underwent surgery for right TLE and 90 had surgery for left TLE. The groups were comparable with regards to demographic variables. There were no significant changes in BNT Z-scores following right temporal lobectomy. Patients who underwent left-sided resection showed an average BNT Z-score decrease of –1.15 ($n = 90$). Patients with complete left hippocampal resection ($n = 18$; Z-score, –2.33; SD, 2.34) had a significantly more severe drop in their BNT Z-scores than patients without hippocampal resection ($n = 10$; Z-score, –0.19; 1.84, $p < 0.019$). To investigate the relative contributions of variable amounts of resected temporal gyri, a stepwise multiple regression analysis was performed. This analysis revealed that the amount of hippocampal resection of the language-dominant hemisphere was significantly related to a decrease in BNT Z-scores ($R = –0.266$; $p = 0.011$). Interestingly, a slightly better predictor of language outcome was the multiplicative hippocampus–fusiform gyrus interaction. This means that the combined extent of resection of these gyri was even more strongly associated with postoperatively impaired naming function ($R = 0.280$; $p < 0.001$). **Conclusions:** Naming deficits appear to occur only following dominant temporal lobe surgery. The resection of the dominant side hippocampus is associated with significant naming decrements. The interaction of fusiform gyrus and hippocampus improved the predictive power of postoperative naming dysfunction in patients who are undergoing dominant mesial temporal lobe surgery.

3.215
PATIENTS WITH PERIVENTRICULAR NODULAR HETROTOPIA AND MEDICALLY INTRACTABLE FOCAL EPILEPSY: SURGICAL APPROACHES AND OUTCOME

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Rationale: Patients with PNH often have intractable focal epilepsy and electroclinical features suggestive of temporal lobe (TL) seizures. All but one of 10 had poor outcome after TL resection (Li et al., *Ann Neurol* 1997;41:662). **Methods:** We reviewed surgical outcome in six patients (four men, mean age at seizure onset, 15.3 years) with PNH. The nodules were bilateral, diffuse and contiguous in one patient (1), unilateral focal in two (2, 3), and bilateral focal in the remaining three (4, 5, 6). **Results:** The first patient (1) had epileptic ictal discharges originating in the right and left hippocampi with an 85% right-sided preponderance. She underwent right selective amygdalohippocampectomy (SAH) with satisfactory outcome after 8 years of follow-up (Li et al, case 5). Patient 2 with focal and unilateral heterotopia had no seizure recorded from a nodule and no interictal spiking arose in it. He had two adjacent occipital nodules, active interictal and ictal discharges from the adjacent occipital cortex (within 2 cm). He had removal of the nodules and part of the overlying occipital cortex. In patient 3, a single nodule was found in the right trigone, and the epileptic discharges originated in the left contralateral, atrophic hippocampus. He underwent left SAH. Both patients 2 and 3 have a 5-year follow-up with a satisfactory outcome. Patients 4 and 5 had focal bilateral temporal–occipital PNH, and showed bilateral and widespread temporo-parieto-occipital interictal and ictal discharges. Patient 6 had in addition scattered nodules along the body of both lateral ventricules, and bilateral epileptic activity. In two the nodules were found retrospectively and in none of these three patients was a nodule explored. They underwent anterior temporal resections and all had poor results (Li et al., cases 3, 4, 6, follow-up 8–15 years). **Conclusions:** Patients with PNH often have "pseudo-temporal localization and epilepsy". This explains the failure of temporal resections in patients with PNH. On the other hand, they may have additional abnormalities such as hippocampal atrophy that act as the primary epileptogenic substrate. When few congruent unilateral nodules are present investigation may suggest a focal resection and good outcome. Dual pathology with mesial temporal resection may also lead to a good result. Some nodules seem inert or not related to epileptogenesis. Bilateral multiple nodules often lead

to widespread epileptogenesis where classical surgical approaches are unlikely to be effective.

3.216
TEMPORAL LOBECTOMY FOR REFRACTORY EPILEPSY IN THE U.S. MILITARY

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Rationale: Epilepsy surgery outcomes have not been previously reported from military institutions. The current study was performed to determine the seizure outcome, quality of life outcome, and predictors of seizure outcome in patients undergoing temporal lobectomy for refractory epilepsy at Walter Reed Army Medical Center, the only U.S. military medical center with a comprehensive epilepsy surgery program. **Methods:** Eighty-one of 84 consecutive patients treated with anterior temporal lobectomy at Walter Reed Army Medical Center between 1986 and 2000 were followed for a minimum of 1 year and a mean of 4 years. Outcome measures included seizure frequency according to the Engel classification system, driving, employment, and use of anticonvulsant medications. The association between seizure outcome and the results of preoperative EEG, MRI, SPECT, and surgical pathology was assessed by univariate analysis. **Results:** Following temporal lobectomy, 90% of patients had improvement in seizures (Engel class 1, 2, or 3) and 70% of patients had remission of seizures (Engel class 1). The driving rate increased from 2.5% to 60% ($p < 0.0001$), the employment rate increased from 35 to 62% ($p < 0.017$), and anticonvulsant use decreased from 2.03 AEDs per patient to 1.26 AEDs per patient ($p < 0.0001$). Five of 10 (50%) patients serving on active duty in the military at the time of surgery achieved complete seizure remission postoperatively and continued to serve in the armed forces. Complications occured in 6% of patients and included hemiparesis, dysphasia, and memory impairment. Interictal epileptiform discharges confined to the ipsilateral temporal lobe, neuroimaging abnormalities in the ipsilateral temporal lobe, and mesial temporal sclerosis on pathology were each associated with postoperative seizure remission. Bilateral interictal EEG abnormalities and normal pathology were associated with a less favorable seizure outcome. **Conclusions:** Temporal lobectomy for refractory epilepsy produces seizure remission and improves quality of life in most patients who undergo this procedure in the U.S. military. The outcomes are similar to those reported from non-military institutions. Seizure remission after temporal lobectomy enables some active duty military personnel to continue serving in the armed forces. (Supported by U.S. Army.)

3.217
OUTCOME FOLLOWING FRAMELESS, STEREOTACTIC, IMAGE-GUIDED, SELECTIVE AMYGDALOHIPPOCAMPECTOMY FOR INTRACTABLE PARTIAL EPILEPSY

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Rationale: Selective amygdalohippocampectomy has been shown to be a safe and effective procedure for patients with intractable partial epilepsy of mesial temporal origin. Utilizing a stereotactic approach may improve patient tolerance of the operation and be associated with a lower postoperative morbidity. At the end of this activity the participants should be able to discuss operative outcome following stereotactic, selective amygdalohippocampectomy. **Methods:** We reviewed the clinical histories, presurgical evaluations, and follow-up of consecutive patients with intractable partial epilepsy of temporal lobe origin who underwent stereotactic, selective amygdalohippocampectomy at the Washington University School of Medicine between 1997 and 2001. The mesial structures were accessed in all patients via a stereotactic middle temporal gyrus approach with hippocampal resection to the level of the colliculi. Patients with lesional epileptic syndromes and those followed for less than 6 months postoperatively were excluded. **Results:** A total of 38 patients were identified (mean age at surgery: 38.6 years; 22 male, 16 female). Thirty-three patients (86.6%) had mesial temporal sclerosis on seizure protocol MRI. Twenty-eight (73.7%) had unilateral concordant, interictal epileptiform activity while 10 patients (26.3%) had bilateral abnormalities. Seventeen patients (44.7%) had a history of febrile convulsions. Twenty-eight patients (73.7%) were seizure free following surgery while 31 (81.6%) experienced an Engel class I–II outcome. Mean duration of follow-up was 16.3 months. MRI identified mesial temporal sclerosis was significantly associated with seizure freedom (27 of 33) compared to patients with normal MRI (one of five; Fisher's Exact test, $p = 0.01$). No perioperative complications occurred in these patients. **Conclusions:** Frameless, stereotactic, image-guided, selective amygdalohippocampectomy is an effective surgical approach for patients with intractable partial epilepsy of mesial temporal origin. The rates of seizure freedom approximate those of commonly used and more invasive temporal lobe surgical procedures. Further research is necessary to determine whether there is significantly improved patient tolerance and decreased utilization of health care resources using this approach.

3.218
TYPICAL SEIZURES INDUCED BY CORTICAL STIMULATION THROUGH IMPLANTED SUBDURAL ELECTRODES ARE PREDICTORS OF GOOD SURGICAL OUTCOME

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Rationale: Cortical stimulation is usually performed as part of the invasive neurophysiological investigation in patients with refractory extratemporal epilepsy and normal or nonlocalizing MRI submitted to subdural electrodes implantation. **Methods:** Twenty patients with refractory extratemporal epilepsy and normal or nonlocalizing MRI submitted to extensive coverage of the brain surface with subdural electrodes were studied. Four patients had anterior quadrant, three posterior quadrant, five hemispheric, four rolandic, and four bifrontomesial epileptic syndromes. The number of electrodes ranged from 64 to 256. Mean follow-up time was 1.6 years. Cortical stimulation was carried out in the awake patient with square pulses at 100 Hz, 0.1 ms duration, and 4–8 mA. **Results:** The patient's habitual seizures could be triggered by stimulation of one to three electrodes in 13 of 20 patients. In one patient with supplementary motor area (SMA) epilepsy, seizures could be elicited from both SMA areas. Overall, 75% of the patients were rendered seizure free by surgery. Ninety-three percent of the patients in whom the habitual seizures were obtained during cortical stimulation have been seizure free, while 40% of the patients in whom no seizures were triggered did so. There was no major neurologic morbidity or mortality related to cortical stimulation. **Conclusions:** Cortical stimulation is safe and very effective in triggering the patients' habitual seizures when an extensive coverage of the brain surface was used. Misdiagnosis or failure to induce seizures are very likely to occur in patients with limited or erratic coverage of the cortical surface with invasive electrodes. Seizures were generally elicited from a very small number of electrodes. Patients in whom the habitual seizures were elicited by cortical stimulation had a better surgical outcome. (Supported by Sao Paulo Secretary of Health.)

3.219
MESIAL TEMPORAL SCLEROSIS AND OUTCOME AFTER ANTERIOR TEMPORAL LOBECTOMY

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Rationale: Anterior temporal lobectomy (ATL) is an accepted form of treatment for patients with intractable temporal lobe epilepsy (TLE).

Magnetic resonance imaging (MRI) evidence of mesial temporal sclerosis (MTS) has been shown to predict seizure-free outcome postoperatively. We wanted to evaluate patients with TLE and MTS who underwent ATL but did not become seizure free. After this program, participants should be able to appreciate characteristics of patients with TLE and MTS who do not become seizure free after ATL. **Methods:** All patients undergoing ATL for intractable TLE at the Duke Epilepsy Center between 1985 and 2001 were reviewed. Patients that had MTS on presurgical MRI and continued to have seizures postoperatively were enrolled. Clinical characteristics of these patients were noted. **Results:** A total of 13 patients were identified that met inclusion criteria. All had histologically proven hippocampal sclerosis. The mean age of onset of epilepsy was 13.5 years; the mean age at the time of surgery was 35.9 years. The mean duration of follow-up was 4.6 years. Eight of 13 (62%) patients had <10 seizures per year after ATL. Five of 13 (38%) patients had >10 seizures per year after TLE surgery. All patients had complex partial seizures postoperatively; three patients also had generalized tonic–clonic seizures. Eight (62%) patients had a history of febrile seizures. Ten (77%) patients had a left ATL, whereas only three (23%) had a right ATL. **Conclusions:** Not all patients with MRI evidence of MTS become seizure free after ATL. There do not appear to be remarkable differences in these patients in comparison to those who are seizure-free after ATL (as reported in literature), other than a higher proportion of patients undergoing left ATL in this group.

3.220
OUTCOME FROM TEMPORAL LOBECTOMY FOLLOWING INVASIVE EEG MONITORING IN PATIENTS WITH DISCORDANT NONINVASIVE PRESURGICAL STUDIES

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Rationale: Temporal lobectomy for medically intractable epilepsy results in a high success rate for seizure reduction when noninvasive presurgical evaluation shows concordant data. We sought to determine the surgical outcome of patients with clinically suspected temporal lobe epilepsy who underwent invasive EEG monitoring after discordant scalp video EEG monitoring and neuroimaging studies. **Methods:** Forty-three patients were evaluated for temporal lobectomy with invasive EEG due to discordant noninvasive data.Followup ranged from three months to six years. Scalp EEG, MRI, PET and SPECT findings were analyzed to determine the predictive value of these studies in terms of surgical candicacy following invasive EEG and seizure free outcome in those who underwent temporal lobectomy. Patients were analysed in the following groups: Group A, seizure free postop, group B, persistent seizures postop, group C, no resective surgery due to inadequate localization of seizure onset. **Results:** Thirty patients (70%) underwent temporal lobectomy after invasive EEG monitoring of whom 17 (56.6%) became seizure free (group A). Thirteen patients (30%) did not have resective surgery (group C). Group A (seizure free) showed abnormalites on MRI in 53%, PET in 67%, and SPECT in 57%. Group B (persistent seizures) showed abnormal MRI in 46%, PET in 54%, and SPECT in 77% of patients. In group C (no resective surgery due to inadequate localization of seizure onset), abnormalities were seen on MRI in 23%, PET in 54%, and SPECT in 82%. **Conclusions:** Temporal lobectomy following invasive EEG monitoring after discordant noninvasive data can result in significant seizure reduction. Structural and nuclear neuroimaging studies do not show high predictive value for seizure-free outcome postoperatively in these patients.

3.221
INTRAOPERATIVE ECoG AND FRAMELESS STEREOTACTIC-GUIDED SINGLE-STAGE SURGERY FOR CORTICAL DYSPLASIA

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Rationale: Cortical dysplasia is a common pathological substrate of medically intractible neocortical epilepsy. Because of the previously documented intrinsic epileptogenicity of human dysplastic cortex (Palmini et al.), we have adopted a single-stage surgical approach to many patients with cortical dysplasia. **Methods:** Patients with medically intractable, scalp EEG lateralized neocortical epilepsy and MRI-documented cortical dysplasia were managed with a single-stage surgical approach. Intraoperative electrocorticography (EcoG) and MR-based frameless stereotaxy were used to delineate the electrophysiologic and anatomic areas of abnormality, respectively. **Results:** Fifteen patients (age 1–24 years) were managed by this approach. Intraoperative ECoG identified patterns of ictal or continuous epileptiform discharges (I/CEDs). With ≥24 months of follow-up (range, 24–64 months), eight patients are seizure free (Engel class IA), three have rare seizures, and three have ≥75% reduction in seizure frequency. Seven of eight seizure-free patients had complete resection of their anatomic and electrophysiologic areas of abnormality. Of the non–seizure-free patients, four of seven had incomplete lesion resection, while three of seven had incomplete resection of the electrophysiologically abnormal area. The extent of the dysplastic abnormality affected outcome: six of nine patients with lesions limited to one lobe were seizure free in contrast to two of six patients with multilobar lesions. **Conclusions:** A combination of intraoperative electrophysiologic and frameless stereotactic-guided anatomic localization can be used to carry out single-stage epilepsy resections in many patients with cortical dysplasia. This approach avoids the need for electrode implantation and provides at least comparable results. If the anatomical lesion and area of I/CEDs can be completely resected, excellent outcome can be anticipated.

3.222
SIGNIFICANCE OF INTERICTAL EPILEPTIFORM ACTIVITY AFTER SELECTIVE AMYGDALOHIPPOCAMPECTOMY

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Rationale: The mechanism of temporal spike generation in patients with temporal lobe epilepsy (TLE) is not fully understood. We attempted to determine the significance of the pre- and postoperative interictal epileptiform activity (IEA) and its relation with surgical outcome in patients with medically refractory TLE who underwent selective amygdalohippocampectomy (SAH). **Methods:** We retrospectively reviewed the records and EEGs of TLE patients from the Montreal Neurological Hospital and Institute database with medically refractory epilepsy who had transcortical SAH. Inclusion criteria were (a) patients with nonlesional TLE; (b) at least one preoperative routine EEG showing IEA; (c) at least two postoperative EEGs; and (d) a minimum of 1 year follow-up. Patients who had insufficient data, a foreign-body, congenital or vascular lesion, or multiple or palliative surgeries were excluded. Patients were classified as being seizure free (Engel's class Ia) or having persistent seizures (classes Ib–IV). **Results:** Among 170 patients who underwent SAH between 1985 and 2001, we identified 55 (25 men; mean age ± SD at seizure onset, 13.2 ± 8.7; at surgery, 35 ± 12; at last evaluation, 41.9 ± 11.7) who fullfilled the inclusion criteria. Etiological factors were described in 29 patients: febrile convulsions, 18; and head trauma, meningitis, family history of epilepsy, pre- or perinatal, four each. Forty-two patients had unilateral and six bilateral hippocampal atrophy (HA), six had a normal MRI, and in one patient, MRI was not available. The number ± SD of preoperative EEGs were 6.5 ± 4.0 and of postoperative EEGs, 2.8 ± 1.4. Mean follow-up was 4.3 years (range, 1–11.5). Twenty-four patients had IEA in at least one postoperative EEG. Twenty-two of them had persistent seizures after SAH compared to two seizure-free patients ($\chi 2$ test, Yates corrected, $p = 0.013$). There were no significant difference between the postoperative spiking and nonspiking groups with respect to the following variables: age at onset of seizures and at surgery, duration of follow-up, number of pre- and postoperative EEGs, etiologic factors and proportion of patients with HA. **Conclusions:** In nonlesional TLE patients who underwent SAH, a large fraction of them have persistent postop-

erative IEA. This activity is probably not the result of mesial TL epileptogenesis and when these spikes are present it is very likely that patients will continue to have seizures. Therefore, neocortical epileptogenesis must play an important role in TLE.

3.223
EARLY ANTIEPILEPTIC DRUG REDUCTION FOLLOWING ANTERIOR TEMPORAL LOBECTOMY FOR MEDICALLY INTRACTABLE COMPLEX PARTIAL EPILEPSY

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Rationale: The goal of anterior temporal lobectomy (ATL) in medically intractable complex partial epilepsy is a seizure-free status. Once this is achieved, a secondary goal is reduction in number and dosage of antiepileptic drugs (AEDs), in order to reduce the burden of associated side effects. **Methods:** Thirty-one patients underwent ATL for medically intractable complex partial epilepsy at Loma Linda University Medical Center (LLUMC) from December 1991 to November 2001. In a retrospective review, patients were considered "seizure-free" if they did not experience complex partial seizures while taking the prescribed medications until AED reduction was initiated, or until the time of most recent clinic or mail follow-up. We provide descriptive data of the patients, their outcomes, and the timing and results of AED reduction in patients rendered seizure free. **Results:** Twenty-five of the 31 patients became seizure free on their preoperative AEDs after one operation (81%). Three other patients required additional ipsilateral temporal lobe resection to become seizure free. AEDs were not reduced in these three patients. AEDs were increased in two patients to control simple partial seizures. AEDs were reduced in the remaining 23 patients (74% of the 31 patients). Their characteristics were similar to those of the entire group. Follow-up averaged 2.9 ± 2.4 years (mean ± standard deviation [M+/-SD]) after surgery. AED reduction was initiated 4.7 ± 7.2 (M ± SD) months after surgery. This occurred within 1 month of surgery in 43% of patients, within 2 months in 65%, within 6 months in 84%, and within 12 months in 91%. As a result, polytherapy use dropped from 61% preoperatively to 22% 6 months postoperatively, rising slightly to 26% at last follow-up. Seizures emerged in six patients who followed the AED reduction as prescribed. Seizures stopped in five of these patients after AEDs were increased or alternative AEDs introduced. Medication adjustment continues in the sixth patient. **Conclusions:** Early medication reduction to ameliorate side effects was successful in most patients who became seizure free after ATL. Early reduction of AEDs was initiated in response to patients requests. Once they became seizure free, they were unwilling to tolerate the same burden of AED side effects that they accepted when they were experiencing seizures preoperatively. We conclude that early, gradual, postoperative medication reduction in patients who become seizure free after ATL may be accomplished with relative safety to the degree needed to ameliorate AED side effects.

3.224
SEIZURE OUTCOME AFTER TEMPORAL LOBECTOMY IN 381 ADULT PATIENTS: THE CLEVELAND CLINIC EXPERIENCE (1991–2001)

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Rationale: Intractable temporal lobe epilepsy (TLE) is the most common presentation for epilepsy surgery. Published studies of patients who underwent anterior temporal lobectomy (ATL), showed seizure free rate of 60–70% at 6 months and 52–58% at 2 years. **Methods:** A retrospective study of the seizure outcome in patients who underwent temporal lobectomy at the Cleveland Clinic between 1991 and 2001 was performed. The records of 427 adult patients (age older than 18 years) were reviewed. Only patients with documented seizure outcome (≥6 months of postoperative follow-up) and in whom pathological diagnosis was available were included in the study. Average age at the time of surgery was 32 years (range 18–65 years). There were 193 female and 234 male patients. Engel's classification for seizure outcome was used for outcome assessment **Results:** Follow-up was available in 381 patients. Overall 273 of 381 (71%) patients were seizure free (Engel's class I) at the last follow up (>6 months), and 39% continued to have seizures (Engel's class II, 11%, III, 6%, IV, 12%). The seizure-free outcome relative to the underlying pathology was as follows: HS (74%), tumors (77%), cortical dysplasia (69%), nonspecific changes/other diagnosis (69%). **Conclusions:** Our results in a large group of adult TLE patients operated on at the same institute after 1991 show an improvement in seizure outcome of 71%. A significant seizure control (Engel's class I and II) was achieved in 82% of patients. In addition, seizure outcome was not related to the pathological diagnosis. Studies to identify the predictors of both success and failure in seizure control after ATL are under way. At the end of this activity, the participitants should be able to discuss the outcome of temporal lobectomy performed at our institute between 1991 and 2001.

3.225
LONGITUDINAL COGNITIVE OUTCOME IN CONSERVATIVELY OR SURGICALLY TREATED CHILDREN AND ADOLESCENTS WITH FOCAL EPILEPSIES

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Rationale: To evaluate the longer-term impact of treatment (medical vs. surgical) and seizures on cognition in children and adolescents with pharmacoresistant focal epilepsies. **Methods:** 17 medically and 54 operatively treated children/adolescents (mean age, 12 ± 3 years) had follow-up evaluations between 2 and 12 years (mean, 5 years). Groups were not randomized to treatment and differed at baseline with respect to seizure severity, age at onset and duration of epilepsy, pathology, and lateralization of epilepsy. 63% of the operated-on children had temporal lobe epilepsy (conservative, 59%). The medical group had two (T1 baseline/T3 long-term) and the operated-on group three evaluations (T1 baseline/T2 1 year/T3 long-term). Patients were evaluated with respect to seizures, drug therapy, cognition (attention, memory, language, visuoconstruction), school/job/carreer, quality of life, and behavior. **Results:** 72% of the operated-on patients became seizure free, and 22% had >50% seizure reduction (medical: 12% seizure free, additionally 47% responders). AED had been withdrawn in 37% of the operated-on patients, and 18% changed from polytherapy to monotherapy (medical group 6%). At baseline (T1), 30–50% of the patients showed impairment in one or more cognitive domains, an earlier onset, grand mal seizures, polytherapy, and greater seizure frequency being associated with poorer performance levels. At the long-term follow-up (T3), attention and higher cognitive functions improved in the medical group (20–36%) and even more in operated-on patients (62–65%). Losses in these functions were rare (2–14%). As for memory, a comparabe number of patients in both groups showed deteriorated (35% medical, 39% operated) or improved (both groups 41%) performance at the long-term follow-up (T3). In the operated-on group, memory losses were more frequent (55 vs. 25% gains) immediately after surgery (T2). However, there was a considerable number of children who showed improved memory later on in the time between T2 and T3 (52 vs. 27% losses). Predictors of a better cognitive long-term outcome were better baseline performance, better seizure control, temporal lobe surgery, and surgery at younger age. Within the temporal resection group, two of three resections and selective surgery caused more memory impairment than lesionectomies. After surgery, and particularly when patients became seizure free, superior outcome was also observed with respect to career, behavior, self reported mood, and QOL. **Conclusions:** Epilepsy surgery is very successful in achieving sustained freedom from seizures and reduction or withdrawal of AED in children with chronic epilepsy.

Cognition and behavior show significant improvement particularly after temporal lobe surgery and when seizures are successfully controlled. As in adults, memory is most vulnerable to epilepsy surgery. Although, in the long run, surgical defects can be largely compensated, it appears that even younger patients are often operated too late. Thus, early surgery should be considered in order to prevent mental retardation due to uncontrolled chronic epilepsy on the one hand and loss of acquired functions due to late surgery on the other hand. [Supported by Deutsche Forschungsgemeinschaft DFG (EL-122/6-2).] (Disclosure: Grant: The study was supported by the Deutsche Forschungsgemainschaft DFG.)

3.226
TRANSIENT POSTOPERATIVE NEUROLOGIC DEFICIT AFTER SUPPLEMENTARY MOTOR AREA RESECTION

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Rationale: Supplementary motor area (SMA) resection is a commonly performed surgical procedure in epilepsy surgery. A postoperative transient neurologic deficit has been reported in 0–100% of patients. **Methods:** Retrospective review of postoperative neurologic deficit in 10 patients after SMA resection for epilepsy surgery. All patients underwent intracranial EEG monitoring with coverage of the SMA. Resections were tailored to EEG onset. **Results:** All patients had a postoperative deficit. Eight patients (80%) had a functional motor deficit of the contralateral extremities. In all of those patients this predominantly involved the lower extremity. Seven patients (70%) patients had a speech and language deficit. The postoperative deficit lasted between 2 and 65 days (mean, 13.3 days). The longest deficits were seen in a 20-year-old (21 days) and a 59-year-old patient (65 days), both with cortical dysplasia. Three other patients with cortical dysplasia had shorter deficits. The pathology of the remaining patients showed normal tissue (three), gliosis (one), and previous hemorrhage (one). All postoperative deficits resolved completely, and patients did not have detectable functional motor or speech deficits on neurologic examination in follow-up. All patients underwent intracranial functional motor mapping and the primary motor cortex was preserved in all patients. Eight patients (80%) were seizure free, one Engel class II and one Engel class IV due to a complication of a dural leak. **Conclusions:** After SMA resection for epilepsy surgery, a postoperative motor and speech deficit can be expected. Patient should be well aware of this complication before undergoing epilepsy surgery. Deficits are transient. Factors that determine extent and length of deficit are not clear. (Supported by Hitchcock Foundation.)

3.227
LONG-TERM OUTCOME OF MOOD AND PSYCHOPATHOLOGY FOLLOWING EPILEPSY SURGERY

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Rationale: Although research has established predictors of mood and psychopathology in adult populations with epilepsy, these long-term outcomes have not been well investigated in young adults with onset of epilepsy in childhood, nor have they been examined after early surgery. The objective of this study was to examine these variables in a group of young adults who had epilepsy surgery in childhood and a nonsurgical epilepsy control group. **Methods:** Twenty-four male (21 surgical and three nonsurgical) and 40 female (28 surgical and 12 nonsurgical) individuals with epilepsy of childhood onset, age 18–29, participated in this study. Sixteen individuals in the surgical group and all individuals in the nonsurgical group have experienced seizures in the past year. All subjects completed two questionnaires measuring the individual's psychological and physical well-being. The Profile of Mood State (POMS) is a self-administered adjective rating scale that provides information about mood and feelings people may experience. The Symptoms Checklist Revised (SCL-90-R) is a 90-item self-report symptom inventory designed to reflect a respondent's psychological and psychiatric symptoms. **Results:** Stepwise regression analyses demonstrated that predictors contributed in the following way (all p values <0.05): The surgical group was less prone to depressive symptoms on the POMS ($R^2 = 0.06$), phobic anxiety ($R^2 = 0.06$), and number of expressed symptoms ($R^2 = 0.21$). The presence of seizures was predictive of higher degrees of somatization ($R^2 = 0.12$), confusion and bewilderment ($R^2 = 0.11$), hostility ($R^2 = 0.10$), and the global severity score of the SCL-90-R ($R^2 = 0.09$). Females reported higher levels of hostility ($R^2 = 0.09$) and symptom distress on the SCL-90-R ($R^2 = 0.06$). Greater numbers of antiepileptic drugs (AEDs) were predictive of obsessive–compulsive traits ($R^2 = 0.09$), symptom distress on the SCL-90-R ($R^2 = 0.09$), and depression ($R^2 = 0.07$). Among individuals who underwent surgery, greater number of AEDs was predictive of obsessive–compulsive traits ($R^2 = 0.13$) and symptoms of depression ($R^2 = 0.09$). Females reported higher levels of fatigue ($R^2 = 0.13$). The presence of seizures was predictive of confusion and bewilderment ($R^2 = 0.22$), the SCL-90-R symptom distress score ($R^2 = 0.18$), hostility ($R^2 = 0.16$), somatization ($R^2 = 0.12$), and the SCL-90-R global severity score ($R^2 = 0.10$). The proportion of the individual's life with epilepsy, as well as seizure localization and lateralization did not contribute to the predictive model. **Conclusions:** These results provide preliminary support that epilepsy surgery in childhood reduces the risk for symptoms of psychological distress during early adulthood, in those individuals who are seizure free. At the end of this study, participants should be aware of the variables that predict psychopathology and mood disturbance in young adults with childhood onset epilepsy, and the effects of childhood surgery on these outcomes. (Supported by Ontario Mental Health Foundation.)

3.228
OUTCOMES OF SURGERY IN PATIENTS WITH PARADOXICAL TEMPORAL LOBE EPILEPSY

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Rationale: A paucity of data exists on patients with apparent medial temporal lobe epilepsy (MTLE) but whose MRI scans do not disclose mesial temporal sclerosis. This entity has been termed paradoxical temporal lobe epilepsy (PTLE). In this study, seizure outcomes following intracranial electrode monitoring and resective surgery in these patients is examined. **Methods:** Ten consecutive patients (ages 16–62 years) were included in this study who fulfilled the following criteria: normal brain MRI scan using high-resolution techniques, video-EEG monitoring with scalp and sphenoidal electrodes demonstrating temporal onset, and intracranial electrode monitoring. Bilateral hippocampal depth and temporal subdural strip electrodes were placed when the laterality was in question, in six patients. Unilateral temporal recording with a grid array, subdural strips, and a hippocampal depth electrode was performed when the laterality was known but medial versus lateral localization was unclear, in four patients The average time of follow-up is 9.8 months (range, 1–23 months). **Results:** Unilateral hippocampal seizure onset was observed in five of the six patients with bitemporal monitoring, with bilateral independent hippocampal seizure onsets in one patient. Of the four patients with unilateral monitoring, seizure onsets were in hippocampus alone in one, hippocampus and parahippocampal gyrus in one, hippocampus, parahippocampal gyrus, and orbitofrontal cortex in one, and parahippocampal gyrus in one. Eight patients underwent anteromedial temporal resections (one with additional orbitofrontal resection), and two patients underwent transsylvian selective amygdalohippocampectomy. Pathological analysis revealed mild MTS in five, moderate MTS in two, severe MTS in two, and was normal in one. Overall, nine patients are seizure free, and one patient has moderate improvement. **Conclusions:** Medial temporal resection in patients with PTLE may result in excellent seizure-free outcomes. Intracranial electrode monitoring is recommended because of the possi-

bility of neocortical seizure onset or bilateral temporal onsets. Further study of this patient population is required to elucidate the relationship of this entity to medial temporal lobe epilepsy caused by mesial temporal sclerosis.

3.229
PALLIATIVE TEMPORAL RESECTION IN BIOCCIPITAL LOBE EPILEPSY

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Rationale: Temporal resection is usually ineffective in patients with occipital seizures. When seizures are unilateral occipital resection are now at times considered. When bilateral seizures and field defect exist occipital resection can not be considered. When temporal seizure onset can be shown in such patients, palliative temporal resection may be justified. **Methods:** We report two patients with medically refractory bilateral occipital lobe seizures. Clinical and electrophysiologic patterns suggested spread to temporal lobe structures. Long-term EEG video monitoring was followed by stereoencephalography to assess involvement of temporal and occipital regions symmetrically. **Results:** Both patients had nonlateralized elementary visual aura followed by loss of contact, automatism and occasionally secondary generalization. The MRIs of the brain revealed bilateral parietooccipital ischemic lesions without concomittant temporal volumetric abnormalities. They had bilateral or unilateral altitudinal field defects. Scalp EEGs showed independent bilateral temporal or temporooccipital interictal epileptic abnormalities. Scalp ictal recording in one patient revealed bilateral temporal seizure onset. The second patient had bilateral occipital or left parietooccipital onsets. Intracranial EEG recordings showed multifocal interictal epileptic abnormalities. In both, all disabling seizures originated in, or rapidly spread to the right hippocampus. Since occipital resections were unadvisable both patients underwent selective amygdalohippocampectomy. Seizures continued in both (2-year follow-up) but were much less severe, not associated with falling, shorter, less frequent, not followed by fatigue or headache, and with faster recovery. **Conclusions:** When occipital resection is unadvisable because of bilateral or diffuse visual problems, palliative temporal resection may be considered in patients with lesional bilateral occipital lobe epilepsy and rapid seizure spread to mesial temporal structures.

3.230
SURGICAL OUTCOME AFTER LEFT SELECTIVE AMYGDALOHIPPOCAMPECTOMY VERSUS TAILORED LEFT TEMPORAL LOBECTOMY

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Rationale: Selective amygdalohippocampectomy is an attractive surgical alternative to standard temporal lobectomy in patients with hippocampal sclerosis, because it spares lateral temporal structures and obviates the need for language mapping. It is not clear if amygdalohippocampectomy is associated with a less favorable surgical outcome. **Methods:** We reviewed seizure outcome in patients with dominant mesial left temporal lobe epilepsy and hippocampal sclerosis by MRI, who had epilepsy surgery at our institution. We included patients who had a tailored left temporal lobectomy after subdural grid implantation and those who underwent selective amygdalohippocampectomy through a transcortical approach. We included only patients with ≥ 1 year of follow-up. An image-guided transcortical approach to the temporal horn was performed for all selective amygdalohippocampectomies. **Results:** 23 of 29 (79%) of patient with a tailored temporal lobectomy had excellent seizure outcome (Engel class I), compared to eight of nine (89%) patients with selective amygdalohippocampectomy. No patient had persistant language disturbance after either selective amygdalohippocampectomy or standard lobectomy 1 year after surgery. **Conclusions:** Transcortical selective amygdalohippocampectomy is a safe and effective alternative to tailored temporal lobectomy in patients with dominant hemisphere mesial temporal epilepsy with hippocampal sclerosis. At least a similar outcome was reached, without invasive language mapping.

3.231
LONG-TERM OUTCOMES OF HEMIDECORTICATION IN CHILDREN

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Rationale: Hemidecortication has been performed for several decades to treat intractable unihemispheric epilepsy. A prior case series focused on the outcomes after 58 surgeries at our institution in 1997. At the end of this activity the participants should be able to discuss the long-term outcomes of hemidecortication. **Methods:** Charts were reviewed and families were contacted of the 106 hemidecortications performed by the Pediatric Epilepsy Center from 1975 to 2001. Follow-up ranged from 6 months to 22 years. Three children were unavailable for follow-up. Pre- and postoperative neuropsychological test results were available for 53 subjects, with a mean interval between surgery and most recent evaluation of 5.4 years (SD, 5.05). **Results:** Three children died in the immediate perioperative period; two children died several years later due to intractable seizures. Overall, 63% are seizure free, 22% have occasional, nonhandicapping seizures, and 15% have residual, troublesome seizures. The average patient is taking 0.67 medications and has 89% improvement in seizure frequency; 88% of patients are able to walk without assistance; 63% of patients with Rasmussen and 79% of those with congenital strokes were seizure free, compared to 50% of those with cortical dysplasias (40% of hemimegalencephaly specifically). The overall mean presurgical IQ was 68 (SD, 27) and follow-up IQ was 65.9 (SD, 25). IQ change was not significantly related to etiology of seizures (Rasmussen/cortical dysplasia) or to side of surgery. The most significant predictor of IQ at follow-up was presurgical IQ. **Conclusions:** Hemidecortication continues to be a beneficial procedure in reducing seizure frequency in cases of unilateral cortical epilepsy. The large majority of children have both seizure and medication reduction without major impact on ambulation. Children with Rasmussen syndrome and congenital strokes had a better response than those with dysplasias. There was no change in IQ after surgery, nor was change in IQ related to etiology. (Supported in part by funds for the Roxanne Fellowship.)

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3.232
PREDICTORS OF SOCIAL ADJUSTMENT AFTER PAEDIATRIC EPILEPSY SURGERY

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Rationale: Families of children with intractable epilepsy who are surgical candidates perceive surgery as an opportunity to improve their child's overall health. One of the areas comprising child health is that of social experience. The objective of this study is to ascertain what changes children experience in their social adjustment one year after epilepsy surgery using a unique blend of quantitative and qualitative findings. Another objective is to examine pre surgical predictors of social adjustment 1 year after surgery. **Methods:** The participants included 23 children who received surgery (mean age, 13.3 years) and a matched cohort of 18 children with intractable epilepsy but who did not undergo this procedure (mean age, 13.0 years). Data were collected

prospectively, at baseline, and 1 year after surgery. Three subscales from the parent rated Child Behaviour Checklist that address social adjustment were chosen for this analysis. Repeated measures analysis, controlling for age and sex was conducted to examine change by group over time. Given the exploratory nature of this study, bivariate analysis of epilepsy, child and family correlates of social adjustment at time 2 was also conducted. These were submitted to stepwise regression to ascertain time 1 predictors of functioning at time 2. In addition, ethnographic interviews were conducted with parents at both times during which they were asked to reflect on their child's social experience. These interviews were coded and analyzed using NVIVO. **Results:** There is no difference in the change in social functioning experienced by children in the surgical group when compared to the comparison group. Significant epilepsy correlates ($p < 0.05$) of social adjustment at time 2 included proportion of life with seizures ($r = –0.322$), frequency of seizures at time 1 ($r = –0.447$), and seizure outcome at time 2 ($r = –0.33$). Performance IQ was associated with social problems ($r = –0.285$). Family variables included state and trait anxiety ($r = –0.391$; $r = 0.304$), family active orientation ($r = 0.4$). The strongest predictor of two of the indicators of social adjustment is the same indicator at time 1. Family Active Orientation predicted the Activities scores on the CBCL. Seizure frequency at time 1 and seizure outcome predicted an additional 13.7% and 8.5% variance, respectively. It is important to note that in the surgical group, being seizure free was associated with more social problems. **Conclusions:** Children undergoing epilepsy surgery do not experience any major improvement in their social functioning. With the exception of family active orientation, the strongest predictor of how well children will do socially after surgery is how well they are doing before surgery. In addition, those who have more frequent seizures at time 1 and those who experience better seizure control have more difficulty in this area of health. The qualitative findings illuminate some of the processes involved in this finding and suggest that children return to the same peer context after surgery and so assume the same social position. Furthermore, their improved attunement to their social world may cause them to connect with and experience some of the harsh realities they are faced with such as isolation, bullying and teasing. (Supported by Ontario Mental Health Foundation.)

3.233
THE QUALITY OF LIFE OF CHILDREN FOLLOWING EPILEPSY SURGERY

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Rationale: The quality of life (QOL) of children following epilepsy surgery has received little attention in the literature. Previous pediatric studies exclusively evaluate the effect of seizure outcome on QOL without considering other important clinical variables. The aim of this study was to determine the factors that were predictive of improved QOL outcomes. A second aim was to provide further external validation of the psychometric properties of the Quality of Life in Childhood Epilepsy questionnaire. (QOLCE) (Sabaz M, et al. *Epilepsia* 2000;41: 765–74). **Methods:** The study design was a retrospective cross-sectional analysis with the entry criteria being children (age 4–18 years) who had epilepsy surgery at Miami Children's Hospital >12 months ago. Parents were asked to complete the QOLCE. Demographic variables included family income, ethnic origin, marital status and parental education level. Clinical factors included, for example, age at surgery, duration of epilepsy, cognitive ability, surgical site, pathology and outcome. Univariate analysis of these variables correlating with the total QOL scores and subscales was performed. **Results:** Fifty-five children were enrolled, 28 boys. The mean age at surgery was 8 years with a mean duration of epilepsy of 5.3 years. The postoperative outcomes were that 31 children were seizure free, and nine had a >90% reduction. Univariate analysis of clinical variables revealed only seizure outcome as a significant factor in predicting total QOL score. Seizure freedom or a >90% reduction in seizures postepilepsy surgery explained 35% of the variance of the total QOL scores ($p = 0.001$). There was no significant difference between the seizure free and >90% seizure-reduction groups. The QOL domains that surgery outcome significantly influenced were physical restrictions, energy/fatigue, perception of general health, social activities and other cognitive processes ($p < 0.003$). A longer duration of epilepsy prior to surgery did not have a negative effect on QOL scores. No other demographic or clinical factor exerted a significant effect. **Conclusions:** Children who achieve a greater than 90% reduction in seizures following epilepsy surgery have a significantly higher QOL as measured by the QOLCE. No other clinical or demographic variables significantly influenced outcome. This study further validates the QOLCE as a specific instrument sensitive to the measurement of quality of life change following epilepsy surgical intervention. [Supported by National Health and Medical Research Council (Australia) (grant number 209512).]

3.234
EPILEPSY SURGERY OUTCOME AMONG UNITED STATES VETERANS

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Rationale: Epilepsy surgery is an effective therapy for patients with refractory epilepsy of temporal origin. The veteran population is biased toward older age at onset of epilepsy and other comorbidities including substance use or other psychiatric diagnoses. We retrospectively studied the outcome of anterior temporal lobectomy (ATL) among a population of veterans and evaluated outcome related to co-morbidities. **Methods:** The database at the Veterans Memorial Hospital, in Madison, WI was used to identify patients who underwent ATL for intractable epilepsy between 1990 and 2000. Chart review was conducted on all identified patients, who were contacted to review their clinical history and obtain their seizure history and vocational status. End points measured were postoperative seizure outcome, current quality of life using the QOLIE-31 questionnaire, and vocational status. Multiple regression analysis evaluated factors associated with outcome. **Results:** A total of 29 patients underwent ATL. Two of the patients died postsurgically and therefore were not included in the study. The mean age at onset was 25 years (±10.2). Mean duration of epilepsy prior to surgery was 16.5 years (±8.9), and mean age at surgery was 43.8 (±8.7). Fifteen patients underwent left ATL, and 12 right ATL. The pathological diagnoses were mesial temporal sclerosis with or without heterotopias (16), vascular malformations (three), contusion (one), infarct (one), and six patients had either normal hippocampus tissue or nonspecific findings. Seven of the 27 (26%) had a presurgery history of a nonsubstance abuse psychiatric diagnosis (depression, posttraumatic stress disorder, personality disorder, psychosis, or anxiety disorder). Eight of 27 (30%) had a history of substance abuse prior to surgery (three of these eight had an additional psychiatric diagnosis). Eighteen of the 27 (67%) had a good outcome [Engel's class I (56%) or class II (11%)], and the remaining nine patients (33%) had poor outcome (class III or IV). There was no difference in the frequency of good outcome among the patients with a history of substance abuse (63%), other psychiatric diagnosis (71%), or no psychiatric diagnosis (67%). There were significant correlations between seizure outcome and quality of life score ($r = 0.67$, $p < 0.001$) and postop vocational status ($r = 0.48$, $p = 0.01$). **Conclusions:** In this study of veterans who underwent ATL, seizure outcome was consistent with that reported in the literature for the general population. Although the sample size was small, the data suggest that post-ATL seizure outcome can be satisfactory among veterans even in the context of the late mean age of epilepsy onset and the psychiatric diagnoses that were present in this sample.

3.235
REOPERATION AFTER FAILED PRIMARY LESIONECTOMY IN PATIENTS WITH REFRACTORY EPILEPSY
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Rationale: The adequate management of brain lesions associated with refractory epilepsy has been intensively discussed over the years. Series favoring lesionectomy alone or including margins have been published. A recent extensive meta-analysis suggested that additional margins should be included in the resection. The method for margin determination has varied among centers but intraoperative electrocorticography has been the preferred option. **Methods:** Nine adult patients with refractory epilepsy previously submitted to lesionectomy in other center were reoperated. Three patients had meningioma (frontal convexity, sphenoid wing and parietal parasagital, respectively), three had temporal lobe cavernoma (one mesial, two lateral), and three had low-grade glioma (two parietal and one temporal). The patients with meningioma and glioma were submitted to additional resection guided by intraoperative electrocorticography. The patients with temporal lobe cavernoma were submitted to additional corticectomy up to the level of the central artery and amygdalohippocampectomy, without electrocorticography. Mean seizure frequency was two/week. Mean follow-up time was 1.3 years. **Results:** All patients previously operated for cavernoma and meningioma have been rendered seizure free after reoperation. Two of the patients with glioma have been seizure free after surgery. There was only a 50% improvement in seizure frequency in the third patient with glioma. This patient had a xanthoastrocytoma and presented with malignant deterioration of the lesion 8 months after surgery and is now undergoing adjunctive radiotherapy and chemotherapy. **Conclusions:** Lesionectomy alone may fail to eliminate seizures in patients with preoperative refractory epilepsy. Combined seizure and anatomic surgery should be offered to the patient whenever technically possible. If lesionectomy alone would be performed, the patient should be aware the a second procedure might be necessary to take care of seizures. (Supported by Sao Paulo Secretary of State.)

3.236
SURGICAL OUTCOME FOR TEMPORAL LOBE EPILEPSY IN THE PEDIATRIC POPULATION
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Rationale: To evaluate seizure outcome in children undergoing surgery for intractable temporal lobe epilepsy. **Methods:** Eight children who underwent temporal resections for intractable partial onset epilepsy between 1997 and 2001 at University of Michigan were studied. Clinical features including age at onset; duration of epilepsy; seizure semiology; interictal/ictal EEG; MRI findings; pathologic substrate, and seizure outcome were identified. **Results:** Seizures were characterized primarily by loss of awareness and automatisms. A single patient also had nocturnal myoclonic jerks. The average age of seizure onset was 8 years (range, 2 and 17 years). . MRI showed hippocampal sclerosis (three), hippocampal sclerosis and focal cortical dysplasia (one), and an enhancing temporal lobe lesion (four). Interictal EEG identified unilateral temporal spikes (six), bilaterally independent spikes (two). One patient with unilateral temporal spikes also had myoclonic jerks and generalized spike-and-wave discharges. Pathology revealed hippocampal sclerosis (three), cortical dysplasia (one) patient and low-grade tumors with or without associated hippocampal sclerosis (four). Two of the three patients with hippocampal sclerosis identified by MRI and histo pathology, had class III A outcome, and the third had a one class I B outcome (Engel classification). The remaining five patients are seizure free at 1 or 2 years of follow-up. **Conclusions:** Temporal lobe epilepsy surgery in children offers an exceelent chance of seizurefreedom which seems to be best correlated with complete resection of the abnormality identified by imaging studies and the noninvasive EEG evaluation.

3.237
QUANTITATIVE MRI (qMRI) PREDICTS SURGICAL OUTCOME FOLLOWING TEMPORAL LOBECTOMY FOR REFRACTORY EPILEPSY
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Rationale: Patients with medically refractory temporal lobe epilepsy can be successfully treated with surgery. However, ≤30% of even the most suitable candidates, with concordant electroclinical data and apparently isolated hippocampal sclerosis, are not rendered seizure free following surgery despite complete resection of the visualised lesion. Preoperative identification of these patients would avoid exposing them to the risks of surgery and allow for more rational use of resources. qMRI can reveal subtle structural abnormalities not seen on visual inspection of optimised MRI, which may reflect underlying epileptogenic tissue, and be useful as a prognostic indicator in these patients. **Methods:** We analysed T1 volumetric images of 74 consecutive patients from our epilepsy surgery program and 100 age/sex-matched controls. All patients had isolated unilateral hippocampal volume loss on preoperative MRI and pathologically proven hippocampal sclerosis. Fully automated postprocessing of MR data were performed to obtain measures of regional grey/white matter distribution. The data was segmented using SPM99, a probabilistic anatomical atlas registered to each subject data set and the volumes extracted. Regional grey and white matter volume was corrected for brain size and the normal range defined from the control data. Processing time for each patient was <1 h. Surgical-outcome data were collected blind to MRI and pathology data. In 38 subjects, quantitative pathological measures of cortical and white matter gliosis were obtained blind to MRI and clinical data. The presence of extralesional qMRI abnormalities was correlated with surgical outcome. **Results:** The mean postsurgical follow-up period was 36 months (SD, ±11 months); 44 patients had quantitative abnormalities of grey and white matter distribution; in 23 patients, there were additional extralesional abnormalities. Only eight of these 23 patients were seizure free (Engel class Ia) at follow-up. 28 seizure-free patients had no extralesional abnormalities. The sensitivity of qMRI was 39% and specificity 78% (positive predictive value, 0.65). Extending the seizure-free group to include Engel class I and II, those with worthwhile improvement, the sensitivity increased to 62%, with a specificity of 79%. There was no significant correlation of abnormal qMRI measures or postoperative outcome with quantitative pathologic measures. **Conclusions:** Abnormal qMRI can guide post surgical prognosis. Only eight of 23 with abnormal qMRI were seizure free postoperatively, whereas 40 of 51 patients with a normal qMRI achieved a Engel class I outcome. We did not find a correlation between qMRI and quantitative pathological measures. This suggests that the volume differences detected are not merely reflective of a gliotic process secondary to seizures. Our automated method provides a fast, reliable, objective method that could be a valuable prognostic tool in the presurgical evaluation of patients with hippocampal sclerosis. New methods have been developed to detect occult epileptogenic foci, but none has been proven to provide prognostic information. [Supported by MRC (U.K.).]

3.238
REFRACTORY EPILEPSIES WITH PERIROLANDIC EPILEPTOGENIC ZONES: ETIOLOGIES, CONTRIBUTION OF INTRACRANIAL RECORDINGS, SURGICAL TECHNIQUES, AND OUTCOME
Fabiana Mugnol, Andre Palmini, Eliseu Paglioli-Neto, Jaderson Costa da Costa, Eduardo Paglioli, Victor Martinez, Mirna Portuguez, Ney Azambuja, Gilberto Trentin, Ligia Coutinho, Sergio Raupp, and João-Rubião Hoefel-Filho (Porto Alegre Epilepsy Surgery Program, Hospital São Lucas da PUCRS, Porto Alegre, RS, Brazil)

Rationale: Refractory seizures with a sensorimotor semiology suggestive of an epileptogenic zone (EZ) around the rolandic sulcus are often seen in patients referred for preoperative evaluation. There is hardly a consensus on how to evaluate these patients and whether they may or may not be suitable surgical candidates. We wanted to define the spectrum of etiologies of medically refractory perirolandic epilepsies, and to address some debatable issues pertaining to neurophysiological evaluation and surgical candidacy. **Methods:** We reviewed the medical and surgical records and personally interviewed 17 operated-on patients whose preoperative seizure semiology and noninvasive EEGs were strongly suggestive of an EZ around the rolandic sulcus. Patients were followed up from 1 to 9 years (mean, 5.18). Seven had subdural strips and grids to further localize the EZ and eloquent cortex. Resection of the lesion and of the putative EZ were rated as complete or partial. Outcome was analyzed according to Engel's classification. **Results:** MRI showed lesions in 12 of the 17 patients (70.5%). Eleven of the 15 (64.7%) in whom both pathology and MRI were available had malformations of cortical development (MCDs: nine Taylor-type focal cortical dysplasia, one non-Taylor FCD, and one hemimegalencephaly). Three others had gliotic lesions and one had a normal pathological examination. Intraoperative cortical stimulation was performed in 12 patients, and elicited functional responses in eight (66.6%). Overall, six patients (35.3%) were in outcome class I, and all the others were in classes III or IV, including four of the five (80%) MRI-negative patients. Two of the seven patients (28.5%) in whom subdural electrodes were implanted were seizure free, while the same results were achieved by four of the eight (50%) who had only noninvasive evaluation. Complete resection of the lesion was feasible in only four of the 12 patients (33.3%) in whom MRI identified a structural lesion. Three of them are seizure free (75%), contrasting with only one of the other eight (12.5%) who had only partial resections ($p < 0.05$). **Conclusions:** MCDs are the foremost etiology of medically refractory perirolandic epilepsies and, not unexpectedly, surgical outcome is heavily related to the feasibility of complete lesion resection, often precluded by functional constraints. Subdural electrode implantation had no positive impact on outcome. (Supported by FAPERGS.)

3.239
THE OCCURRENCE OF ONE OR TWO SEIZURES AFTER A TEMPORAL RESECTION FOR EPILEPSY DOES NOT NECESSARILY HERALD THE RECURRENCE OF MEDICALLY REFRACTORY SEIZURES

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Rationale: After temporal lobe resection for epilepsy, some patients have a recurrence of seizures after a seizure-free period. Although often an emotionally upsetting event, there may be only one or two seizures in the year of recurrence. The objective of this study is to determine how often this recurrence of rare seizures represents a return of medically refractory epilepsy. **Methods:** Data from our earlier study of a 5- and 10-year follow-up outcome of 93 patients with medically refractory temporal lobe epilepsy treated with surgical resection versus a matched group of medically treated patients were examined (Haglund MM, Ojemann LM. *Neurosurg Clin North Am* 1993;4:337–44). In that study, year-by-year seizure counts were obtained. These were examined in the 67 patients in the 5-year surgically treated group and the 26 patients in the 10-year surgical group. Cases with one or two seizures in the first postoperative year, or those with ≥1 seizure-free years immediately after operation, followed by a recurrence were identified. The subsequent course of those patients was ascertained. Patients with postop seizures were kept on or placed back on antiepileptic drugs (AEDs). We reviewed the history for major events and for AED tapering. **Results:** Eleven patients had one or two seizures in the first year following surgery. Five of these 11 (45%) were seizure free for the ensuing 4 years of maximum follow-up. Twenty-one patients were seizure free ≥1 years postop and had a recurrence of ≥1 seizures. Fifteen of the 21 (72%) had a single seizure in the year of recurrence. Eighteen of 21 these patients had a follow-up of ≥2 years after the year of recurrence: nine of 18 (50%) with a 2-year follow-up were seizure free in those 2 years after recurrence; 13 were followed up for 3 years after recurrence, five (38%) were seizure free for the 3 years. Three were followed up for 6 years after recurrence, one (33%) was seizure free for those 6 years. Thirteen of the 18 had a single seizure during year of recurrence. Of the 13, eight (62%) were seizure free for the 2-year follow-up. Ten of these were followed up for 3 years after recurrence, five (50%) were seizure free in those 3 years. Three of these had a 6-year follow-up after recurrence, and one (33%) was seizure free for those 6 years. **Conclusions:** The occurrence of one or two seizures in the first postoperative year does not necessarily mean the return of medically refractory epilepsy; almost half of these patients will have no seizures in the next 4 years. Recurrence of seizures after ≥1 seizure-free years immediately following the operation also does not mean return of medically refractory seizures. Most recurrences will be only a single seizure in that year. Half of these patients with a recurrence will be seizure free for the next two years. Having only a single seizure in the year of recurrence improves this outcome. There was no statistical correlation of major stressful events, or of AED tapering with the reccurrence of these rare seizures.

3.240
DIFFERENT SURGICAL TECHNIQUES IN REFRACTORY TEMPORAL LOBE EPILEPSY DUE TO HIPPOCAMPAL SCLEROSIS: A PROSPECTIVE COMPARISON OF THE RESULTS IN THE FIRST 3 YEARS AFTER SURGERY

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Rationale: There is a paucity of direct comparisons of the effectiveness and safety of the two most commonly performed surgical techniques for treatment of temporal lobe epilepsy/hippocampal sclerosis (TLE/HS) in patients homogeneously evaluated by the same neurophysiological team, and operated on by the same neurosurgeon. **Methods:** We prospectively collected surgical outcome data in an yearly basis for the first 3 postoperative years of 131 patients consecutively operated on for TLE/HS by the same neurosurgeon. Seventy-seven underwent an ATL, and 54, a SAH. All had unilateral HS unequivocally detected by preoperative MRI and/or postoperative histopathology. Engel's outcome classification was used to analyze the surgical results, which were compared through survival analyses and contingency tables. **Results:** The application of survival analyses to the 77 patients operated on through an ATL and to the 54 who had a SAH showed that postoperative survival in outcome class IA for the former was 83%, 78%, and 75%, respectively, for years 1–3, while the figures for the latter, at the same time points, were 83, 76, and 70%, Contingency tables did not disclose any significant differences between the proportion of patients operated through each technique, separately analyzed in years 1, 2, and 3, and considering outcome classes IA, I, and I+II. Mortality and major neurologic deficits (hemiparesis or language abnormalities) did not occur with any of the two techniques. Two patients who had ATL spontaneously complained of a restriction in the contralateral visual field. **Conclusions:** These data suggest that SAH is as effective and safe as ATL for control of medically refractory seizures in patients with TLE /HS, at least during the first postoperative years. (Supported by FAPERGS.)

3.241
LONG-TERM SURGICAL OUTCOME IN TEMPORAL LOBE EPILEPSY DUE TO HIPPOCAMPAL SCLEROSIS: A SURVIVAL ANALYSIS SPANNING 9 YEARS

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Rationale: Subsyndromic specificity allows and calls for the delineation of reliable long-term outcome expectations in patients undergoing epilepsy surgery . Survival analyses of patients remaining in strict outcome classes may help with such delineation. This work aimed at evaluating the stability of surgical results over the years in a consecutive series of patients undergoing surgery for TLE/ HS. In addition, it looked for the variables potentially associated with the best scenarios regarding long-term seizure control. **Methods:** Yearly data on the degree of seizure control was prospectively collected for 131 patients with TLE/ HS followed up for 1–9 years after operation. Number of patients included in the analysis for years 1–9 were, respectively, 131, 115, 82, 66, 52, 34, 20, 12, and five. All had unilateral HS unequivocally detected by preoperative MRI and/or postoperative histopathology. Seventy-seven underwent an anterior temporal lobectomy (ATL), and 54, a selective amygdalohippocampectomy (SAH). Engel's outcome classification was used to analyze the surgical results. **Results:** Survival in outcome class I for years 1–9 was seen, respectively, in 91, 91, 89, 89, 89, 84, 84, 84, and 84% of the patients, with a mean survival time of 8.58 years (CI 8.02–9.14). More specifically, survival in outcome class IA was seen in 83, 77, 77, 73, 71, 71, 71, 71, and 71% in the same time period (mean survival, 7.08 years; CI, 6.37–7.79). For those patients who remained in outcome class IA after the first postoperative year, there was a 93% probability of retaining this result for the remainder of the follow up period (mean survival, 8.51 years; CI, 7.94–9.09). Younger age at epilepsy onset ($p = 0.02$) and a >90% lateralization of interictal spikes ($p = 0.01$) were the only variables significantly associated with outcome class IA at last visit, in comparison with all other outcome classes. No significant correlations were found for outcome class I with demographic or neurophysiologic variables, in comparison with all other less favorable results. Surgical results did not significantly differ in patients who underwent an ATL in comparison with those who had a SAH. **Conclusions:** When adequate resection of mesial temporal lobe structures is performed, clearcut clinical and MRI delineation of TLE/HS is strongly suggestive of a most favorable and stable postoperative long-term course, irrespective of other variables. (Supported by FAPERGS.)

3.242
THE NATURAL HISTORY OF THE SURGICAL TREATMENT OF MEDICALLY REFRACTORY EXTRATEMPORAL EPILEPSIES DUE TO TAYLOR-TYPE FOCAL CORTICAL DYSPLASIA

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Rationale: The major determinants of surgical success and particularly the long-term outcome of patients with medically refractory extratemporal epilepsies due to Taylor-type focal cortical dysplasia (MRETE/TTFCD) are still unclear. **Methods:** Fifty-six consecutive patients with MRETE/TTFCD who presented for evaluation and surgery from 2 to 38 years of age (mean, 17.05; SD, 8.4) were included. They all had (a) bona fide MRI and/or histopathologic features characteristic of TTFCD; (b) ETE; (3) ≥3 years of overall postoperative follow-up (mean, 8.4; SD, 4.0), and (d) specific outcome analysis at 1 year postop, and at the last visit (or before reoperation), 1–14 years later. The impact of several surgical strategies on both short- and long-term outcome was studied, taking into account the feasibility of complete resection of the lesion and of the cortex displaying epileptogenic discharges. Finally, the results obtained with reoperations in a subset of patients with unfavorable evolution were analyzed. **Results:** At year 1, 23 patients (41%) were seizure free (class A), and overall 32 (57%) were seizure free or greatly improved (A+B). In contrast, only 17 patients (30%) were in class A, and overall 21 (38%) demonstrated significant improvement (A+B) in the long-term (short-term vs. long-term outcome $p = 0.07$). Completeness of resection of the lesion, and of the cortical regions displaying electrocorticographic abnormalities (continuous and discontinuous) correlated significantly with the degree of seizure control in both the short and the long-term (all $p < 0.00$), as well with a stable satisfactory postoperative course ($n = 18$; 32%), as opposed to a "running up" (recurrence) of seizures ($n = 15$; 27%) (all $p < 0.00$). On the basis of seizure recurrence or unsatisfactory results from the beginning, 21 patients (38%) were reoperated on. Of 19 with ≥1 year postop follow-up (mean, 4.2; SD, 1.7), five were rendered seizure free, and overall 11 (52%) have improved greatly (classes A+B). **Conclusions:** Short- and long-term surgical outcomes differ with a trend toward statistical significance in patients with MRETE/ TTFCD. Since "running up" of seizures is common with incomplete resections of the epileptogenic zone, reoperations have a definite role in the management of these difficult cases. (Supported by FAPERGS.)

3.243
SIZE OF MESIAL TEMPORAL LOBE ICTAL GENERATOR AND SEIZURE OUTCOME

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Rationale: To assess if the size of the ictal generator has a prognostic value in terms of surgical outcome in patients with unilateral temporal lobe epilepsy investigated with scalp and depth electrodes. **Methods:** We retrospectively studied 25 patients with strictly unilateral temporal lobe epilepsy who underwent long-term EEG-video monitoring with scalp electrodes and subsequently with depth electrodes (64 channels). Bilateral depth electrode implantation was performed stereotactically or using a 3D neuro navigational system, targeting : amygdala (25 pts), hippocampus (25 pts) and parahippocampus (13 pts). Surgical procedures included: anterior temporal lobectomy (seven patients) and selective amygdalectomy hippocampectomy (18 patients). Follow-up after surgery ranged from 1 to 10 years (mean, 4.5 years). Engel's classification was used to rate outcome. **Results:** Focal onset (most commonly hippocampal, amygdaloid and parahippocampal in respective order) was documented in nine of 25 patients (36%); regional onset (most frequently amygdalohippocampal or hippocampal–parahippocampal) was recorded in 12 of 25 (48%), a lobar onset was seen in four of 25 patients (16%). A good outcome (Engel I or II) was seen in 17 patients of these series (68%) regardless the size of the ictal generator. In four of these patients, the size of the ictal generator was larger than the surgical removal (SAH), including lobar onset (one), temporal neocortex involvement (one), and parahippocampus in addition to amygdala and hippocampus involvement (two). Only in one of eight failures, the surgical removal was smaller than the ictal generator as documented by depth-EEG. **Conclusions:** In a pure culture of patients with unilateral temporal lobe epilepsy as evidenced by depth electrode recordings, the size of the ictal generator within the mesial temporal lobe network, does not provide a prognostic implication regarding surgical outcome. Selective amygdalectomy–hippocampectomy is an effective surgical procedure even in patients with large (regional and lobar) ictal generators and therefore one could postulate that this technique produces a critical disconnection of the temporolimbic network, which results in elimination or significant reduction of seizures. One could explain the surgical failures assuming that this network is much larger than its electrographic expression on depth recordings, possibly involving subcortical structures in keeping with recent MRI changes. (Supported by Montreal Neurological Institute–McGill Montreal Swiss EPI Center.)

3.244
COMPLICATIONS OF INVASIVE SUBDURAL GRID MONITORING IN CHILDREN

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Rationale: To evaluate the complications of invasive subdural grid monitoring during epilepsy surgery in children. **Methods:** We retrospectively reviewed the records of 35 consecutive children with intractable localization-related epilepsy who underwent invasive video EEG (IVEEG) with subdural grid electrodes at The Hospital for Sick Children between 1996 and 2001. Following subdural grid monitoring and the identification of the epileptic regions, cortical excisions and/or multiple subpial transections (MSTs) were performed. Complications after these procedures were then categorized as either surgical or neurologic. **Results:** There were 17 boys and 18 girls with a median age of 11.7 years. The duration of epilepsy before surgery varied between 2 and 17 years (mean, 8.3 years). Fifteen children (43%) had prior surgical procedures for epilepsy. The number of electrodes on the grids ranged from 40 to 117 (mean, 95). During IVEEG, CSF leaks occurred in seven patients. Cerebral edema (five patients), subdural hemorrhage (five), and intracerebral hematoma (three) were observed on postprocedural imaging studies but did not require surgical intervention. Hypertrophic scars on the scalp were observed in nine patients. There were three infections including one osteomyelitis, and two superficial wound infections. Blood loss and subsequent blood transfusion correlated directly with the size of and number of electrodes on the grids ($p < 0.001$). Transient unilateral motor weakness (24 patients), dysphasia (18), and facial weakness (17) were the most common neurologic deficits after cortical excision and MSTs. One child had exacerbation of a preoperative dysphasia, which was permanent. Twenty-nine children derived significant benefit from cortical resections and MSTs with >50% reduction of seizures and a mean follow-up period of 30 months. **Conclusions:** Our study suggests that carefully selected pediatric patients with intractable epilepsy can benefit from subdural invasive monitoring procedures with definite but acceptable risks.

3.245

POSTSURGICAL SEIZURE OUTCOME IN NON–HIPPOCAMPAL SCLEROSIS TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy (TLE) is the main type of surgically treatable epilepsy syndrome and encompasses two group of patients: hippocampal sclerosis (HS TLE) and non–hippocampal temporal lobe epilepsy (non-HS TLE). Postop seizure outcome of the HS group is convincingly favorable and already well known. However, results of surgery of other etiologies of TLE despite their importance are much less reported. In this study we addressed the seizure outcome after surgery of non-HS temporal lobe epilepsy. **Methods:** Thirty-one consecutive non-HS TLE patients, 3–49 years old, 13 males and 18 females, were surgically treated from 1995 to 2000. Postsurgical follow-up ranged from 2 to 7 years. Duration of epilepsy ranged from 1 to 37 years; 14 surgeries were performed in the dominant and 17 in the nondominant temporal lobe. We analyzed age, sex, age at onset, age at surgery, side of surgery, duration of epilepsy, IQ, etiology, frequency of seizures, EEG, and seizure outcome according to Engel classification schema. **Results:** Age at onset varied from 6 months to 37 years old, and duration of epilepsy ranged from 1 to 37 years. IQ varied from 63 to 114, and 14 patients were not tested or testable. Main etiologies included abnormalities of cortical development (12 cases), dysembryoplastic neuroepithelial tumor (nine cases), other tumors (five cases), gliosis (one case), hamartoma (one case), and cavernous angioma (one case). Pathological examination was inconclusive for two cases. Seizure outcome disclosed 24 patients classified as Engel class I, four patients as Engel class II, one patient as Engel class III, and two patients as Engel class IV. **Conclusions:** We concluded that overall seizure outcome is similar to HS TLE series, and that there is no presurgical predictor of outcome. (Supported by FAEPA, CNPq, and FAPESP.)

3.246

SUDDEN HEALTH: THE EXPERIENCE OF FAMILIES WITH A MEMBER WHO HAS SURGERY TO CORRECT EPILEPSY

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Rationale: Intractable epilepsy has a deleterious effect on patients and their families, including psychological, psychiatric, behavioral, and interpersonal difficulties. Corrective surgery is highly successful in eliminating or reducing the frequency of seizures. Yet it is unclear what effect this change in the health status of the individual has on family functioning. This qualitative study of six families explored their presurgery and postsurgery experiences. At the end of this presentation, participants will understand the impact of epilepsy on family functioning and the problematic noncumulative psychosocial changes that occur postsurgically when the patient and family experience "sudden health." **Methods:** An exploratory qualitative study was conducted to answer the following question: What is the experience of families with a member who elects to have surgery to correct epilepsy? Fourteen patients and families were screened for the study meeting the sample criteria: (a) 20 years old or older; (b) intractable seizures for 5+ years; (c) living with family members; (d) eligible for corrective surgery; (e) able to engage in an interview. Six families were enrolled. Pre- and postsurgery (6–8 months) semistructured interviews were conducted and videotaped in the subjects' homes. The interviews were transcribed and summaries of each set of family interviews were written. These summaries were reviewed by the families for corrections or changes. The videotapes, transcripts and summaries were reviewed by six outside reviewers to validate the data. A constant comparative method was used to analyze the data which included rereview of all data for key word phrases, which were them combined into categories and finally into broad themes. **Results:** Findings to be presented are (a) families develop two broad forms of organization in response to epilepsy: families with an adult spouse/parent whose epilepsy originated in childhood/adolescence develop a nesting phenomenon in which the member is both protected by and isolated from the family; family functioning around other issues follows a similar structure; the epilepsy is integrated into the family and determines how the family functions around a variety of issues; families in which the member develops epilepsy in adulthhood do not nest; their orgaization reflects a crisis functioning mode in which the epilepsy is never integrated into the family structure; (b) the postsurgery phase is characterized by an expereince of "sudden health" that includes noncumulative psychosocial changes in the patient and family that can not be predicted and which often create difficulties with adjustment; these changes are most disruptive for families with a nesting structure because they more directly challenges the normative role that epilepsy has played in family life. **Conclusions:** These findings regarding family structure and post-surgical adjustment have not been reported anywhere in the literature. Further study is called for to determine the generalizability of these exploratory findings.

3.247

THE ROLE OF INTRAOPERATIVE DEPTH ELECTRODE RECORDING IN TAILORED HIPPOCAMPAL RESECTION AND AS A PREDICTOR OF PROGNOSIS FOLLOWING EPILEPSY SURGERY

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Rationale: The prognosis for seizure freedom following temporal lobe resection is influenced by multiple variables, including seizure localization, MRI findings, results of Wada testing, and possibly the extent of hippocampal resection. There is no clear consensus as to how much of the mesial temporal structures must be resected in order to optimize surgical outcomes. Intraoperative depth electrode recording

(IDER) is an electrocorticographic technique that may improve the ability to tailor hippocampal resection and prognosticate seizure freedom following resection. At the end of this activity, participants should be able to discuss the use of IDER in tailored hippocampectomy and prognosis following epilepsy surgery. **Methods:** All temporal lobectomy patients from 1997 to 2002 were reviewed and patients with IDER were selected. In these patients, following resection of the appropriate temporal neocortex, a depth electrode was placed freehand into the hippocampal region parallel to its long axis. Following a brief recording, it was removed and tissue was resected. The depth electrode was then replaced and recorded from with additional resection performed until no further spikes were seen or no additional resection was possible. Patient outcomes were correlated with the presence or absence of spike activity by IDER at the conclusion of the resection. **Results:** Thirty-seven patients were identified as having undergone temporal lobe resections with IDER, with one patient lost to follow-up. Of the remaining 36 patients, 21 resections were on the right and 15 on the left. There were 14 men and 22 women with an age range of 8–54 years and a mean age of 30 years. The duration of follow-up ranges from 3 to 63 months with a mean follow up of 35 months. Twenty-four patients of the 36 that had IDER had their resections extended beyond the planned resection based upon the result of the IDER. Of these 24 patients, 18 (75%) have a class I or II outcome (Engel criteria). Of the 12 patients without further extension of the resection, 10 (83%) are class I or II; 32 (89%) patients had no spike activity at the conclusion of the resection and, of these, 26 (81%) have a class I or II outcome. Of the four patients with continued spikes following the resection, two (50%) have a class I or II outcome. **Conclusions:** Intraoperative depth electrode recording may be a valuable technique for determining the optimal extent of hippocampal resection, and the prognosis of seizure outcome in patients undergoing temporal lobe resection for epilepsy. Regardless of the extent of hippocampal resection, these data suggest that it is important to eliminate residual spike activity in the remaining hippocampus for optimum surgical outcome. Further studies of IDER are warranted for better comparison with alternative electrocorticography tehniques. (Supported by The Rosen Fund.)

TABLE 1. *Outcome data*

	Resection extended	Resection NOT extended	Spikes present after resection	Spikes absent after resection
Class I/II	18 (75%)	10 (83%)	2 (50%)	26 (81%)
Class III/IV	6 (25%)	2 (17%)	2 (50%)	6 (19%)

All outcomes used the Engel classification.

3.248
DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMORS: IS THERE ANY FACTOR FOR PREDICTING THE MOST SUITABLE SURGICAL STRATEGY? A STUDY OF 40 CASES

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Rationale: To identify, retrospectively, factors that could guide the surgical strategy in patients with epilepsy related to a dysembryoplastic neuroepithelial tumor (DNT). **Methods:** We evaluated the medical records of 40 patients surgically treated between 1990 and 2000 with histological diagnosis of DNT. **Results:** Thirty-two DNTs were located in the temporal lobe (TL) and eight in extratemporal (ET) regions. Surgery was performed without any recordings in 27% of the cases (10 TL, one ET), following video-EEG only in 38% (14 TL, one ET), and after depth EEG recordings in 35% (eight TL, six ET). Lesionectomy alone was proposed in only 10 cases (five TL, five ET), and was complete in all. A more extended cortical resection was judged necessary in the remaining 30 patients, among whom the lesion was fully removed in 24. Overall, 70% of our patients were seizure free (Engel class IA) following surgery (follow-up >2 years), a complete removal of the lesion leading to better results (73% IA) than incomplete resection (33% IA). There was no difference between TL (69% IA) and ET patients (75% IA). The global results were similarly satisfactory and seemed independent from the performance (64% IA) or not (73% IA) of invasive recordings. **Conclusions:** Predicting factors for the surgical strategy of epileptogenic DNTs are yet to be fully defined. Our study indicates that surgical results can be good in both temporal and extratemporal DNTs following seizure recording with video-EEG and provided that the lesion can be fully removed. A standardized larger resection seems preferable for TL lesions. Such a strategy is not feasible for extra-temporal areas, rendering invasive recordings mandatory.

3.249
MEMORY ABILITIES IN CHILDREN AND ADOLESCENTS WITH TEMPORAL LOBE EPILEPSY BEFORE AND AFTER TEMPORAL LOBECTOMY

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Rationale: In adult epilepsy, the study of memory functions and correlates with biological variables has proven fruitful in helping to predict losses following surgery. Memory measurement is less well developed in pediatric epilepsy, and the relationship of memory tests to biological variables is poorly documented with inconsistent findings. In the current multicenter retrospective chart-review study, we evaluated a widely used memory measure in pediatrics, the Wide Range Assessment of Memory and Learning (WRAML), to address the following questions. Do verbal versus nonverbal memory scores discriminate between left and right TLE patients? Prior to or following surgery, are verbal memory scores significantly lower than nonverbal memory scores in left TLE patients, and are nonverbal memory scores significantly lower than verbal memory scores in right TLE patients? Is there a decrement in verbal or nonverbal memory following left or right TL, respectively? **Methods:** We retrospectively examined the charts of 20 children/adolescents with left and right TLE who had undergone TL for seizure remediation. Average age of seizure onset was 5.9 years (SD, 4.2). Average age at surgery was 12.2 years (SD, 3.1). Each subject had undergone neuropsychological assessment prior to and ~6 months following surgery ($X = 0.9$ years). The mean Full Scale IQ score for the group was 97 (SD, 15). WRAML subtests included: Story Memory, Design Memory, Verbal Learning, and Visual Learning. Using *t* tests we compared left vs. right TLE memory scores, verbal vs. nonverbal memory scores (i.e. Story vs. Design Memory and Verbal vs. Visual Learning) within each TLE group, and pre vs. post surgical scores. **Results:** For the most part, right and left TLE patients did not differ significantly on any presurgical or postsurgical measures. While the right TLE Visual Learning scores were significantly lower than the Verbal Learning scores ($X = 7.33$ vs. 12.67; $p = 0.00$), the n for this comparison was only three. Surgery resulted in declines in both TL groups. Left TL patients differed significantly on pre- vs. post–Story Memory ($X = 8.79$ vs. 7.29; $p = 0.03$; $n = 14$) and Verbal Learning ($X = 10.91$ and 7.40; $p = 0.01$; $n = 11$). Right TL patients differed significantly on pre- vs. post–Design Memory (8.7 vs. 6.2; $p = 0.05$; $n = 6$). **Conclusions:** This exploratory, descriptive study suggests that the four subtests of the WRAML mentioned above may not be helpful in discriminating left vs. right TLE patients prior to surgery, except possibly in the right TLE group. However, WRAML data may be helpful in documenting postsurgical changes. Results suggest that both left and right TL groups of patients may show decrements post TL, with left TL patients showing declines on verbal measures and right TL patients showing declines in design memory. Results will be discussed with respect to age of seizure onset and age at surgery as well as other medical variables. The small sample size of the current investigation, particularly with respect to right TLE cases, is a limitation, and caution should be taken when generalizing these findings, particularly to right TLE patients. Further exploration of these issues is warranted.

3.250

RESULTS OF THE TEMPORAL LOBE EPILEPSY SURGERY IN A DEVELOPING COUNTRY

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Rationale: Surgical treatment seems to be the best option for patients with refractory symptomatic temporal lobe epilepsy (TLE). The aim of this study was to analyze the surgical results in a population of patients from Ramos Mejía hospital in Buenos Aires, Argentina, that were operated between October 1996 to March 2001. At the end of this activity the participants should be able to discuss about the outcome after surgery in temporal lobe epilepsy in a country with limited resources. **Methods:** We selected 24 patients who were operated on due to a diagnosis of medically intractable TLE and who had ≥1 year of postsurgical follow-up. All the patients were evaluated using a multidisciplinary approach that include a complete medical and neurological history, outpatient EEG, MRI of the brain, neuropsychological tests, and video-EEG. Intracarotid amobarbital test was performed in only one patient. Deep electrodes were implanted in one patient, in both temporal lobes, to lateralize the epileptogenic zone. Seizure outcome was assessed using Engel's classification. **Results:** There were 14 females and 10 males; mean age, 36 years. In 22 patients an anterior temporal lobectomy (ATL) was performed, and in two patients a lesionectomy was done. Twelve patients were operated on the right side and 12 on the left side. The histopathologic findings showed a low-grade tumor in four patients, hippocampal sclerosis in 17, dual pathology in two, and cavernous angiomas in one patient. The mean follow-up period was 3.4 years (range, 1–5 years). Nineteen patients (79.2%) were in class I, two patients were in class II, two patients were in class III, and one patient was in class IV. **Conclusions:** Our results showed a postoperative outcome comparable with series of developed countries. The number of patients that were operated during the period of analysis was significantly lower than the potential candidates. The implementation of an surgical epilepsy program in public hospitals in our country is necessary to increase the number of patients who benefits with this kind of therapy. (Supported by CONICET-UBA.)

3.251

OUTCOME OF ANTERIOR TEMPORAL LOBECTOMY IN PATIENTS WITH TEMPORAL LOBE EPILEPSY AND GENERALIZED EPILEPTIFORM EEG ABNORMALITIES

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Rationale: Anterior temporal lobectomy (ATL) is an effective surgical option for patients with medically refractory temporal lobe epilepsy (TLE). The typical EEG abnormalities in this population include focal anterior temporal spikes and sharp waves. The presence of generalized interictal epileptogenic discharges (IEDs) in a patient with TLE may suggest a concurrent diagnosis of idiopathic generalized epilepsy. The outcome of temporal lobectomy in such patients is not known. In this study, we reviewed the outcome of ATL in patients with TLE who showed generalized IEDs in addition to focal temporal IEDs. The reader will learn the prognosis of ATL in patients with TLE and generalized IEDs after reviewing this study, and be able to identify the factors predictive of outcome. **Methods:** We retrospectively reviewed the EEG reports of all 608 patients who underwent ATL for medically intractable TLE at our institution from 1989 to 2000, and selected those who showed generalized IEDs on any pre-operative Mayo EEG. All patients underwent MRI with a special protocol designed to evaluate hippocampal volume, and underwent a comprehensive presurgical evaluation including video-EEG monitoring to confirm seizure localization. Patient demographics, pre-surgical epilepsy duration, seizure types, the presence of aura and febrile seizures, MRI results, pre and post-operative EEG findings, and outcome were determined by review of the medical records. The modified Engel classification system was used to classify post-operative seizure outcome. An excellent outcome was defined as a post-operative score of ≤4, and a nonexcellent outcome, >4. A favorable outcome was defined as an improvement of ≥2 points, and an improvement of <2 points designated a poor outcome. Fisher's Exact test (two-tailed) was used to compare the frequency of different clinical variables with respect to outcome. **Results:** Twenty patients were identified (11 female and nine male patients), with a mean age (±1 SD) of 28.5 ± 13 years (range, 10–54 years). The mean presurgery epilepsy duration was 22.6 ± 14.1 years (range, 2–52 years) and mean postsurgery follow-up was 45.9 ± 33.9 months (range, 5–150 months). MRI showed mesial temporal sclerosis (MTS) in 14 patients, anterior temporal glioma in one, postencephalitic changes in one, and was normal in four. Seizure outcome was excellent in 10 (50%), favorable in six (30%), and poor in four (20%). Factors correlating with an excellent outcome were the presence of an aura ($p = 0.03$), and complex partial seizures (CPS) only without generalized tonic–clonic seizures ($p = 0.02$). The presence of focal MRI abnormalities approached but did not reach statistical significance as a favorable prognostic factor ($p = 0.08$). The presence of generalized IEDs on follow-up EEG correlated with a nonexcellent outcome ($p = 0.005$). **Conclusions:** Fifty percent of patients in this series with TLE and generalized IEDs had an excellent outcome following ATL. The presence of CPS only and aura correlated with an excellent outcome. The persistence of generalized IEDs following ATL correlated with a nonexcellent outcome. A focal temporal lobe abnormality on MRI favored an excellent outcome, but this did not reach statistical significance.

3.252

SEIZURE OUTCOME FOLLOWING TEMPORAL LOBECTOMY IN TEMPORAL LOBE CORTICAL DYSPLASIA

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Rationale: Standard temporal lobectomy achieves favorable result in medically intractable epilepsy with hippocampal sclerosis. Cortical dysplasia (CD) is increasingly recognized as a cause of drug resistant epilepsy. We report the seizure outcome of temporal lobectomy in patients with temporal lobe cortical dysplasia. **Methods:** All data on patients who underwent temporal lobectomy from 1990 to 2001 with pathologically verified cortical dysplasia were reviewed. The patients who had multilobar CD, tumor associated with CD or tuberous sclerosis were excluded. **Results:** There were 45 patients who underwent temporal lobectomy and had pathological evidence of cortical dysplasia. There were 23 patients (51.1%) who had cortical dysplasia and hippocampal sclerosis. The mean age at surgery was 27.2 years (range; 1-65 years). The mean age at seizure onset was 10.5 years (range, 3 months–47 years) and the mean duration of epilepsy was 16.6 years (range, 7 months–56 years). The MRI was abnormal in 16 patients with CD and 21 patients with CD & HS. Six patients had invasive monitoring (two depth electrodes and four subdural electrodes). Standard temporal lobectomy was performed in 42 patients. Lateral temporal lobectomy and selective amygdalohippocampectomy were performed in two and one patients, respectively. The mean duration of follow-up was 2.1 years (range, 6 months–6 years). Twenty nine of 45 patients (64.4%) were seizure free, and four patients (8.9%) were seizure free but had aura only. Six patients (13.3%) had rare seizure, four patients (8.9%) had 50–90% seizure reduction, and two patients (4.4%) had no worthwhile improvement. There was no significant different in seizure outcome between patients with CD and CD-HS ($p > 0.05$). There were no mortality or major morbidity. **Conclusions:** Temporal lobectomy for temporal lobe cortical dysplasia had favorable seizure outcome. Cortical dysplasia appears to be an important cause of temporal lobe epilepsy and should be considered in those patients without evidence of hippocampal sclerosis on preoperative MRI.

3.253
EPILEPSY SURGICAL OUTCOME AT THE UNIVERSITY OF IOWA
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Rationale: Surgical therapy has become a standard consideration in patients with medically intractable localization-related epilepsy. We describe our recent experience with epilepsy surgery at the University of Iowa. **Methods:** We retrospectively reviewed our epilepsy surgery database, and included patients with operations performed by a single neurosurgeon (M.H.) between 1993 and 2001. All patients received a standardized preoperative investigation, including a seizure protocol magnetic resonance image (MRI) of the brain, electroencephalography (EEG) and inpatient prolonged video-EEG monitoring, positron emission tomography (PET) scanning, and neuropsychological and sodium amytal (Wada) testing. Selected patients also received ictal single-photon emission computed tomography (SPECT). Patients subsequently received either anterior temporal lobectomy (ATL), extratemporal resection (ETR), or multiple subpial transections (MST) after localization of the surgical epileptic focus and determination of functional anatomy. A modified Engel outcome classification was utilized (1, seizure free or auras only; 2, >90% improvement; 3, >75% improvement; 4, no significant improvement or worse). We attempted to contact all patients by telephone who had >1 year follow-up. **Results:** 93 patients underwent epilepsy surgery. Follow-up of >1 year was available in 84 patients; 72 (86%) completed a telephone survey regarding seizure outcome. The long-term seizure outcomes for 61 ATL patients (mean follow-up, 3.6 years) were class 1, 47 (77%); class 2, seven (11%); class 3, four (7%); and class 4, three (5%). No significant difference in excellent outcome was observed between side of resection (left, 33; right, 28), by underlying pathological substrate, or whether patients received phase 1 (n = 42) or phase 2 (n = 19) evaluation. Forty-two (90%) of class 1 outcome patients following ATL rated their overall quality of life as "significantly better" or "better." The seizure outcomes for patients with ETR (n = 10) were class 1, two (20%); class 2, two (20%); class 3, one (10%); and class 4, five (50%). One patient received multiple subpial transections (MST) and had a class 4 outcome. **Conclusions:** Our surgical outcome was comparable to recently published large series, reaffirming the value of epilepsy surgery for carefully selected patients with medically intractable localization-related epilepsy. (Supported by The Roy A. and Lucille J. Carver College of Medicine.)

3.254
COMBINED OPERATIONS FOR COMPLEX INTRACTABLE EPILEPSY
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Rationale: A single operative method is very hard to achieve statisfactory control for some complex intractable epilepsy. We pilot to study the combined several operations for complex intractable epilepsy during one surgery, including leision resection or hippocampectomy, callosotomy and bipolar coagulation on functional cortexes (BCFC). The surgical outcomes were evaluated. **Methods:** The 230 seizure patients were surgically treated in Beijing Tiantan Hospital from 2000 to 2001,and 15 of them underwent combined operations. All of them wre medicated with multiple anticonvulsants (AEDs) and had more than two or three kinds of medicines before surgery. All patients wre evaluated by video/EEG monitoring and MRI and PET. Thirteen patients underwent anterior callosotomy combined with anterior temporal lobectomy, hippocampectomy, and BCFC, one occipital lobe resection combined with anterior callosotomy, hippocampectomy, and BCFC, and one basal cistern tumor resection and anteriotemporal lobectomy combined with hippocampectomy, callosotomy, and BCFC. **Results:** Follow-up from 3 to 12 months was available for all patients. No permanent complication and mortality occurred. The fact that seizure free results in 14 patients and two seizures in one patient with one medicine in 12 patients and two medicines in three patients indicated the surgical outcome was execellent. **Conclusions:** For complex intractable epilepsy, the combined operations were effective for seizure contral and as safe as regular seizure surgery. (Supported by Beijing Neurosurgerical Institute.)

3.255
WADA PREDICTION OF SURGICAL OUTCOME IN ANTERIOR TEMPORAL LOBECTOMY
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Rationale: This study's goal was to examine the ability of Wada results to predict surgical outcome following left or right anterior temporal lobectomy. We expected our Wada lateralization index to be a better predictor of seizure control than more general measures of cortical integrity. As the left and right hemisphere may have different capacities for altering cognitive processes and compensating for surgery, we assessed prediction of outcome separately for left and right temporal lobectomy patients. **Methods:** Wada scores from a 176 left and 181 right temporal lobectomy patients were used with separate analysis for the left and right side surgery groups. Discriminant function analyses were used to determine the relative power of the variables to predict postsurgical seizure control using a six-level scheme for classifying outcome: the isolated ipsilateral and contralateral Wada scores, the Wada lateralization ratio, measures of general cortical integrity (verbal and performance IQ), and handedness. We examined the predictive power of isolated ipsilateral (operated on) and contralateral (nonoperated on) hemisphere Wada performance, the ratio between them (difference in the Wada scores, divided by the total score), and measures of general cortical integrity (VIQ and PIQ scores) to predict seizure control, because IQ has been found to be related to seizure outcome with higher IQ indicating a better prognosis. We viewed the Wada ratio as an index of memory lateralization, more reflective of the consequences that ensue following temporal lobe surgery due to shifts in the neurocognitive demand placed on each hemisphere. **Results:** The discriminant function analysis in left temporal lobectomy patients was significant and contained three factors (Wilks'λ, 822; $\chi 2 = 32.2$; df = 18; $p < 0.05$). The largest canonical function explained 67.4% of the variance in surgical outcome with the loading for the Wada ratio highest (standardized coef. = 0.91, 27.6% higher than others) and Verbal IQ second in strength (stand. coef. = –66). Performance IQ and handedness also loaded significantly on this factor. The second canonical function explained 23.3% of the variance in surgical outcome with handedness (stand. coef. = –0.54) and contralateral Wada scores (stand. coef. = 0.55) the significant loadings. The discriminant function analysis with the right temporal lobectomy patients was not statistically significant. **Conclusions:** Measures of memory lateralization and general measures of cortical integrity have predictive power in terms of postsurgery seizure control. The best predictor was the asymmetry between Wada scores for the two hemispheres. This Wada ratio data suggested that when the contralateral side possessed a larger advantage in memory the surgical outcome was worse; conversely, when ipsilateral memory was superior the surgical outcome was better. The results suggest (a)Wada memory variables that take into account the context of overall Wada performance provide better predictive power than the Wada memory scores from the isolated hemispheres, (b) Wada memory asymmetry predicts surgical outcome more strongly than measures of general cerebral integrity or gross indices of cerebral dominance, (c) if the asymmetry in Wada scores reflects good functional reserve for memory in the hemisphere undergoing surgery than the prognosis for outcome is improved.

3.256

SEIZURE OUTCOME AFTER RESECTIVE SURGERY FOR EPILEPSY IN CHILDREN

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Rationale: At the end of this activity the participants should be able to discuss results of resective surgery for epilepsy in children, and relationship of cause and type of surgery. Surgery is a well-established treatment for adults with intractable seizures arising from a resectable focus. The available data suggest that children should be considered for surgical evaluation at whatever age they present with intractable focal epilepsy. We present seizure outcome following resective surgery for epilepsy in children. **Methods:** Forty-three patients underwent resective surgery for epilepsy at Hacettepe University Children's Hospital between June 1994 and February 2001. The region for resection was localized by neuroimaging and scalp EEG/video-EEG. We present the results of remaining 33 patients with a minumum postoperative follow-up of 6 months. **Results:** Age at the time of surgery was 13 months–18 years (mean, 10.8 years). Nineteen patients were between 1 and 12 years of age, and 14 patients were between 13 and 17 years of age. Nineteen patients were boys, and 14 were girls. Fifteen patients underwent temporal resection, 13 patients underwent extratemporal resection, and five patients had hemispherectomy. Two patients were lost after hemispherectomy, one within the first 24 h, other at 10 months. Age at onset of seizures was between 2 days and 8 years (mean, 3.4 years) for patients who had temporal resection, 3 days and 11 years (mean, 5.1 years) for patients who had extratemporal resection, and 1 month and 5 years (mean, 2.2 years) for patients who had hemispherectomy. Postoperative follow-up duration ranged between 8 months and 6.25 years (mean, 3 years). Neuropathological data showed tumor in nine patients; four of nine were diagnosed with dsyembryoplastic neuroepithelial tumor. Eight patients had encephalomalacia, and six patients showed temporal gliosis or cyst. Five patients showed neuropathological features of Rasmussen encephalitis. Infarct, hamartoma, cortical dysplasia, and pial angiomatosis were found, each in one patient. Sixteen patients (52%) were seizure free (class I), six patients achieved class II outcome, nine patients showed class III–IV outcome. Nine of 15 patients (60%) with temporal resection were seizure free, whereas six of 13 patients (46%) with extratemporal resection, and two of five patients (40%) with hemispherectomy were seizure free. **Conclusions:** Available results in pediatric epilepsy surgery series are encouraging, with most patients seizure free at all ages. In our patients, the frequency of good outcome was highest for patients with tumoral cause or temporal localization, in accordance with previous reports. Assessment of risk/benefit ratio, and extensive presurgical evaluation is mandatory.

3.257

LACK OF PRESURGICAL PREDICTORS OF SEIZURE OUTCOME IN A HOMOGENEOUS GROUP OF MESIAL TEMPORAL SCLEROSIS EPILEPSY SURGERY

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Rationale: Mesial temporal lobe epilepsy (MTLE) due to hippocampal sclerosis (HS) is the main type of surgically treatable epilepsy syndrome. There are many reports analyzing seizure outcome after temporal lobectomy; however, larger series with long-term follow-up generally included pre-MRI and post-MRI cases, which may have led to the inclusion of non-HS cases, while more recent series usually comprise small number of cases and/or short-term follow-up. Presurgical predictors of outcome is essential for patient and family counseling. In this report we analyzed a large and homogeneous group of pathologically confirmed HS-MTLE and address specifically the possibility of presurgical predictors of seizure outcome. **Methods:** The 207 consecutive HS-MTLE patients, 101 males and 106 females, were operated on from 1994 to 2000. Postsurgical follow-up ranged from 2 to 7 years. Duration of epilepsy ranged from 4 to 46 years. All patients were submitted to standardized presurgical evaluation which included clinical history, MRI, video-EEG monitoring, and neuropsychological testing. Ictal SPECT was obtained for most cases, and Wada test whenever necessary. We analyzed history of febrile convulsion or initial precipitating injury, family history of epilepsy and febrile convulsion, age, sex, age at onset, age at surgery, side of surgery, duration of epilepsy, IQ, etiology, frequency of seizures, EEG, and seizure outcome according to Engel classification scheme. **Results:** Age at onset varied from 5 to 57 years, and duration of epilepsy ranged from 4 to 46 years. IQ varied from 48 to 120. Seizure outcome disclosed 171 (82%) patients classified as Engel class I, 20 (10%) patients as Engel class II, 12 (6%) patients as Engel class III, and four (2%) patients as Engel class IV. **Conclusions:** No presurgical data were predictive of postsurgical seizure outcome in this study. (Supported by FAEPA, CNPq, and FAPESP.)

3.258

COMPLETE CORPUS CALLOSOTOMY IN PATIENTS YOUNGER THAN 5 YEARS

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Rationale: Epilepsy surgery has been a resource with increasing acceptance in developing countries as a valuable resource for intractable epilepsy. Complete corpus callosotomy is an effective procedure to treat the central bilateral synchrony associated with atonic seizures. The procedure is usually done involving the anterior two thirds of the corpus callosum, and the side effects include the well-known disconnection syndrome. To identify the cases were the procedure was done in a complete fashion, and review the indications and the neurophysiologic findings that motivated this type of surgery at an early age. **Methods:** The sample included the patients that were operated with a complete corpus callosotomy for intractable seizures. All the patients had preoperative video telemetry and MRI of the brain. In all cases the procedure was done to alleviate head and truncal atonic seizures. Whenever other types of seizures were identified, they were always in a ratio of <8:1. All patients had a history of >10 seizures per day. The cases with a metabolic or degenerative disease were excluded. **Results:** Of a population of 15 patients with corpus callosotomies, we included the ones with a complete section and no additional epilepsy surgery procedures such as corticectomy, performed; three patients were therefore enrolled. The mean age was 5 years. The seizure focus in all cases was located posteriorly, either posterior temporal/parietal or occipital. All cases developed a disconnection syndrome that included a right–left incoordination that eventually improved within the next 10 days following the procedure. The follow-up was for ≥6 months in all cases; the seizure-free outcome was >90%. **Conclusions:** Complete callosotomy is a valuable procedure for patients with intractable atonic seizures of posterior origin; the disconnection syndrome that typically occurs in older patients has a shorter duration and better recovery in early ages.

3.259

PROGNOSTIC FACTORS IN TEMPORAL LOBE EPILEPSY: A CORRELATION BETWEEN ILAE AND ENGEL'S CLASSIFICATION OF SURGICAL OUTCOME

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Rationale: To correlate Engel's classification of postoperative outcome and the proposal for a new classification of outcome with respect to epileptic seizures of ILAE in a study of prognostic factors in temporal lobe epilepsy surgery. **Methods:** We analyzed 41 consecutive patients who underwent temporal lobe epilepsy surgery between 1997 and 2000 in our Epilepsy Unit. We analyzed the following parameters: age at onset, time passed since first nonfebrile seizure, presence of simple partial seizures, risk factors for developing epilepsy, presurgery seizure frequency, type of lesion in brain MRI, distribution of interictal epileptiform activity, type of ictal EEG onset, use of intracranial EEG recordings, results of neuropsychological assessment and Wada test, surgical procedure and type of lesion in pathological study. For evaluating outcome we used the class assigned in the last visit using both Engel's and ILAE's classification of outcome. T-test and ANOVA test were used for statistical analysis. **Results:** Similar results were obtained with both classifications. The presence of unilateral interictal epileptiform activitity and of temporal unilateral ictal EEG onset as well as the lack of use of intracranial recordings were associated ($p < 0.05$) with a better prognosis using both classifications. Having >20 seizures per month presurgery and the presence of nontumoral lesions were associated ($p < 0.05$) with a worse prognosis using both classifications. The rest of parameters were not associated with outcome in either classification. **Conclusions:** Both outcome classifications, Engel's and ILAE's, were equally useful for correlation purposes in our series. New studies with more patients are necessary for corroborating our findings. [Supported by a fellowship (V.V.) from the Spanish Neurological Society.]

3.260
MEMORY OUTCOME AFTER ANTERIOR TEMPORAL LOBECTOMY IN PATIENTS WITH POOR BIOHEMISPHERIC MEMORY ON INTRACAROTID AMYTAL TESTING

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Rationale: Patients undergoing anterior temporal lobectomy (ATL) are at risk for material-specific memory loss. While memory preservation is likely in those who have good memory contralateral to the resection, there are few data describing memory outcome in patients with poor bihemispheric memory. Our objective was to analyze material-specific memory outcome in ATL patients who demonstrated extremely poor memory function with both hemispheres during intracarotid amytal testing (IAT). **Methods:** All patients who underwent ATL and who had pre- and postoperative neuropsychological testing at MINCEP Epilepsy Care were considered for the study ($n = 354$). Patients whose IAT memory score was <40% with each hemisphere were included in the study. Demographic data and seizure outcome were obtained by chart review. Verbal and nonverbal memory were measured using RAVLT (cumulative learning score, post interference recall and delayed recall) and Rey–Osterrieth Complex Figure Test, respectively. Memory decline was defined as >1 standard deviation decrease in postoperative memory score. **Results:** Twenty-nine patients (16 female/13 male, 19 left ATL, 10 right ATL) were included in the study (29 of 354, 8.2%). All patients were left hemisphere dominant for language. MRI results demonstrated normal in 12, MTS in 10, and structural lesion in seven. Seizure outcomes were 14 of 29 (48%) Engel I, five of 29 (17%) Engel II, five of 29 (17%) Engel III, and five of 29 (17%) Engel IV (average follow-up, 3.4 years). Left ATL patients had significant postoperative declines noted on the following RAVLT tests: cumulative learning score, eight of 19 (42%) patients; postinterference recall, six of 19 (32%) patients; delayed recall, four of 19 (21%) patients. Six (32%) left ATL patients demonstrated postoperative decline on the Rey–Osterrieth Complex Figure Test. Few right ATL patients had verbal or nonverbal memory decline (two of 10 patients, all scores considered). Left ATL patients were more likely than right ATL patients to have significant decline on RAVLT cumulative learning score ($p = 0.016$). **Conclusions:** Approximately one-third of left ATL patients with extremely poor bihemispheric memory testing on IAT demonstrated significant postoperative verbal and nonverbal memory decline. Right ATL patients were significantly less likely than left ATL patients to experience postoperative memory decline. Complete seizure freedom after ATL was noted in slightly less than half of the patients in our study. This data suggests that temporal lobectomy involving the dominant hemisphere in patients with severe bitemporal memory dysfunction carries the risk of further memory decline. (Supported by MINCEP Epilepsy Care.)

3.261
COLLATERAL STIMULATION OF ADJACENT NEURAL STRUCTURES DURING VAGUS NERVE STIMULATION: CLINICAL MANIFESTATIONS AND POSSIBLE NEUROANATOMIC CORRELATES

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Rationale: Vagus nerve stimulation (VNS) is a widely used procedure for the treatment of medication-resistant epilepsy. During VNS, collateral spread of the applied current is practically inevitable, with the potential of stimulating other neural structures in the vicinity of the vagus nerve. Since the currents applied during VNS are very small, the probability of collateral stimulation appears to be low. However, we found several patients that were reporting very specific signs and symptoms that could be best explained by this phenomenon. We reviewed our experience with collateral stimulation during VNS therapy. **Methods:** The medical records from 78 patients on VNS for the treatment of epilepsy were reviewed looking for signs or symptoms consistent with collateral stimulation of adjacent nerves. These symptoms had to occur exclusively during "ON" periods of stimulation. A detailed description was obtained and, whenever possible, the patients were examined while experiencing the symptoms. A neuroanatomic correlation of the symptoms was attempted based purely on the clinical findings. No neurophysiologic techniques were used in this study. **Results:** Eight patients were found to have signs or symptoms consistent with collateral stimulation. Clinical manifestations (probable nerve/muscle involved) were as follows: twitching or spasm of muscles in the left supraclavicular region (ansa cervicalis/infrahyoid muscles, or ventral rami of spinal nerves/longus colli, longus capitis, scaleni): five cases; left upper abdominal twitching, jerky respiration (phrenic/hemidiaphragm): three cases; left shoulder twitching, abduction (upper trunk of brachial plexus or suprascapular/deltoid or supraspinatus): one case; left upper extremity tingling (upper trunk of brachial plexus): one case. Range of VNS settings at the time of the symptoms was 1–2.25 mA, 30 Hz, and 250–500 μs. Symptoms were present during every "ON" period in only one patient. They were triggered by a certain posture (head turning to left or left lateral decubitus) in five patients. Symptoms were relieved by a change in head/neck position in four patients. Reduction of the output current resolved the symptoms in two patients; the rest did not require any specific intervention. **Conclusions:** Symptoms attributable to collateral activation of adjacent neural structures are relatively common during VNS. The two most common presentations were activation of muscles in the left supraclavicular region and the left hemidiaphragm. Symptoms were mild or moderate and rapidly resolved when the output current was reduced. In most patients, symptoms were only observed when the stimulation occurred while in a certain head, neck, or body posture. Most patients did not require any specific adjustment of the VNS settings and were able to control the problem by avoiding those specific postures. A spontaneous, gradual improvement with time was seen in most patients. (Disclosure: Honoraria: Cyberonics.)

3.262
STATUS EPILEPTICUS PRECIPITATED BY TURNING OFF THE VAGUS NERVE STIMULATOR FOR ELECTIVE BRAIN MRI

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Rationale: A 40-year-old woman with intractable complex partial seizures with secondary generalization underwent an elective brain

MRI to evaluate for possible right mesial temporal sclerosis that was suggested on a prior study. The patient was taking valproic acid (VPA; Depakote) and zonisamide (ZNS; Zonogram). She had a VNS placed 2 years prior with significant improvement in her seizure control. As per the recommendations given by Cyberonics physician's manual regarding MRI procedure, the pulse generator output was programmed to 0 mA (from 2 mA), and the patient went directly to the MRI suite. The procedure was terminated when the patient began having tonic–clonic seizure activity. She was taken immediately to the emergency room (ER). In the ER, the patient continued to have seizures. The stimulator was turned back from 0 to 2 mA, but her seizures did not stop until she received a total of 4 mg of lorazepam (LZP; Ativan) i.v. Seizure control was unstable for the next 48 h requiring admission and additional doses of LZP. An MRI was later completed successfully with the VNS off (0 mA) after premedication with 2 mg of i.v. LZP. **Methods:** We contacted the manufacturer and reviewed the literature regarding similar cases of status epilepticus after turning the VNS off for an elective MRI procedure or for any other reasons. **Results:** There was no reported similar complication under any circumstances. **Conclusions:** Due to the risk of status epilepticus, abrupt cessation of antiepileptic drugs (AED) is not recommended, especially in patients with intractable seizures. Such a recommendation has not been made for the VNS, although there has been concern of increased seizures when a patients' battery wears out. This was certainly our first experience with such a dramatic increase in seizures when the stimulator was briefly disabled. After our experience with this case, we can recommend that in patients with intractable epilepsy with a well-defined response to the VNS, when there is a need to turn off the device, i.v. access should be obtained, and a benzodiazepine (BZD) should be either available or preadministered. Further similar cases need to be reported before any formal guidelines can be issued.

3.263
VAGUS NERVE STIMULATION: A REVIEW OF THE CURRENT PRACTICE IN EUROPE

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Rationale: Because of a lack of understanding of the mechanism of action of vagus nerve stimulation (VNS) and responder-identification studies, establishing practical guidelines for the use of VNS may lead to more adequate prescription and increased availability of VNS to larger patient populations. A first step in developing such guidelines is a review of current practice of VNS in Europe. **Methods:** Neurologists, neuropediatricians, and neurosurgeons associated with 110 epilepsy centers in 17 European countries currently implanting devices were sent a structured questionnaire containing 28 questions with regard to diagnostic infrastructure, patient selection, specific therapeutic practice, patient follow-up, efficacy, and side effects of VNS. **Results:** Between 9/2001 and 12/2001, 83 of 110 questionnaires from 17 of 17 countries were returned; 57 centers (71%) were academical; 73 centers (87%) had a monitoring unit with a mean number of three monitoring beds (range, 1–11), and a mean number of 117 monitoring sessions per year (range, 2–1,000). 67 centers (81%) reported having a dedicated multidisciplinary epilepsy team; 58 (70%) commonly perform epilepsy surgery. Since 1989, a total number of 2,639 devices was implanted; the mean number of implantations per center was 28 (range, 1–160). The main indications were refractory epilepsy not amenable by resective surgery and preferred alternative treatment for callosotomy (87% and 66% of centers, respectively). The main contraindications were acute psychosis and cardiac conditions; 90% of centers use general anesthesia. The mean duration of admission was 4 days (range, 1–60 days); the mean delay between implantation and activation of the device was 9 days (range, 0–125 days). The mean frequency of postoperative visits was seven per year (range, 1–52). The reported efficacy of VNS matched results published in the literature in 63% of cases; results were felt to be worse in 30% and better in 8% of cases. Reported acute and chronic side effects matched the literature in 88% of centers; in 12% of centers other side effects were reported such as paralytic ileus, SUDEP, anorexia, and sexual disturbances. Funding of the device was the main practical operational problem encountered by 40% of centers; 89% of centers estimated VNS to be a valuable addition the therapeutic armamentarium for refractory epilepsy **Conclusions:** There seems to be a consensus among European epilepsy centers that VNS can be performed in patients with medically refractory epilepsy who are no surgical candidates. VNS is considered a preferred treatment option before callosotomy in 2/3 of European epilepsy centers. This wide-scale review revealed no divergent results in terms of efficacy and side effects of VNS when compared to the presently available literature. (Supported by grant 01105399 from the Research Fund of Ghent University, by grants 1.5.236.99 and 6.0324.02 from the Fund for Scientific Research–Flanders, and by the Clinical Epilepsy Grant of Ghent University Hospital 1998-2001.)

3.264
VAGUS NERVE STIMULATION OUTCOME: 24-MONTH FOLLOW-UP

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Rationale: Antiepileptic drugs (AEDs) are reported most effective during the first 3 months taken, and then effectiveness sometimes declines. This analysis charts the effectiveness of VNS therapy over 24 months. **Methods:** The VNS patient outcome registry was queried for a constant cohort of patients with data available at baseline and after 3, 12, and 24 months of VNS therapy. Changes in seizure frequency and physician-assessed quality of life were reported for each interval. **Results:** As of February 2002, data were available for 465 patients at all 4 time points. Median seizure frequency reduction increased with time: 40.0% at 3 months, 52.0% at 12 months, and 62.5% at 24 months. Seizure reductions of $\geq$50% were reported for 46% of patients at 3 months, 53% at 12 months, and 62% at 24 months; reductions of $\geq$75% were reported for 27% at 3 months, 34% at 12 months, and 38% at 24 months. No seizures were reported for 5% of the patients at 3 months, 6% at 12 months, and 7% at 24 months. By 24 months, improvements in alertness were noted in 59% of patients, postictal period in 54%, seizure clustering in 46%, verbal skills in 37%, mood in 39%, achievement at work or school in 28%, and memory in 33%. **Conclusions:** Unlike AEDs, for which effectiveness sometimes declines with time, median and proportional seizure frequency reduction for patients receiving VNS therapy continued to increase over the 24 months of the analysis. The automatic delivery of VNS Therapy facilitates, if not ensures, patient compliance, an advantage over AEDs. Nonetheless, patient compliance alone cannot account for the steady improvement in seizure frequency reduction over time. Therefore, additional studies of long-term VNS therapy outcome and possible physiologic changes should be undertaken. (Disclosure: Grant : Cyberonics Inc.; Honoraria : Cyberonics Inc. 2000, 2001, 2002.)

3.265
NEUROPSYCHOLOGICAL OUTCOME IN MULTIPLE SUBPIAL TRANSECTION

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Rationale: This study sought to determine cognitive outcome in a sample of medically intractable epilepsy patients who underwent either left frontal topectomy (LFT) or left temporal lobectomy (LTL) in combination with multiple subpial transection (MST). Postsurgical neuropsychological (NP) performance was compared to a sample of patients who underwent focal resective surgery alone. The objective of this study was to assess the cognitive risk of MST to cortical speech areas. **Methods:** The sample consisted of 11 patients who underwent either LFT ($n = 8$) or LTL ($n = 3$) and MST of speech and in some case, motor areas as determined by intraoperative mapping. The control sample consisted of eight patients who had only LFT ($n = 5$) or LTL ($n = 3$). All patients in this study were left speech dominant as determined by Wada procedure. Demographic, seizure, medical, and surgi-

cal data were retrospectively collected for both the presurgical and postsurgical periods. The two groups were compared on both verbal and nonverbal measures of NP function. Desciptive, parametric, and nonparametric statistical analyses were utilized to assess group differences and NP outcome following surgery. **Results:** There were no significant differences between the two groups in terms of gender, age of seizure onset, age at surgery, education, number of presurgical and postsurgical antiepileptic drugs (AEDs), postsurgical interval, and presurgical and postsurgical seizure frequency. Ninety-percent or greater improvement in postsurgical seizure control was achieved by 63% and 75% of the MST and focal resection-only groups, respectively. Presurgical neuropsychological performance was comparable between the two groups, except for the MST group performing significantly worse on a measure of visuospatial construction. Postsurgical NP outcome for the MST group revealed moderate to substantial (10–30%) declines on measures of verbal fluency ($p < 0.05$), verbal reasoning, and vocabulary. All other measures of verbal and nonverbal cognitive function showed either no change or modest improvements. In contrast, the focal resection-only group demonstrated no change or improved performance on all verbal and nonverbal cognitive measures. On postsurgical neurologic exam, 64% of the MST group showed clinical language deficits, 71% of which were judged to be persistant. **Conclusions:** These preliminary data support previous findings of adverse cognitive risk, especially to langauge, associated with MST plus additional resective surgery to the frontal or temporal lobe of the speech-dominant hemisphere. These findings should be considered when counseling patients regarding postoperative risk. There is a need to replicate this study with a larger series of patients.

3.266

VAGUS NERVE STIMULATION FOR REFRACTORY SEIZURES IN DEVELOPMENTALLY DELAYED ADULTS

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Rationale: Patients with developmental delay (DD) and seizures pose special challenges in the treatment of epilepsy. Many patients with DD have medically refractory seizures, but due to their diffuse or multifocal neuronal dysfunction, these patients may be poor candidates for resective epilepsy surgery. Further treatment alternatives are clearly needed in these patients. Only limited published data are currently available regarding vagus nerve stimulation (VNS) in adults with epilepsy and DD. We present data on all adult VNS patients implanted at the University of Michigan with epilepsy, DD, and ≥3 months' follow-up. **Methods:** 24 patients with DD underwent placement of VNS for medically refractory seizures. Strict seizure calendars were kept, beginning 3 months prior to surgery. Patients were excluded if they had <3 months' postsurgical follow-up (two patients). Their devices were activated 2 weeks after implant procedure, stimulation parameters were gradually titrated up as tolerated, and medicines were not increased. **Results:** The 22 patients included in this study ranged in age from 18 to 50 years, and six patients (27%) were female. Eight patients (36%) resided in a supervised living environment; three patients had undergone prior resective surgery; 10 patients (45%) had symptomatic generalized epilepsy, and 12 patients (55%) had focal epilepsy. At latest postimplant follow-up, 13 patients (59%) had a ≥50% improvement in seizure frequency, including three patients (14%) who had a ≥75% improvement, and one patient (5%) who was seizure free. No patients had worsening of seizure frequency. In 13 patients (59%), a majority of seizures were aborted or shortened with magnet-induced, on-demand stimulation. Behavioral improvement was noted in four patients (18%), while behavioral worsening was not noted in any patients. No surgical complications were seen in this group. **Conclusions:** VNS has been successful in providing substantial improvement in seizures for the majority of developmentally delayed patients in this series. Additional benefits seen in a number of patients included termination or shortening of seizures with on-demand therapy, as well as improvement of behavior. VNS appears to be a safe and effective adjunctive treatment for seizures in developmentally delayed adults. (Disclosure: Honoraria: Cyberonics, Inc.)

3.267

VAGUS NERVE STIMULATION IN REFRACTORY EPILEPSY PATIENTS: ETIOLOGIES AND RESPONSE RATES

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Rationale: Vagus nerve stimulation (VNS) has been well accepted as an alternative measure to treat refractory epilepsy. Previous studies have showed >50% seizure-reduction rate. However, the relationship between the etiologies and the efficacy of VNS is uncertain. The objective of this study is to discuss the relationship of etiologies of epilepsy and the outcome of seizure control with VNS. **Methods:** Seizure frequency data from 22 patients (10 male and 12 female; 17–71 years) with refractory complex partial seizures (+ secondary convulsion, atonic, tonic seizures) were obtained prospectively at our university center (VNS implants were placed between 4/1998 and 4/2001). Seven patients had also undergone previous epileptic surgeries. All patients had had long-term video-EEG monitoring. All patients (except one) have >10-year seizure history at the time of VNS placement. They continue with two (or more as necessary) antiepileptic drugs (AEDs) during the follow-up period. The pre-VNS minimum number of seizures per month was 10 except one (average, three). **Results:** Twelve patients had >75% seizure reduction, and one more had >50% reduction. Of these responders, there were two of five patients with encephalitis, two of four with congenital cerebral anomalies (CCA), four of four with traumatic brain injuries, and six of nine with idiopathic epilepsy. All patients in the traumatic brain injury group responded well, while ~40–50% of the other three groups responded. Twelve of 14 responders showed significant seizure reduction within the first month after VNS use. One patients has remained seizure free for >8 months. **Conclusions:** VNS implant appears to be a useful therapeutic adjunctive measure in patients with intractable epilepsy regardless of etiology. Most responders in our small series demonstrated improvement within the first month of VNS use.

TABLE 1. *VNS implant activation and latency of positive responses*

Group	Patient no.	1 mo	3 mo	6 mo	No positive response
Head injury	4	4	—	—	0
Unknown etiology	9	6	—	—	3
Encephalitis	5	2	—	—	3
CCA	4	0	1	1	2
Total	22	12	1	1	8

3.268

ACADEMIC PERFORMANCE CHANGES WITH VAGUS NERVE STIMULATION IN PEDIATRIC PARTIAL SEIZURE PATIENTS

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Rationale: We report on the changes in academic performance for 12 refractory pediatric partial seizure patients, with implantation of the vagus nerve stimulator (VNS). Current anticonvulsant medications (AEDs) were not removed until significant changes were already recorded due to the addition of the VNS. These academic changes were clearly not the result of decreases in or removal of cognitively impairing medications. **Methods:** These observations are the result of a retrospective chart review of 12 patients with refractory partial seizures. All took multiple medications before and after the implantation of the VNS. They ranged in ages from 11 to 17 years (six girls, 6 boys) and had to be able to answer questions about their academic situations and their treatment. Every patient had a normal IQ on the WISC R. All patients were interviewed during routine clinic visits for improvements over the first 6 months of VNS placement in many areas of their lives. Specifically questions regarding class room placements (regular vs. resource classes vs. home school) were asked of both the patient and

the parents. Finally, each child/adolescent was questioned about future academic plans. **Results:** Twelve pediatric-aged refractory partial seizure patients were reviewed for academic improvements since the placement of the VNS. Nine of the 12 children/adolescents reported positive changes in their school performance since the VNS implantation and activation. Only three students lacked improvement or regressed during their first 6 months with the VNS. Two students, who were home schooled for the previous year due to their inability to pass resource course material, were now in a normal classroom setting and passing the material. Three students who were failing resource classes were now passing that academic material. One other student moved from vocational trade school to regular classes. Three students are now confident enough in their academic abilities to be planning to attend junior college. These improvements were not due to a reduction in seizure medications after the implantation of the VNS, because no changes were made with medications until after these improvements were seen. Other improvements such as a memory of the child's newspaper route were also reported by these children. **Conclusions:** It has been suggested that improvements in alertness and sleep cycle seen after the implantation and activation of the VNS are due to cholinergic mechanism which are stimulated by the VNS (Malow et al., 2001). Holmes et al., 2001, have shown in animal models that cholinergic neurons responsible for memory are destroyed in kindling models of epilepsy. They have additionally suggested that in kindled epilepsy animal models, the pharmacologic augmentation of cholinergic neurons seems to slow the kindling process. Perhaps these academic improvements are also the result of protection of the forebrain cholinergic neurons by the VNS currents. At the end of this activity the reader should be able to answer questions about the VNS's ability to show academic improvements in refractory seizure children. They should also be able to discuss possible cholinergic mechanisms which would explain these findings. (Disclosure: Other: Consulting and Beta testing PDA program.)

3.269
VAGUS NERVE STIMULATION IN PERSONS OLDER THAN 65 YEARS

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Rationale: As the world's population ages, the proportion of patients with a history of stroke, dementia, and tumor increases. Such underlying illnesses are highly associated with seizures in the elderly. Treating the older patient with seizures presents several challenges. Medications prescribed for co-morbid conditions and diseases increase the likelihood of drug interactions among patients who are also receiving antiepileptic drugs (AEDs) for seizures. The elderly may be more sensitive to the side effects of AEDs, which can exacerbate problems with cognition and activities of daily living (Sirven JI. Acute and chronic seizures in patients older than 60 years. *Mayo Clin Proc* 2001; 76:175–83). VNS therapy, delivered by a pulse generator implanted in the chest, neither interacts with drugs nor impairs cognitive function. **Methods:** The VNS Therapy Outcome Registry, which collects data on patients receiving VNS for seizures, was queried for changes in seizure frequency and quality of life (QOL) for a constant cohort of patients aged 65 years and older with data at baseline and 3- and 12-month follow-up. **Results:** Query of the registry identified 15 patients who met analysis criteria. After 3 months of VNS therapy, seizure frequency was reduced from that at baseline by a median of 56% (range, 0–100%). Seizures were reduced 50% in nine (60%) of the patients, 75% in three (20%), 90% in two (13%), and no seizures were reported in one (7%). After 12 months of VNS therapy, median seizure frequency was reduced by 59% (range, 25–100%). Seizures were reduced 50% in eight (53%) of the patients, 75% in five (33%) of the patients, 90% in three (20%) of the patients, and no seizures were reported in one (7%). After 3 months of VNS Therapy, QOL measures were reported as better or much better among nine (60%) of patients for alertness, seven (47%) for verbal, three (20%) for memory, three (20%) for achievement, six (40%) for mood, nine (60%) for postictal period, and three (20%) for seizure clustering. After 12 months, QOL improvements were reported among eight (53%) of patients for alertness, five (33%) for verbal, three (20%) for memory, one (7%) for achievement, four (27%) for mood, seven (47%) for postictal period, and two (13%) for seizure clustering. No measure of QOL was reported as "much worse" for any patients at either time point. **Conclusions:** Although the number of patients in this analysis is small, reductions in seizure frequency and improvements in quality of life are notable. Between 3 and 12 months of VNS therapy, the median reduction in seizure frequency increased, and the number of patients with robust (≥75% reductions) increased from three to five patients. Alertness was reported as improved among more than half the patients at both time points. VNS Therapy has potential for treating seizures in patients aged 65 years and older.

3.270
VAGAL NERVE STIMULATION INDUCES END-TIDAL HYPOCAPNEA: HYPOTHETICAL IMPLICATIONS FOR ANTI-SEIZURE EFFECTS

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Rationale: Studies have shown that changes in respiratory patterns may have powerful effects on brain excitability by through end-tidal CO_2 alterations. Recent reports have documented that vagal nerve stimulation (VNS) may have significant effects on respiration. With this background, we examined the effects that VNS may have on end-tidal CO_2, through changes in respiratory patterns. **Methods:** We studied 14 patients (10 males; age range, 17–55 years) with medically refractory epilepsy who were undergoing VNS therapy. All subjects were studied during daytime sleep in an outpatient setting. The patients underwent a polygraphic recording that consisted of a 10-channel EEG, ECG, electrooculogram, nasal airflow monitoring by thermocouple, and capnograph with nasal probe. Activation of the VNS device was monitored with an ECG lead so placed that the stimulation-induced artifact was clearly discernible. VNS parameters included current flows that ranged from 2.00 to 3.50 mA. In all cases current flow was "on" for 30 s, "off" for 5 min. The capnographs automatically measured end-tidal CO_2 ($EtCO_2$) and respiratory frequency (RF) with a nasal probe. Capnographic data were analyzed visually and consistency of changes in $EtCO_2$ was assessed. In subjects with consistent drops in $EtCO_2$ the average values of $EtCO_2$ and RF were taken from points before and after VNS, as well as the highest/lowest peaks during VNS. One patient was excluded from analysis because of severe sleep apnea and three excluded from analysis of changes in $EtCO_2$ because of severe snoring in one case (resulting in unreliable $EtCO_2$ nasal measurements), inability to achieve sleep in another case, and constant aperiodic breathing in the third case that made association with VNS epochs unreliable. **Results:** Of the 10 subjects with reliable CO_2 recordings, five showed clear and consistent drops in $EtCO_2$ with simultaneous increases in RF, with maximal CO_2 decreases ranging from 5 to 22% during VNS epochs. Three patients had occasional decreases in $EtCO_2$ during VNS epochs, and two others showed no VNS-related CO_2 changes. Twelve of the patients showed alterations in respiratory patterns (rhythm, amplitude, etc.) that often varied considerably. There were no consistent changes in EEG, ECG, or heart rate related to VNS activation. **Conclusions:** This study provides evidence that VNS may exert significant physiologic effects in some patients by reducing CO_2 through respiratory mechanisms. We speculate that this may be lead to intermittent, transient mild changes in neuronal excitability, and by modulating the early pre-ictal stages, such reductions may participate in the antiepileptic effects of VNS. (Supported by Finnish Academy, Finnish Cultural Foundation, Arvo and Lea Yippo Foundation, the University of Washington Regional Epilepsy Center.)

3.271
STEREOELECTROENCEPHALOGRAPHY (SEEG)-GUIDED CORTICAL THERMOCOAGULATION: A NEW TECHNIQUE FOR FUNCTIONAL NEUROSURGERY OF EPILEPSY

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Rationale: In presurgical assessment of epilepsy intracranial EEG recordings proved useful in a large number of patients, peculiarly those whose epileptogenic area (EA) is suspected to be located close to, or inside, functional eloquent areas. In our department these recordings are carried out using stereotactically implanted depth electrodes (SEEG). Our purpose was to explore the possibility of using these electrodes to produce TC lesions inside the EA and to evaluate the therapeutic efficiency of this procedure. **Methods:** Five consecutive patients in whom epileptic discharges with focal onset had been identified by Video-SEEG recordings were enrolled in this study. Lesions were produced by inducing a Joule effect between the electrode contacts where discharges onsets had been recorded in each individual. The procedure proved painless and could be performed in an awake patient, able to cooperate, under EEG and clinical monitoring. Two to five TC lesions were performed per patient, immediately before the removal of intra-cranial electrodes. The lesion size and location was assessed by brain MRI 24 h later. **Results:** Three of the five patients presented with a left temporal lobe epilepsy (TLE) without hippocampal sclerosis (HS), seizures originated from the operculoinsular cortex in the fourth patient and in a left periventricular heterotopia facing the language area in the fifth one. Therefore, targets locations were different according to patients : entorhinal area in two patients in the group of TLE without (HS) hippocampus and temporo-polar neocortex in the third patient of this group; insula and frontal operculum in the fourth case; heterotopia and left parietal neocortex in the fifth one. No complication occurred during the procedure and no clinically detectable side effect was observed in any patients after TC. Eight months after TC, two patients with TLE and the patient with heterotopia are in Engel's class 2b, the patient with operculoinsular onset seizure is in class 1b, and the third TLE patient is seizure free (1a). **Conclusions:** This study reports on a therapeutic protocol based on the use of intracranial SEEG recording electrodes to perform focal TC lesions. It shows that (a) this procedure is feasible, safe, and well tolerated; it gives access to regions of which the surgical removal is risky (insular cortex in patient 4) or impossible (language area in patient 5); in case of failure it does not preclude a complementary surgical procedure; (b) TC lesion of the EA has a therapeutic effect. Despite the limited number of lesions per patients performed in the evaluation phase of the procedure, preliminary results are encouraging. The next step consists in assessing whether larger TC lesions in the EA are able to improve the therapeutic efficiency. (Supported by Hospices Civiles de Lyon.)

3.272

LOSS OF SEIZURE CONTROL PRECEDES VNS BATTERY END OF SERVICE

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Rationale: Vagal nerve stimulation (VNS) has been shown to be a safe and effective adjunctive therapy for medically intractable epilepsy. More than 10,000 patients have been implanted with the NeuroCybernetics Prosthesis (NCP) worldwide. However, accurately determining whether the battery is approaching end of service can be difficult. Older models (NCP model 100 with serial number <10,000) rely on chart calculations. Newer models (NCP model 100 serial number >10,000 or model 101) have an elective replacement indicator. We propose there is a clinical pattern that suggests the battery is approaching end of service or is at least insufficient to deliver the required output to maintain seizure control. **Methods:** A retrospective chart review was performed of the first 22 patients who underwent battery replacements at USC Medical Center between July 1998 and November 2001. Monthly seizure counts were compiled from time of implantation to the time of replacement. The average monthly seizure count over the three month period prior to replacement was then compared to the average monthly seizure count over the six month period of best seizure control. **Results:** There were 23 battery replacements and one mortality in these 22 patients (14 male and eight female). Eight patients were excluded: four subjects had insufficient seizure calendars, two patients were VNS nonresponders, one patient had two replacements due to high lead impedance, and one patient had significant medication noncompliance. Of the remaining 14 battery replacements, eight were performed due to clinical deterioration or status epilepticus (n = 3). The one mortality was due to an additional case of status epilepticus. Of these nine adverse events, five (56%) had an average monthly increase in seizures between 30 and 100% in the prior 3-month period, three (34%) had an increase >100%, and one patient had no increase. Six battery replacements were done prophylactically. None of these patients had a seizure increase >30%. **Conclusions:** VNS is relatively safe as adjunctive therapy for intractable epilepsy, although accurately determining if the VNS battery is approaching end of service or generating sufficient output for the device settings selected may be difficult. Of the 14 battery replacements reviewed, nine adverse events were identified. Adverse events included seizure exacerbation, status epilepticus, or death. Eight of nine patients (89%) who experienced an adverse event showed a ≥30% increase in seizure frequency in the prior 3 months. Our institution tends to use higher duty cycles and rapid cycling. It may be that patients at these settings are more sensitive to reductions in battery output before complete battery depletion. To ensure patient safety when utilizing VNS therapy, a clinical judgment should supercede device diagnostics. When seizure control is lost and no other provoking factors can be identified, one should procede with VNS battery replacement. Long-term prospective studies evaluating clinical outcomes with thorough explanted battery testing is warranted. (Disclosure: Grant : Cyberonics ; Honoraria : Cyberonics.)

3.273

VAGUS NERVE STIMULATION FOR THE TREATMENT OF EPILEPSY: RESULTS OF A PATIENT SURVEY ON THE EFFICACY OF MAGNET-INDUCED MANUAL ACTIVATION

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Rationale: Vagus nerve stimulation (VNS) is considered an effective therapy for patients with intractable seizures. Magnet-induced manual activation of the stimulator is an important component of VNS. Even though the efficacy of VNS has been well established in controlled studies, the efficacy of the magnet activation has been difficult to evaluate. We conducted a survey on the perceived efficacy and degree of satisfaction with the magnet use among patients treated with VNS at our institution. **Methods:** Of 78 patients who received VNS therapy for the treatment of epilepsy, 59 were able to complete the survey. Patients or caregivers were interviewed during regular office visits or over the phone. A standard questionnaire was used and an effort was made by the interviewers not to influence the patient's responses. **Results:** Mean age of the population was 30.4 years (range, 9–59 years). Thirty-eight (64.4%) subjects had partial epilepsy, 18 (30.5%) had secondarily generalized epilepsy, and three (5.1%) had primary generalized epilepsy. Mean duration of VNS therapy was 30.9 months. Survey results: overall efficacy of VNS was rated as "very good" or "excellent" by 23 patients (39.0%), and "fair" or "poor" by 21 (35.7%). Of 59 patients, 55 reported using the magnet. Magnet efficacy was rated as "very good" or "excellent" by 15 (31.3%) patients when used in partial seizures (PSs; n = 48) and 13 (25.5%) in generalized tonic–clonic seizures (GTCs; n = 51). Magnet use was considered "ineffective" by 21 (43.8%) patients in PSs, and 16 (31.4%) in GTCs. When patients (n = 59) were asked how much the possibility of magnet use influenced their decision to proceed with VNS, 31 (52.5%) answered as "very much", 13 (22.0%) "not at all." When they (n = 55) were asked if the magnet use has met their expectations, 29 (52.7%) responded "yes." When they (n = 55) were asked how much the magnet use changed their feeling of safety or confidence, 19 (34.5%) answered "very much," 27 (49.1%) answered "not very much." **Conclusions:** Results of our survey indicate that almost 40% of the patients considered VNS therapy as very effective. As for the magnet use, between a fourth to a third of the patients considered it as very effective, whereas, close to half of the patients considered it essentially ineffective. Interestingly, the prospect of magnet use to control seizures heavily influenced the decision to proceed with VNS therapy in slightly more than half of the patients. Despite a relatively low efficacy, only about half of the patients considered that the magnet use did not meet their expectations. About one third of the patients reported an increase

in their self confidence because of the magnet use. These findings may be of help to physicians when counseling patients about the possibility of VNS. [Disclosure: Honoraria: Cyberonics (Jorge Asconapé).]

3.274
POSITIVE EFFECTS OF VNS ON WEIGHT REGULATION

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Rationale: The ability of vagus nerve stimulation (VNS) therapy to improve motor speed, psychomotor function, language, and executive functions (Sackeim HA et al. *Neuropsychiatry Neuropsychol Behav Neurol* 2001;14:53–62) may help individuals who are developmentally disabled (DD) regulate their weight. **Methods:** Client body weight was measured at baseline and compared with each client's ideal body weight range (IBWR) (n = 39). Following implantation with the NeuroCybernetic Prosthesis (NCP) device, client body weight was monitored at 3-month intervals. **Results:** Routine evaluation of client weight following implantation showed that clients who were below IBWR had better appetites and increased body weights. Clients who were at IBWR or above did not markedly increase their body weights. In addition, professional staff stated that the clients were feeding themselves, had improved oral motor control, and that food spillage had reduced markedly. Twenty-three clients had an increase in weight within the first 6–12 months following implant. Only two had no change in weight, and 12 had a decrease. No data were available on two clients. The range of weight difference was +19 lbs to –13 lbs. Clients who gained weight averaged a 6.98 lb increase, and those losing averaged a 5.23 lb decrease. **Conclusions:** Weight and nutrition is an important issue for many DD clients. This positive weight change may be attributed to increased cognition, allowing better oral motor control and fine motor control needed for clients to feed themselves. Therefore, the weight control could have to do with the acquisition of a new skill by these clients. Clients may also be easier to feed due to better muscle control while swallowing or decreased extraneous movement. In many cases, these results were achieved before medication reduction. (Disclosure: Honoraria: Cyberonics, Inc.)

3.275
ONE-YEAR FOLLOW-UP ON 668 PATIENTS TREATED WITH VAGUS NERVE STIMULATION AND UNCHANGED ANTIEPILEPTIC DRUGS

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Rationale: Previous studies of long-term vagus nerve stimulation (VNS) for epilepsy allowed concurrent antiepileptic drug (AED) changes. We studied VNS used for 1 year as the sole new adjunct to unchanged AEDs . We specifically wondered whether VNS might have unique additive effects with any particular AED. From our work we hope neurologists gain insight into VNS use as sole new adjunctive antiepileptic therapy. **Methods:** A pilot exploration of the VNS registry was carried out to identify treated patients with 1 year of completed data and no changes in AEDs. We assessed seizure rates at baseline, and at 3 and 12 months' follow-up. We compared patients on various baseline AEDs. **Results:** 668 patients were culled from the VNS registry. Median seizure rate reductions were 46% at 3 months and 57% at 12 months ($p = 0.126$). Baseline AEDs were carbamazepine (n = 273 patients), lamotrigine (238), valproate (201), topiramate (190), and phenytoin (151) (some patients were taking multiple AEDs). Seizure rates did not differ according to baseline AEDs. **Conclusions:** This is the first long-term study of a large patient population with VNS as the sole new adjunctive antiepileptic therapy without concomitant AED changes allowed. The seizure rate changes can be attributed to VNS. We did not see significant improvement between 3 and 12 months of therapy. No particular AED appears to have unique additive antiepileptic effects with VNS. (Supported by Cyberonics.) (Disclosure: Grant: Dr. Labar has clinical research grants from Cyberonics; Consulting: Dr. Labar consults for Cyberonics; Honoraria: Dr. Labar is on the speakers bureau for Cyberoncs.)

3.276
130-HZ ELECTRICAL STIMULATION OF THE SUBTHALAMIC NUCLEUS ACTIVATES AN ANTICONVULSANT SUBCORTICAL NETWORK

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Rationale: To determine the mechanism of anticonvulsant action of subthalamic electrical stimulation. **Methods:** Concentric bipolar stimulation electrodes were implanted unilaterally in the subthalamic nucleus of adult male rats. Rats were allowed to recover 48 h after surgery, and were then fasted overnight. On the day of testing, rats received 0.5-mCurie/kg dose of ^{14}C-2-deoxyglucose subcutaneously at the onset of continuous 130-Hz electrical stimulation. Stimulation consisted of a 130-Hz train of 60-μs bipolar rectangular waves (30 μs per half-wave) lasting 45 min delivered to the electrode implanted in the subthalamic nucleus. Stimulation intensity was adjusted in each animal to the maximum level that did not produce motor side effects. At the conclusion of stimulation, each animal was rapidly decapitated, and the brain was removed and rapidly frozen at –35°C. Brains were sectioned into 40-μm slices which were exposed to autoradiography film for 7 days. Resultant images were scanned using a flatbed scanner at 1,200 dpi, and images were analyzed using NIH Image (as adapted for the PC by Scion, Inc). Calculated values included the ratio of intensities between the specific structures ipsi- and contralateral to the site of stimulation and the entire section of brain containing the structure. ANOVA analysis was used to determine whether the relative intensities of glucose utilization differed between stimulated animals and unstimulated controls, and between ipsi- and contralateral structures. **Results:** The 130-Hz subthalamic stimulation significantly increased glucose utilization ipsilaterally in the subthalamic nucleus, globus pallidus, substantia nigra pars reticulata, and the superior colliculus. **Conclusions:** The 130-Hz electrical stimulation increases activation in the subthalamic nucleus and in nuclei receiving subthalamic input directly and indirectly, via polysynaptic pathways. Subthalamic stimulation may increase the seizure threshold by activating extrapyramidal circuits rather than by inhibiting subthalamic neurons. [Supported by NIH grant K08-NS41340 (F.A.L.), NIH grant NS-20253 (S.L.M.), SURP fellowship from the Albert Einstein College of Medicine (J.A.).] [Disclosure: Grant: F. Lado has a unrestricted educational grant from Medtronic, Inc. that is being used to fund separate research (i.e., not the data discussed in this abstract) into the effects of thalamic and subthalamic electrical stimulation on seizures.]

3.277
RADIOSURGERY IN THE TREATMENT OF MEDIAL TEMPORAL LOBE EPILEPSY

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Rationale: Radiosurgery delivers focused radiation using stereotaxic guidance to targets within the brain. Prior studies have documented seizure reductions when vascular malformations and hypothalamic hamartomas have been treated with radiotherapy. A multicenter European trial of radiosurgery to treat temporal lobe epilepsy has demonstrated potential clinical utility. A NIH sponsored U.S. multicenter clinical trial utilizing gamma knife treatment of medically refractory medial temporal lobe epilepsy (mTLE) was started in October 2000, and the study progress is reported here. The purpose of the study was to determine whether gamma knife radiosurgery is effective in reducing or eliminating seizures in mTLE. **Methods:** Patients with very well defined mTLE with evidence of mesial temporal sclerosis on MRI, who were otherwise excellent candidates for seizure surgery, were offered the alternative of treatment with focused radiation. After informed

consent was obtained, the patients were screened and then randomized to treatment with either 20 or 24 Gy directed to the medial temporal lobe (treatment volume, 5.5–7.5 cc), with appropriate shielding to protect the brainstem (<10 Gy) and optic nerve (<8 Gy). The patients were then followed up with serial assessments including seizure counts, neurologic exams, neuropsychological testing, and neuroimaging. **Results:** To date 10 patients (six right, four left; seven female, three male patients) have been treated at four centers with the longest follow-up 18 months (median, 14 months). Although none is completely seizure free to date, four of the patients have experienced >80% reductions in complex partial seizures. After a latent period of 9–15 months, the patients typically reported headaches, followed by a dramatic increase in auras, and then a decrease in complex partial seizures. MRIs performed when the patients were symptomatic demonstrated dramatic cerebral edema including shift of midline structures, and three patients have required steroids to ameliorate their symptoms. One patient developed chronic papilledema, refractory to decadron and, at 14 months after radiosurgery, underwent a temporal lobectomy with resolution of symptoms. **Conclusions:** A NIH-sponsored, multicentered feasibility study of the use of radiotherapy to treat refractory epilepsy is underway with the preliminary findings demonstrating significant reductions in seizure frequency and severity. A single significant adverse event has been reported. The clinical features and neuroimaging results will be presented. At the end of this presentation the audience will be updated on this new treatment modality and on the role radiotherapy will potentially play in the future treatment of refractory epilepsy. (Supported by NIH and Elekta Corporation.) (Disclosure: Grant: Grant support from Elekta Corporation.)

3.278
PARASYMPATHETIC TONE IN PATIENTS RECEIVING VAGUS NERVE STIMULATION FOR THE TREATMENT OF REFRACTORY EPILEPSY

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Rationale: Left vagus nerve stimulation (VNS) has been used over the last years in the treatment of refractory epilepsy. The physiological mechanism involved in the antiepileptic effect is still unknown, as are the causes for the lack of response in many patients. Presumably, an increased parasympathetic tone should be involved in the VNS-mediated antiepileptic effect. We report on the autonomic effects findings of VNS in men. **Methods:** Three adult epileptic patients submitted to VNS were studied. Patient 1 had bilateral perisylvian polimicrogyria and daily complex partial seizures. EEG showed interictal bilateral independent centrotemporal spikes and nonlocalizing seizure onset. He was submitted to VNS as primary treatment and had 90% seizure-frequency reduction. Patient 2 had multiform secondary generalized seizures (Lennox-like syndrome) and has been previously submitted to maximized callosal section. A 40% reduction in seizure frequency was noted after surgery. After VNS, she had additional 85% of generalized seizure reduction. Patient 3 had refractory versive seizures and had been previously submitted to left frontal lobe resection. An 85% reduction of seizure frequency was noted after surgery. VNS showed no antiepileptic effect in this patient. All patients were stimulated with 2-mA, 100-Hz, and 0.5-ms pulses for 30 s, every 5 min. All patients were submitted to 24-h continuous ECG monitoring (Holter) and tilt table test (TTT) with the stimulator turned on or off. The heart rate variability (HRV) was studied during the Holter using SDNN (standard-deviation of RR interval) and pNN >50 (percentage of RR intervals >50 ms) indexes. HRV was studied during the TTT by power spectral analysis obtained over the last 5 min of a 20-min resting baseline and over the first 5 min after passive postural stress. **Results:** Patients 1 and 2 disclosed an increased parasympathetic tone after VNS. Patient 3 showed no autonomic response to VNS. Stimulator off SDNN values (ms) were 63, 88, and 144 for patients 1, 2, and 3, respectively. SDNN values were 89, 97, and 114 for patients 1, 2, and 3, respectively, after the stimulator was turned on; pNN >50 values (%) were 1.03, 0.56, and 6.34 with the stimulator turned off and 11.29, 0.59, and 4.10 with the device turned on, for patients 1, 2, and 3, respectively. The sympathetic/parasympathetic ratio (S/P) calculated with the stimulator off during TTT was 0.98, 1.33, and 1.38 in the resting state, and 1.96, 1.48, and 1.59 after table inclination, for patients 1, 2, and 3, respectively. After the stimulator was turned on, S/P was 1.59, 1.72, and 3.74 during the resting state and 0.85, 0.70, and 3.21 after table inclination, for patients 1, 2, and 3, respectively. **Conclusions:** Despite including a small sample, this report suggests that VNS was effective only in patients in whom an actual increase in parasympathetic tone could be documented during Holter and TTT studies. The evaluation of autonomic changes in cardiovascular system induced (or not) by VNS might be an indicator of outcome in relation to seizures in these patients. (Supported by Sao Paulo Secretary of Health.)

3.279
COMBINED PERIROLANDIC MULTIPLE SUBPIAL TRANSECTIONS AND IMMUNOLOGIC TREATMENT STRATEGIES IN NONHEMISPHERECTOMY CANDIDATES WITH LATE-ONSET RASMUSSEN ENCEPHALITIS

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Rationale: Patients with Ras are usually candidates for functional HFx, unless the disorder starts during adolescence, when brain plasticity is less reliable. Therapeutic alternatives for such patients are not fully defined. We herein report the value of perirolandic multiple subpial transsections (MSTs) associated or not with immunologic treatment (IT) for patients with adolescent-onset Ras. **Methods:** We have evaluated three patients with adolescent-onset Ras (one right, two left hemisphere) who had refractory partial motor and secondarily generalized seizures, as well as prolonged bouts of epilepsia partialis continua or negative myoclonus. Seizures led to prolonged or recurrent ICU admissions in all. Motor and language functions were largely preserved, mitigating against HFx. Perirolandic MST coupled with IT (IV methylprednisolone, IVIg, and/or ganciclovir) was the chosen therapeutic strategy in all. **Results:** All patients have stabilized their motor function, and only sporadic seizures have remained, after 3, 4, and 5 years of follow-up, respectively. Remarkably, there were no further ICU admissions for staus epilepticus or epilepsia partialis continua. Only one patient still receives ganciclovir and methylprednisolone every 6 months. However, all three take maximum tolerated dosages of two or more antiepileptic drugs. **Conclusions:** Perirolandic MST coupled with IT is well tolerated and may prove to be a most valuable alternative for non-HFx candidates with late-onset Ras. (Supported by FAPERGS.)

3.280
ROLE OF THE MAGNET IN ABORTING SEIZURES IN PATIENTS WITH VAGUS NERVE STIMULATION

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Rationale: Vagus nerve stimulation (VNS) is approved as adjunctive therapy for various partial epilepsies. The NeuroCybernetic Prosthesis NCP device has various settings that provide chronic stimlation to control seizures. These settings include output current, signal on and off time, signal frequency, and pulse width. A magnet may be used on demand by patients or care givers to abort seizures. The neurogenerator has independent settings for use of the magnet:magnet output current, magnet on time, and magnet pulse width. Very little is described in the literature regarding actual magnet settings used to abort seizures. Our objective is to study the most clinically effective VNS magnet current

settings to abort intractable partial onset seizures. At the end of this activity, participants should be able to discuss the variety of settings that can be sucessful in aborting intractable partial seizures. **Methods:** Prospective analysis of VNS magnet settings parameters necessary to abort various partial seizures was done. While the emphasis of this presentation is on demand magnet use, chronic parameters will be reviewed. Nine patients were followed up. There were seven females and two males. The age ranged from 26 years to 55 years. Duration of VNS therapy was 1 month to 3 years. **Results:** Magnet settings of 2.75–3.0 mA were found to abort 100% of simple seizures. Approximately 98% of secondarily generalized clonic–tonic seizures were aborted. Complex partial seizures without secondarily generalized seizures were aborted with output current ranges of 1.5–2.25 mA with variable results. **Conclusions:** We conclude highter magnet current should be strongly considered in patients with poorly controlled secodarily generalized clonic–tonic seizures. Further studies should be done to confirm these results.

3.281

VAGUS NERVE STIMULATION USE IN PATIENTS WITH EPILEPSY AND MENTAL RETARDATION

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Rationale: Among individuals with epilepsy who are cognitively challenged (IQs of <75), intractability is a problem in ≤45% of patients. Evaluation of treatment success may be difficult to assess secondary to multiple medical problems, behavioral problems and communication difficulties. Families, guardians and care staff have been reluctant to pursue invasive aggressive thrapies including the VNS, and have requested data regarding how this population fares to make treatment decisions. After review of our findings, readers should be able to discuss how patients with multiple retardation respond to and tolerate VNS therapy. **Methods:** All our adult patients with IQs <75 implanted with the VNS between 11/97 and 04/02 were retrospectively reviewed. History, seizure frequency and severity, medications, post-op course, generator settings, reports of Quality of Life (QOL) measures, and alertness were tabulated. **Results:** Fifty patients between the ages of 19 and 52 years were implanted under general anesthesia: 19 were mild/borderline (MB), 10 moderate (MO), 21 severe/profound (SP). Seven batteries have been replaced; one turned off. There were three uncomplicated superficial post-op skin infections. One had prolonged hoarseness for several months postimplant. There were no serious complications. Staff/families trained/learned how to use the magnet without problems. Two patients died 2+ years after implant: one SP with SUDEP and one MO with aspiration pneumonia/sepsis. Medications were not held constant through the time periods. Duty-cycles used were "Routine" (5 min off/30 s on) in 24% MB, 20% MO, 42% SP. "Intermediate" cycles were used in 29% MB, 50% MO, 5% SP. "Rapid" cycles (7 s on/≤1 min off) were used in 47% MB, 40% MO, 47% SP. Fifty-percent of the whole group had ≥50% decrease in seizure frequency. Four percent became seizure-free; 20%, >75% decrease; 26% had 50–75% decrease. Twelve percent had no clear change; 24% had such variable rates of seizure occurrence that the response rate was not clear (variability). In the MB group, 71% had >50%, and 17% had variability. In MO group, 40% had >50% response and 40% had variability. In SP group, >52% had >50% response, and 21% had variability. In 44%, seizures were described as shorter, less intense, having shorter postictal recovery times, or were improved by use of the magnet. Alertness was improved in 71% MB, 60% MO, 65% SP. **Conclusions:** Patients with mental retardation of any severity who have refractory epilepsy can benefit from VNS with decreased frequency and severity of seizures at rates equivalent to the general refractory population, tolerate the procedure and the stimulations well, and also achieve improved alertness, including other factors contributing to improved QOL. [Disclosure: Grant: VNS Research Study Grant (ongoing).]

3.282

PATIENT TOLERANCE TO REPROGRAMMING OF VAGUS NERVE STUMULATOR CURRENT, AFTER PULSE-GENERATOR REPLACEMENT

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Rationale: We studied stimulation parameters tolerated by patients undergoing vagus nerve stimulator (VNS) pulse-generator reimplant. **Methods:** Patients who had VNS generators replaced when approaching end of service, or for actual end of service, were assessed for tolerance of their pre-reimplant current. Stimulation was programmed in the operating room to the following parameters: current, 0.25 mA; frequency, 30 Hz; pulse width, 250 μs; time on, 7 s; time off, 30 min. Within the next week the patient's pre-reimplant parameters, with the exception of the current, were programmed. Next the current was increased by 0.25-mA increments to patient tolerance or pre-reimplant current. With each current increase, the patient was observed for 4 times the duration of their time off. Patients that were unable to achieve pre-reimplant current initially were seen again for further programming within one week and then monthly. Statistical analyses were $\chi 2$ with cross-tabulation, one-way ANOVA, and Pearson's bivariate correlation. **Results:** Twenty-eight patients were evaluated (14 males, 14 females). The mean age was 35 years (range, 16–56). The mean duration of VNS therapy before reimplant was 39 months (range, 23–80). Twenty-one patients were reimplanted electively, and seven were reimplanted because of end of service. Twenty-six of 28 patients had VNS "model 100" replaced with "model 101." Mean baseline current was 1.85 mA (range, 0.25–3.25). Mean baseline off time was 1.0 min (range, 0.2–5.0). We were able to achieve pre-reimplant current within 1 week postoperatively in only seven of 28 patients (25%). An additional two patients achieved their baseline current after 4 months and 1 year, respectively. The other 19 patients did not tolerate their pre-reimplant current after a mean follow-up of 2.5 months (range, 1 week–52 months.). Adverse events limiting current were coughing in 10 patients and throat pain in nine patients. Patients with a higher baseline current were less likely to return to their current within 1 week. Patients with shorter off times also were less likely to return to their baseline current within 1 week. **Conclusions:** Most patients undergoing VNS replacement are unable to tolerate their pre-reimplant current settings within the first week post operatively. This is most noticeable in patients with higher baseline currents and shorter off times. These results may be helpful for selecting stimulation parameters after VNS replacement. (Disclosure: Honoraria: Cyberonics.)

3.283

EVIDENCE THAT REFRACTORY PARTIAL-ONSET AND GENERALIZED EPILEPSY SYNDROMES RESPOND COMPARABLY TO ADJUNCTIVE VAGUS NERVE STIMULATION THERAPY

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Rationale: Medically refractory generalized epilepsy can be a devastating condition, with few treatment options. Adjunctive vagus nerve stimulation (VNS) therapy is indicated in the United States for patients with refractory partial epilepsy based on double-blind randomized multicenter trials (Cyberonics E03/E05). Some multicenter data (Cyberonics E04; Labar et al. *Neurology* 1999;52:1510–2) suggest that patients with generalized syndromes also benefit. The current study directly compares the response of patients with refractory partial and generalized epilepsy syndromes at one experienced center. At the end of this activity, participants should be able to compare response rates in these syndromes and apply this knowledge in considering VNS therapy. **Methods:** Partial and generalized syndromes were classified by UCSD epileptologists based on clinical history, exam, family history, EEG, neuroimaging and ictal video-EEG recordings. Patients offered VNS were not candidates for resective surgery. Outcome data was retrospec-

tively analyzed for 81 sequential patients aged 7–63 years implanted with VNS since FDA approval in 1997. Seizure calendars for 3 months prior to implant provided a mean baseline seizure frequency (MBSF). Percentage seizure reduction (%SR) from MBSF was calculated for the 1- to 4-, 5- to 8-, and 9- to 12-month periods postimplant. Responders were defined those with %SR ≥50%. Median %SR comparisons were made for the groups using independent unmatched Student's *t* tests. Multiple regression analyses were performed to compare demographic and etiologic variables to the dependent variable of %SR at 9–12 months. **Results:** Nine patients were excluded (six noncompliant, two infections, one new nonepileptic seizures). Adverse events were similar to published series; 72 patients were classified with partial (n = 43) and generalized (n = 29) syndromes. Groups had balanced gender ratios with similar duration of epilepsy (25 years) and medication burdens. They differed in percentage with mental retardation (Part/Gen = 35%/79.5%), average seizure-onset age (Part/Gen = 12/5, p = 0.003), and MBSF (Part/Gen = 28/85 per month; p = 0.003). Multiple regression analyses revealed higher MBSF (p = 0.003) and earlier age at onset of seizures (p = 0.027) as significantly correlated with a good %SR at 9–12 months. Comparative seizure reductions: At 1–4 months: Median %SR (Part/Gen = 29.9%/43.3%, p = 0.1566); %Responders (Part/Gen = 34.9%/44.8%); at 5–8 months: Median %SR (Part/Gen = 61.5%/45.2%, p = 0.7171); %Responders (Part/Gen = 53.5%/51.7%); at 9–12 months: Median %SR (Part/Gen = 59.1%/57.5%, p = 0.8176); %Responders (Part/Gen = 53.5%/55.2%). **Conclusions:** Patients with partial and generalized epilepsy syndromes respond comparably to adjunctive VNS, with >50% of each group achieving ≥50% seizure reduction during the first year. There was a trend for the partial group to respond later, but no statistically significant differences were seen at any time point. The generalized group did well despite a higher MBSF and more cognitive impairment. These results support the use of VNS in generalized epilepsy and suggest the need for more trials in this group. (Supported by NIH Summer Research Training Grant to CQ.) [Disclosure: Honoraria: Cyberonics (E.S.T.).]

3.284

CHANGES IN QUALITY OF LIFE IN PEDIATRIC PATIENTS RECEIVING VAGUS NERVE STIMULATION: PRELIMINARY RESULTS

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Rationale: Physicians treating patients with vagus nerve stimulation (VNS) therapy for refractory seizures have noted improvements of varying degrees in patient quality of life. Our goal was to determine whether standardized tests administered to pediatric patients receiving VNS therapy would reflect such improvements. **Methods:** We administered the Pediatric Quality of Life Inventory Version 4.0 (PedsQL 4.0) by JW Varni and the Behavior Assessment System for Children (BASC) by CR Reynolds and RW Kamphaus to pediatric patients with medically refractory seizures before they received VNS Therapy and after 3 months of treatment. The patient's parent or guardian completed questionnaires tailored for parents. Results between time points and between parent and child were compared. Increased scores on the PedsQL 4.0 were considered to indicate improvement. **Results:** Results were available at both time points for four parents and three patients. One severely impaired patient was unable to complete the forms. PedsQL: physical function scores from patients, median change in was +6 (range, –19 to +6); from parents, +19 (–3 to 69). Median change in psychosocial health summary score from patients was +3 (–34 to 32); from parents, 84 (20–109). BASC scores showed a tendency toward improvement, especially as rated by the parents. **Conclusions:** Results of the PedsQL, similar to the BASC, showed a tendency toward improvement. We expect that test results from a greater number of patients and parents and over a greater period of time will provide a clearer picture of the effects of VNS Therapy on health-related quality of life in children. (Supported by Cyberonics Inc.) (Disclosure: Grant: Research grant to study use of VNS in this project; Equity: family owned stock of $50,000, now $5,000; Honoraria: Various honoraria for speaking.)

3.285

RESULTS OF THE VAGUS NERVE STIMULATION IN THE TREATMENT OF THERAPY-RESISTANT EPILEPSIES

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Rationale: The vagus nerve stimulation (VNS) represents a treatment method for patients with intractable focal or symptomatic generalized epilepsies. At the epilepsy center of the University of Greifswald 33 patients have been implanted with a Neurocybernetic Prosthesis System TM. We present our clinical results of 26 patients observed for a period of 1–3 years after implantation. **Methods:** Twenty-six patients (aged 12–53 years) have been implanted, including patients with intractable nonoperable focal epilepsies, patients with intractable unsuccessfully operated on focal epilepsies, and refractory Lennox–Gastaut syndrome. The parameters of stimulation concerning standard parameters varied individually between 0.25 and 3.5 mA, in case of rapid cycle parameters between 0.25 and 1.25 mA. A change of the antiepileptic drug (AED) treatment was undertaken only in case of clinical indications. **Results:** One year after implantation (26 patients) a reduction of the seizure frequency was realised in 46.1% (>20%, n = 8; >50%, n = 3; >75%, n = 1). After 2 years (19 patients), the reduction of the seizure frequency was observed in 47.4% (>20%, n = 3; >50%, n = 4; >75%, n = 2). The highest rate of seizure reduction was found after 3 years (six patients) of treatment with 66.7% (>20%, n = 1; >50%, n = 2; >75%, n = 1). Further results were noticed in the form of extension of the seizure-free period, in the form of reduction of the seizure intensity, duration, and period of reorientation. The quality of life has been improved. Side effects such as hoarseness, coughing, voice alteration, pain, paresthesia, and dyspnea were rare. In two patients, the VNS had to be removed. **Conclusions:** Our results confirm that the VNS represents a supplementary treatment which is as effective as the new AEDs. The VNS is characterized by a good tolerance. Interactions with AEDs and problems with patient compliance have not yet been observed. We confirm the good results of the VNS presented by other centers of epilepsy.

3.286

VAGAL NERVE STIMULATION IN CHILDREN WITH INTRACTABLE EPILEPSY: PRELIMINARY FINDINGS ON ATTENTION, MENTAL STATUS, AND QUALITY OF LIFE

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Rationale: A small number of studies and anecdotal reports suggest that vagal nerve stimulation (VNS) for the treatment of epilepsy is associated with improvements in alertness and attention as reported by patients or parents. The only study to date using objective measurements of attention did not find VNS-associated improvements in adults (Dodrill and Morris. *Epilepsy Behav* 2001;2:46–53). The goal of this study was to test the assumption that VNS is associated with improvements in alertness and attention in children and to determine whether any postoperative improvements in attention are related to quality of life. **Methods:** Nineteen children and adolescents aged 8–18 years were assessed pre- and post-VNS (mean age, 13.3; SD, 3.3). Participants had severe, medically refractory epilepsy and had been through multiple medication trials and/or epilepsy surgery (n = 2) without substantial improvement in seizure control. Participants were administered a measure of auditory attention (digit recall task), a parent-rated measure of attention and impulsivity (ADHD-RS-IV), a measure of general mental status consisting of a modified Mini-Mental State Exam for children (3MS) and measures of general and temporal orientation from the

Children's Orientation and Amnesia Test (COAT). Parent ratings of global and epilepsy-specific quality of life were also obtained (Impact of Neurologic Handicap Scale). Post-VNS scores were obtained ~5 months after implantation. Eight of the 19 children (42%) had improvements in seizure control based on Engel seizure-outcome classification. Nonparametric tests for paired samples were used to assess for significance of pre- and post-VNS differences in variable means (i.e., Wilcoxon Signed Ranks Test). **Results:** No pre-post differences in either an objective test of auditory attention (digit recall task) or in subjective ratings of attention by parents (ADHD-RS-IV) were found. General mental status was also unchanged post-implantation. However, temporal orientation as measured by the COAT was significantly improved ($p < 0.03$), as was the overall COAT score ($p < 0.03$). Both global quality of life and epilepsy-specific quality of life were improved post-VNS ($p < 0.05$). However, post-VNS attentional functioning, mental status, and general orientation scores were not associated with changes in quality of life or with improvements in seizure control as measured by Engel outcome classification. **Conclusions:** There was minimal evidence for improvements in attention and mental status post-VNS in this sample of children with intractable seizures. Improvements in both global and epilepsy-specific quality of life were found, but these improvements did not relate to attention, mental status or general orientation levels. Some improvements were suggested in terms of temporal orientation as a result of VNS. However, given the small sample size and possibility of confounding from maturation and practice effects, these findings need replication using both a larger sample and control children with intractable seizures tested over time. (Supported by British Columbia Medical Services Foundation/Vancouver Foundation.)

3.287

LONG-TERM OUTCOME OF PATIENTS RECEIVING VAGUS NERVE STIMULATION: EXPERIENCE AT AN EPILEPSY CENTER

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Rationale: To describe the long-term outcome of patients receiving vagus nerve stimulation (VNS) therapy. The efficacy of VNS therapy is widely thought to continue to improve through the first 12 months, but reports of long-term outcome are scarce. This study traces the 5-year and greater outcome of VNS patients followed at an epilepsy center. **Methods:** We reviewed records to identify and characterize patients receiving VNS Therapy for ≥5 years and followed up at our university-based epilepsy center. We compared changes in seizure frequency between baseline and 1 year, between baseline and long-term follow-up (ranging from 5 to 7 years), and between 1 year and long-term follow-up with the Wilcoxon signed rank test. **Results:** Twenty-six patients receiving VNS therapy and followed up for ≥5 years were included in the study. Epilepsy syndrome was classified as partial epilepsy in 23 patients, as primary generalized epilepsy in two, and as atypical absence in one. Median patient age was 40 years (range, 23–60 years). Median age at onset of epilepsy was 8 years (0–44). Median number of antiepileptic drugs (AEDs) was two (none to four) at baseline, 1 year, and long-term follow-up. At baseline, the median number of seizures per month was 16.5 (two to 2,800). After 1 year of VNS therapy, the median reduction in seizure frequency was 27.6% (–100 to 100) ($p = 0.0053$), at long-term follow-up, 72.5% (–100 to 100) ($p < 0.0001$), and from 1 year to long-term follow-up, 33.3% (100 to 0) ($p < 0.0001$). After 1 year of VNS therapy, only six patients had no changes in seizure frequency or type. However, by long-term follow-up, seizure frequency had decreased for four of the six. In addition, between 1-year and long-term follow-up, seizure frequency decreased for 19 of the 26 patients. By long-term follow-up, 22 of the 26 patients had experienced ≥50% reduction in seizure frequency. **Conclusions:** Although the median number of AEDs remained constant, median seizure frequency declined after patients in this study completed 1 year of VNS therapy. Most patients with unchanged seizure frequencies after 1 year did experience reductions by long-term follow-up. Therefore, the seizure-reducing effect of VNS therapy seems to continue beyond 1 year. On the basis of these findings, we suggest that physicians continue VNS therapy in patients who have not shown a response after 1 year.

3.288

THE CLINICAL COURSE OF VAGUS NERVE STIMULATION END OF SERVICE

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Rationale: Vagus nerve stimulation (VNS) is an adjunctive therapy for patients with refractory epilepsy and utilizes intermittent electrical pulses delivered to the left cervical vagus nerve. Limited capability exists to determine when VNS battery deterioration becomes clinically significant. Initial generator models employed batteries lasting between 2 and 5 years. We evaluated 14 patients following VNS reimplantation to examine the clinical course observed during generator end of service (EOS). **Methods:** We evaluated nine males and six females with medically refractory epilepsy with a mean age of 25.1 years. These 15 patients had epilepsy for a mean of 17.9 years, and 14 of 15 underwent reimplantation with VNS after reaching EOS. Ten patients had partial epilepsy (PE) and five patients had symptomatic generalized epilepsy (SGE) failing a mean of 11.3 AEDs. Four patients had epilepsy surgery (one had successful surgery following VNS) including two callosotomies and two extratemporal topectomies. Reimplantation was performed after a mean of 2.64 years in 14 patients. Clinical symptoms prior to VNS reimplantation were examined potentially denoting EOS. Symptoms were assessed with a 12-question survey given to the patient or primary caretaker following replacement. VNS stimulus parameters were compared before and after reimplantation. **Results:** Seventy-two patients were implanted with VNS. Fifteen patients were suspected to be near EOS and candidates for reimplantation. One was found in follow-up to be at EOS with an inability to interogate the generator. EOS was predicted based upon the duration of use and stimulus parameters. Eight of nine PE patients and one of five SGE patients had complaints of altered VNS function. Five patients with SGE were nonverbal. An increase in seizures was the most frequent sign and was noted in eight of 14 (57.1%). A change in seizure pattern was noted in six of 14 (42.9%), and seizure intensification was observed in four of 14 (28.6%). Less intense, missed, or erratic stimulation was noted by six of 14 (42.9%). Painful stimulation and behavioral worsening each occurred in two of 14 (14.3%). Following reimplantation, improvement of stimulator function was noted by nine of 14 (64.3%), with a greater stimulus intensity perceived in six of 14 (42.9%) and improved stimulus regularity and magnet consistency in five of 14 (35.7%). Overall, stimulus current averaged –0.48 mA less when compared to initial parameters. All patients (or their caretakers) felt surgical reimplantation should be performed before EOS became clinically evident. **Conclusions:** We conclude that clinical features may become evident in patients using VNS for refractory epilepsy that signify battery deterioration heralding EOS. Seizure increase or change in seizure pattern was the most frequent sign observed in our series. Reimplantation yielded more intense stimulation after replacement suggesting a graded battery decay and prompting a reduction in re-implant curent intensity. Battery replacement before EOS becomes clinically evident appears desirable from a patient perspective.

3.289

PROLONGED DEEP-BRAIN STIMULATION IN REFRACTORY TEMPORAL LOBE EPILEPSY

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Rationale: Short-term deep-brain stimulation (DBS) in medial temporal lobe structures has recently been shown to be efficacious in patients with medically refractory temporal lobe epilepsy. To date there is little information on chronic DBS in these structures. The purpose of the present study was to evaluate the efficacy and safety of long-term DBS in medial temporal lobe structures and to evaluate the feasability of using chronic DBS electrodes for the localisation of the ictal onset zone prior to DBS. **Methods:** In four patients with refractory complex

partial seizures (CPSs) and negative MRI findings, four DBS electrodes were bilaterally implanted in the amygdalohippocampal region to identify and subsequently stimulate the ictal onset zone. Mean monthly CPS frequency was compared before and after long-term DBS. Side effects were carefully monitored. **Results:** DBS electrodes yielded high-quality EEG recordings that showed unilateral focal or regional seizure onset in medial temporal lobe structures. In all patients unilateral amygdalohippocampal stimulation was performed. After a mean follow-up of 7 months (range, 3–8 months), all patients had a >50% reduction in seizure frequency. None of the patients reported side effects. **Conclusions:** This study shows the feasibility of consecutive EEG recording and DBS in medial temporal lobe structures using DBS electrodes implanted during a single surgical procedure. Long-term DBS is an efficacious and safe treatment for refractory temporal lobe epilepsy. (Supported by Junior Research Grant, Fund for Scientific Research Flanders.) (Disclosure: Materials: Medtronic Europe Inc.; Royalties: Medtronic Europe, Inc.)

3.290
PEDIATRIC PATIENTS IN THE VAGUS NERVE STIMULATION PATIENT OUTCOME REGISTRY: COMPARISON OF AGES 0 THROUGH 11 WITH 12 THROUGH 17 YEARS

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Rationale: Physicians treating patients with vagus nerve stimulation (VNS) therapy voluntarily submit information to the manufacturer-maintained patient outcome registry, which records baseline demographic data and tracks changes in seizure frequency and quality of life. This analysis compares pediatric registry patients aged 0 through 11 years with those aged 12 through 17. **Methods:** The registry was queried for a constant cohort of pediatric patients with data available at baseline and after 3 and 12 months of VNS Therapy. Demographics and changes in seizure frequency and quality of life of patients aged 0 though 11 years (younger) were compared with those of patients aged 12 though 17 (older). **Results:** The younger group had 297 patients (56.6% males) and the older group had 263 (53.2% males). Epilepsy syndromes were distributed as follows: localized, 39.7% younger, 50.6% older; generalized, 27.6% younger, 22.4% older; Lennox-Gastaut, 28.3% younger, 24.0% older; other, 4.4% younger, 3.0% older. Median duration of epilepsy before VNS was 6.3 years in the younger group and 12 years in the older group. Median age at onset was 1year in the younger group and 2 years in the older group. Reductions in seizure frequency were similar between groups. Median seizure frequency reduction after 3 months was 47% younger, 50% older; after 12 months, 60% younger, 62% older. Proportional seizure reductions were ≥50% after 3 months, 48% younger, 51% older; after 12 months, 61% for both groups; ≥75% after 3 months, 30% for both groups, after 12 months, 40% younger, 36% older. After 12 months 8% of the younger and 5% of the older group reported no seizures. After 12 months physicians reported improvements in quality of life for 48% of both groups for seizure clustering and achievements at school. Improved alertness was reported for 75% younger, 71% older; postictal period for 51% younger, 57% older; verbal communication skills for 49% younger, 38% older; mood for 46% younger, 42% older; memory for 38% younger, 35% older. **Conclusions:** The younger and older groups were fairly well matched for demographics and outcome, and only slight differences were apparent. This larger study confirms previous findings that patients younger than 12 years seem to respond similarly to those aged 12 to 18 years (Helmers SL, et al. *J Child Neurol* 2001;16:843–8). (Disclosure: Grant : Cyberonics Inc. ; Honoraria : Cyberonics Inc.)

3.291
BODY MRI AND VAGUS NERVE STIMULATION

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Rationale: The objective of this study is to determine the safety of magnetic resonance imaging (MRI) spine imaging in patients implanted with a vagus nerve stimulator (VNS) by using a cold pack placed over the patient's neck. **Methods:** Three children with medically refractory epilepsy aged 5, 8, and 14 years who had previously been implanted with VNS, underwent MRI spine imaging for evaluation of gait disturbances. Informed consent was obtained in each case. Cervical and thoracic MRIs were performed with a Signa 1.5-T MRI Unit (General Electric; Waukesha, Wisconsin) scanner using standard pulse sequences with a 256 × 192 matrix and 2 Nex: 1) Axial T1-weighted Spin Echo (SE) sequence; TR (relaxation time), 600; TE (echo time), 9; 2) Coronal T1-weighted Fast Spoiled Gras (FSPGR) sequence with a 60-degree flip angle; TR, 115; TE, 3.2; 3) sagittal T1-weighted SE sequence; TR, 400; TE, 8. Before scanning, the VNS was programmed to 0 mA output for the duty and magnetic activation cycles and a large water and ammonium nitrate cold pack (Allegiance, McGaw Park, Illinois) was placed over the left side of the patient's neck. **Results:** High-quality spine MRI images were obtained in each case without interference from the VNS generator or stimulation lead. The patients tolerated the procedure without incident. **Conclusions:** The physician's manual for the VNS allows MRI to be performed, but recommends MRI only with use of a transmit and receive head coil. However, some patients implanted with a VNS will inevitably require an MRI scan of the spine using a body coil. In the three patients described here, placing a cold pack over the left side of the neck seemed to protect the vagus nerve from heat that could have theoretically been generated by the body coil MRI. Additional studies can provide greater insight into the safety and feasibility of this method. (Disclosure: Grant : Cyberonics, Inc. ; Honoraria : Cyberonics, Inc.)

3.292
DIFFERENTIAL EFFECTS OF ANTICONVULSANT THALAMIC DEEP-BRAIN STIMULATION ON SEROTONERGIC AND NORADRENERGIC MICROCHEMISTRY

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Rationale: The anterior thalamic nucleus (AN) is a key thalamic site mediating experimental seizures. Studies have demonstrated that AN DBS is effective in raising seizure threshold. Little is known about the anticonvulsant mechanisms of DBS, or the specific biochemical and synaptic mechanisms underlying seizure propagation. We proposed to determine the alterations in the underlying regional microchemistry of the AN resulting from experimental seizures and the anticonvulsant action of AN electrical stimulation. We tested the hypothesis that AN has a distinct neurochemical response, particularly serotonergic inhibition and facilitation of noradrenergic systems, early during EEG seizure propagation, and a unique response to local electrical stimulation compared to other brain regions. **Methods:** Paralyzed and ventilated Sprague–Dawley male rats (200–300 g), anesthetized with halothane, underwent stereotactically guided bilateral placement of bipolar stimulating steel electrodes in AN and posterior thalamus (PT), introduction of dialysis probes-guide cannulae in AN and PT, and placement of four epidural EEG screw electrodes 24 h prior to experiments. Both stimulated (STIM) and nonstimulated (NOSTIM) animals ($n = 7$ per group), under 0.5% halothane, were infused with i.v. pentylenetetrazol (PTZ) (5.5 mg/kg/min). Simultaneous AN and cortical EEG were recorded and microdialysis samples (2 μl/min) were collected in AN and PT every 20 min. AN Stimulation was delivered using a Grass Instruments Constant Current stimulator: 0.1–10 V; 150 mA; 0.1-ms pulse duration beginning 40 min prior to PTZ infusion. **Results:** Bilateral AN stimulation delayed the onset of EEG seizures by 82 ± 8 vs. 58 ± 5 min ($p = 0.02$) despite low current settings. PTZ infusion alone resulted in a steady increase in norepinephrine (NE), but not dopamine, in both STIM and NOSTIM animals. The rise in NE was maintained following onset of PTZ seizures. Although levels of serotonin were extremely low and did not change with PTZ or seizures, extracellular levels of 5-hydroxyindoleacetic acid (5-HIAA) increased in AN (but not PT) with PTZ and decreased following the first seizure to very low levels. The difference between 5-HIAA levels in AN and PT was significant in both STIM ($p = 0.03$) and NOSTIM ($p = 0.04$) groups. AN stimulation did not alter serotonin levels as much as the effects of PTZ

infusion. Levels of glutamate and other measured amino acids showed no substantive change during PTZ or stimulation. **Conclusions:** This data suggests that seizures enhance NE activity while suppressing serotonin-mediated AN transmission. Low serotonin levels at baseline and during PTZ infusion may indicate efficient re-uptake systems for serotonin, with 5-HIAA serving as a surrogate marker for serotonergic activity. This data suggests that manipulation of AN serotonergic activity may alter PTZ seizure threshold. (Supported by NIH grant RO1-NS35528.) (Disclosure: Grant: NIH grant RO1-NS35528.)

3.293
AUDITORY NAMING SITES: TAKE THEM OR LEAVE THEM?

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Rationale: In addition to traditional visual naming sites in language dominant temporal cortex, we, and others, have identified sites where stimulation disrupts auditory naming (e.g., "The yellow part of an egg"), yet does not interfere with visual (picture) naming. However, it is currently unknown whether it is necessary to spare auditory naming sites from resection in order to preserve language function postoperatively. We hypothesized that resection of auditory naming sites would result in postoperative auditory naming decline, whereas sparing these sites would preserve word finding ability. **Methods:** Subjects were 16 left temporal lobe epilepsy (TLE) patients who underwent preoperative cortical language mapping (seven intraoperative, nine extraoperative) utilizing both visual and auditory naming tasks. Surgical resections were carried out regardless of auditory naming data. Auditory naming sites were spared in seven patients, resected in six patients, and fell within 2 cm from the resection boundary in three patients. Visual naming sites were preserved in all patients. All patients underwent extensive testing of word finding before surgery and 1 year postoperatively. Naming tasks included a 50-item auditory description naming task, a 50-item visual naming task, and the Boston Naming Test (BNT). Performance measures included accuracy, RT and tip-of-the-tongue scores for the auditory and visual naming tasks, and accuracy scores for the BNT. Reliable change indices were calculated for all seven word-finding measures to identify significant postoperative change. Fisher's Exact test was used to determine whether auditory naming site resection was associated with postoperative naming decline (i.e., significant decline on at least one naming measure). **Results:** None of the seven patients in whom auditory naming sites were spared declined on any naming measure, whereas five of the six patients in whom auditory naming sites were resected declined on at least one naming measure ($p < 0.01$). Two of the three patients in whom auditory naming sites fell within 2 cm from the resection boundary each declined on one measure. Most intriguing, significant decline was evident on visual naming as well as auditory naming measures, despite the fact that visual naming sites were preserved in all patients. **Conclusions:** These preliminary findings suggest that sparing auditory naming sites preserves postoperative word finding, whereas resecting these sites causes a fairly general word-finding decline. These results might also explain why patients whose resections are tailored based on mapping using solely visual naming sometimes show word finding decline postoperatively (i.e., untested auditory naming sites may have been removed). (Supported by National Institute of Neurological Disorders and Stroke, grant number: NS35140-01A1.)

3.294
THE USEFULNESS OF MOTOR EVOKED POTENTIAL MONITORING IN THE IMAGE-GUIDED AND COMPUTER-ASSISTED OPERATION OF THE CEREBRAL LESIONS AROUND THE CENTRAL SULCUS

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Rationale: Surgery for resection of the lesions around the central sulcus carries an associated risk of causing significant motor deficits. The use of motor evoked potential (MEP) monitoring in the image-guided and computer-assisted operation allows these lesions to be removed with maximal safety and efficacy. **Methods:** In 30 patients with cerebral lesions adjacent to the central lesions, the surgical resection was performed. We oriented the lesion site anatomically using the neuronavigation. It was oriented through the scalp within 2-mm error, and skin incision was designed. After craniotomy, central sulcus was determined by N20 phase reversal on sensory evoked potential (SEP) recording following the median nerve stimulation. Cortical motor mapping was performed by monopolar anodal stimulation with a train of 500 Hz (three to five pulses; stimulation intensity, 8–25 mA). Action potentials were recorded from facial, thenar, biceps arm, and quadriceps femoralis muscles. Following the mapping procedure, MEP recording continued for the intraoperative monitoring of the motor system until radical lesion resection was macroscopically achieved. Intraoperative CT was taken to confirm the radical lesion resection using a mobile CT. **Results:** No new postoperative motor deficits were seen in 93% of the patients in this series. **Conclusions:** This combination of intraoperative imaging, neuronavigation, and MEP monitoring enhanced the safety of the operation of lesion resection around the central sulcus.

3.295
MINIMALLY INVASIVE SURGICAL MANAGEMENT OF HYPOTHALAMIC HAMARTOMAS IN GELASTIC EPILEPSY

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Rationale: Hypothalamic hamartomas can be associated with precocious puberty and gelastic epilepsy. Over the past several years, the syndrome of and hypothalamic hamartoma and gelastic seizures (HHGS) has been refined by a number of investigators. Most characteristically, patients with HHGS syndrome present with gelastic seizures early in life followed by a progressive epileptic syndrome most typically with multifocal seizures or a secondary generalized epileptic encephalopathy. Resistance to antiepileptic drugs (AEDs), ketogenic diet, and other nonsurgical treatments is common. Because of the high morbidity associated with traditional procedures, we have developed a minimally invasive surgical approach to these patients with relatively low morbidity and good results. **Methods:** Twelve patients with hypothalamic hamartomas and intractable seizures were evaluated and received surgery at the UAB Epilepsy Center. Presurgical evaluation included routine EEG, extended EEG video monitoring with scalp and sphenoidal electrodes and neuropsychological studies, MRI, and ictal/interictal SPECT studies. Patients 1–8 underwent stereotactic depth EEG electrode implantation studies and subsequently underwent radiofrequency lesioning. Patients 9–12 underwent endoscopic surgical approach with acute intraoperative depth EEG followed by radiofrequency and resection. For the first eight patients, the procedure consisted of a two-stage investigation. In stage I, a stereotactic frame-based MRI was obtained, and under sedation stereotactic electrode placement was performed through the frontal approach into the hamartoma. Prolonged EEG video monitoring was obtained until seizures were recorded. During stage II, a stereotactic MRI frame was again placed under mild sedation. A stereotactic radiofrequency thermocoagulation probe was placed using the same coordinates of the depth electrode placement. Following stimulation, stereotactic thermocoagulation was carried out by heating the probe to 80°F for 1min. The probe and frame were then removed, and the patient was taken to the NICU for recovery. Postoperative follow-up was obtained at 1 month and thereafter every 3 months. Medication adjustments were done according to the patient's clinical status. **Results:** Patients 1–8 received stereotactic radiofrequency lesioning preceded by chronic depth electrode recordings. At the time of follow-up (mean, 33 months), three patients were in class 1, two patients were in each class 2 and 3, and one patient was in class 4. Complications in this group included transient third-nerve palsy in patient 7. Four patients underwent endoscopic visualization of the hamartoma with a combination of both radiofrequency and partial resection. Two patients are class 1, one patient is class 2, and one patient is class 3. Complications included brainstem infarction and transient memory loss in one patient. Overall, eight patients (67%)

were either class 1 or 2 with the remaining patients (33%) class 3 or 4. Major improvements in social disposition have been reported by the families. No endocrinologic abnormalities were observed in the long term. **Conclusions:** Endoscopic and sterotactic thermocoagulation are safe and effective in the surgical management of HHGE syndrome. For large lesions, the endoscopic approach has advantages since it permits visualization.

3.296
MEASURES OF CORTICAL SYNCHRONIZATION CAN HELP PREDICT WHEN BRIEF PULSE STIMULATION WILL SUPPRESS AFTERDISCHARGES

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Rationale: The authors previously have reported that brief pulse stimulation (BPS) can terminate the afterdischarges (ADs) caused by localizing stimulation (LS) during extraoperative functional mapping (Lesser et al. *Neurology* 1999;53:2073–81). In this study, we analyzed the synchronization status of cortex manifesting ADs and not manifesting ADs, to determine under which conditions BPS can suppress ADs. **Methods:** Electrical cortical stimulation was performed in six patients undergoing presurgical evaluations using subdural electrodes. We evaluated the conditions altering BPS efficacy in 194 electrodes showing, and not showing ADs. We investigated interelectrode synchronization for consecutive 2-s periods before LS, and between LS and BPS, in extended frequency ranges between 2 and 100 Hz, using a new measure called "neighbor correlation count" (NCC) based on wavelet theory. NCC analyzes the individual correlation between an electrode and its surrounding electrodes to evaluate the synchronization status of the ADs. For each electrode, we measured wavelet correlations amplitude (WC-amp), absolute time lag (WC-atl), and the fraction of channel pairs that exceed a predetermined threshold of 90% of maximum WC-amp (%-NCC). Alternating logistic regression (ALR) and generalized linear model (GLM) were used for statistical analysis. **Results:** In the 4- to 8-Hz frequency band, assessment of periods 0–2 and 2–4 s before BPS showed that BPS efficacy improved with increases in WC-amp (odds ratios, 73.2 and 18.2, respectively, $p = 0.060$ and 0.073). BPS could stop ADs 14.9 and 12.6 s faster per unit WC-amp increase during the same period ($p < 0.001$). In the 8- to 16-Hz band, assessment of the 2–4 and 4–6 s before BPS also showed that BPS efficacy improved with increases in WC-amp (odds ratios, 12.6 and 34.9, respectively, $p = 0.067$, 0.022). BPS could stop ADs 15.6 and 9.7 s faster per unit WC-amp increase during this time ($p = 0.049$ and $p < 0.001$, respectively). In the 4- to 8-Hz band, BPS efficacy improved by 8–11% per unit %-NCC increase over the period 0–8 s before LS ($p < 0.001$ to $p = 0.013$). **Conclusions:** BPS was more effective when WC-amp and %-NCC values were higher in the 4–8 and 8–16 Hz bands, in other words when ADs were more synchronized in these frequency bands. NCC analysis may help predict conditions during which BPS is more likely to be effective. NCC analysis also may help elucidate mechanisms underlying seizure generation, spontaneous termination, and external blocking. [Supported by postdoctoral fellowship from Korean Science and Engineering Foundation (KOSEF).]

3.297
RESECTING COMBINED WITH BIPOLAR COAGULATION FOR THE TREATMENT OF TEMPORAL LOBE EPILEPSY

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Rationale: Resecting the epileptic foci combinning with thermocoagulation, a new methods had been used to treat temporal lobe epilepsy, especially for those epileptogenic foci related with the functional cortexes, because the resecting will cause serious dysfunction of the cortexes. In addtion, we are trying to evaluate the possibility and effectiveness of the new method and to summarize the experiences. **Methods:** 86 cases with temporal lobe epilepsy had been treated with the new method , after resecting the epileptic foci on the nonfunctional areas, the extratemporal functional areas with epileptic waves discharging were carried out with thermocoagulation. The output power of the electrocoagulation was 4–8 U, and the duration, 1–2 s at intervals 5 mm apart. The EcoG technique was used before and after operation to mornitor the activity of epileptic waves; 59 cases had been followed up for 1–6 years, and the effectiveness were evaluated with Engel's criteria. **Results:** The total dfficiency is ~93.22%; seizure free, ~71.3% (42 of 59), the seizures are <25%, and having no effects, 7.6%, and no significant side effects occurred among of them. **Conclusions:** The method is a new pathway to cure temporal lobe epilepsy, and it is safe, useful, and worth clinical use. (Supported by Beijing Neurosurgical Institute.)

3.298
FIRST REPORTED USE OF VAGUS NERVE STIMULATION IN BATTEN DISEASE: A CASE REPORT

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Rationale: One of eight variants of neuronal ceroid lipofuscinous (NCL), Batten disease, an autosomal recessive disorder, affects lysosomal storage. Loss of vision, epilepsy, and cognitive/motor regression characterize NCLs. The incidence rate varies by country from 0.1 to 7 per 100,000 live births. A male patient, aged 15 years, with a history of Batten disease, scoliosis corrected by surgery, and depression presented with medically refractory epileptic seizures. Patient was initially diagnosed at age 5 for Batten disease and began having epileptic seizures at age 7. Caregiver has reported ~140 seizures per month of varying types: partial complex, generalized tonic–clonic, myoclonic, and grand mal. He was taking oxcarbazepine, clonazepam, and levetiracetam for seizures, and paroxetine HCl and citalopram hydrobromide for depression. The patient was implanted with the NeuroCybernetic Prosthesis (NCP) system (Cyberonics, Inc.; Houston, Texas), which delivers vagus nerve stimulation (VNS). In the 4 months since device was turned on, the caregiver has reported a marked decrease in seizures. At the most recent visit, the only seizure type reported was myoclonic jerks, of which only a few occurred. The patient's caregiver has been successful in aborting seizures by applying the magnet furnished by the manufacturer. In addition, aggressive behavior, mood swings, and postictal state have markedly improved. Since implantation, the patient switched from Paxil to Celexa for depression. Drugs have remained constant. **Methods:** Case report. **Results:** To our knowledge, this report is the first known use of VNS in Batten disease. In this patient, VNS therapy has been effective in reducing seizures and lessening aggressive tendencies and mood swings. **Conclusions:** Ongoing studies suggest that VNS may also be effective over time for the treatment of depression, which is also symptomatic of Batten disease. Given the success of VNS in this patient with Batten disease, further investigation into the effectiveness of VNS for all variations of NCL disorders would be of great interest.

3.299
CENTRAL LOBULE SEIZURES: UTILIZATION OF AWAKE CORTICAL MAPPING AND SUBDURAL GRID MONITORING FOR SEIZURE FOCUS RESECTION

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Rationale: Surgical treatment options for intractable seizures secondary to an epileptogenic focus located in the central sulcus region are limited. Described here is an alternative surgical approach for treating

medically refractory nonlesional perirolandic epilepsy. **Methods:** We studied five consecutive patients with presumed nonlesional partial epilepsy of central lobule origin from 1996 to 2001. Preoperative assessment included prolonged video-scalp electroencephalography and single photon emission tomography (SPECT) scan coregistered with high-resolution MRI. Patients then underwent an awake stereotactic craniotomy guided by the EEG and SPECT/MRI studies, followed by cortical stimulation to identify the sensorimotor cortex and to reproduce the patient's aura. A subdural grid was then implanted based on these results. Subsequent postoperative recordings further delineated the site of seizure onset and functional cortex. During a second awake craniotomy, a limited resection of the central lobule region was performed. During the resection, neurologic function was continuously monitored. **Results:** Five patients were 16 to 56 years old (mean, 28.6 years, four men and one woman). The duration of their epilepsy ranged from 8 to 39 (mean, 20.2) years with a mean frequency of 19 seizures per week. There were one limited resection in the precentral and two in the postcentral cortex. In two other cases, the excisions involved both the pre- and postcentral gyri. Histological examination revealed nonspecific gliosis in all five patients. Postoperatively, three patients had a hemiparesis immediately following surgery. At follow-up, four recovered from their motor weakness, but one had persistent left upper extremity weakness. In four patients with the focus in the postcentral gyrus, the postoperative cortical sensory loss and apraxia resolved. Two patients were completely seizure free and two had nondisabling seizures (modified Engel classification I). One patient had reduction in his seizure frequency (modified Engel class IV). The follow-up period ranged from 6 months to five years (mean, 3.1 years). **Conclusions:** An awake limited resection of the nonlesional epileptogenic sensorimotor cortex can be performed with acceptable neurologic morbidity and may offer an alternative therapy to multiple subpial transection in the patients with intractable epilepsy.

3.300
EXTENSIVE FRONTAL DISCONNECTION: A SURGICAL ALTERNATIVE FOR PEDIATRIC FRONTAL LOBE EPILEPSY WITH DIFFUSE CORTICAL DYSPLASIA

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Rationale: In the surgical treatment for pediatric intractable epilepsy associated with extensive cortical dysplasia, it is often difficult to choose a suitable surgical procedure. We experienced three cases of intractable frontal lobe epilepsy in early childhood associated with diffuse cortical dysplasia who were treated by extensive frontal disconnection (i.e., resection of premotor and supplementary motor areas and total disconnection of the rostral frontal lobe) and obtained good postoperative outcomes. The point and indication of the extensive frontal lobectomy are also described. **Methods:** Case 1: A 3-year 5-month-old boy. His seizure started as brief tonic seizure at 10 days after birth. Daily epileptic spasms and complex partial seizures also developed at the age of 3 months and 18 months, respectively. Case 2: A 2-year 2-month-old girl. Her seizure started as generalized tonic–clonic seizure at 7 months after birth. Daily generalized tonic seizures developed at the age of 14 months. Case 3: A 2-year 4-month-old boy. His seizure started as myoclonic seizure in the face and bilateral arms at 20 days after birth. Daily epileptic spasms and nocturnal generalized tonic–clonic seizure also developd at the ages of 1 month and 18 months, respectively. All of three cases showed very similar findings in preoperative studies including physical examination, neuropsychological studies, and imaging studies. They exhibited developmental delay and mild paresis in the upper extremity contralateral to the cerebral lesion side. In MR imaging, corticomedullary demarcation was not clear in the lesion-side frontal lobe. In [^{18}F]fluorodeoxyglucose ^{18}FDG-PET scan the finding of hypometabolism was detected more extensive area including the part of parietal lobe than the abnormal area shown in MRI. In magnetoencephalography and ictal SPECT showed the accumulation of spike dipoles and hyperperfusion in the frontal lesion, respectively. **Results:** An extensive frontal disconnection was performed on all of three patients. After resecting the premotor and supplementary motor corteices rostral to the precentral sulcus totally, residual frontal cortex was disconnected from the genu and the subcallosal area medially to the anterior border of the insular cortex along the sphenoidal ridge laterally. Postoperatively, the disappearance of seizures and developmental catch-up were obtained in all patients. The pathological diagnosis was cortical dysplasia in all patients. **Conclusions:** Total frontal disconnection rostral to the precentral sulcus may be a good surgical alternative for the treatment of intractable pediatric frontal lobe epilepsy associated with diffuse cortical dysplasia.

3.301
IN VIVO MODULATION OF EPILEPTIFORM ACTIVITY WITH RADIAL HIPPOCAMPAL ELECTRIC FIELDS

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Rationale: Adaptive electrical fields have been demonstrated to suppress in vitro seizures (*J Neurosci* 2001;21:590–600). We investigated translating these results to in vivo modulation of epileptiform activity using radial electrical fields generated from depth electrodes within the central axis of the hippocampus. **Methods:** Male Sprague–Dawley rats were anesthetized and a bilateral craniotomy performed. Bilateral epileptiform activity was induced by unilateral injection of kainic acid into the right hippocampus. A left neocortical window was created to enter the lateral ventricle and expose the dorsal surface of the left hippocampus. A field-generating Ag-AgCl depth electrode was inserted along the central axis of the left hippocampus to a depth of 2–3 mm. A current return plate electrode was placed within an artificial cerebrospinal fluid layer in the neocortical window. Neural activity was monitored through differential amplification of paired tungsten microelectrodes (0.24-mm spacing). Two electrode pairs were placed in the CA1 region of the exposed hippocampus, and a third electrode pair was placed homologously within the right hippocampus. The left hippocampus was stimulated with both sinusoidal and biphasic square waveforms of varying amplitude and frequency while neuronal activity was simultaneously recorded bilaterally. Brains were fixed in formalin and histologically sectioned and stained. **Results:** Analysis of the recorded hippocampal activity indicated clear modulation of neural activity in phase with the sinusoidal field in five of six experiments, and in all six experiments with the biphasic stimuli. In one of six experiments, we simultaneously observed similar modulation in the right hippocampus (contralateral to stimulation). Histologic analysis of the trajectories suggests that variability of the electrode placement correlated with different stimulation results. At the highest current densities (>1.5 mCoulombs per square mm per phase), AgCl deposition and cavitation were observed along the electrode track. **Conclusions:** We have demonstrated in vivo electric field modulation of hippocampal epileptiform activity. This finding suggests that such electric field control of seizure is technically feasible. An important next step will include establishing an accurate lesion threshold using human-compatible electrode materials. (Supported by Whitaker Foundation, NIH 2R01MH50006 and 7K02MH01493.)

3.302
INTERSTITIAL RADIOTHERAPY IN THE TREATMENT OF EPILEPSY DUE TO HYPOTHALAMIC HAMARTOMA

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Rationale: Symptomatic focal epilepsies due to hypothalamic hamartomas have remained remarkable refractory to any medical treatment so far. Open surgery, on the other hand, has a high risk of side effects. As the epilepsy often compromises also the patient's behavior negatively, there is a need for other treatment options. Recently, radiotherapy of hypothalamic harmartomas using gamma-knife has been reported to be promising. We report the effects of interstitial radiotherapy on seizure outcome in a series of six patients with gelastic epilepsy due to hypothalamic hamartomas treated in Freiburg. **Methods:** Six patients (five male, one female, 9–32 years of age) with pharmacorefractory epilepsy suffering from gelastic, complex partial, and secondarily generalized seizures due to a sessile hypothalamic hamartoma were treated using interstitial radiotherapy. The hamartoma was identified using T1-weighted 3D MRI data sets. In addition to noninvasive presurgical monitoring, five of six patients had invasive recordings from the hamartoma using depth electrodes. Treatment was performed by stereotactic insertion of 125J-seeds into the hamartoma for a mean period of 26 days. **Results:** Two of six patients have remained seizure free a follow-up period of 1 year. One patient had an initial reduction in seizure frequency but remitted; he has had a second seed implantation and has remained seizure free for 6 months. One more patient had a seizure reduction by >50%. In one patient, the seed could not be placed in the hamartoma, and one patient did not profit from an implantation so far. Serious side effects did not occur, in particular there were neither emerging endocrine disorders nor visual field defects. **Conclusions:** As far as can be presently judged by these data, steretotactic interstitial radiotherapy seems to offer an effective alternative in the therapy of pharmacorefractory epilepsy due to hypothalamic hamartoma. Due to the lack of significant side effects, it may be preferable to open surgery at least in the sessile type of hamartoma.

3.303
PERCUTANEOUS THERMOCOAGULATION OF HYPOTHALAMIC HAMARTOMAS: SAFETY AND BENEFICIAL EFFECT ON SEIZURES

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Rationale: We present a minimally invasive method of treatment for hypothalamic hamartomas. Hypothalamic hamartomas may present with medically intractable epilepsy, typically with a complex seizure disorder including gelastic seizures, behavioral disturbance, and precocious puberty. Open surgery is difficult, and its risks may be unacceptable to patients. **Methods:** Two patients presented with a severe seizure disorder and MRI evidence of a hypothalamic hamartoma. They underwent stereotactic placement of depth electrodes into the hamartoma and areas that appeared semiologically or electrically to be involved in their seizures. Direct recording from the lesions confirmed them to be the site of seizure onset. Electrical stimulation of the lesions reproduced their habitual seizures at low threshold. Using local anesthetic, the electrode in the hamartoma was replaced with a thermocoagulation electrode. Gradually increased thermal lesions were created within the hamartomas $\leq$80°Celsius. **Results:** The procedures were halted when in one case unilateral pupillary dilatation occurred, and in the other, facial flushing was produced. Both settled when the electrode temperature reduced. Subsequent electrical stimulation could not reproduce seizures. Postoperatively there were no complications. One patient gained immediate benefit in terms of seizure frequency, although at 6 months, continues to have ~30% of baseline frequency. The other had little immediate change but a progressive reduction over 6 months also to 30% of baseline. **Conclusions:** Stereotactic thermocoagulation is a promising minimal access technique for the treatment of hypothalamic hamartomas.

3.304
LONG-TERM IMPLANTATION OF THE RESPONSIVE NEUROSTIMULATOR LEAD SYSTEM IN THE SHEEP MODEL TO DEMONSTRATE ESSENTIAL SAFETY PRIOR TO A HUMAN CLINICAL TRIAL

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Rationale: The RNS Lead System consists of quadripolar depth and cortical strip leads and is a component of the NeuroPace RNS System, which is intended for prolonged implantation as a therapy for intractable epilepsy. The objective of this study is to demonstrate the essential safety of the lead system through chronic implantation and stimulation in the sheep model. **Methods:** Using a protocol approved by the Purdue Animal Use and Care Committee and consistent with FDA and USDA guidelines, a consecutive series of eight male, castrated Suffolk sheep (aged 5–16 months) were bilaterally implanted with strip and depth leads (four leads per animal). Sedation with xylazine and sodium pentothal, followed by intubation and isoflurane maintenance anesthesia were utilized. Hippocampal depth lead placements were performed stereotactically 5 mm anterior to the interaural line with the head in a 15-degree down angle. Coordinates were determined using a sheep brain atlas in conjunction with MRI scans performed following two initial feasibility procedures. Lead introduction was made through 14-mm burr holes. Subdural cortical strip lead placements were performed in the same burr holes with the leads advanced rostrally and positioned over the parietal and frontal lobes. Leads were stabilized with burr hole covers. To assess the differential neural response resulting from stimulation, one side (consisting of a depth and strip lead) was externalized for periodic electrical stimulation whereas the other side was totally implanted and was not stimulated. Lead position was documented via dual plane radiographs. Postoperative analgesia using i.m. torbugesic was administered for 3 days, and the animals were allowed to recover for 7 days. The externalized leads received 30 min of continuous stimulation per lead each week (50-Hz, 2.5-mA, 300-μs phase duration, biphasic), and weekly impedance measurements and signal recordings were performed. After survival periods ranging from 6 to 9 months, the brains will undergo histopathologic examination at the UCLA Medical Center using multiple staining techniques (hematoxylin & eosin, Kluver–Barrera, glial fibrillary acidic protein, and a microglial marker). **Results:** Implantations began in December 2001 and will be completed in May 2002. Initial results (survival to 5 months) show stable impedance and ECoG recordings. Preliminary histopathologic data from an animal that survived 2 months showed expected reactions consistent with published results for deep-brain stimulation leads. The results from the full series including histopathologic examination will be presented. **Conclusions:** The RNS represents a novel approach for the treatment of epilepsy. This study is an important part of the preclinical work required to begin the clinical trial of the system in patients. (Supported by NeuroPace, Sunnyvale, CA.) (Disclosure: Salary: NeuroPace; Consulting: NeuroPace; Materials: NeuroPace; Stock: NeuroPace; Royalties: NeuroPace.)