Third Annual
Yale Comprehensive
Epilepsy Research
Retreat
April 3-4, 2014

Madison Beach Hotel,
Madison CT
A very special thank you to our sponsors...

Gold Star Sponsor 🌟🌟🌟

Silver Star Sponsor 🌟🌟

by Cyberonics®

Supernus Pharmaceuticals®
Exhibitors

- Eisai
- PMT Corporation
- natus neurology
- EGI dense array EEG
- QUESTCOR
The Yale Epilepsy Research Retreat is a two day meeting in which clinical and basic science researchers from Yale and collaborators from other institutions will discuss the latest advances in cutting-edge epilepsy research. In addition, Dr. James McNamara, an outstanding leader in epilepsy research, concentrates on mechanisms of "epileptogenesis" -- the process by which a normal brain becomes epileptic, will speak at the Retreat, provide feedback and guidance, and serve as an external Moderator and reviewer for the research program. The Retreat will consist of investigator slide presentations, poster session, and discussions on new research approaches and collaborations.
2014 EPILEPSY RETREAT GUEST SPEAKER

James McNamara, MD
Carl R. Deane Professor of Neuroscience
Duke University School of Medicine

Jim McNamara is a Duke School of Medicine Professor in the Departments of Neurobiology and Neurology. His research focuses on the mechanisms of epileptogenesis. A member of the Institute of Medicine of the National Academy of Sciences and a recipient of the American Epilepsy Society Research Recognition Award, Jim has received two National Institutes of Health Jacob Javits Neuroscience Investigator Awards, an American Epilepsy Society Research Recognition Award, and a Freedom to Discover award from Bristol-Myers Squibb. Jim graduated from Marquette University and from the University of Michigan Medical School where he was elected to Alpha Omega Alpha. He served as chief resident in neurology and completed his postdoctoral work in neuroscience at Duke.
AGENDA
Thursday, April 3rd

10:00-11:00 a.m.  **Registration, coffee and cookies, Poster Display**

11:00-12:20 p.m. **Slide Session I: Neuroimaging**  
*Moderator: Dennis Spencer, MD*

11:00-11:20 a.m. **EEG and fMRI Predicts Behavioral Impairment in Absence Seizures**  

11:20-11:40 a.m. **fMRI Changes in a Ferret Model of 3-4 Hz Spike-Wave Seizures**  

11:40-12:00 p.m. **Multiphoton Microscopy of Cellular and Network Brain Activity in Awake Mouse During Epileptic Convulsion**  
Michael Levene, Markus Wolfel, Hal Blumenfeld

12:00-12:20 p.m. **Mechanisms of Cortical fMRI Decreases in Absence Seizures Investigated in the Awake Mouse**  
Florian Serout, Jeanette Chin, Hiam Naiditch, Qiong Zhan, Abhijeet Gummadavelli, Eric Chen, Peter Herman, Basavaraju G. Sanganahalli, Fahmeed Hyder, Hal Blumenfeld

12:20-1:20 p.m. **Lunch and Annual Yale Comprehensive Epilepsy Center Clinical, Research, and Surgical Updates**  
*Lawrence Hirsch, MD; Hal Blumenfeld, MD, PhD; Dennis Spencer, MD*
1:20-3:00 p.m.  
**Slide Session II: Animal Models**  
*Moderator: Tore Eid, PhD*

1:20-1:40 p.m.  
**Physiology of Slack Sodium-Activated Potassium Channels in Epilepsy**  
Imran Quraishi, Grace Kim, Jack Kronengold, Leonard Kaczmarek

1:40-2:00 p.m.  
**Decreased Subcortical Cholinergic Arousal in Limbic Seizures**  
Zaina Zayyad, Joshua E. Motelow, Wei Li, Asht M. Mishra, Robert N. S. Sachdev, Geoffrey Liu, Abhijeet Gummadavelli, Hyun Seung Lee, Victoria Chu, Dario J. Englott, Peter Herman, Basavaraju G. Sanganahalli, Fahmeed Hyder, Hal Blumenfeld

2:00 -2:20 p.m.  
**Deep Brain Stimulation to Prevent Impaired Consciousness in Epilepsy**  
Abhijeet Gummadavelli, Joshua E. Motelow, Niko D. Schiff, Dennis D. Spencer, Jason Gerrard, Hal Blumenfeld

2:20-2:40 p.m.  
**State-dependent Cardio-Respiratory Consequences of Seizures**  
Gordon Buchanan, Michael Hajek, Kumiko Claycomb

2:40-3:00 p.m.  
**Cortical and Subcortical Mechanisms of Impaired Breathing in a Rodent Partial Seizure Model and Implications for SUDEP**  
Qiong Zhan, Joshua E. Motelow, Moran Furman, Wei Li, Abhijeet Gummadavelli, John Andrews, Gordon F. Buchanan, George B. Richerson, Hal Blumenfeld

3:00-5:00 p.m.  
**Poster Session with Wine and Passed hors d’oeuvres Reception**

*Posters will be available for viewing by Thursday 9:00am and remain up until the end of the retreat*

**Distinct Contribution of Different Interneuron Subtypes to Network Stability in Vivo**  
M.Miri, JA Cardin

**Examining the Intracranial EEG Second Spectrum for Evidence of Support for the Default Mode Network**  
Rasesh B. Joshi, Nicolas Gaspard, Irina I. Goncharova, Jason L. Gerrard, Dennis D. Spencer, Lawrence J. Hirsch, Hitten P. Zaveri

**The Relationship Between Intracranially Detected Interictal Spikes and Extracellular Glutamate in Patients with Medically Intractable Epilepsy**  
Nimisha Ganesh, Caroline Ong, Irina I. Goncharova, Clayton Haldeman, Eyiymesi Damisah, Ognen A. C. Petroff, Dennis D. Spencer, Tore Eid, Hitten P. Zaveri
Factors Influencing Driving Impairment in Persons with Refractory Epilepsy  
Vineet Punia, Pue Farooque, William Chen, Lawrence J. Hirsch, Anne T. Berg, the Multi-Center Study of Epilepsy Surgery, Hal Blumenfeld

Reliability of Patient Report of Impaired Consciousness During Seizures  
Yang Si, Adeolu Morawu, Yigit Baykara, Rahiwa Gebre, William Chen, Petr Vitkovskiy, Ningcheng Li, Michelle Johnson, Eric Chen, Dan Kluger, Hal Blumenfeld

Cosmetic Adverse Effects of Anti Epileptic Drugs in Adults With Epilepsy  
Baibing Chen, Kamil Detyniecki, Richard Buchsbaum, Hyunmi Choi, Asif Javed, Lawrence Hirsch

Seizure Control for Intracranial Arteriovenous Malformations is Directly Related to Treatment Modality: A Meta-Analysis  
Jacob F Baranoski, Ryan A Grant, Lawrence J Hirsch, Paul Visintainer, Jason L Gerrard, Murat Günel, Charles C Matouk, Dennis D Spencer, and Ketan R Bulsara

Advances in Neuropsychological Testing in Epilepsy; the Importance of Non-Neurological Variables While Interpreting Tests  
Franklin C. Brown

Glutamine Synthetase inhibition and the Methionine-Sulfoximine Rat-Model of Epilepsy  
Edgar Perez, Helen Wang, Hitten Zaveri, Ronnie Dhaher, Tore Eid

5:00-5:30 p.m.  
General Discussion and Day 1 Summary  
Moderator: James McNamara, MD

5:45-6:30 p.m.  
Group Beach Run or Kayaking

7:00-11:00 p.m.  
Dinner and Social Event
Friday, April 4th

7:00-8:30 a.m.  
*Breakfast*

8:30-10:30 a.m.  
**Slide Session III: Clinical/Electrophysiology**  
*Moderator: Lawrence J. Hirsch, MD*

8:30-8:50 a.m.  
**Characteristics of Patients with "Poorly - Localized" Ictal Onset on Intracranial EEG**  
Adithya Sivaraju, MD, MHA; Hitten Zaveri, PhD; Irina Goncharova, PhD; Jeremy J. Moeller, MD; Robert B. Duckrow, MD

8:50-9:10 a.m.  
**Investigating Consciousness Using Human Intracranial Recordings**  
Wendy Xiao, Reba Watsky, William Chen, Erik Levinsohn, Dennis D. Spencer, Jason Gerrard, Hal Blumenfeld

9:10-9:30 a.m.  
**Functional Connectivity, the Default Mode Network, and the Seizure Onset Area**  
Hitten P. Zaveri, Steven M. Pincus, Irina I. Goncharova, Nicolas Gaspard, Jason Gerrard, Lawrence J. Hirsch, Dennis D. Spencer

9:30-9:50 a.m.  
**The Failure of More Than a Dozen new AEDs to Improve Total Seizure Control**  
Richard Mattson

9:50-10:10 a.m.  
**Progressive Change in Sleep Quality During Intracranial EEG Monitoring and the Impact of Seizures and AEDs**  
Rasesh B. Joshi, Nicolas Gaspard, Irina I. Goncharova, Milena Pavlova, Jason L. Gerrard, Dennis D. Spencer, Lawrence J. Hirsch, Hitten P. Zaveri

10:10-10:30 a.m.  
**Prospective Evaluation of Driving During Seizures Using Driving Simulation on the Video/EEG Monitoring Unit**  
William C. Chen, Andrew Bauerschmidt, Mark W. Youngblood, Courtney Cunningham, Cel Ezeani, Zachary Kratochvil, Jared Bronen, James Thomson, Dan Kluger, Ningcheng Li, Katherine Riordan, Ji Yeoun Yoo, Romina Shirka, Louis Manganas, Andres Fernandez, Anupama Alareddy, Rup Sainju, Adithya Sivaraju, Imran Quraishi, Lawrence J. Hirsch, Hal Blumenfeld

10:30-11:00 a.m.  
*Coffee Break*
11:00-12:00 p.m.  Slide Session IV: New Directions aka “Data Free Zone”

11:00-11:15 a.m.  Auditory Discrimination and Physiology in an Awake Behaving Mouse Absence Seizure Model
Eric Chen, Alex Kwan, Jeanette Chin, Hal Blumenfeld

11:15-11:30 a.m.  Gut-Brain Axis in Epilepsy: Role of Microbiota on Seizures
Eid Tore

11:30-11:45 a.m.  Defining the Risk Factors, Prevalence, and Consequences of Seizure Clusters
Tenzin Choezom, Jennifer Bonito, Lawrence J. Hirsch, and Kamil Detyliecki

11:45-12:00 p.m.  EEG Sonification for the Detection of Seizures
Psyche Loui, Mark Frick, Matan Koplin-Green, Mike Massone.

12:00-1:30 p.m.  Lunch Buffet and Final Discussion

THANK YOU ALL FOR PARTICIPATING IN THE THIRD ANNUAL EPILEPSY RESEARCH RETREAT

A SPECIAL THANKS TO DR. JAMES MCNAMARA
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:30-1:45 p.m.</td>
<td>Welcome and introduction</td>
<td>Emily J Gilmore and Nicolas Gaspard</td>
</tr>
<tr>
<td>1:45-2:10 p.m.</td>
<td>EEG Biomarkers of Sleep and Delirium in the Critically Ill</td>
<td>Melissa Knauert</td>
</tr>
<tr>
<td>2:10-2:35 p.m.</td>
<td>Pathophysiology of Sepsis Associated Brain Dysfunction</td>
<td>Emily J Gilmore</td>
</tr>
<tr>
<td>2:35-3:00 p.m.</td>
<td>The Value of CEEG for Predicting Outcome after Cardiac Arrest</td>
<td>Adithya Sivaraju</td>
</tr>
<tr>
<td>3:00-3:15 p.m.</td>
<td>BREAK</td>
<td></td>
</tr>
<tr>
<td>3:15-3:40 p.m.</td>
<td>Metabolomics Approach to Vasospasm</td>
<td>Ketan Bulsara</td>
</tr>
<tr>
<td>3:40-4:05 p.m.</td>
<td>Towards the Next Generation of Delayed Cerebral Ischemia Detection</td>
<td>M Brandon Westover</td>
</tr>
<tr>
<td>4:05-4:30 p.m.</td>
<td>EEG Biomarkers of Epileptogenesis After Acute Brain Injury</td>
<td>Rup Sainju</td>
</tr>
<tr>
<td>4:30-4:55 p.m.</td>
<td>The Treatment of Refractory Status Epilepticus</td>
<td>Andres Fernandez</td>
</tr>
<tr>
<td>4:55-5:20 p.m.</td>
<td>The Spectrum of New-Onset Refractory Status Epilepticus</td>
<td>Nicolas Gaspard</td>
</tr>
<tr>
<td>5:20-5:30 p.m.</td>
<td>Closing remarks</td>
<td></td>
</tr>
</tbody>
</table>
Slide Session I: Neuroimaging
EEG and fMRI Predicts Behavioral Impairment in Absence Seizures


*Rationale:* Childhood absence epilepsy (CAE) is often characterized by brief episodes of impaired consciousness and 3–4 Hz spike and wave discharges on EEG. Several neuroimaging studies have found involvement of cortical/subcortical attentional systems along with default mode networks in patients diagnosed with CAE. In this study, we employ data-driven methods to relate EEG and fMRI changes to behavioral impairment observed during absence seizures.

*Methods:* Two task designs were used to measure cognitive impairment from patients with CAE during simultaneous EEG-fMRI recordings with 32 EEG channels, and high-density out-of-magnet EEG systems. In the first task paradigm (repetitive tapping task; RTT), patients were asked to press a button in response to letters displayed on a screen every second. In the second task design (continuous performance task; CPT), patients were instructed to respond only when presented with the target letter “X”.

*Results:* A data-driven method applied to fMRI percent change signals yielded three networks of closely related timecourses during absence seizures: default mode networks, task positive networks, and primary sensory cortices and thalamus. fMRI BOLD changes from these three clusters were significantly greater in absence seizures with impaired performance (< 25% correct) than in seizures associated with spared performance (> 75% correct) for both CPT and RTT. Similarly, high-density EEG power changes in the slow-wave frequency range (2.5–4 Hz) were higher for impaired performance seizures.

*Conclusions:* These results suggest that greater changes in fMRI BOLD signals and EEG power are closely related to greater cognitive impairment.
fMRI Changes in a Ferret Model of 3-4 Hz Spike-Wave Seizures


Functional neuroimaging studies have provided key insights on the changes in neurovascular activity associated with human absence seizures. Previous work has identified widespread cortical decreases in blood oxygen-level dependent (BOLD) signal during absence seizures, however the meaning of these decreases remains to be elucidated. Rodent models of epilepsy have failed to replicate this finding, which could be due to several important differences between human and rodent seizures. Human absence seizures occur at a frequency of 3-4 Hz and involve changes in developed cortical regions. Pharmacologic and genetic rodent models produce seizures occurring at 7-8 Hz, and lack a developed cortex capable of replicating human findings. To further investigate the meaning of ictal decreases in BOLD signal, we developed a ferret model of generalized epilepsy. This species contains a gyrated cortex, and previous in-vitro studies have shown ferret thalamic slices are capable of generating a 3-4 Hz rhythm in response to bicuculline. We used 9.4 T BOLD imaging with simultaneous recording of EEG to characterize changes in neurovascular activity during ictal periods. To our surprise, the presence of 3-4 Hz discharge in this model was not sufficient to replicate the BOLD decreases seen in humans. This finding was consistent across seizures of different duration, frequency, and with various analytical techniques. However this model was capable of generating previously described post-ictal decreases during tonic-clonic seizures, reducing the likelihood that technical factors played a role. The mechanism and meaning of ictal decreases during absence seizures will require further study.
Multiphoton Microscopy of Cellular and Network Brain Activity in Awake Mouse During Epileptic Convulsion

Authors: Michael Levene, Markus Wolfel, Hal Blumenfeld

Imaging of neuronal activity in the brain in vivo has provided fundamental insight into information processing in single cells and neural networks. However, forceful movement during epileptic convulsions prevents conventional imaging due to excessive motion artifacts and risk of injury. Therefore, we designed a suspension platform for motion-stabilized imaging of brain activity with sub-cellular resolution. With the animals head fixed in place using an implanted head mount, the animal rests on a suspension platform underneath. This protects the animal from force exerted against the implant, and removes motion artifacts in the recorded images. The stabilization system was combined with micro-prism implants to image neurons throughout the full cortical depth. We were able to record activity of neurons throughout tonic-clonic seizures in the awake, convulsing mouse. Single cells stayed in place during recording sessions, and no further motion correction was needed to track cells over time.
Mechanisms of Cortical fMRI Decreases in Absence Seizures Investigated in the Awake Mouse

Authors: Florian Serout, Jeanette Chin, Hiam Naiditch, Qiong Zhan, Abhijeet Gummadavelli, Eric Chen, Peter Herman, Basavaraju G. Sanganahalli, Fahmeed Hyder, Hal Blumenfeld

Numerous animal models of childhood absence epilepsy exist but none have shown perfect similarity to human patients, especially regarding the fMRI changes associated with spike-wave seizures. Previous work on children with absence epilepsy has shown a marked decrease in the cortical fMRI signal persisting long after the seizure’s end. However, experiments in rat, ferret and non-human primate animal models have shown mainly cortical fMRI increases in spike-wave seizures. Our hypothesis is that the anesthesia is responsible for the differences between animal models and human absence seizures. Anesthetic agents may prevent a normal physiological response to absence seizures and could mask the resulting fMRI decreases in the cortex. In order to assess this hypothesis and provide an animal model of absence seizures more similar to the human condition, we have begun to perform EEG-fMRI, as well as Laser Doppler Flowmetry and Multi-Unit Activity (MUA) recordings on awake C3H/HeJ mice, a relatively pure absence seizure model. Initial results have shown the feasibility of obtaining spike-wave seizures in head-fixed C3H/HeJ mice both in the high field fMRI setting with simultaneous EEG, as well as the opportunity to directly record neuronal physiology and cerebral blood flow through bench experiments. Ongoing investigations with this model may determine whether the fMRI decreases observed in human patients in absence seizures are associated with decreased electrical activity of cortical neurons, or another mechanism for altered cerebral blood flow following seizures.
Slide Session II: Animal Model
Physiology of Slack Sodium-Activated Potassium Channels in Epilepsy

Authors: Imran Quraishi, Grace Kim, Jack Kronengold, Leonard Kaczmarek

I will present the current state of our research into how sodium-activated potassium channels contribute to epilepsy. Slack (Kcnt1) is a potassium channel that is unique because of its sodium activation and unusually large C-terminal cytoplasmic domain that interacts with Fragile X Mental Retardation Protein (FMRP), which is essential for normal cognitive development. Slack mutations have been identified in patients and families with a variety of epilepsy syndromes, including migrating malignant partial seizures of infancy (MMPSI), Ohtahara syndrome, West syndrome, and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Slack-associated epilepsies may lead to severe epileptic encephalopathy, epilepsy with neuropsychiatric features, or less commonly epilepsy without cognitive or psychiatric manifestations. All of the epilepsy-associated mutations are associated with gain of function as determined by increased Slack conductance in a heterologous expression system (Xenopus oocytes). Single channel conductance is either unchanged, increased, or decreased by different mutations. The increased whole cell conductance may be explained in part by positive cooperativity between neighboring channels and by constitutive phosphorylation behavior. Slack knockout mice display marked learning deficits and a small reduction in maximum electroshock seizure thresholds as compared to wild type. Future studies will address the influence of mutated channels in neuronal culture, animal models, and simulated epileptic cortical networks. We believe these studies of Slack physiology will provide insights into the mechanisms of epileptogenesis and cortical development, as well as a potential new therapeutic target for antiseizure medications.
Decreased Subcortical Cholinergic Arousal in Limbic Seizures

Authors: Zaina Zayyad, Joshua E. Motelow, Wei Li, Asht M. Mishra, Robert N. S. Sachdev, Geoffrey Liu, Abhijeet Gummadavelli, Hyun Seung Lee, Victoria Chu, Dario J. Englot, Peter Herman, Basavaraju G. Sanganahalli, Fahmeed Hyder, Hal Blumenfeld

Subcortical arousal systems play a critical role in the normal operation of the waking brain. During loss of consciousness in deep sleep and coma, slow waves arise in the cortex, accompanied by reduced subcortical arousal. These same phenomena are observed during complex partial limbic seizures arising in the temporal lobe. We are interested in understanding the mechanism for impaired consciousness and cortical slow oscillation during these focal seizures with impaired consciousness. In experiments using blood oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI), we observed broad suppression of arousal systems during hippocampal seizures in a rodent model. We conducted juxtacellular recordings in the brainstem and observed reduced firing of cholinergic neurons in focal limbic partial seizures. Furthermore, using enzyme-based amperometry, we found reduced choline levels in the cortex and thalamus. Consequently, the mechanism for impaired consciousness during complex partial limbic seizures resembles slow-wave sleep initiation as opposed to seizure propagation to the cortex.
Deep Brain Stimulation to Prevent Impaired Consciousness in Epilepsy

Authors: Abhijeet Gummadavelli, Joshua E. Motelow, Nicholas D. Schiff, Dennis D. Spencer, Jason Gerrard, Hal Blumenfeld

Abstract: For patients with medically refractory epilepsy, the ability to remain conscious despite seizure occurrence would provide a dramatic improvement in quality of life, morbidity and mortality. Our lab developed a rodent model of complex partial seizures which mimics the human cortical electroencephalographic signature of ictal neocortical slow waves (0-2 Hz) and behavioral arrest associated with loss of consciousness (Englot et al, 2008). Using this model, we measured suppression of subcortical arousal systems including the brainstem cholinergic and intralaminar thalamic nuclei (Motelow et al, 2014). Stimulation of central lateral thalamic nuclei has improved measures of consciousness in a patient from minimally conscious state after traumatic brain injury (Schiff et al, 2007). We show restored measures of consciousness in the anesthetized and awake-behaving animal model by stimulating the central lateral thalamic nuclei under anesthesia and during seizures. We stereotactically implanted electrodes and confirmed localization with histology. We stimulated at varying current intensities (ranging from 0.1 μA to 3mA, unilaterally and bilaterally) at 100 Hz while synchronously recording behavior with video and electrophysiology with electrodes in the lateral orbitofrontal cortex and hippocampus. Thalamic stimulation under anesthesia shows loss of cortical slow waves in a current dose-responsive fashion, and behavioral arousal with head, tail and limb movement. Ictal and post-ictal stimulation shows similar decrease in cortical slowing, associated behaviorally with increased arousal. These data suggest a novel therapeutic approach for restoring consciousness during seizures. If paired with responsive neurostimulation, it may lead to rapid implementation of a therapy for preventing impaired consciousness in patients.
State-Dependent Cardio-Respiratory Consequences of Seizures

Authors: Gordon F. Buchanan, Michael A. Hajek, Daniel A. Rappoport and Kumiko I. Claycomb

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in refractory epilepsy patients. In most cases the direct cause of death is likely seizure-induced respiratory arrest, though cardiac arrest or suppression of cerebral activity may be responsible in some patients. Intriguingly, SUDEP tends to occur at night. Why this is the case is not known, but there is a complex relationship between seizures, sleep-wake state, circadian phase, regulation of breathing, cardiac control, and regulation of the neurotransmitters involved in modulation of all of these. Here we aimed to determine whether there are state-dependent effects of seizures on cardiac and respiratory function that may contribute to seizure-related death. Seizures were induced with maximal electroshock (MES) in seizure naïve mice or amygdala stimulation (AS) in kindled mice. EEG, EMG, EKG, breathing and video were recorded before, during and after seizures. Vigilance state was determined in real-time using EEG, EMG and behavioral parameters. Preliminarily, we have found that seizures induced via MES during sleep were more likely to be fatal, especially those induced during REM sleep. Mice that survived seizures induced by MES or AS displayed increased post-ictal respiratory rate variability and a greater number of apneas when seizures were induced during NREM sleep. Furthermore, mice that eventually died when seizures were induced during sleep tended to have more irregular baseline breathing. There was no state-dependent difference in effects of seizures on cardiac activity. These data support that there are state-dependent effects on breathing that may contribute to seizure-related death.
Cortical and Subcortical Mechanisms of Impaired Breathing in a Rodent Partial Seizure Model and Implications for SUDEP

Authors: Qiong Zhan, Joshua E. Motelow, Abhijeet Gummadavelli, Moran Furman, Wei Li, John Andrews, Gordon F. Buchanan, George B. Richerson, Hal Blumenfeld

Seizures have both local and remote effects on nervous system function. Focal seizures can propagate from the site of onset to engage a larger network and induce severe consequences including impaired arousal, cardiorespiratory changes and in some cases death. Impaired breathing during and following seizures is increasingly recognized as an important cause of sudden unexpected death in epilepsy (SUDEP). Impaired breathing in seizures has been compared to sudden infant death syndrome (SIDS), in which deficits in serotonergic arousal may contribute to impaired respiratory drive and impaired arousal in response to CO2 retention while lying face down, leading to asphyxia and death. We now utilize an acute rat model of limbic seizures to measure changes in breathing and in the firing patterns of brainstem nuclei using extracellular multiunit and juxtacellular recordings. We found that during limbic seizure the breathing is markedly impaired, possibly related to seizure propagation beyond the site of onset. The firing of neurons in the midbrain and medullary raphe nuclei is dramatically decreased during the ictal and post-ictal period. Based on these results, we suggest that seizures may propagate to inhibitory circuits which depress the ascending and descending arousal systems. Failure of the ascending arousal system to maintain consciousness and of the descending arousal system to stimulate the respiratory network may both be important factors in SUDEP. Improved mechanistic understanding of these pathways may lead to improved treatments to prevent this significant cause of death in people living with epilepsy.
Poster Session
Distinct Contribution of Different Interneuron Subtypes to Network Stability in Vivo

Author: M. MIRI*, J. A. CARDIN

GABAergic inhibition is critical for regulation of excitation and is thought to maintain neural network stability through a precise balancing process. Loss or dysfunction of inhibitory interneurons is thought to lead to abnormal activity patterns and ultimately to seizure initiation. Two major interneuron classes are the Parvalbumin-expressing (PV), fast-spiking cells and Somatostatin-expressing (SOM), low-threshold spiking cells. Due to differing physiology, biophysical properties, and synaptic targeting, they may contribute differently to ongoing computations in the surrounding local network. Previous studies have examined preferential interneuron vulnerability leading to or resulting from seizures, but there the roles of specific sources of inhibition in seizure generation remain unclear. Using combined optical and electrophysiological tools, we can investigate network dynamics during the development of seizures by monitoring the activity of individual interneurons and synchronization between multiple hippocampal cell types.

Here we used two transgenic mouse lines: PV-Cre and SOM-Cre. Using AAVDIO-ChR2-mCherry, we selectively targeted optogenetic tools to PV or SOM interneurons in CA1. During experiments, we used stereotrode arrays to extracellularly record the activity of many simultaneous cells in hippocampal CA1 in animals lightly anesthetized with ketamine/xylazine. We identified targeted ChR2-expressing PV and SOM interneurons in the recorded population by stimulating with brief pulses of blue light at 473nm. Light pulses were continued throughout the experiment to track identified neurons without altering the pattern of spontaneous activity. Using a pharmacological model of seizure induction (PTZ), we performed measurements of neural activity during three periods: 1) baseline 2) early preictal and 3) late preictal. We first assessed the recruitment of local excitatory neurons by ictal activity. We further assessed the temporal pattern of identified interneuron activity during each period and the relationship between interneuron and excitatory neuron activity.

To examine the relationship between local network activity and interneuron spiking,
we calculated the spike-triggered LFP average for each cell during each period. We find that PV+ cells have a lower spike probability in response to blue light pulses that progressively decreases from baseline to late preictal stages. Additionally, we find that average local synaptic activity increases surrounding spike times of identified RS cells during both early and late preictal periods, as compared to baseline. These preliminary results demonstrate that these combined approaches provide a powerful set of tools for dissecting network activity during seizure initiation.
Examining the Intracranial EEG Second Spectrum for Evidence of Support for the Default Mode Network

Authors: Rasesh B. Joshi, Nicolas Gaspard, Irina I. Goncharova, Jason L. Gerrard, Dennis D. Spencer, Lawrence J. Hirsch, Hitten P. Zaveri

It has been shown previously that the intracranial EEG (icEEG) relationship within the default mode network (DMN) was not significantly greater than between DMN locations and a control location, indicating a lack of support for the DMN in the icEEG. However, recent literature suggests that the electrophysiological basis of these networks may lie in coherent slow amplitude modulations of different frequency bands, i.e. in the second spectrum, rather than in synchronization of the icEEG. In particular, studies performed with resting state magnetoencephalography (MEG) suggest that the electrophysiological correlates of the DMN can be observed in the alpha band second spectrum. We examined the icEEG second spectrum for evidence of support for the DMN.

We first sought to characterize the magnitude-squared coherence (MSC) estimator to determine a threshold for when an MSC value can be considered significantly nonzero and to determine the ideal parameters to be used in the MSC calculation. We studied a total of 12 patients. For each patient, we selected a one-hour icEEG epoch when the patient appeared to be resting quietly with eyes open. For each one-hour segment, we calculated the running power, at a one-second resolution, in different frequency bands (delta, theta, alpha, beta, and gamma). For each band power time-series, we then calculated the average coherence in frequencies less than 0.15 Hz for every possible electrode contact pair. We aggregated these values for all patients and examined how second spectrum connectivity changes with distance, second spectrum relationships between different lobes of the brain, as well as whether DMN-specific contacts exhibit enhanced connectivity in the second spectrum.

Interestingly, we found that second spectrum coherence is relatively high in the delta band for short distances (less than 5 cm). Furthermore, we observed that second spectrum coherence decreases in higher frequency bands, with the lowest values in the gamma band. Analysis of DMN-specific contacts did not show any evidence in support of the DMN. Second spectrum coherence in the DMN contacts was significantly nonzero only in the delta, theta, and alpha bands. In these bands, there was no significant difference between relationships within the DMN locations and between the DMN location and a control location.
The Relationship Between Intracranially Detected Interictal Spikes and Extracellular Glutamate in Patients with Medically Intractable Epilepsy

Authors: Nimisha Ganesh, Caroline Ong, Irina I. Goncharova, Clayton Haldeman, Eyiyemisi Damisah, Ognen A. C. Petroff, Dennis D. Spencer, Tore Eid, Hitten P. Zaveri

Abstract: Recent research from our laboratory suggests that interictal spikes may represent inhibition rather than excitation. Research from our center has also established the presence of elevated basal levels of extracellular glutamate in the epileptic brain. Here we sought to correlate interictal spikes and basal extracellular glutamate concentrations in patients (n=20) undergoing intracranial EEG (icEEG) monitoring for epilepsy surgery. Spike counts were documented for the two icEEG contacts on either side of the microdialysis membrane, all contacts within 3cm of each probe, and all contacts within the region surrounding the probe. Additionally, basal glutamate and glutamine values were correlated with the probe distance from the seizure onset area. The basal glutamate and basal glutamine values were negatively correlated with the probe distance to seizure onset area with correlation coefficient values of 0.2 (p=0.06) and 0.4 (p=0.001), respectively. We observed a slightly negative correlation between the basal glutamate values and spike counts. The correlation coefficient values for the probe contacts, contacts within 3cm, and regional contacts were 0.07, 0.08, and 0.14, respectively. In areas of high spiking, basal glutamate values were particularly low. The higher basal glutamate and glutamine values closer to the seizure onset area suggest a correlation between increased glutamate and glutamine levels and the seizure onset area. The slight negative correlation observed between basal glutamate level and spike counts, moreover, support the suggestion that spikes may instead be a measure of brain inhibition. This study suggests considerable value for co-local in-vivo measurements of electrophysiology ad neurochemistry to improve our understanding of the pathophysiology of medically intractable epilepsy.
Factors Influencing Driving Impairment in Persons with Refractory Epilepsy

Authors: Vineet Punia, Pue Farooque, William Chen, Lawrence J. Hirsch, Anne T. Berg, the Multi-Center Study of Epilepsy Surgery, Hal Blumenfeld

Objectives: To evaluate factors related to seizures that potentially impair driving leading to motor vehicle accidents (MVA) in people with medically refractory epilepsy.

Methods: We used the Multicenter Study of Epilepsy Surgery (MSES) database to identify patients who reported having seizures while driving. We divided this population in two groups: ones in whom seizures while driving led to a MVA (“Accident” group) and those who had seizures while driving that did not lead to a MVA (“No Accident” group). We then compared these two sub-groups for different variables that could potentially affect the risk of MVA.

Results: 215 patients out of a total of 553 patients reported having seizure(s) while driving. 74 formed part of the “No Accident” group and 141 were in the “Accident” group. The two groups did not differ in terms of age, sex distribution, seizure localization, ictal duration, motor impairment during seizure and AED history. Interestingly, they also did not differ (p = 0.76; OR = 0.89, CI 0.49 – 1.61) based on presence of reliable auras. We found that patients were more likely to have MVA due to a seizure if they had a history of complex partial seizure (CPS) (p = 0.029; OR = 2.83, CI 1.14-7.09) or if they had one or more CPS on an average each month for last 3 months prior to interview (p = 0.01; OR = 2.52, CI 1.22-5.21). Patient in “No accident” group were found to have longer duration (>1 minute) of post-ictal state (p = 0.05; OR = 2.53, CI 1.04 – 6.19).

Conclusions: Our study shows that reliable auras do not provide protective benefit against MVA, which questions the long held belief that the reliability of auras is a favorable modifier in preventing MVAs. We also found that CPS, possibly implying impaired consciousness, may be the most salient feature of seizures affecting the ability to drive safely.
Reliability of Patient Report of Impaired Consciousness During Seizures

Authors: Yang Si, Adeolu Morawu, Yigit Baykara, Rahiwa Gebre, William Chen, Petr Vitkovskiy, Ningcheng Li, Michelle Johnson, Eric Chen, Dan Kluger, Hal Blumenfeld

Epileptic seizures often cause loss of consciousness (LOC). However, patient report of their mental state during seizures can be unreliable, making diagnosis of epilepsy and guidance on patient safety issues difficult for clinicians. The present study used a daily questionnaire administered to epilepsy inpatient undergoing continuous video-EEG monitoring to study the reliability of patient report of their consciousness during seizures. Patients with episodes during the monitoring were questioned whether they were aware of their surroundings, were responsive, and were able to speak during their seizures. These subjective reports were compared with their actual ictal behavior on video EEG. A total of 37 seizures in 17 patients were analyzed. Among those with ictal unconsciousness, self-report of loss of awareness, inability to respond and speak during the events was highly accurate. Among those with spared consciousness, self-report was not always consistent with the real ictal performance and tended to overestimate ictal impairment of consciousness. These findings indicated that epilepsy patients with ictal LOC may be able to report this fact correctly.
Cosmetic Adverse Effects of Antiepileptic Drugs In Adults With Epilepsy


Introduction Adverse cosmetic effects (ACEs) can occur in patients taking antiepileptic drugs (AEDs). The objective of the study was to compare the ACE profiles among both older and newer AEDs.

Methods We reviewed patient records including demographics, medical history, AED use, and side effects for 1903 adult epilepsy patients (age ≥ 16 years). ACEs included were acne, gingival hyperplasia, hair loss, hirsutism, and weight gain. We compared the AED-attributed ACEs and intolerable ACE (i.e. ACE that led to AED dosage reduction or discontinuation) in patients newly started on an AED after controlling for gender.

Results Overall, ACEs occurred in 110/1903 (5.8%) patients, and led to intolerability in 70/1903 (3.7%) patients. 37.2% of patients who had at least one ACE developed additional ACEs. Female patients (7.0%) reported more ACEs than male patients (4.3%; P < 0.05). Weight gain was more commonly reported in patients using pregabalin (8.4%; P < 0.001) and valproic acid (13.0%; P < 0.001), hair loss was more commonly seen in patients taking valproic acid (8.9%; P < 0.001), and more patients taking phenytoin developed gingival hyperplasia (2.5%; P < 0.001) compared to average.

Conclusion There is significant variability amongst all AEDs in terms of their ACE profiles. Particular attention should be paid to pregabalin, phenytoin, and valproic acid when considering ACEs. Patients who have had an ACE to an AED and/or are female may be more susceptible to AED-attributed ACEs. Our findings may help clinicians to better assess the risk/benefit ratios in the AED selection process.
Table 1. Comparison of AED-attributed ACEs in adults with epilepsy newly started on an AED.

<table>
<thead>
<tr>
<th>AED</th>
<th>n</th>
<th>ACE % (n)</th>
<th>‡P-value</th>
<th>‡OR</th>
<th>IACE % (n)</th>
<th>‡P-value</th>
<th>‡OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>326</td>
<td>1.5 (5)</td>
<td>0.031*</td>
<td>0.40  (0.18, 0.92)</td>
<td>0.6 (2)</td>
<td>0.045*</td>
<td>0.31  (0.10, 0.97)</td>
</tr>
<tr>
<td>CLB</td>
<td>80</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>FBM</td>
<td>53</td>
<td>1.9 (1)</td>
<td>NS</td>
<td>0.89  (0.21, 3.64)</td>
<td>1.9 (1)</td>
<td>NS</td>
<td>1.37  (0.33, 5.72)</td>
</tr>
<tr>
<td>GBP</td>
<td>251</td>
<td>2.8 (7)</td>
<td>NS</td>
<td>0.74  (0.36, 1.52)</td>
<td>1.2 (3)</td>
<td>NS</td>
<td>0.55  (0.20, 1.52)</td>
</tr>
<tr>
<td>LCM</td>
<td>86</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>LEV</td>
<td>524</td>
<td>1.3 (7)</td>
<td>0.002*</td>
<td>0.32  (0.15, 0.65)</td>
<td>1.0 (5)</td>
<td>0.019*</td>
<td>0.37  (0.16, 0.85)</td>
</tr>
<tr>
<td>LTG</td>
<td>521</td>
<td>1.9 (10)</td>
<td>0.012*</td>
<td>0.45  (0.24, 0.84)</td>
<td>1.0 (5)</td>
<td>0.020*</td>
<td>0.37  (0.16, 0.86)</td>
</tr>
<tr>
<td>OXC</td>
<td>160</td>
<td>0.6 (1)</td>
<td>NS</td>
<td>0.28  (0.07, 1.13)</td>
<td>0.6 (1)</td>
<td>NS</td>
<td>0.43  (0.11, 1.78)</td>
</tr>
<tr>
<td>PB</td>
<td>98</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>PGB</td>
<td>143</td>
<td>9.8 (14)</td>
<td>&lt; 0.001**</td>
<td>2.85  (1.63, 5.01)</td>
<td>5.6 (8)</td>
<td>0.011*</td>
<td>2.51  (1.24, 5.09)</td>
</tr>
<tr>
<td>PHT</td>
<td>404</td>
<td>4.2 (17)</td>
<td>NS</td>
<td>1.07  (0.65, 1.78)</td>
<td>3.2 (13)</td>
<td>NS</td>
<td>1.32  (0.74, 2.34)</td>
</tr>
<tr>
<td>PRM</td>
<td>14</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>TGB</td>
<td>25</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>TPM</td>
<td>230</td>
<td>1.7 (4)</td>
<td>NS</td>
<td>0.49  (0.20, 1.20)</td>
<td>1.7 (4)</td>
<td>NS</td>
<td>0.77  (0.31, 1.92)</td>
</tr>
<tr>
<td>VGB</td>
<td>32</td>
<td>3.1 (1)</td>
<td>NS</td>
<td>1.48  (0.35, 6.26)</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>VPA</td>
<td>270</td>
<td>21.9 (59)</td>
<td>&lt; 0.001**</td>
<td>10.40 (7.26, 14.88)</td>
<td>13.3 (36)</td>
<td>&lt; 0.001**</td>
<td>8.55 (5.54, 13.18)</td>
</tr>
<tr>
<td>ZNS</td>
<td>230</td>
<td>0.9 (2)</td>
<td>0.033*</td>
<td>0.29  (0.09, 0.91)</td>
<td>0.0 (0)</td>
<td>NS</td>
<td>-</td>
</tr>
</tbody>
</table>

Average: 3.7

Abbreviations: AED: Antiepileptic Drug; ACE: Adverse Cosmetic Effects; CBZ: carbamazepine; CI: Confidence Interval; CLB: clobazam; FBM: felbamate; GBP: gabapentin; IACE: Intolerable Adverse Cosmetic Effects; LCM: lacosamide; LEV: levetiracetam; OR: Odds Ratio; OXC: oxcarbazepine; PB: phenobarbital; PGB: pregabalin; PHT: phenytoin; PRM: primidone; TGB: tiagabine; TPM: topiramate; VGB: vigabatrin; VPA: valproate; ZNS: zonisamide

** Significant: p < 0.003
*Trend: 0.003 < p < 0.05

‡ controlled for gender

** Significant: p < 0.003
*Trend: 0.003 < p < 0.05
Seizure Control for Intracranial Arteriovenous Malformations is Directly Related to Treatment Modality: A Meta-analysis

Authors: Jacob F. Baranoski, B.S., Ryan A. Grant, M.D., M.S., Lawrence J. Hirsch, M.D., Paul Visintainer, Ph.D., Jason L. Gerrard, M.D., Ph.D, Murat Günel M.D., Charles C. Matouk, M.D., Ketan R. Bulsara, M.D.

Object – Seizures are a common presenting sign of intracranial arteriovenous malformations (AVMs). The object of this meta-analysis was to determine if the modality selected to treat AVMs affects the rate of seizure-free outcomes.

Methods – All published data describing seizure status as an outcome goal over the last 20 years were included in this study. Seizure outcomes following microsurgery (MS), endovascular embolization for cure (EVE), or stereotactic radiosurgery (SRS) were compared using a validated random-effect logistic regression approach.

Results – Twenty-four studies, with a total of 1157 patients, were analyzed. Overall, the microsurgical group had the best seizure control (p<0.01), with the relative predicted rates of seizure-free outcome as follows: MS 78.3% [95% CI, 70.1-85.8%]; SRS 62.8% [95% CI, 55.0-70.0%]; EVE 49.3% [95% CI, 32.1-66.6%]. However, further analysis revealed that for patients with unruptured AVMs, MS and SRS were equally efficacious. Patients in the SRS group who had complete obliteration of their AVMs achieved the highest rate of seizure-free outcomes at 85.2% [95% CI, 79.1-91.2%] (p<0.01). The development of new-onset seizures occurred more frequently in patients undergoing EVE (39.4% [95% CI, 8.1-67.8%]) compared to MS (9.1% [95% CI, 5.0-13.1%]) and SRS (5.4% [95% CI, 3.0-7.8%]) (p<0.3 and p<0.01, respectively).

Conclusions – This is the first meta-analysis designed to study relative rates of seizure-free outcomes following the currently utilized AVM treatment modalities. In general, microsurgery results in the highest proportion of seizure-free outcomes. However, if stereotactic radiosurgery results in successful obliteration of the AVM, then this modality is the most effective in achieving seizure-control.
Forrest Plot for Seizure-Free Outcomes

Percent of Patients with Seizure-Free Outcomes

MS
- Pipgras et al., 1993
- Hoh et al., 2002
- Hyun et al., 2012
- Thorpe et al., 2000
- Nagata et al., 2006
- Yeh et al., 1993
- Englot et al., 2012

SRS
- Zeller et al., 2012
- Gertszten et al., 1996
- Nataf et al., 2003
- Kurita et al., 1998
- Silander et al., 2004
- Yang et al., 2012
- Steiner et al., 1992
- Hyun et al., 2012
- Falkson et al., 1997
- Kida et al., 2000
- Elschenbenk et al., 1998
- Lim et al., 2006
- Schaub et al., 2004
- Andrade-Souza et al., 2006
- Hoh et al., 2002
- Sutcliffe et al., 1992

EVE
- Lv et al., 2010
- Hyun et al., 2012
- Hoh et al., 2002
- De Los Reyes et al., 2011
- Le Feuvre et al., 2007
Advances in Neuropsychological Testing in Epilepsy; the Importance of Non-Neurological Variables While Interpreting Tests

Author: Franklin C. Brown

Neuropsychological evaluations are an important part of presurgical evaluations. In addition to being useful to better understand cognitive correlates with epileptogenic and irritative zones. In addition, presurgical memory tends to be as good, if not better, a predictor of postsurgical memory. However, such tests are only useful if the performance is a valid representation of neurological functioning, and not due to confounding variables. This presentation discusses some advances in studying factors that can affect performance such as medications, anxiety, age effects, and the degree to which tests can actually measure their purported construct. Furthermore, several published studies and case reports will be provided to demonstrate the impact that such variables have on performance.
Glutamine Synthetase inhibition and the Methionine-Sulfoximine Rat-Model of Epilepsy

Authors: Edgar Perez, Helen Wang, Hitten Zaveri, Ronnie Dhaher, Tore Eid

Glutamine synthetase (GS) has been found to be deficient in the hippocampus of patients with MTLE. The role of glutamine synthetase deficiency in the generation of seizures is being explored in a newly developed rat model of MTLE involving infusion of methionine sulfoximine (MSO), an inhibitor of GS, in the entorhinal cortex. We are assessing the effects of MSO after a chronic infusion (28 days) and after an acute infusion (72 hours) on seizure outcome and pathology. The goal is to assess whether restoration of GS leads to cessation of seizures in the presence of extensive brain pathology. In a subset of rats infused for 72 hours, seizures were still observed after an extensive latent period, suggesting a possible secondary process involved in epileptogenesis assuming that GS has been restored to normal. We hope that we can leverage this knowledge to determine time-sensitive perturbations leading to epilepsy and when it might be appropriate to intervene in terms of treatment.
Slide Session III:
Clinical/Electrophysiology
Characteristics of Patients with “Poorly – Localized” Ictal Onset on Intracranial EEG

Authors: Adithya Sivaraju; Jeremy J. Moeller; Irina Goncharova; Hitten Zaveri; Robert B. Duckrow

Introduction: Intracranial EEG monitoring offers a unique and precise way of localizing seizure onset in humans. Various patterns of seizure onset & propagation have been well described in the literature. However, most of this data has been devoted to describing well-defined ictal onset patterns/seizure onset zones (SOZ). We seek to identify & describe the characteristics of patients with poorly localized ictal onset on Intracranial EEG. The extensive degree of electrode coverage at our institution offers us a unique opportunity to conduct this study.

Methods: Retrospective chart review of prospectively collected patient data. This includes all patients who underwent intracranial EEG monitoring for seizure localization at Yale New Haven Hospital, from January 2002 to March 2014. The raw EEG data was reviewed by three independent board certified neurophysiologists, with extensive experience in interpreting intracranial EEG’s. 9 Zones were defined as Medial frontal (MF), Dorsolateral frontal (DF), Orbito frontal (OF), Lateral temporal (LT), Medial temporal (MT), Inferior temporal (IT), Lateral parietal (LP), Medial parietal (MP), & Occipital (O). We defined poorly localized as involving ≥ 2 of the above defined zones (contiguous or non-contiguous) with a minimum of 10 electrode contacts at onset; and without a clear lead in of at-least 200 ms. After patient identification based on EEG findings, we reviewed clinical, radiologic and electrophysiologic data (including scalp EEG) for each patient.

Results and Conclusion: Pending
Investigating Consciousness using Human Intracranial Recordings

Authors: Wendy Xiao, Reba Watsky, William Chen, Erik Levinsohn, Dennis D. Spencer, Jason Gerrard, Hal Blumenfeld

The mechanism by which perceived stimuli are processed and encoded into consciousness has been extensively studied with behavioral tasks. The addition of imaging and electrophysiology methods can elucidate the temporal and spatial location of the sequences necessary to study the process by which some stimuli are consciously perceived and later reportable while others are not. We hypothesize that this selection mechanism is related to memory circuits interacting with sensory and attentional circuitry. We have developed a behavioral task paradigm with which to study the mechanism of conscious report by showing a face stimulus image titrated to threshold perception levels of transparency. Subjects validate their subjective perception of the stimulus by also objectively reporting the location of the face. While subjects report perceiving the face about 48% of the time, they are able to locate the stimulus 90% of the time when they do perceive it. We have collected intracranial EEG data from two subjects, and have been able to successfully elicit an N170 event-related potential (ERP) following the face stimulus in the fusiform face area as well as visual cortex ERPs after the presentation of the stimulus. We plan to use this behavioral task in conjunction with imaging methods such as functional MRI and intracranial EEG to elucidate the brain activity patterns in memory and attention regions associated with conscious experience.
Functional Connectivity, the Default Mode Network, and the Seizure Onset Area

Authors: Hitten P. Zaveri, Steven M. Pincus, Irina I. Goncharova, Nicolas Gaspard, Jason Gerrard, Lawrence J. Hirsch, Dennis D. Spencer

Purpose: To determine the relationship between band-related local functional connectivity (LFC) of the background intracranial EEG (icEEG) and the seizure onset area (SOA).

Method: This study was conducted on 1 hr icEEG epochs recorded from 18 unselected adult patients with localization related epilepsy (LRE) undergoing monitoring for possible epilepsy surgery. The LFC of each electrode contact was estimated as the average coherence between it and all electrode contacts within a specified distance of it. In a separate study, we tested if a relationship between distant parts of the default mode network (DMN), a resting state network defined by fMRI studies, could be observed in the icEEG.

Key Findings: A graded relationship was observed between band-related LFC and distance to the SOA such that electrode contacts with the greatest connectivity were closest to the SOA and those with the lowest connectivity were at a distance of several cm from the SOA. This relationship between distance to the SOA and connectivity was present primarily in the theta, alpha, beta, gamma and high frequency bands, with lesser effect being seen in the delta frequency band. We did not observe a relationship in the icEEG between distant parts of the DMN, suggesting a lack of icEEG support for the DMN.

Significance: There is altered band-related LFC, spatially co-localized with the SOA, in the background icEEG of patients with LRE. This altered band-related LFC may be a marker of the SOA in LRE, and may suggest a role for aberrant connectivity in the generation of seizures.
Antiepileptic Drug Development: Failure?

Author: Richard H. Mattson, M.D.

More than a century and a half ago bromides were discovered to be effective in preventing seizures in symptomatic epilepsy with focal (partial) onset seizures. Twenty one (21) compounds are currently available to treat the problem, but no clear evidence shows one drug possesses significantly more efficacy. A third of patients can not be controlled. Serendipity, “brute force” and designer methods have not changed this fact. Drugs decreasing neuronal excitability or enhancing inhibition via multiple mechanistic targets all have similar results. A final pathway may limit the efficacy due to adverse effects.

New approaches are needed. Methods to prevent tolerance, new models, genetic manipulation and non pharmacological tools may help.
Objective: We sought to understand how sleep structure changes during intracranial EEG (icEEG) monitoring of epilepsy patients and the effect of seizures and antiepileptic drugs (AEDs) on these changes.

Methods: We developed a metric of sleep structure calculated from relative delta power to evaluate sleep quality during continuous icEEG monitoring. We used this metric to analyze trends in sleep quality over multiple nights in the icEEG of 15 patients. We then analyzed subsets of these patients to determine the effect of seizures and AEDs on these trends.

Results: There was a significant increase in sleep quality over the term of icEEG monitoring. We further observed that seizures and AEDs did not have a significant effect on this trend.

Conclusions: Our results suggest that sleep quality improves during icEEG monitoring, regardless of seizures and AEDs. It is possible that this improvement is due to the patient recovering from surgical implantation of intracranial electrodes and acclimating to the epilepsy monitoring unit (EMU), and that the effect of this adjustment outweighs the detrimental effects of seizures and AEDs.

Significance: Our study suggests the presence of a considerable normalizing trend in sleep during long-term icEEG monitoring. This suggests that icEEG epochs for sleep analysis should be selected from later in the term of monitoring, when the patient is more likely to be sleeping properly. This observation may help guide analysis of interictal spikes and other epileptiform discharges, the study of high-frequency oscillations, and the evaluation of the relationship between sleep and epilepsy, all of which depend directly on patient state.
Prospective Evaluation of Driving During Seizures Using Driving Simulation on the Video/EEG Monitoring Unit

Authors: William C. Chen, Andrew Bauerschmidt, Mark W. Youngblood, Courtney Cunningham, Cel Ezeani, Zachary Kratochvil, Jared Bronen, James Thomson, Dan Kluger, Ningcheng Li, Katherine Riordan, Ji Yeoun Yoo, Romina Shirka, Louis Manganas, Andres Fernandez, Anupama Alareddy, Rup Sainju, Adithya Sivaraju, Imran Quraishi, Lawrence J. Hirsch, Hal Blumenfeld

Restrictions to driving due to a diagnosis of epilepsy can have significant impact on the everyday lives of people living with epilepsy. There is a need for prospective studies of driving ability in people with epilepsy to inform decision making by patients, health providers, and regulators. In this study, telemetry data from a driving video game played by patients undergoing continuous video/EEG monitoring was captured. 19 patients had a total of 30 seizures during driving gameplay. Quantitative criteria and video review were used to determine the presence or absence of impairment in driving, consciousness, and motor control before, during and after seizures. Seizures causing loss of consciousness were invariably associated with severe driving impairment and crash. 100% (8/8) of seizures with loss of consciousness and 36% (4/11) of seizures without loss of consciousness were associated with driving impairment (p≤0.05, Fisher’s exact test). In addition, 57% (4/7) of seizures with disruptive motor impairment and 28% (5/18) of seizures with non-disruptive or no motor impairment were associated with severe driving impairment. This difference was not significant (p≥0.2, Fisher’s exact test). However, seizures causing severe driving impairment tended to have a greater degree of motor impairment. Among seizures with any motor impairment, those associated with severe driving impairment tended to cause impairment in a greater number of body parts (2.7±0.5 vs 1.0±0.0, p≤0.05, two-tailed Mann-Whitney U-test). These findings and further prospective evaluation of driving ability during seizures may ultimately provide improved evidence-based guidelines for driving restrictions in people with epilepsy.
Slide Session IV: New Directions
aka "Data Free Zone"
Absence seizures are brief periods when the patient loses normal consciousness and is “absent.” These seizures are categorized by generalized spike-wave discharges (SWD) around 10 seconds in duration with abrupt onsets and offsets. Behavioral studies have shown that severe deficits are observed when complex decisions are required while simple repetitive actions are not affected. Electrical recordings and fMRI studies in rodent models have confirmed that deficits are only seen in some specific areas while other areas are spared. To study the effects of absence seizures on behavior, the C3H/HeJ mouse strain can be used due to its spkw1 allele having a mutation in Gria4 (an AMPA glutamate receptor subunit), making the strain prone to absence seizures. The C3H/HeJ mice are trained to complete a licking auditory discrimination task. By running physiological tests concurrently with the behavioral task, we can not only determine the effects of absence seizures on behavior, but also establish which groups of neurons are impaired and which are spared during absence seizures. Preliminary results show that the C3H/HeJ mice can learn the discrimination task and that EEG can be recorded simultaneously to determine seizure durations. It appears that the mice cease licking during absence seizures (Fig. 1). Future direction will involve looking at whether the seizures affect discrimination between the auditory stimuli. We also hope to study how the severity of seizures can affect behavior and to refine the spatial characterization of SWDs to determine the exact subsets of neurons involved in absence seizures.
Figure 1. Lick rate before and after seizures.
Gut-Brain Axis: A Role for Microbiota in Epilepsy?

Author: Tore Eid, M.D., Ph.D.

The human gastrointestinal tract is colonized by over 100 trillion microorganisms, many of which are bacteria (also known as the gut microbiota). Colonization occurs at birth with modest changes in the bacterial composition over the lifespan of the individual. More dramatic changes can occur in response to antibiotic treatment, infection, diet, and stress. The microbiota has important physiological roles in metabolism of nutrients and drugs prior to entry into the systemic circulation, in production of vitamins, and in modulating the immune system. Furthermore, the microbiota has been implicated in an increasing number of pathological conditions such as pseudomembranous colitis, type 2 diabetes, obesity, and autism. We now propose the novel idea that perturbations in the gut microbiota may alter brain excitability and trigger epileptic seizures. We will discuss three possible mechanisms for such a scenario: (1) bacterial synthesis of neuroactive molecules which enter the CNS and modulate synaptic function; (2) effects of bacterial metabolites on the enteric nervous system with signaling to the CNS via the vagus nerve; and (3) immune modulation.
Defining the Risk Factors, Prevalence, and Consequences of Seizure Clusters

Authors: Tenzin Choezom, Jennifer Bonito, Lawrence J. Hirsch, and Kamil Detyniecki

Seizure clusters often occur as a component of a patient’s seizure disorder. Seizure clustering is a phenomenon described as the occurrence of repetitive seizures over a brief period of time, but there is a lack of consensus on a uniform definition. This is a prospective observational study to define the prevalence and characteristics of seizure clustering in the Yale Epilepsy Center patient population.

Patients are categorized according to their reported seizure frequency over the year prior to enrollment into one of the three groups: high risk (prior clusters), Intermediate risk (active epilepsy) and low risk (seizure free). We anticipate recruiting 100 patients in each group for a total of 300 patients. Patients record their seizure descriptions, frequency, episodes of medication non-compliance, use of rescue medications and ER visits using a paper or electronic diary and are followed for a period of one year. Quality of Life in Epilepsy Inventory (QOLIE-31) and seizure severity Questionnaire (SSQ) are administered at baseline and every 6 months. Quality of Life questionnaire (QOLIE-31) is scored out of 100 points where higher scores indicated better function and seizure severity questionnaire (SSQ) is measured on a 7-point scale, where higher scores indicate more severity.

We present preliminary results at baseline for the pattern of clustering, use of rescue medications, seizure severity, and quality of life on the 148 patients recruited so far. Overall, 48 out of 148 (32.4%) patients reported seizure clustering in the year prior to enrollment and of those, 15 (31.3%) had prescribed rescue medication whereas 33 (69.7%) did not. There was no significant difference in the mean total QOLIE-31 score (p=0.881) and the total SSQ score (p=0.062) between the prior clusters group (57.2, SD 20.3; 3.95, SD 1.36) and the active epilepsy group (56.5, SD 18.2; 4.15, SD 1.56). The seizure free group (72.5, SD 16.5) had a significantly better mean total QOLIE-31 score compared to the prior clusters (p=0.01) and the active epilepsy groups (p=0.003).

Seizure clustering is not uncommon among patients with epilepsy and rescue medications are underutilized for those patients. This prospective study is ongoing to define risk factors, the use of rescue medications, prevalence and consequences of seizure clusters.
EEG Sonification for the Detection of Seizures

Authors: Psyche Loui, Mark Frick, Matan Koplin-Green, Mike Massone

Abstract: The ability to detect seizures automatically using EEG may present a route towards biofeedback-based clinical interventions for epilepsy. However, in their daily lives patients with epilepsy may rarely use biofeedback due to lack of access and inability to interpret their own EEGs. We propose that sonifying EEG signals (i.e. converting EEG signals into musical sounds) may enable patients to monitor their own EEG signals through the auditory system, thereby providing a biofeedback-based intervention for epilepsy.

Our overall hypothesis is that patients with epilepsy may be able to use auditory biofeedback of their own EEG signals to detect and eventually control their seizures. Here we present some new algorithms to sonify EEG recordings. We define a mapping system to convert EEG to music, and apply this mapping on EEG data from epilepsy patients. In this talk we will present music that is converted from EEG data from epilepsy patients, which contain baseline activity as well as episodes of seizures, obtained from a publicly available archive at from the Children’s Hospital Boston-Massachusetts Institute of Technology Scalp EEG Database (Shoeb, 2009). These data are sonified via a mapping algorithm that combines music theory and signal processing to create music from frequency-domain and time-domain information in EEG signals. This mapping system is implemented in the Max/MSP programming environment, combined with MATLAB-based data access routines. Preliminary testing shows that listeners who are unskilled in reading EEGs are nevertheless able to distinguish ictal activity from baseline activity by listening to sonified EEGs alone.