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This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through a joint providership of the The Yale School of Medicine and Yale Departments of Neurology and Neurosurgery. The Yale School of Medicine is accredited by the ACCME to provide continuing medical education for physicians. The Yale School of Medicine designates this live activity for a maximum of 8 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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LEARNING OBJECTIVES

Upon completion of this program, participants should be able to:

1. Utilize newer epilepsy medications with a firm grasp of mechanisms, benefits and side-effects
2. Effectively use the latest technologies and devices for epilepsy diagnosis and treatment
3. Correctly interpret new clinical and basic science literature pertaining to epilepsy
4. Develop well-designed clinical trials for evaluating new approaches to epilepsy care
5. Apply cutting-edge neuroimaging and electrophysiology methods for research and clinical care
6. Improve surgical care of epilepsy patients through advanced technologies
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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, this year’s retreat will be moderated by Amy Brooks-Kayal, MD., Chief and Ponzio Family Chair in Pediatric Neurology; section head for child neurology; and Co-Director of Translational Epilepsy Research, all at the University of Colorado. She is a former Vice-President of the American Epilepsy Society, and a world renowned epileptologist and neuroscientist. The Retreat will consist of investigator slide presentations, poster session, and discussions on new research approaches and collaborations.
Amy Brooks-Kayal, MD is Professor of Pediatrics, Neurology and Pharmaceutical Sciences, Co-director of the Translational Epilepsy Research Program, and Chief and Ponzio Family Chair of Pediatric Neurology at the University of Colorado School of Medicine, Skaggs School of Pharmacy and Pharmaceutical Sciences, and Children's Hospital Colorado. Dr. Brooks-Kayal trained at Johns Hopkins University, University of Pennsylvania and Children's Hospital of Philadelphia. She joined the University of Colorado in 2008 after 13 years on the faculty at University of Pennsylvania and Children’s Hospital of Philadelphia. Her area of clinical focus is pediatric epilepsy. Her research focuses on regulation of neurotransmitter systems during epilepsy and epileptogenesis, with particular emphasis on GABA<sub>A</sub> receptor expression regulation by the JAK/STAT pathway, and targeting these molecular changes to develop disease modifying therapy. Dr. Brooks-Kayal is chair of the Development Council and a Past President of the American Epilepsy Society, a member of the NIH/NINDS Advisory Council and Commission on North American Affairs of the ILAE, a Director of the American Board of Psychiatry and Neurology, and is an active member of the American Neurological Association, Child Neurology Society, Society for Neuroscience and American Academy of Neurology.
AGENDA
2018 SIXTH SESQUIENNIAL
YALE COMPREHENSIVE EPILEPSY CENTER
RESEARCH RETREAT
AGENDA
October 25-26, 2018
Old Saybrook Inn and Spa, Old Saybrook, CT

Thursday, October 25th

10:00 - 10:40 a.m. Registration, Coffee and Cookies, Poster Display

10:40 – 12:20 p.m. Slide Session I: Animal Models
Moderator: Tore Eid, PhD.

10:40 – 11:00 a.m. Focal Brain Glutamine Synthetase Inhibition Leads to Epilepsy and Glutamate-GABA Perturbations levels in the Distant Epileptic Network
Roni Dhaher, Ph.D.

11:00 – 11:20 a.m. Seizures and GABA rhythmically oscillate in a rodent model of temporal lobe epilepsy
Roni Dhaher, Ph.D

11:20 – 11:40 a.m. mTOR Activity Levels Influence the Severity of Epilepsy and Associated Neuropathology in a Mouse Model of Complex and Focal Cortical Dysplasia
Lena Nguyen

11:40 – 12:00 p.m. Intralaminar thalamic neuromodulation in epilepsy
Abhijeet Gummadavelli

12:00 – 12:20 p.m. Neocortical in vivo whole-cell recordings to investigate mechanisms of slow wave activity and impaired arousal in focal hippocampal seizures
Zongwei Yue

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

1:20 - 1:40 p.m.  
**Intracranial Slow Wave Activity in Focal Epilepsy**  
*Brian Nils Lundstrom*

1:40 - 2:00 p.m.  
**Seizure susceptibility and infraslow activity in the intracranial EEG**  
*Rasesh B. Joshi*

2:00 – 2:20 p.m.  
**Smartphone Interaction in Epilepsy**  
*Robert Duckrow*

2:20 – 2:40 p.m.  
**Increased short range functional MRI connectivity in limbic network correlates with seizure frequency and cognitive impairment in temporal lobe epilepsy patients**  
*Melanie Boly*

2:40 – 3:00 p.m.  
**Intracranial EEG provides a direct window to investigate auditory conscious perception**  
*Kate L. Christison-Lagay*

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.

**Network Analysis in Responsive Neurostimulation (RNS) Patients**  
*Abiha Jafri*

**Temporal dynamics of electrophysiological recordings in visual conscious perception**  
*Sharif I. Kronemer*

**Attentional network switching in intracranial EEG**  
*Jiajia Li*

**HEP2 Study Progress Update**  
*Alma Rechnitzer*

**NORSE Study Progress Update**  
*Alma Rechnitzer*

**A Review of Ongoing Anti-Epileptic Drug Trials**  
*Rija Aziz*
Mechanisms of impaired consciousness in absence seizures
Cian P. McCafferty

Investigation of EEG features of generalized spike-wave discharges that impair behavioral responses using a high fidelity driving simulator
Eli Cohen

Electrically induced focal limbic seizures with impaired consciousness in mice
Lim-Anna Sieu

5:00 – 5:30 p.m. General Discussion and Day 1 Summary Moderator: Amy Brooks-Kayal, MD

5:45 – 6:30 p.m. Group Beach Run

7:00 – 11:00 p.m. Dinner and Social Event
Friday, October 26th

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

8:30 – 9:50 a.m.  **Slide Session III: Clinical Epilepsy 1,**  
**Moderator: Dennis Spencer, MD**

8:30 – 8:50 a.m.  **Regional Asymmetries in Quantitative FDG-PET Predict Poor Surgical Outcome in Medically Refractory Medial Temporal Lobe Epilepsy**  
*Sidrah Mahmud*

8:50 – 9:10 a.m.  **Yale and Columbia Anti-epileptic drugs Database and the Computer-Assisted Rational Epilepsy Therapy (CARET)**  
*Hatem Tolba*

9:10 - 9:30 a.m.  **Psychosocial Outcomes after Surgery for Refractory Epilepsy due to Focal Cortical Dysplasia**  
*Rija Aziz*

9:30 – 9:50 a.m.  **Progress Towards a Feasibility Study of Thalamic Stimulation to Prevent Impaired Consciousness in Epilepsy**  
*Natnael Dolicho*

9:50 – 10:30 a.m.  **Coffee Break and Poster Session Revisit**

10:30 – 12:10 p.m.  **Slide Session IV: Clinical Epilepsy Part 2**  
**Moderator: Lawrence Hirsch, MD**

10:30 – 10:50 a.m.  **NeuroProbe: A brain implantable electronic multi-sensor solution for rapid, sensitive, co-localized, in vivo measurement of brain physiology for acute brain injury**  
*Hitten P. Zaveri*

10:50 – 11:10 a.m.  **Noninvasive skin volatilomics for forecasting and diagnosing seizures**  
*Deshpande Ketaki*

11:10 – 11:30 a.m.  **Randomized controlled trial of motivational interviewing for psychogenic nonepileptic seizures**  
*Benjamin Tolchin, MD*
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| 11:30 - 11:50 a.m. | Evaluation of driving performance with a portable driving simulator on the epilepsy monitoring unit  
Reese Martin |
| 11:50 –12:10 a.m. | Data Driven Prediction of Behavioral Impairment in Absence Epilepsy  
Peter Vincent |
| 12:10 - 1:10 p.m. | Lunch Buffet and Final Discussion Moderated by Amy Brooks-Kayal, MD |
Slide Session I: Animal Models
Focal Brain Glutamine Synthetase Inhibition Leads to Epilepsy and Glutamate-GABA Perturbations levels in the Distant Epileptic Network

Authors:
Roni Dhaher, Ph.D.¹, Shaun Gruenbaum, M.D.², Mani R. Sandhu, M.D.¹, Hitten Zaveri, Ph.D.³, Tore Eid, M.D., Ph.D.¹
Departments of Laboratory Medicine¹, Anesthesiology² and Neurology³, Yale School of Medicine, New Haven, CT 06520, USA

Rationale: In vivo brain microdialysis studies of epilepsy patients demonstrate elevated basal glutamate levels in epileptogenic foci when compared to non-epileptogenic regions (Ann Neurol 2016; 80: 35-45). The hypothesized mechanism of action by which this occurs is through deficiency in glutamine synthetase, the enzyme that metabolizes glutamate to glutamine, as this enzyme has been shown to be deficient in epileptogenic foci (Lancet 2004; 363: 28-37). The objective of this study was to evaluate the effect of inhibition of glutamine synthetase on basal and seizure associated levels of extracellular glutamate, glutamine, and GABA in the GS deficient vs. GS-intact hippocampus. In addition, seizure propagation from these two hippocampi was also studied.

Methods: Male Sprague Dawley rats were implanted with an osmotic pump infusing either phosphate buffered saline (PBS) or glutamine synthetase inhibitor, methionine sulfoximine (MSO), into the entorhinal cortex for a period of up to 28 days. Guide cannula were also placed in the hippocampus proper both ipsilateral and contralateral to the infusion location. Some animals were also implanted with unipolar stainless-steel depth electrodes in bilateral hippocampi.

Results: Basal levels of glutamate were significantly higher on the contralateral side of the MSO treated rats compared to the ipsilateral side (p=0.01), and compared to the PBS control (p=0.02). Glutamine was significantly lower in the ipsilateral (p=0.004) and contralateral hippocampi (p=0.01) in the MSO treated animals compared to the PBS control. GABA levels were not significantly different between the groups. When observing the chemistry around a seizure, in the contralateral hippocampus, the glutamate/GABA ratio in the MSO treated rats gradually increased from 5 hours before the seizure, peaking three hours after the seizure (p<0.0001), followed by a 29 % drop (p=0.006) and stabilization. On the ipsilateral side, the ratio remained stable from seven hours prior to the seizure, increased by 56 % at the third hour following the seizure (p<0.01), followed by a decrease to baseline levels at the fifth hour after the seizure (p=0.01). The EEG from the depth electrodes also suggested both a similarity between the two hippocampi, with the seizure initiating from the ipsilateral hippocampus, and then propagating to the contralateral hippocampus, with the time delay between seizure propagation decreasing over days.

Conclusions: The results suggest that the GS-deficient and GS-intact hippocampi of the MSO model of temporal lobe epilepsy share both similarities and differences with respect to both chemistry and seizure propagation. While the GS-intact contralateral hippocampus has elevated glutamate, it is the ipsilateral GS-deficient hippocampus from which the seizures initiates. Furthermore, the glutamate/GABA ratio progresses similarly around the seizure in both the ipsilateral and contralateral hippocampi. These findings are significant because they help to elucidate the effect of unilateral glutamine synthetase inhibition on bilateral basal glutamate, glutamine, and GABA levels, and seizure propagation from the two hippocampi.
Seizures and GABA rhythmically oscillate in a rodent model of temporal lobe epilepsy

Authors: Mani Ratnesh S. Sandhu1, Shaun E. Gruenbaum2, Roni Dhaher3, Hitten P. Zaveri4 and Tore Eid11
Department of Laboratory Medicine, Yale University, CT 2 Department of Anesthesiology, Yale University, CT 3 Department of Neurosurgery, Yale University, CT 4 Department of Neurology, Yale University, CT

Rationale: Many physiological processes and diseases exhibit intriguing periodic (rhythmic) changes, such as cortisol secretion, body temperature, sleep/wakefulness, cancer, Alzheimer's disease and epilepsy. It is well known that seizures can occur in clusters, followed by long periods of seizure freedom and many focal epilepsies exhibit circadian (~24-hrs) vulnerability to seizure. The mechanism underlying circadian periodicity in seizure likelihood is not well understood. The objective of this study was to test a hypothesis linking periodicity in seizure likelihood to rhythmic changes in the metabolome of the brain.

Methods: Seizures in a rodent model of mesial temporal lobe epilepsy (the methionine sulfoximine (MSO) model, n = 23), were detected through visual evaluation of the video-intracranial EEG record over 21 days. To collect extracellular fluid, a microdialysis probe was inserted in the dentate gyrus of the right hippocampus of this focal epilepsy model (n=7). Microdialysate was collected continuously in 1-hr fractions for up to 7 days. The sampled brain extra-cellular fluid was analyzed using liquid chromatography-tandem mass spectrometry(LC-MS/MS). The temporal distribution of seizures was assessed by evaluating seizure frequency in eight three-hour bins over 24 hours. The neurochemistry was similarly arrayed into eight three-hour bins. The distribution of seizures vs time and metabolome vs time was tested for non-uniformity using the chi-square statistic.

Results: A total of 1535 seizures were documented by continuous video-icEEG. The seizure frequency of epileptic rats (n=23) was plotted over the 24-hr cycle, and a distinct rhythmic pattern was discovered (p < 0.0001, Fig. 1). There was a steady increase in seizure frequency during the light cycle (during sleep), and then a decrease towards the start of the dark cycle (the end of wake). With regard to neurochemistry, there was a striking rhythmic oscillation in GABA levels in the hippocampus of epileptic rats (p< 0.0001, Fig. 2). There was a steady decrease in GABA levels during the beginning of the light cycle and subsequent increase towards the end of the light cycle. The GABA levels continued to rise in the dark cycle, where seizure frequency was at its lowest and relatively stable.

Conclusion: An increase in GABA levels over 24 hours corresponded with a concomitant decrease in seizure likelihood, while a decrease in GABA levels corresponded with an increase in seizure likelihood. This relationship suggests that the circadian oscillation of GABA may underly the circadian vulnerability to seizure in these animals.

Support: Swebilius Foundation Grant
mTOR Activity Levels Influence the Severity of Epilepsy and Associated Neuropathology in a Mouse Model of Complex and Focal Cortical Dysplasia

Authors:
Lena Nguyen and Angelique Bordey

Tuberous sclerosis complex (TSC) and focal cortical dysplasia (FCD) are characterized by focal malformations of cortical development (MCDs) that are highly associated with intractable epilepsy. TSC and FCD are caused by a spectrum of pathogenic variants in the mTOR pathway genes leading to differential activation of mTOR signaling during cortical development. However, it remains unclear whether the degree of mTOR hyperactivity influences disease severity. Here, we examined the effects of differential mTOR activity levels on epilepsy and associated neuropathology in a mouse model of TSC and FCD. Constitutively active Rheb (Rheb\textsuperscript{CA}), the canonical activator of mTOR complex 1 (mTORC1), was expressed in mouse embryos via \textit{in utero} electroporation at low, intermediate, and high concentrations to induce different mTORC1 activity levels in developing cortical neurons. Video-EEG monitoring was performed in adult mice to assess seizure frequency. Histological analyses were performed post-hoc to evaluate neuropathological features. We found that Rheb\textsuperscript{CA} expression induced mTORC1 hyperactivation and increased neuronal size in a dose-dependent manner. Low Rheb\textsuperscript{CA} mice had no seizures while intermediate and high Rheb\textsuperscript{CA} mice displayed spontaneous, recurrent seizures that significantly increased with Rheb\textsuperscript{CA} concentration. Similarly, neuronal misplacement and microglial activation were present in the intermediate and high, but not low, Rheb\textsuperscript{CA} mice. Overall, our studies show that mTOR activity levels influence the severity of epilepsy and associated neuropathology in TSC and FCD. These findings emphasize the importance of genotype-phenotype correlations to establish personalized medicine approaches based on patients’ gene variants and mTOR activation level.
Intralaminar thalamic neuromodulation in epilepsy

Authors: Abhijeet Gummadavelli, Cian McCafferty, Benjamin Gruenbaum, Lim-Anna Sieu, Jingwen Xu, Jason Gerrard, Dennis Spencer, Hal Blumenfeld

Approximately one-quarter of patients with epilepsy have seizures refractory to appropriate medical anti-epileptic treatment. For these patients, the loss of consciousness associated with seizures is a major source of impaired quality of life, morbidity, and even mortality. Extensive mechanistic investigations in an animal model of temporal lobe seizures have shown functional imaging, biochemical, and electrophysiological evidence supporting a ‘network inhibition’ hypothesis. The behavioral arrest and remote cortical slowing (seen in states of altered consciousness, such as sleep, anesthesia and coma) of a seizure with its focus of onset in the temporal lobe are mediated by subcortical structures such as the ascending reticular activating system and intralaminar thalamic nuclei. Single- and multi-unit activity recordings in the thalamic intralaminar central lateral nucleus (CL) during focal temporal seizures have shown both decreased firing rate and switch in firing state in the ictal and post-ictal periods. Stimulation of the intralaminar nuclei and reticular structures during and after seizures have shown reversal of cortical slow waves and improved qualitative measures of behavioral arousal. Further investigation to characterize behavioral restoration of awareness requires an awake model of inducible focal temporal lobe seizures. To do this, we train rats to respond to an auditory stimulus (clicking) with a behavioral response, licking a spout, to receive a sucrose reward. After implantation of electrodes in the intralaminar thalamus targeting CL, we induce focal seizures with dorsal hippocampal stimulation, followed by ictal and post-ictal thalamic stimulation to quantitatively assess behavioral response in the licking task. These studies will have two major impacts: (1) in generating a model of temporal lobe seizures without confounds of anesthesia and serve to test nodes of stimulation; (2) improve on on-going efforts to translate intralaminar thalamic stimulation to clinical therapy.
Neocortical in vivo whole-cell recordings to investigate mechanisms of slow wave activity and impaired arousal in focal hippocampal seizures

Authors:
Zongwei Yue, Isaac G. Freedman, John P. Andrews, Garrett Neske, Quentin Perrenoud, David A. McCormick, Jessica Cardin, Hal Blumenfeld

ABSTRACT
Background: The mechanism by which focal limbic seizures impair consciousness is unknown. Slow oscillations in the neocortex during sleep and anesthesia, characterized by slow, synchronized transitions between vigorous synaptic activity (Up states) and relative silence (Down states), have long been reported and implicated in loss of consciousness. Previous extracellular recordings in multiple neocortical regions have revealed similar large-amplitude 1-2 Hz slow oscillations during focal limbic seizures in a rat model. The membrane potential synaptic activity changes in neocortical neurons during focal limbic seizures are unknown. The purpose of this study is to investigate the electrophysiological properties and synaptic input changes of cortical neurons exhibiting Up and Down states during hippocampal focal seizures.

Methods: Whole-cell recordings were obtained in neurons of the left secondary motor cortex (M2), 0.8-1 mm deep from the cortical surface (pia). Micropipettes were pulled with an approximately 4-mm taper and 4-6 MΩ resistance. Intrapipette positive pressure was maintained at 300 mbar throughout the descent and reduced to <25 mbar at the target region. A K-gluconate-based internal solution was used for all recordings. Multiunit activity (MUA) and local field potential (LFP) signals were recorded from the right M2 simultaneously with whole-cell recordings. Seizures were triggered using a 2-second 60 Hz stimulation of the hippocampus through a twisted bipolar electrode with current titrated to seizure threshold. Continuous recordings were made using Spike2, with signal digitized using a Micro1401 (CED). Whole-cell recordings in current clamp mode were obtained during seizures. Brains were fixed and stained for Cy3-biocytin to confirm histologic recovery via immunofluorescent microscopy.

Results: We recorded 23 seizures from 11 neurons in 11 rats. Immunohistological recovery was confirmed for 9 neurons (81.8% recovery). Up and Down states were seen in M2 LFP during hippocampal seizures, which correlated with simultaneous membrane potential fluctuations, a finding not previously demonstrated in a rat focal seizure model. Single neuron activity during seizures resembled slow waves recorded in the same neuron during periods of deep anesthesia. In contrast, neuronal activity during baseline pre-ictal periods of light anesthesia did not resemble either deep or ictal epochs.

Conclusions: Subthreshold membrane potential fluctuations of neurons in M2 during hippocampal seizures are indicative of cortical slow waves in this rat model. Ictal intracellular recordings resemble those seen during periods of deep anesthesia and are different from those seen during periods light anesthesia. In further work we plan to investigate the synaptic mechanisms of this altered state of cortical function.
Slide Session II: Network & Neurophysiology
Intracranial Slow Wave Activity in Focal Epilepsy

Author: Brian Nils Lundstrom

Abstract:
Although it is increasingly appreciated that broadband EEG contains helpful information for localizing the seizure onset zone (SOZ), the potential benefit of low-frequency EEG has been less well-studied. Prior work suggests that slow oscillation (0.1-1 Hz) and infraslow activity (0-0.1 Hz) from scalp and invasive EEG can localize to the SOZ. Previous in vitro and in vivo animal research suggest links between inhibitory and excitatory neuronal processes and macroscale EEG slow oscillations. In work with Hal Blumenfeld, we find that slow oscillation activity is reduced near the SOZ, while 2-4 Hz activity is increased. These changes are related to disrupted spatial correlations and a decreased modulatory effect of slow oscillation activity on higher frequencies. In work with Greg Worrell, short-term decreases in delta power from electrical stimulation applied to the SOZ were associated with improved long-term clinical outcomes from chronic stimulation. These findings suggest that some low-frequency bands may be more closely related to inhibitory neural processes than others, and that the composition of low-frequency EEG could provide localizing information about the SOZ.
Seizure susceptibility and infraslow activity in the intracranial EEG

Authors:
Rasesh B. Joshi, Robert B. Duckrow, Irina I. Goncharova, Jason L. Gerrard, Dennis D. Spencer, Lawrence J. Hirsch, Dwayne W. Godwin, Hitten P. Zaveri

Few studies have explored the role played by infraslow activity (typically defined as <0.2 Hz) in the context of normal physiology and in pathological conditions like epilepsy. Prior work has suggested that infraslow oscillations, which are present widely across cortex, may exert a modulatory influence on overall cortical excitability and affect the frequency of interictal spikes. Subsequent studies showed that it may serve some utility in lateralizing, and in some cases, localizing seizure activity. Infraslow oscillations have also recently been shown to exhibit unique spatiotemporal dynamics that are distinct from higher-frequency activity. Specifically, infraslow oscillations modulate delta activity through phase-amplitude coupling in a state-dependent manner, suggesting a hierarchical nesting of oscillations in the brain. We examined correlations in infraslow activity in human intracranial EEG (icEEG) to characterize its timescale. We also determined how infraslow envelope correlations vary during periods of increased seizure vulnerability.

We studied icEEG data from 13 medically refractory adult epilepsy patients who underwent monitoring and seizure localization at Yale-New Haven Hospital. We estimated average magnitude-squared coherence (MSC) below 0.15 Hz of band power time-series to quantify slow envelope correlations between them. We computed this on hour-long background icEEG epochs before and after AED taper when patients appeared to be resting quietly with eyes open (based on video-icEEG). For these segments, we also used time lag analysis to determine to what extent long-term correlation structure is preserved with increasing lag between signals. We also calculated infraslow envelope MSC over the entire record for each patient and examined variations related to time of day. Finally, for each patient, we reviewed the clinical record to find any seizures that were at least 6 hours removed from any other seizures, and analyzed the icEEG before and after these seizures using our measures.

Our time lag analysis showed that we were able to capture correlations in oscillatory activity in icEEG as slow as approximately 0.015 Hz, which matches with prior observations of infraslow oscillations. There was a small, but significant increase in infraslow envelope MSC with AED taper. The infraslow envelope MSC increased on average during the night, and decreased during the day. In our seizure-related analyses, we studied 61 seizures across all patients. Interestingly, infraslow envelope MSC was significantly increased in all frequency bands except theta for hours before and after seizure, as compared to background icEEG epochs. The seizure onset area also exhibited its own connectivity profile in relation to seizure. Our analysis indicates that infraslow envelope MSC can provide a unique understanding of long-term changes and seizure generation during icEEG monitoring. We also expect that these measures will prove useful in the development of robust, physiologically relevant seizure prediction algorithms.
Smartphone interaction in epilepsy

Authors:
Duckrow RB, Brooks C, Quraishi I, Zaveri H, Ghosh A.

Background: Surveys show that people with epilepsy are bothered most by the unpredictable nature of their seizures. This has motivated the study of factors that contribute to seizure susceptibility with the eventual goal of creating personalized algorithms capable of forecasting daily seizure probability. One such factor is the inherent interplay between the behavioral state of the patient and the occurrence of seizures. Unconstrained day-to-day activities are difficult to quantify but smartphone use is now one human activity that is nearly universal. Accordingly, patterns of smartphone use, such as touchscreen interaction, can provide a window to observe human behavior on an extended time scale in an unobtrusive fashion. Our hypothesis is that behavioral states characterized by smartphone tapping patterns will vary in systematic ways in relation to the onset of epileptic seizures.

Methods: A free tap-sensing App, QuantActions TapCounter, was placed on subjects’ Android-based smartphones to allow continuous monitoring of touchscreen interaction with 5 millisecond resolution. The inter-touch interval was used to indicate tapping speed. Subjects were recruited from our population of patients previously implanted with the RNS® System (NeuroPace, Inc.). This allowed correlation of touchscreen interactions with epileptiform electrographic discharges measured continuously over weeks and months. RNS System long episodes tracked with one-hour time resolution were used as a surrogate for clinical seizures. The protocol was IRB approved and subjects gave written informed consent.

Results: Of 22 patients being treated with the RNS System at Yale, 6 used Android-based smartphones and 5 were able to implement the TapCounter App, individually for 128, 128, 67, 63, and 46 days. Long episodes occurred at an average rate of 7.36, 1.76, 0.28, 1.98, and 0.00 per day, respectively. Data from 3 subjects who averaged more than 1 long episode per day were analyzed. At slower time scales (19 h bin, with 3 step Gaussian smoothing), tapping speed inversely correlated with the number of long episodes. When the inter-touch interval was aligned with long episodes counts on the time scale of hours, there was a surprising 'speeding-up' of touches 2 hours after long episodes.

Conclusions: These preliminary data show the feasibility and utility of tracking smartphone touchscreen interactions in persons with epilepsy. Patterns of smartphone use vary with the frequency of epileptiform discharges recorded intracranially and may provide an index of seizure susceptibility.
Increased short range functional MRI connectivity in limbic network correlates with seizure frequency and cognitive impairment in temporal lobe epilepsy patients

Authors: Joshua C Pankratz, Shuntaro Sasai, Aaron F Struck, Kevin Dabbs, Gyujoon Hwang, Jed Mathis, Veena A. Nair, Gengyan Zhao, Taylor M. McMillan, Dace N. Almane, Andrew Nencka, Elizabeth Felton, Rasmus Birn, Rama Maganti, Megan Rozman, Lisa Conant, Colin Humphries, Manoj Raghavan, Edgar A. DeYoe, Jeffrey R. Binder, Bruce Hermann, Vivek Prabhakaran, Beth Meyerand, Melanie Boly

Rationale: Focal epilepsy is associated with significant morbidity and cognitive impairment. A recent high density EEG study suggested the presence of local connectivity increases in focal epileptic patients compared to controls (Boly et al., Brain 2018). As focal seizures propagate in a nearest-neighbor fashion intracranially, increases in cortico-cortical connectivity may be more pronounced for short distance ranges. We aimed to determine if increases in short range functional MRI (fMRI) connectivity could differentiate the epileptic network from the rest of the brain in patients with temporal lobe epilepsy (TLE). We also assessed the correlation between abnormal increases in fMRI connectivity, seizure frequency and cognitive impairment.

Methods: Data from 35 TLE patients and 31 controls (age range 20-57) from the Epilepsy Connectome Project (ECP) were analyzed. High resolution anatomical and resting state fMRI data were obtained using 3T MRI Human Connectome Project (HCP) sequences and were preprocessed using the HCP pipeline. For each subject, vertex-wise matrices of correlation between each voxel and its neighbors at predefined short (0-5 mm) and long (150-200 mm) distances were computed. Spatially Z-scored topographies of short and long distance connectivity were compared between TLE patients and controls. In the TLE group, short and long distance connectivity topographies were then correlated with seizure frequency. Finally, average connectivity strength (from 0 to 200 mm) was correlated with IQ, verbal memory (Rey-AVLT) and motor (Grooved Pegboard) performance in both TLE patients and controls, and topographies were compared between the two groups. All analyses used non-parametric statistics and were thresholded at p<0.05 corrected for multiple comparisons using Threshold Free Cluster Enhancement (TFCE) in the HCP workbench.

Results: Compared to controls, TLE patients showed increased short range connectivity in bilateral limbic networks and increased long range connectivity in bilateral motor networks (corrected p<0.05, Figure 1). In the TLE group, seizure frequency was also correlated with increased short range connectivity in bilateral limbic networks and with increased long range connectivity in bilateral motor networks (Figure 2A). While in controls, average connectivity strength in limbic networks was positively correlated with both IQ and memory scores, it was paradoxically negatively correlated with IQ and memory scores in the TLE group (corrected p<0.05, Figures 2B-C). While in controls, motor performance positively correlated with average connectivity strength in bilateral motor cortices, it was positively correlated with connectivity in extra-motor areas in patients with TLE (corrected p<0.05, Figure 2D).

Conclusions: Compared to controls, TLE patients displayed increased short range connectivity in the epileptic (limbic) network and increased long range connectivity in motor networks. Connectivity changes correlated with both seizure frequency and cognitive impairment in TLE patients. These findings suggest that increased short range connectivity may help localize focal epileptic networks. The correlations between increased connectivity and both seizure frequency and cognitive impairment in TLE patients also suggest that seizures may induce maladaptive changes. Future studies should correlate short range fMRI connectivity with surgical outcomes to validate this approach clinically.
Figure 1. Comparison of distance-specific connectivity between TLE patients and controls. Red-yellow regions exhibit increases and green-blue indicate decreases in distance-specific connectivity in TLE patients compared to controls. Short (left panel) refers to 0-5 mm and long (middle panel) refers to 150-200 mm distances. Short-long (right panel) refers to the difference between short and long distance connectivity changes. Color scale refers to group mean T-values; all results are thresholded for display at non-parametric whole-brain TFCE corrected p < 0.05.

Figure 2. A. Correlation between distance-specific connectivity and seizure frequency in TLE patients. Red-yellow regions exhibit positive correlation and green-blue regions exhibit negative correlation between seizure frequency and distance-specific connectivity in TLE patients. Short refers to 0-5 mm and long refers to 150-200 mm distances. Short-long refers to the difference between short and long distance connectivity. Color scale refers to group mean T-values; results are thresholded for display at non-parametric whole-brain TFCE corrected p < 0.05. Scatter plots display correlation between change in short-long distance connectivity and seizure frequency in left and right medial temporal lobe (MTL).

B. Correlation between average connectivity and IQ in controls (left panel), TLE patients (middle panel), and difference between the two groups (right panel). Red-yellow regions exhibit positive correlation and green-blue regions exhibit negative correlation between connectivity and IQ. Color scales refer to group mean T-values and Z-values for differences between groups; results are thresholded for display at non-parametric whole-brain TFCE corrected p < 0.05. Scatter plots display correlation between connectivity and IQ in left and right MTL in controls (left panel) and patients (right panel).

C. Correlation between average connectivity and Rey-AVLT memory scores in controls (left panel), TLE patients (middle panel), and difference between the two groups (right panel). Red-yellow regions exhibit positive correlation and green-blue regions exhibit negative correlation between connectivity and Rey-AVLT memory scores. Color scales refer to group mean T-values and Z-values for differences between groups; results are thresholded for display at non-parametric whole-brain TFCE corrected p < 0.05. Scatter plots display correlation between connectivity and Rey-AVLT memory scores in right and left MTL in controls (left panel) and patients (right panel).

D. Correlation between average connectivity and Purdue Pegboard motor scores in controls (left panel), TLE patients (middle panel), and difference between the two groups (right panel). Red-yellow regions exhibit positive correlation and green-blue regions exhibit negative correlation between connectivity and Purdue Pegboard motor scores. Color scales refer to group mean T-values and Z-values for differences between groups; results are thresholded for display at non-parametric whole-brain TFCE corrected p < 0.05. Scatter plots display correlation between connectivity and Purdue Pegboard motor scores in right and left motor cortex in controls (left panel) and patients (right panel).
Intracranial EEG provides a direct window to investigate auditory conscious perception

Author:
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Rationale: Significant headway has been made in understanding the temporal and spatial dynamics of the neural mechanisms of consciousness. Our lab has reported on a visual perceptual threshold task that used a face stimulus calibrated to a subject’s 50% detection rate (Herman et al., Cerebral Cortex, 2018). Following each trial, subjects were prompted to report whether they perceived the visual stimulus and the stimulus’ location to validate perception. This paradigm was used in conjunction with intracranial EEG (icEEG) in patients with intractable epilepsy. We found initial activation of early visual cortex for both perceived and not perceived stimuli; in perceived trials only, this was followed by a decrease in both the early visual areas and the default mode network and a posterior to anterior wave of activity that swept through the cerebral cortex, followed by a late reactivation of the early visual areas—a pattern that we call the “switch-and-wave.” Our present goal is to determine whether a similar “switch-and-wave” phenomenon may be common across conscious sensory perception by performing an analogous study of auditory perception using icEEG.

Methods: We developed an auditory counterpart to our visual task, in which three target sounds (a whistle, a ‘laser’, and a waterdrop) are calibrated to a subject’s 50% detection threshold and embedded in white noise. After each trial, subjects are prompted to report whether they perceived the sound, and the sound’s identity, to validate perception. If they did not hear a sound, they are instructed to randomly guess on the second forced-choice question about sound identity.

Results: In behavioral studies (n=25), we found that the stimulus perception rate was 57.5% (2.7% standard error of the mean (SEM)) when the target was present whereas false positive rate was 10.9% (2.9% SEM) for blank trials. Subjects correctly indicated the sound’s identity in 89.5% (2.3% SEM) of perceived trials; in non-perceived trials, sound identification accuracy was approximately chance (36.7%, 2.2% SEM). Having established this as a robust behavioral paradigm for testing conscious auditory perception, we are now using this paradigm with epilepsy patients with icEEG at multiple centers. Preliminary analyses of broadband gamma power in the first second following the stimulus suggest there are similarities in the conscious perception of auditory and visual stimuli. Namely, activity is present at early times in the sensory cortex regardless of perception status. At later times, perceived trials show greater activity in the association cortex than not perceived trials.

Conclusions: Conscious perception in both visual and auditory paradigms may involve a broad network of activity changes in the association cortex which can be measured in the first second following perceived stimuli. Analyses of broadband gamma power in relation to our auditory task are ongoing to gain further insights into shared mechanisms of conscious perception across modalities.
Poster Session
Network Analysis in Responsive Neurostimulation (RNS) Patients

Authors:
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Network changes in patients with multifocal epilepsy based on long-term ambulatory electrocorticography were evaluated at the Yale Comprehensive Epilepsy Center with Neuropace responsive neurostimulation (RNS) devices and electrodes implanted for two epileptic foci. The most common type of epilepsy in this cohort is expected to be bitemporal. The tested hypothesis was in multifocal epilepsy, different nodes of an epileptic network predominate over time. Intracranial EEG’s (Electrocorticography) were categorized into scheduled, magnet, and long episodes, and defined the ictal and interictal periods. Preliminary connectivity measures were ran utilizing matlab to find the cross correlation between channels. Future plans include using more advanced correlation and connectivity measures on more data to serve as a replicable model for more patients.
Temporal dynamics of electrophysiological recordings in visual conscious perception

Authors:
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The neural mechanisms of consciousness remain unknown. A fundamental question is the precise temporal dynamics of electrophysiological signal that correspond to the sequence of neural activity for conscious perception. A previous intracranial EEG study shows an anterior to posterior wave of gamma signal (40-115 Hz) over 1000 ms after the onset of a consciously perceived and reported visual stimulus (Herman et al., Cerebral Cortex 2018). Early (~125 ms) primary visual cortex gamma activity was similar for both perceived and not perceived stimuli. This suggests that the temporal dynamics for the ignition of consciousness should occur at approximately 150-300 ms post-stimulus. The current investigation aims to study the spatiotemporal dynamics for the consciousness ignition mechanisms that may drive the non-linear propagation of activity from sensory to association cortices, as found by Herman and colleagues (2018). In addition, this study examines how precursor fluctuations in brain state influence subsequent activity among detection and perceptual processing networks. Simultaneous electrophysiological signals with 256-channel high-density scalp EEG (Electrical Geodesics, Inc.) and binocular pupillometry (SR Research) were recorded with healthy, adult participants (N = 57, females = 37) while completing an at-threshold, report-based visual perception task. To improve spatial resolution of scalp electrophysiological signals, individual T1-weighted, whole-brain anatomical MRI (Siemens Medical Systems, Germany) and photogrammetry were collected to model scalp sensor three-dimensional locations and predict the cortical location of scalp EEG signals. Sustained potentials from 300 ms post-stimulus onset (P300) were found when comparing perceived versus not perceived stimuli that replicate findings from previous studies. Source localization of broadband gamma activity reveals similar patterns of activity as shown in previous intracranial EEG and fMRI studies, including early visual cortex signal 100-200ms post-stimulus onset for both perceived and not-perceived stimuli, and intermediate changes in association cortex signal >300ms for perceived stimuli only. Additional preprocessing is necessary to remove possible muscle artifact signals that correlate to cognitive load and can disguise as gamma activity. With ongoing analyses, we hope to gain further insights into normal mechanisms of consciousness which may be impaired in epilepsy and other brain disorders.
Transitions in attentional states are necessary to guide behavior towards salient stimuli in the environment. Experimental attention paradigms that focus on either event (e.g., individual stimuli) or state-related (e.g., active vs. rest phases) designs are commonly used to study task-specific transient or sustained changes in attention networks, respectively. The current study aims to utilize intracranial EEG (icEEG), the gold-standard for human brain recording, and a mixed block and event-related attention task to examine the attention network responses at both the state and event-specific levels. Adult, intractable epilepsy patients (n = 11; females = 6) undergoing icEEG implantation (100-300 subdural electrodes; sampling frequency = 1024 Hz) were recruited from the Yale Epilepsy Surgery Program at the Yale-New Haven Hospital. Patients were asked to complete a two-phased computerized task: rest and active phases. During the rest phase (32 seconds) the patients were asked to fixate on a cross. The active phase (32 seconds) required participants to make a button press for a target stimulus (“X”) in a stream of English letters. Thus, this paradigm combines state (rest versus active phases) and event (letter stimuli) attention network demands. Broadband gamma (40-115Hz) power change, corresponding to population neuronal firing was analyzed in reference to task block phases and individual stimuli. In addition, data-driven k-means clustering was performed to correlate gamma power time courses among brain networks. Our results demonstrate transient increases in gamma power in the supplementary motor area, primary visual cortex, precentral gyrus, and anterior insula at task onset and offset. Sustained increases were noted during the active phase in motor regions (e.g., primary motor cortex) and sustained decreases in the default mode network (e.g., the precuneus and ventral medial prefrontal cortex). Target-stimuli k-means clustering analysis of gamma power changes shed light on spatially distinct responses, including visual, motor, and association cortex clusters. These results imply that attention networks are transiently modulated to optimize performance at the block and event levels when attention is required and to disengage these same networks during rest. Attentional impairment in brain disorders including epilepsy may be related to aberrance in the switching dynamics observed in the current investigation.
HEP2 Study Progress Update

Author: Alma Rechnitzer

The Yale Comprehensive Epilepsy Center is currently participating in the Human Epilepsy Project 2 (HEP2) study, a multi-site prospective, observational study led by the Epilepsy Foundation. The study aims to better characterize the challenges of living with medication-resistant focal epilepsy. We are following patients over the course of two years to measure changes in their seizure frequency, treatments used, adverse events experienced, presence of comorbidities like depression and anxiety, healthcare costs, and quality of life. Blood samples will also be collected to study biomarkers of epilepsy severity and treatment response. In this presentation, I will provide a progress report on Yale’s enrollment totals and share preliminary data.
New-onset refractory status epilepticus (NORSE) is defined as refractory status epilepticus without an obvious cause after initial investigations. NORSE has been described mostly in young adults but it can occur at any age during adulthood. Seizures are thought to be due to an excess of pro-inflammatory molecules in the brain, perhaps triggered by a simple viral infection, although no clear cause has ever been demonstrated. Affected individuals are most often treated for weeks in an intensive care unit because they require prolonged anesthesia with coma-inducing drugs to control their seizures. The mortality rate reaches 30%. At least one half of the surviving patients are left with long-term cognitive and functional disability and most will have epilepsy, requiring lifelong treatment with anticonvulsants. The cause of NORSE is currently unknown, and the best treatment plan has yet to be determined. The Yale Comprehensive Epilepsy Center is partnering with 25 affiliate sites to conduct a multi-center, prospective observational study of patients with NORSE. Through the collection of clinical data and the creation of a biorepository, we will enable researchers to understand the cause of cryptogenic new-onset refractory status epilepticus (NORSE), identify the key determinants of outcome, and determine the best management strategy. In this presentation, I will provide an overview of current hypotheses on the cause of NORSE and will give an up-to-date report on the progress of the Yale-led NORSE Study.
A Review of Ongoing Anti-Epileptic Drug Trials

Authors:
Rija Aziz, Hatem Tolba, Terry Xiao, Hamada Hamid Altalib

ABSTRACT:
Yale Epilepsy Department gauges multiple clinical trials. This is an overview of our currently enrolling clinical trials. We have two phase 4 looking at the side-effects of medications and one current phase 3 study. There are multiple other phase 3 studies in the pipeline.

Study 1: Prospective Randomized 12-week Controlled study of Visual Field change in subjects with Partial seizures receiving Pregabalin or Placebo. Our rationale behind this study is concerns were expressed on emerging reports of visual field disturbances with the anti-convulsant vigabatrin, a GABA-transaminase inhibitor (for example Beck RW et al 1998).

Study 2: Non-interventional, observational study of Brivaracetam (BRV) to inform clinical decisions through real-life experiences to achieve better patient outcomes. A small, open-label, phase 3 study evaluating non-psychotic behavioral AEs in patients receiving levetiracetam who switched to brivaracetam showed that, at the end of the 12-week treatment period, 93.1% patients who switched to BRV had clinically meaningful reductions in AEs, which suggest that patients experiencing behavioral AEs associated with LEV may benefit from switching to BREV (Yates et al. 2015).

Study 3: Double-blinded, Placebo-controlled, inpatient, dose-ranging efficacy study of Staccato Alprazolam (STAP-001) in subjects with Epilepsy with a predictable seizure pattern. When seizures are not well-controlled patients might have a need for acute treatment in addition to their maintenance anti-epileptic drug (AED) or might experience seizure emergencies.

We will go over the inclusion/exclusion criteria for the studies in order to recruit more subjects.
Mechanisms of impaired consciousness in absence seizures

Authors:
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Absence seizures are intermittent periods of apparent impaired consciousness accompanied by a distinctive brain-wide electroencephalogram (EEG) pattern. Syndromes involving these seizures cause significant impairment to quality of life, potentially including psychosocial and intellectual developmental issues. Current gold-standard pharmacological therapies are only ~50% effective, and the specifics of the behavioral impairment during seizures is still being fully characterized. Both of these points suggest an improved mechanistic understanding of seizures in a behaviorally-established animal model is necessary for improved therapeutic options. Consequently, we used Genetic Absence Epilepsy Rats from Strasbourg (GAERS), a polygenic model of absence epilepsy, to study the association of neuronal and hemodynamic activity with the behavioral impact of seizures. First, we investigated the validity of the model by comparing non-drugged blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI) and cerebral blood flow (CBF) to the same measures in patients with absence. Cortical and subcortical dynamics were qualitatively similar, supporting the usefulness of the model. Next, we demonstrated that seizures are accompanied by impaired performance in two behavioral paradigms: a spontaneous licking scenario, and a conditioned response task. In both cases the occurrence of a seizure made an animal less likely to act to receive an appetitive stimulus. Finally, we showed that the severity of this performance impairment varied in the spontaneous licking task: in some seizures animals continued to lick at seizure initiation, similar to preserved performance frequently noted during seizures in humans. Crucially, those seizures tended towards lower vRMS EEG amplitude, slower oscillation frequency, and lower spike and wave power, pointing towards potential mechanisms of behavioral impairment. We are currently further investigating these mechanisms on the neuronal and network level, to uncover the causes of absence seizure behavioral severity and thereby suggest potential novel therapeutic targets.
Investigation of EEG features of generalized spike-wave discharges that impair behavioral responses using a high fidelity driving simulator

Authors:
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Rationale: Generalized spike-wave discharges (SWD) are hallmark features of several types of seizures and epilepsies. Typically occurring in brief, seconds-long periods, SWD often affect behavior and cognition. Our previous work involving a Repetitive Tapping Task (RTT) and Continuous Performance Task (CPT) shows that performance on these simple tasks is related to SWD amplitude and duration. Recent work investigating SWD effects on more complex tasks such as driving suggests that SWD prolong reaction time to road obstacles and impair drivers’ ability to maintain a safe car position. Due to SWD persisting as subclinical epileptiform discharges, “seizure-free” patients who are seeking driving privileges may still experience transient cognitive impairment. This possibility poses a challenge to patients, clinicians, and driver licensing authorities. There is a need to study the impact of generalized SWD on driving and to identify clinically-available metrics predictive of driver safety. We have established a paradigm to test driving ability in patients experiencing generalized SWD and to potentially identify EEG features that are predictive of SWD that impair driving.

Methods: Subjects 15 years or older with diagnosed generalized epilepsy and generalized SWD on EEG testing with no clinical seizures in the preceding month drive for an hour in a high-fidelity half-cab simulator (miniSim™) equipped for EEG and video recording. A road obstacle is introduced during each SWD episode. An obstacle is also manually presented every 5 minutes to measure subjects’ baseline functioning. Participants are instructed to pull over when the obstacles appear. The simulator continuously records over 200 variables including vehicle speed, brake force, and rate of steering wheel angle change. These variables are compared between the baseline testing and SWD periods.

Results: We have succeeded in recording reaction time (in milliseconds) between obstacle presentation and brake application and force, vehicle speed (mph) and rate of steering wheel angle change (degrees/sec) at baseline and during 5 SWD episodes in 2 patients. Obstacles were presented during SWD with a mean delay of 1.46 seconds from discharge onset. Variable performance was observed during SWD, with some obstacles responded to appropriately but others completely missed. With further data collection, we expect to obtain sufficient SWD with and without impairment to then use machine learning to classify them as “sparing” and “impairing” driving ability. We hypothesize that SWD that impair driving ability will be characterized by having higher amplitude and longer duration, as well as other EEG features associated with greater physiological severity of SWD.

Conclusions: This study shows that a high-fidelity driving simulator equipped with EEG and video monitoring are practicable tools for studying driving behavior among people with generalized epilepsy. This procedure offers a novel approach to studying driver safety in patients with epilepsy, particularly in identifying EEG features that may be predictive of driving impairment in generalized SWD and subclinical epileptiform discharges.

This work was supported by the Betsy and Jonathan Blattmachr Family, the Loughridge Williams Foundation and the NIH CTSA TL1TR000141.
Focal temporal lobe seizures with loss of consciousness exhibit increased cortical slow-wave activity similar to that of deep sleep. Prior work in rats has shown evidence that decreased activity of subcortical arousal systems can cause depressed cortical function during seizures. One possible explanation for this is an activation of GABAergic neurons from the lateral septum and a cortical reduction of cholinergic neurotransmission. However, the investigation of mechanisms underlying depressed subcortical arousal is limited by the poor availability of genetic tools in the rat model (e.g. methods for direct inhibition or/and removal of excitation). Additionally, the use of anesthetic makes it impossible to assess behavioral performance in relation to level of consciousness. These problems could be solved by an awake mouse model. Here, we present a temporal lobe seizure mouse model with impaired consciousness induced by electrically stimulating the hippocampus in an awake, behaving state. Focal seizures were recorded from the dorsal hippocampus after unilateral induction with a 60 Hz 2 s bipolar stimulus; simultaneously, local field potential signals (LFP) were recorded from orbitofrontal cortex (OFC). Behavioral response during seizure was assessed by training water-restricted mice to lick a spout in response to a click sound (0-50kHz, 12ms) every 10-15s while head-fixed on a running wheel. Focal seizures were repeatable for several weeks (n=190 seizures, 13 animals) and lasted between 5-33s. During seizures, there was a significantly decreased locomotor activity and a decreased response to sound with a reduced number of licks. Additionally, an increase in cortical slow wave activity was correlated to the impaired behavior during seizures. Interestingly, as seen in human patients, behavioral responses were sometimes spared during seizures, suggesting consciousness was not always impaired. To summarize, this mouse model echoes characteristics seen in both humans and in rat models while allowing for novel investigation into the mechanisms underlying loss of consciousness during focal seizures.
Slide Session III: Clinical Epilepsy 1
Regional Asymmetries in Quantitative FDG-PET Predict Poor Surgical Outcome in Medically Refractory Medial Temporal Lobe Epilepsy

Authors:
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Rationale: 18-fluorodeoxyglucose positron emission tomography (FDG-PET) is often used in pre-surgical workup to localize the seizure onset zone for patients with medically refractory focal epilepsy. Its utility has been demonstrated by multiple studies, which have shown that the presence of FDG-PET glucose hypometabolism in the epileptogenic temporal lobe is predictive of seizure freedom after surgery. However, FDG-PET hypometabolism is typically larger than the abnormality identified on structural imaging beyond the temporal lobe. Previous studies have suggested that when extratemporal regions are involved, this typically portends a less favorable post-surgical outcome. However, involvement of specifically which extratemporal regions leading to negative outcomes has not been well defined.

Methods: Thirty-eight patients were studied who underwent medial temporal lobectomies for medically refractory epilepsy due to histopathology-confirmed medial temporal sclerosis (MTS) with at least 5 years of post-operative follow up. Preoperative FDG-PET was segmented and analyzed quantitatively for region-based Z-scores using MIM software. Surgical outcomes were based on Engel scores, and divided into group 1A (complete seizure freedom) and not 1A (incomplete seizure freedom). Regions predictive of post-surgical outcome were determined by ridge regression using Z-scores for asymmetry, ipsilateral regions, and contralateral regions.

Result: A total of 38 cases were identified, including 25 with class 1A outcome after 5 years and 13 with worse outcomes. The average time from FDG-PET to resection was 10.26 years. Of those with a good outcome, 54.2% had a history of generalized tonic clonic seizures, as compared to 38.5% of those with a bad outcome. The most evident differences between the good and poor outcome groups were in four regions: middle frontal gyrus (p=0.002), paracentral lobule (p=0.018), thalamus (0.020), and posterior cingulate (0.032). In the paracentral lobule, the asymmetry was due to higher contralateral than ipsilateral FDG uptake in the poor outcome group relative to good outcomes. In the middle frontal gyrus, thalamus, and posterior cingulate, there was no reliable directionality to the asymmetry. These four regions were also good predictors of outcome (p=0.010, p=0.019, p=0.021, p=0.025 respectively). Additionally, some changes were good predictors of outcome despite being limited to small numbers, such that they did not affect the mean group scores. The most prominent of these changes were asymmetry in the middle occipital gyrus (p=0.005), superior temporal gyrus (p=0.007), and insula (p=0.025), as well as hypometabolism in the contralateral hippocampus (p=0.025).

Conclusions: Quantitative analysis of FDG-PET from patients with medial temporal sclerosis showed increased asymmetries in the middle frontal gyrus, paracentral lobule, thalamus, and posterior cingulate that were associated with worse post-surgical seizure. The findings in this study are significant when tailoring specific patient treatment options, stratifying which patients would be better surgical candidates, and prevent unwarranted harm to those who are not.
Yale and Columbia Anti-epileptic drugs Database and the Computer-Assisted Rational Epilepsy Therapy [CARET].

Authors: Hatem Tolba, Dena Edelman, Anelisa Fergus, Jennifer Bonito, Hamada Altalib

Yale And Columbia AED database [CAERT] database was established more than 15 years ago to help clinicians determine drug efficacy, side effects and interactions. To date the data collected was described as psychiatric and behavioral side effects of anti-epileptics in both children and adolescents beside the most important Cosmetic side effects.

This work is still in progress and we currently conducting multiple studies. Also, we will explore the possibility of the expansion of our database to include VA Hospitals, Miami University and other academic centers as well as describe future potential projects.
Psychosocial Outcomes after Surgery for Refractory Epilepsy due to Focal Cortical Dysplasia

Authors:
Benjamin Blond, Eliezer J. Sternberg, Rija Aziz, Emily Stanford, Anita Huttner, Dennis Spencer, Pue Farooque

Abstract

Rationale: Epilepsy is a condition with a profound impact on quality of life (QOL), with often severe levels of impairment across physical, cognitive, emotional, and social domains. Seizure freedom is the single most important factor in determining QOL in people with epilepsy (PWE), as prior studies show PWE who were seizure free had a QOL comparable to the general population, whereas the presence of any seizures led to impaired QOL at a level comparable to other diseases. Evaluation for epilepsy surgery is therefore essential for potentially improving QOL, most dramatically through achieving seizure freedom. When seizure freedom cannot be achieved, other factors, particularly depression and adverse medication effects, can have a larger impact than seizure frequency, and so comprehensive assessments of QOL are needed. Focal cortical dysplasia presents a spectrum of malformations of cortical development, which are often part of a widespread neurodevelopmental disease process, associated with cognitive and mood impairments, as well as being a frequent cause of medically refractory epilepsy. There is a paucity of research on the results of epilepsy surgery in this specific population. This study is designed to assess epilepsy and psychosocial outcomes, and to evaluate factors associated with positive outcomes.

Methods: Medical records of PWE who underwent epilepsy surgery at Yale New Haven Hospital between 1986 and 2017 were reviewed to obtain clinical data on the following variables: age of epilepsy onset, duration of epilepsy prior to surgery, short- and long-term postsurgical outcomes defined by ILAE Classification, and pre- and postoperative trends of antiepileptic drug use. Data were collected at 1, 2, 3, 4, 5, and 10 years postoperatively and at the most recent available follow-up. Subjects were contacted and completed an online survey designed to comprehensively assess characteristics of their current seizures and their QOL, with subsections of the survey including the QOLIE-31, BDI, and BAI.

Results: Initial results include seizure outcome on 45 subjects and psychosocial outcomes on 13 of those 45. After 1 year, 74% of patients were seizure-free or experiencing only non-disabling auras (ILAE 1, 1a, 2). This rate dropped to 62% after two years, then stabilized (for up to 28 years postoperatively). At latest follow-up, 89% of patients saw at least a 50% improvement in seizure frequency. QOLIE-31 scores had a mean 69+/-14, which is not significantly different from other epilepsy surgery samples reported in the literature (for example, Sajobi et al. 2014). Our early results demonstrate BDI 22+/-14 and BAI 19+/-16. As a comparison, a sample of 373 patients who had epilepsy surgery had BDI 6.8+/-7.6 and BAI 5.9+/-7.5 at 1 year (Hamid et al. 2014), which may suggest elevated anxiety and depression in a dysplasia sample compared to other epilepsy surgery samples.

Conclusion: Early results indicate that our population of patients with cortical dysplasia had similar outcomes to other epilepsy surgery populations, with significant rates of seizure freedom being associated with improved QOL and employment. As we collect more data, we hope to be able to assess the impact of dysplasia subtype and predictors of better psychosocial outcomes.
Temporal lobe seizures with impaired conscious awareness significantly impair quality of life and sometimes cannot be stopped by medications, surgery, or responsive neurostimulation. Consequences include the risk of motor vehicle accidents, drowning, poor (work/school) performance, social stigmatization, and, rarely, death due to postictal cardiopulmonary depression. Preclinical studies have shown that stimulation of the intralaminar central lateral nucleus, a region of the thalamus that modulates arousal, can improve electrophysiological and behavioral markers of arousal during and after temporal lobe seizures. Our goal is to reverse the adverse effects of temporal lobe seizures on conscious arousal to improve quality of life for patients with refractory epilepsy. We will use the Activa RC+S neurostimulator (Medtronic, Inc.) to design and implement a novel treatment that combines conventional responsive neurostimulation with deep brain stimulation of the central lateral thalamus, delivering the latter treatment if real-time sensing reveals that focal responsive neurostimulation has failed to abort the seizure. We are collaborating with the Mayo Clinic group and Medtronic to adapt the (hardware/software) capabilities of the RC+S for our proposed treatment. Once our device is granted an investigational exemption from the FDA, a small, six-patient feasibility trial will commence. We have prepared initial materials for the FDA and will receive feedback on our proposal in October. Next steps will be to secure funding and proceed to an early feasibility clinical trial.
Slide Session IV:
Clinical Epilepsy 2
NeuroProbe: A brain implantable electronic multi-sensor solution for rapid, sensitive, co-localized, in vivo measurement of brain physiology for acute brain injury

Authors:
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Severe TBI is a critical, worldwide, public health and socio-economic problem. It is a major cause of mortality among injured soldiers and civilian young adults, contributes to lifelong disability for its survivors, and has been identified as a significant health issue for service members and veterans. There are more than 5 million people in the USA with TBI related disability, and the incidence of TBI, world-wide, is rising.

Our goal is to develop a portable, single source, single probe, single interface device, single display, multimodal brain monitoring system for TBI. We have developed the modalities indicated for severe TBI (intracranial pressure (icP), intracranial EEG (icEEG), intracranial temperature (icT), brain tissue oxygen (Pbto2) and cerebral blood flow (CBF)) in a brain implantable device called the NeuroProbe with a target diameter, which is equivalent to, or smaller than, current probes.

We are developing a single interface device called the NeuroLink to acquire scalp EEG and digitize and transmit the multi-modal data acquired by the NeuroProbe and NeuroLink. We are also developing a display unit called the NeuroMonitor to display the acquired multimodal data in a synchronized real-time manner. We call the composite solution created by the NeuroProbe, NeuroLink, and NeuroMonitor devices the NeuroProbe Solution. This innovative solution allows integration of the data from multiple intracranial physiological parameters through a standard small tablet creating a simple single end-to-end solution from sensors to multimodal data display in an otherwise fragmented and complex domain thus broadening its application beyond the quaternary referral center and into the field and pre-hospital setting.

The technological development of the NeuroProbe Solution dramatically expands the capabilities of existing icEEG depth electrodes developed at Yale University. The key innovations of the NeuroProbe Solution, developed through collaboration of Yale’s School of Engineering and Applied Sciences and the Departments of Neurology, Neurosurgery, Lab Medicine, and Comparative Medicine at the Yale School of Medicine, are:

1. Integration of multiple physiologic sensors on a single intracranial probe (NeuroProbe)
2. Simplification of NeuroProbe to allow placement at bedside or military field facility
3. Development of a portable multimodal interface device (NeuroLink) which can store and relay digital data acquired simultaneously by the NeuroProbe sensors to a proprietary monitor as well as commercially available monitors
4. Development of a small (iPad sized) portable monitor (NeuroMonitor) to display multimodal data

In future work we will integrate biosensors to allow sensing of neurochemistry on the NeuroProbe, allowing expansion to neuromonitoring in epilepsy. In related work we are developing solutions for the wireless transmission of intracranial EEG, and focal brain cooling. This presentation will discuss the different neurotechnology initiatives with a primary emphasis on the NeuroProbe Solution.
NONINVASIVE SKIN VOLATILOMICS FOR FORECASTING AND DIAGNOSING SEIZURES

Authors:
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Purpose: Volatile organic compounds (VOCs) emitted by the mammalian body are typically small molecule intermediates or end products from metabolism of food, drugs, environmental agents and endogenous constituents of the body. Considering that metabolic perturbations are often associated with seizures we explored the utility of measuring VOCs, emitted through the patient’s skin, as a novel, noninvasive and highly informative “volatilomic fingerprint” for forecasting of impending seizures and for diagnosis of ongoing, or recently completed seizures. VOC can be collected in a rapid, easy and pain-free fashion, making the sample type particularly valuable for frequent monitoring of oscillating disease states such as epilepsy.

Methods: Adult patients (>18 years) admitted to the Yale Comprehensive Epilepsy Program for long-term video-scalp electroencephalogram (EEG) recordings will be recruited for this study. Samples are collected by swabbing the skin with sterile gauze. Swabs will be collected multiple times in triplicates to establish each patient’s baseline (interictal) VOC profile. Additional swabs are collected before and after electrographic seizures to capture seizure-associated VOC changes. Swabs will be analyzed by headspace solid phase microextraction-gas chromatography-mass spectrometry (HS-SPME-GC-MS). Multivariate and univariate statistics with correction for false discovery rate (FDR) will be used to identify statistically significant, “candidate markers”.

Results: We have previously shown the utility of this approach in a different species. In this study we identified 187 VOCs. Many of the VOCs correlated with the individuals’ major histocompatibility complex (MHC) profile. In the present study we are establishing baseline VOC profiles as well as pre-seizure and post-seizure VOC profiles in patients with epilepsy and non-epilepsy control subjects. Our expectation is to identify a gradual change in the VOC profile in the hours leading up to a seizure and in the hours following a seizure. Some VOC changes are expected to be strongly associated with all seizures in all patients, suggesting that certain metabolic changes or pathways represent common seizure mechanisms.

Conclusions: The discovery of easily measurable biomarkers of seizures will be significant because: (a) biomarkers of seizure forecasting will facilitate the development of novel, on-demand treatments for epilepsy, and (b) biomarkers of completed seizures, will fill a critical gap in the way seizures are diagnosed, by eliminating the need to capture a seizure by EEG.
Randomized controlled trial of motivational interviewing for psychogenic nonepileptic seizures

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Abstract: Objective: We conducted a randomized controlled trial of motivational interviewing (MI) as an intervention to improve psychotherapy adherence and outcomes, including seizure frequency, quality of life, and emergency department utilization, among patients with psychogenic nonepileptic seizures (PNES).

Methods: Sixty participants were randomized to receive either conventional psychotherapy alone or MI plus conventional psychotherapy. Participants and therapists were contacted at 16-week follow-up. Participants were considered adherent with psychotherapy if they attended at least 8 sessions within a 16-week period following referral.

Results: Among control participants, 31.0% were adherent, whereas among MI participants, 65.4% were adherent (p=0.015, absolute risk reduction: 34.4%, number needed to treat: 2.9). In the control arm, PNES frequency decreased by 34.8% (SD 89.7%), whereas in the MI arm, PNES frequency decreased by 76.2% (SD 39.2%) (p=0.034). Among control participants, 3 (10.7%) achieved PNES freedom, versus 8 (30.8%) of MI participants (p=0.095). QOLIE-10 scores improved on a 50-point scale by an average of 1.8 (SD 7.9) points among control participants, and by 7.2 (SD 10.0) points among MI participants (p=0.047). Monthly ED visits increased by 0.06 (SD 0.47) visits per month among control participants, versus a decrease of 0.15 (SD 0.76) among MI participants (p=0.23).

Conclusions: MI improved treatment adherence, PNES frequency, and quality of life among our participants with PNES. Our study is limited in that it was conducted at a single quaternary care medical center, and MI was provided by a single neurologist, which may limit generalization of our results.

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Evaluation of driving performance with a portable driving simulator on the epilepsy monitoring unit

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Individuals affected by epilepsy, especially when associated with loss of consciousness, can face significantly limitations when trying to lead normal, independent lives. Because seizures are often associated with loss of motor control and loss of consciousness, people with epilepsy (PWE) are restricted from driving until it can be shown that their seizures are fully controlled. In the U.S. and elsewhere, driving license issuance is dependent on PWE maintaining a seizure-free period whose length depends on local laws. The individual’s physician plays an important role in determining whether the patient should be allowed to drive. However, these decisions are often very subjective, because little data concerning patient driving ability during seizures is available. In this study behavioral data and video-EEG recordings for 36 epilepsy patients from the Yale New Haven Hospital were recorded as the patients used a semi-realistic driving simulator. While patients were using the driving simulator, 39 seizures and 65 subclinical seizures were recorded, with 24 seizures and 55 subclinical seizures having useable data for quantitative analysis purposes. Driving performance data during interictal periods were used as baselines in comparison to ictal driving performance. Impairment was determined using the following quantitative criteria: car velocity, steering wheel movement, application of the brake pedal, and the frequency of crashes. We found that seizures were associated with a higher rate of crashes than driving on the same portions of the track in the interictal period. In addition, longer duration of partial seizures was related to more severe impairment in driving. Subclinical electrographic seizures were not associated with obvious driving impairment. Ongoing analyses will determine if more subtle impairments occur in subclinical seizures. These findings demonstrate the feasibility of testing ictal driving in a prospective manner. In future work we hope to determine whether specific seizure types or localizations present a greater driving risk, with the goal of providing improved guidance to physicians and patients with epilepsy.
Absence seizures present as a temporary loss of normal consciousness, with patients both unable to respond to external stimuli and often unaware they experienced a seizure. These symptoms are associated with epileptic signals on the EEG of the patient; however, these abnormal EEG traces are often present without a loss of consciousness. Here, we employ a range of statistical and machine learning techniques on a large dataset of childhood absence epilepsy gathered from multiple centers to determine if certain features of the epileptic signals on the EEG predict whether the patient’s behavior will be impaired. This will aid in the diagnosis of clinical epilepsy on the basis of EEG recordings.