Fourth Annual
Yale Comprehensive
Epilepsy Research
Retreat
November 5-6, 2015

Madison Beach Hotel,
Madison CT
ACCREDITATION/DESIGNATION STATEMENT

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 7 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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It is the policy of Yale University School of Medicine, through its Center for Continuing Medical Education, to ensure balance, independence, objectivity, and scientific rigor in all its educational programs. All faculty participating in this symposium are required to disclose to the program audience any relevant financial relationship(s) they (or spouse/partner) have with a commercial interest that benefits the individual in any financial amount that has occurred within the past 12 months; and the opportunity to affect the content of CME about the products or services of the commercial interest. The Center for Continuing Medical Education will ensure that any conflicts of interest are resolved before the educational activity occurs.

LEARNING OBJECTIVES

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

1. Discuss the biological mechanisms of seizure generation in patients and in experimental models
2. Utilize clinical research methods to improve understanding of epilepsy diagnosis and treatment
3. Interpret the latest neuroimaging techniques for use in epilepsy research
4. Analyze high-density intracranial electroencephalogram recordings in epilepsy research
This conference is supported by educational grants from

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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, Dr. Tallie Baram, an outstanding leader in epilepsy research, 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.
Tallie Z. Baram is a Professor of Pediatrics, Anatomy/Neurobiology and Neurology at the University of California-Irvine, and holds the Danette Shepard Chair in Neurological Sciences. Baram is the Scientific Director of the UCI Epilepsy Program and the founder of the UCI Epilepsy Research Center. As a child neurologist and developmental neuroscientist, Baram studies seizures and epilepsies of infants and children, focusing on Febrile Seizures and Infantile Spasms.

Baram has been studying how early life febrile status epilepticus can convert a normal brain into an epileptic one. Students in the lab employ molecular and epigenetic techniques to examine how these seizures cause orchestrated and enduring alterations of gene expression programs resulting in abnormal neuronal function and Epilepsy. This has led to discoveries of the role of HCN channels in epilepsy and more recently, to uncovering novel principles of transcriptional regulation in the brain. The lab employs innovative in vivo and in vitro imaging to enable early prediction of individuals who are destined to develop Temporal Lobe Epilepsy following experimental febrile status epilepticus.

Baram’s research contributions have been recognized by prestigious awards including the NIH NINDS Javits Merit Award, AES Basic Science Research Award, the ANA Soriano Award and Child Neurology Society Sachs Award. She has chaired the NIH Developmental Brain Disorders study section and has contributed to numerous others. She has served on the AES Executive Board and leads the Board of the Lennox/Lombroso Epilepsy Research Trust.

Baram has a passion and commitment to mentoring. She is PI of one of two NIH funded T32s focused on epilepsy, and is mentor of several currently funded K awards. Baram’s numerous students from diverse backgrounds are now contributing independently to Neuroscience and Epilepsy research.
Thursday, November 5th

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

10:40 – 12:00 p.m.  
**Slide Session I: Neuroimaging**  
**Moderator: Dennis Spencer, MD**

10:40 – 11:00 a.m.  
Quantitative PET Imaging of Synaptic Vesicle Glycoprotein 2A in Temporal Lobe Epilepsy Patients  
Sjoerd J. Finnema, Kamil Detyniecki, Tore Eid, Dennis Spencer, Anita Huttner, Richard E. Carson, Yiyun Huang

11:00 – 11:20 a.m.  
Preliminary Validation of a Novel Method of Presurgical fMRI Language Localization through Functional Connectivity Analysis  

11:20 – 11:40 a.m.  
PET Findings in Patients with Medial Temporal Lobe Epilepsy (MTLE); Patients with Frequent Secondary Generalizations vs. Not  
Jiyeoun Yoo, Ming-Kai Chen, Adithya Sivaraju, Hal Blumenfeld

11:40 – 12:00 p.m.  
Dynamic Network Changes in Conscious Visual Perception Measured by Intracranial EEG  
Wendy R. Xiao, Rachel E. Smith, George J. Touloumes, Corey Horien, Anusha Raja, Leah Gober, Sharif Kronemer, Adil S. Wafa, Elliot Morse, Rebecca E. Watsky, William C. Chen, Dennis D. Spencer, Jason L. Gerrard, Hal Blumenfeld

12:00 - 1:00 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
Thursday, November 5th

1:00 – 3:00 p.m.  **Slide Session II: Animal Models**  Moderator: Tore Eid, PhD

1:00-1:20 p.m. Epilepsy Due to Gain-of-Function Mutations in the Slack (KCNT1) Channel
Imran Quraishi, Rachael Couture, Jack Kronengold, Grace Kim, Giulia Barcia, Rima Nabbout, Michael Schwartz, Leonard Kaczmarek

1:20 -1:40 p.m. Optogenetic and Morphological Studies of New Neural Circuits formed by GABAergic Interneurons Transplanted into Mice with Temporal Lobe Epilepsy
Janice R. Naegele, Jyoti Gupta, Jake Radell, Elizabeth Paquette, Selena Gonzalez, Ashley Fine, Felicia Harrsch and Gloster Aaron

1:40 – 2:00 p.m. Ivermectin Inhibition of Excitatory Hippocampal Neurons in the Presence or Absence of an Ivermectin-Sensitive Human Glycine Receptor Viral Vector
Anthony van den Pol, Xiaobing Zhang, Andrew Zayachkivsky

2:00 – 2:20 p.m. The Subcortical Control of Cortical Rhythms - Hypothalamus and Basal Forebrain
Nigel P Pedersen, Loris Ferrari, Christelle Anaclet, Anne Venner, Elda Arrigoni, Clifford B Saper, Patrick M Fuller

2:20 – 2:40 p.m. The Role of Increased Branched-Chain Amino Acids in the Blood on Brain Extracellular Fluid Glutamate Concentrations in Naive Rats
Shaun E. Gruenbaum, MD, Roni Dhaher, PhD, Tore Eid, MD, PhD

2:40 – 3:00 p.m. Modeling and Understanding Focal Cortical Dysplasia
Angelique Bordey, Lawrence Hsieh, John Wen

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.

Mechanisms of Widespread Cortical fMRI Decreases in Absence Seizures
Albert Y. Chen, Steven Braun, Jennifer N. Guo, Hal Blumenfeld

First Epilepsy Case of in Vivo Imaging of Synaptic Vesicle Glycoprotein 2A (SV2A) using a Novel PET Radiotracer
Kamil Detyniecki, Sjoerd J. Finnema, Nabeel Nabulsi, Tore Eid, Dennis Spencer, Anita Huttner, Richard E. Carson, Yiyun Huang
Thursday, November 5th
Poster Session with Wine and Passed Hors d’oeuvres

Restoring Consciousness during Focal Seizures with Multi-site, Multi-contact DBS
Adam Kundishora, Abhijeet Gummadavelli, William Biche, Maria Galardi, Chanthia Ma, Mengran Liu, Eric Musonza, Cian McCafferty, Brian Pok, Robert Gross, Jon Willie, Nicholas Schiff, Jason L. Gerrard, and Hal Blumenfeld

Investigating the Physiological Basis of Impaired Consciousness during Absence Seizures in a Rodent Model

Modulation of Thalamic Neuronal Activity during Focal Limbic Seizures
Li Feng, Joshua Motelow, William Biche, Cian McCafferty, Nicholas Smith, Mengran Liu, Qiong Zhan, Ruonan Jia, Alvaro Duque, Hal Blumenfeld

Brain Site Specific Suppression of Glutamine Synthetase in Mice using an Adeno-associated Virus Knockout Approach
Maxwell Farina, Helen Wang, Ronnie Dhaher, Yun Zhou, Siu-Pok Yee, Niels Christian Danbolt, Tore Eid

Effect of Glutamine Synthetase Inhibition in the Central Nucleus of the Amygdala on Anhedonia and Recurrent Seizures in a Rat Model of Temporal Lobe Epilepsy
Roni Dhaher, Shaun E. Gruenbaum, Helen Wang, Hitten P Zaveri, and Tore Eid

Inhibiting Striatal Enriched Phosphatase (STEP) during epileptogenesis suppresses seizures in mice with temporal lobe epilepsy

Hypothermia Associated with Clobazam use in Adult Epilepsy
Angela Gauthier, Imran Quraishi, Richard Mattson
An Update on the Yale Seizure Cluster Study
Chanthia Ma, Tenzin Choezom, Shiliang Zhang, Arpitha Komaragiri, Ben Weiss, Ariella Yazdani, Hitten Zaveri, Rasesh Joshi, Jennifer Bonito, Lawrence Hirsch, Kamil Detyniecki

Comparative Efficacy by Lobe of 13 Antiepileptic Drugs in almost 2000 Adults with Focal Epilepsy

A Novel Inherited SCN1A Mutation Associated with GEFS+ with Benign Encephalopathic Epilepsy
Angela Gauthier, Louis Manganas, Candy Cardoza, Richard Mattson

Intracranial Brief Potentially Ictal Rhythmic Discharges (BIRDs)
Jiyeoun Yoo, Rafeed Alkawadri, Lawrence Hirsch

Changes in autonomic arousal elicited by human amygdala stimulation are parameter-dependent
Jon T Willie; Cory S. Inman; David I Bass; Robert E. Gross; Stephan Hamann

Thursday, November 5th

5:00 – 5:30 p.m.  General Discussion and Day 1 Summary Moderator: Tallie Z. Baram, MD, PhD

5:45 – 6:30 p.m.  Group Beach Run

7:00 – 11:00 p.m.  Dinner and Social Event
Friday, November 6th

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.  Exploring Amygdala Stimulation to Treat Narcolepsy with Cataplexy
Jon Willie

8:50 – 9:10 a.m.  Introducing Automatic Responsiveness Testing in Epilepsy (ARTIE)
George Touloumes, Elliot Morse, William C. Chen, Leah Gober, Jennifer Dente, Rachel Lilenbaum, Emily Katzenstein, Ashley Pacelli, Emily Johnson, Yang Si, Adithya Sivaraju, Eric Grover, Rebecca Khozein, Courtney Cunningham, Lawrence J. Hirsch, Hal Blumenfeld

9:10 - 9:30 a.m.  Results of the TRENDs trial: A Prospective, Randomized, Multicenter Rrial on Lacosamide vs Fosphenytoin for Treatment of Refractory Nonconvulsive Seizures

9:30 – 9:50 a.m.  Effect of Ethnicity on the Pharmacokinetics of Anti-Epileptic Drugs
Qianyu Wang, Aman Ullah, Kamil Detyniecki, Lawrence J. Hirsch

9:50 – 10:10 a.m.  Frontal Lobe Seizures and Impaired Consciousness: Intracranial EEG Markers
Rahiwa Gebre, Leah Gober, Shamma Ahammad, Shivani Ghoshal, Dennis D. Spencer, Jason L. Gerrard, Hal Blumenfeld

10:10 – 11:00 a.m.  Coffee Break and Poster Session Revisit
<table>
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<th>Time</th>
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| 11:00 – 12:00 p.m. | **Slide Session IV: Electrophysiology**  
**Moderator:** Hal Blumenfeld, MD, PhD |
| 11:00 – 11:20 a.m. | **Threshold Concepts in EEG Education**  
Jeremy Moeller |
| 11:20 – 11:40 a.m. | **Prognostication of Post Cardiac Arrest Coma: Clinical and Electroencephalographic Predictors of Outcome**  
Adithya Sivaraju, Emily Gilmore, David Greer, Lawrence Hirsch & Nicolas Gaspard |
| 11:40 – 12:00 p.m. | **A Real-Time EEG Sonification System and its Applications in Epilepsy**  
Psyche Loui, Matan Koplin-Green, Aaron Plave, Michael Massone, Keith Spencer |
| 12:00 – 1:00 p.m.  | **Lunch Buffet and Final Discussion**  
Moderated by Tallie Z. Baram, MD, PhD and colleagues |
Slide Session I: Neuroimaging
Quantitative PET Imaging of Synaptic Vesicle Glycoprotein 2A (SV2A) in Temporal Lobe Epilepsy Patients

Authors: Sjoerd J. Finnema1, Kamil Detyniecki2, Tore Eid3, Dennis Spencer4, Anita Huttner4, Yiyun Huang1, Richard E. Carson1

Affiliations: Departments of Radiology and Biomedical Imaging1, Neurology2, Laboratory Medicine3 and Neurosurgery4, Yale University, New Haven, CT

Objectives: Synaptic vesicle glycoprotein 2A (SV2A) is an essential protein with ubiquitous expression in the CNS, and the site of action for antiepileptic drug levetiracetam. As animal and clinical studies have shown decreased SV2A density in the epileptogenic zone, SV2A may serve as an important biomarker in epilepsy. We recently reported [11C]UCB-J as a novel PET radioligand for imaging of SV2A in non-human primates. Here we present a test-retest reliability evaluation of [11C]UCB-J binding in humans, and first PET measurements with [11C]UCB-J in patients with epilepsy.

Methods: A total of 14 PET measurements were conducted on the HRRT scanner after injection of ~15 mCi of [11C]UCB-J. Five healthy subjects (age: 25-55 years) were scanned twice on the same day. The epilepsy patients, three with temporal lobe epilepsy and mesial temporal sclerosis (MTS) and one with focal cortical dysplasia, were scanned once. Arterial blood samples were collected for measurement of radiometabolites and free fraction (fP) in plasma using HPLC and ultrafiltration methods, respectively.

Results: [11C]UCB-J metabolized fairly quickly, with parent fraction of 28±7% at 60 min post-injection. Plasma free fraction was 32±1%. Brain uptake of [11C]UCB-J was very high. Regional TACs displayed rapid kinetics and were well described by 1TC. Regional VT values were highest in striatum and cortex, moderate in cerebellum and thalamus and lowest in centrum semiovale. The mean of the absolute test-retest differences was <5% for all brain regions. Parametric maps were of high quality and VT values correlated well with ROI-based estimates (R²>0.99). Evaluation of the epilepsy patients indicated a significant reduction of [11C]UCB-J binding in the mesial temporal lobe co-localized with MTS seen on MRI.

Conclusions: The novel radioligand [11C]UCB-J exhibits excellent characteristics as a PET imaging tracer in humans. PET measurement in epilepsy patients confirmed a decrease in SV2A binding in the epileptogenic zone and suggests that [11C]UCB-J may be a suitable biomarker in epilepsy. This radioligand may also have the potential to be a general-purpose tool for measuring synaptic vesicle density in neurodegenerative disorders.
Preliminary Validation of a Novel Method of Presurgical fMRI Language Localization through Functional Connectivity Analysis

Authors: Noble, S.M., Scheinost, D., Bookheimer, S.B., Walshaw, P., Hirsch, L., Spencer, D., Constable, R.T., & Benjamin, C.F.

OBJECTIVE: Neurosurgery is potentially curative in chronic epilepsy but can only be offered to patients if the surgical risk to language is known. Clinical functional magnetic resonance imaging (fMRI) is an ideal, noninvasive method for localizing language cortex yet remains to be validated for this purpose. We have recently presented a novel method for localizing language cortex. Here we present a preliminary evaluation of this method’s validity. We hypothesized language regions identified using this novel method would demonstrate stronger functional connectivity than randomly generated set of proximal networks.

METHOD: fMRI data were collected from sixteen temporal lobe patients (12 left) being evaluated for epilepsy surgery at UCLA (mean age 38.9 [sd 11.4]; 6 female; per Wada 14 left language dominant, 1 right, 1 mixed). Language maps were generated using a recently standardized method relying on a conjunction of language tasks (e.g., visual object naming; auditory naming; reading) to identify known language regions (Broca’s area; inferior and superior Wernicke’s Areas; Angular gyrus; Basal Temporal Language Area; Exner’s Area; and Supplementary Speech Area). With activations defined as network nodes, mean network connectivity was compared via permutation tests with alternate (i) fully random and (ii) proximal random networks. Mean network connectivity was determined in independently-acquired motor fMRI datasets (9 foot, 16 hand, 14 tongue).

FINDINGS: 77% (30/39) of clinician-derived language networks exhibited mean connectivity greater than fully random networks (p<0.05). Similarly, 69% (27/39) of clinician-derived language networks exhibited mean connectivity greater than proximal random networks (p<0.05). Further analysis of networks not passing the permutation test suggests that low connectivity of non-valid networks may be driven not by low connectivity across all nodes, but by individual nodes that may not actually possess membership within the network.

CONCLUSIONS: This study provides preliminary validity for a novel, clinician-based approach to mapping language cortex pre-surgery. This complements our recent work showing this method is reliable, and supports a proposed study comparing fMRI language maps using this technique with the results of direct stimulation mapping."
FDG-PET hypometabolism in MTLE patients with secondary generalized seizures

Authors: Jiyeoun Yoo, Ming-Kai Chen, Adithya Sivarau, Hal Blumenfeld

Secondarily generalized tonic-clonic seizures (SGTCs) have devastating consequences for safety and quality of life. Intracranial EEG analysis of seizures that stay focal vs secondarily generalize in patients with MTLE suggested that the posterior-lateral temporal cortex may serve as an important “gateway” controlling propagation of medial temporal lobe seizures to other cortical regions. In patients with MTLE, FDG-PET scans show typically larger regions of hypometabolism beyond the medical temporal lobe, and it has been suggested that propagation of seizures may be the cause. It has also been suggested that presence of SGTCs is associated with a larger extent of remote hypometabolism and that patients with remote hypometabolism have poorer surgical outcome.

We aimed to examine the pre-operative PET findings in MTLE and compare the extent of hypometabolism with a special focus within the temporal lobe, and investigate their correlation with pre-operative frequency of SGTCs, epilepsy duration, and surgical outcome.

We collected 48 patients who had undergone temporal lobectomy for intractable MTLE with proven MTS pathology and had at least 1 year of postoperative follow up, and who had a pre-operative PET scan in the period of 2004-2015. Pre-operative seizure frequency of SPS/CPS and SGTCs, duration of epilepsy, and surgical outcome were investigated. FDG-PET was analysed using a statistical parametric mapping with MIM software. The results are pending at this time, but we hypothesize that the presence of SGTCs are related to hypometabolism especially in the posterior lateral temporal lobe. We hope that this study will lead to better understanding of the SGTCs in MTLE, which may lead to therapeutic intervention to confine seizure propagation.
Dynamic network changes in conscious visual perception measured by intracranial EEG

Authors: Wendy R. Xiao, Rachel E. Smith, George J. Touloumes, Corey Horien, Anusha Raja, Leah Gober, Sharif Kronemer, Adil S. Wafa, Elliot Morse, Rebecca E. Watsky, William C. Chen, Dennis D. Spencer, Jason L. Gerrard, Hal Blumenfeld

Intracranial EEG provides the ability to directly measure neuronal population firing in localized points across the brain, an advantage over scalp EEG. In order to study brief conscious events, we developed a task paradigm that probes perception with subsequent objective validation using a 50 ms face stimulus titrated to threshold perception levels of contrast for a 50% detection rate. We tested this task in 8 subjects from the Yale Epilepsy Surgery Program with some 100-300 implanted intracranial electrodes sampled at 1024 Hz. When the stimulus was present, it was perceived 53% (±2% SEM) of the time compared to 9% (±4% SEM) for blank trials. In trials in which a present target was detected, its location in 1 of 4 quadrants was accurately discriminated 90% (±3% SEM) of the time. However, when the target was not detected, the location accuracy dropped to 28% (±3%), or near chance levels. Thus, the subjects behaviorally demonstrate appropriate engagement to produce predicted performance. Intracranial EEG analysis was done comparing doubly correctly perceived and located stimuli ("confirmed perceived") and doubly incorrectly perceived and located stimuli ("confirmed not perceived"). While very early ERPs around 100 ms in the primary visual cortex look identical between the two trial types, the evoked signatures quickly diverge as early as 200 ms in the fusiform face area but proceed across the entire brain to involve fronto-parietal as well as medial temporal cortices up to 1000 ms post-stimulus. Spectral analysis of broad-band gamma (40-115 Hz) power follow a similar temporal and spatial progression of increases first in the primary visual cortex followed by visual association areas, then proceeding onto the frontal-parietal association cortices and finally the medial temporal cortex. Interestingly, these increases occur in traditionally identified “task-positive network” areas and are accompanied by power decreases in other “default mode network” areas such as the precuneus, the inferior parietal cortex, and the ventral medial frontal cortex. These results beg the question of how identical information entering the primary visual cortex can quickly diverge so drastically between consciously perceived and not perceived trials. Analysis of the phase of the 5-15 Hz signal at the time of stimulus presentation show that in most of the subjects, there is a phase shift between perceived and not perceived trials. This suggests that the phase of alpha reflecting state-related fluctuations may gate the access of information entering the primary visual cortex by higher association areas to produce conscious awareness of threshold stimuli. Further analysis of the temporal progression of activity may elucidate the influence of network-related activity in producing conscious access.
Slide Session II: Animal Model
Epilepsy due to gain-of-function mutations in the Slack (KCNT1) channel

**Authors:** Imran H. Quraishi (1), Grace E. Kim (2), Jack Kronengold (3), Pawel Licsnerski (4), Rachael Couture (5), Michael Schwartz (5), Rima Nabbout (6), Leonard K. Kaczmarek (3,2) (1) Neurology, (2) Cellular and Molecular Physiology, (3) Pharmacology, (4) Medicine (Endocrinology), and (5) Neuroscience, Yale School of Medicine, New Haven, CT. (6) Pediatric Neurology, Hôpital Necker-Enfants Malades, Paris, France.

Slack (KCNT1) is a neuronal potassium channel that has been implicated in a spectrum of genetic epilepsy syndromes and has been linked to neuronal development and plasticity. 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). In a short time, over 20 epilepsy-associated mutations have been identified. Slack-associated epilepsies range from severe infantile epileptic encephalopathies to focal epilepsy with varying degrees of neuropsychiatric features. All of these mutations are associated with gain of function as determined by increased whole cell Slack conductance in a heterologous expression system (Xenopus oocytes). Although several mechanisms may be contributing, the major reason for the increased whole cell conductance is an increase in cooperative gating interactions between neighboring channels. Slack currents are activated during periods of rapid firing, as in seizures, and contribute to accuracy of high frequency action potentials. The channel also interacts with cellular mechanisms for neuronal translational regulation and is crucial for motor skill learning. There are currently no known Slack-specific antagonists, but Slack channels and related proteins may be good targets for pharmaceutical therapy against seizures and epileptogenesis.
Optogenetic and morphological studies of new neural circuits formed by GABAergic interneurons transplanted into mice with temporal lobe epilepsy.

Authors: Janice R. Naegele, Department of Biology, Program in Neuroscience and Behavior, Wesleyan University, Middletown, CT

Abstract: Transplantation of GABAergic interneuron progenitors into the hippocampus in several different models of epilepsy demonstrated that increasing the number of inhibitory interneurons in hyperexcitable neural circuits could control seizures. The exact mechanisms for seizure suppression are not well understood. We are examining inhibitory synaptic networks between transplanted medial ganglionic eminence (MGE)- derived GABAergic progenitors and endogenous granule cells (GCs) born in the dentate gyrus of adult mice with pilocarpine-induced severe temporal lobe epilepsy (TLE). By conducting continuous V-EEG recordings over 30-90 days, we showed previously that TLE mice with MGE grafts had significantly fewer seizures, compared with TLE controls receiving media injections. However, this effect did not endure beyond 3 months after transplantation, despite survival of the transplanted cells. GCs innervated by the transplants exhibited higher frequencies of IPSCs, compared to non-innervated GCs, and moreover, optogenetic stimulation of ChR2-expressing GABAergic interneuron transplants induced strong IPSCs in GCs, even in the later periods when seizure suppression typically wore off. These findings suggested that inhibitory circuits formed between the transplants and GCs might reduce seizures initially, but over time, neural circuit changes reduced the efficacy of the grafts. To test this hypothesis, we labeled GCs born shortly after induction of TLE with retrovirus, as these GCs are the most likely to develop hyperexcitability. We then transplanted GABAergic progenitors into the DG and allowed them to form mature synaptic connections. We repeated optogenetic stimulation and electrophysiology with biocytin filling to allow us to fully reconstruct retrovirally labeled GCs and obtain 3-D reconstructions of their innervation by the transplants. GCs born shortly after SE had a high number of transplant-derived inhibitory synapses and the number was positively correlated to the strength of post-synaptic currents induced optogenetically. Some GCs exhibited hilar basal dendrites and highly dysmorphic dendritic arbors, previously linked to mossy fiber sprouting and hyperexcitability.

Together these data suggest that inhibitory stem cells selectively wire with GCs born during development of epilepsy, but possibly not at later times. Ongoing studies will investigate whether failure of later-born GCs to incorporate into these inhibitory circuits is responsible for a reoccurrence of seizures. Grant support: CURE Epilepsy, NINDS, and Connecticut Innovations.
Ivermectin inhibition of excitatory hippocampal neurons in the presence or absence of an ivermectin-sensitive human glycine receptor viral vector

Authors: Anthony N. van den Pol, Xiaobing Zhang, Andrew Zayachkivsky
Department of Neurosurgery, Yale University

Here we tested the potential of the drug ivermectin to attenuate activity of neurons in the mouse hippocampus. Ivermectin is already approved for use in humans to kill parasites such as the larvae of worms that cause onchocerciasis (river blindness). We used whole cell electrophysiological recording in brain slices to study the effect of ivermectin. Although a modest direct response to ivermectin was detected in young mice, the response appears reduced or absent in mature mice. Positive current injection induced a series of action potentials. In the presence of 500 nM ivermectin, the frequency of spikes was reduced in 3 week-old mice, but in 6 month-old mice we found little inhibition by the same dose of ivermectin.

To test the hypothesis that we could generate strong inhibition in the mature brain with ivermectin, we employed a gene coding for the human glycine receptor (iGlyR) mutated to reduce glycine responses and to enhance a response to ivermectin. An adenoassociated virus vector was generated that expressed the iGlyR in addition to a fluorescent reporter gene under the control of the human cytomegalovirus immediate early ie1 promoter. When the iGlyR-AAV was injected into the dentate gyrus, substantial gene expression was found in excitatory granule cells. We studied the effects of ivermectin in granule cells expressing the iGlyR fluorescent reporter in adult mice two to five weeks after AAV administration; ivermectin evoked substantial inhibition. Remarkably, even a dose as low as 5 nM inhibited granule cells. In contrast, GABA and glycine even at concentrations 100X greater evoked no substantive inhibition on non-transfected granule cells. The next step in these studies will be to examine the ability of this viral vector to attenuate seizures in seizure models with lab animals given ivermectin. The general idea here is that the AAV-iGlyR could be surgically injected into a seizure initiation site where dose, placement, and spread could be varied. Secondly, ivermectin could then be given orally to selectively inhibit neurons in a particular site; again, dose and timing could be varied to obtain the optimal specific effect.

Support provided by the Swebilius Foundation and NIH.
The Subcortical Control of Cortical Rhythms - Hypothalamus and Basal Forebrain

Authors: Nigel P Pedersen\textsuperscript{1,2,3}, Loris Ferrari\textsuperscript{2,3}, Christelle Anaclet\textsuperscript{2,3}, Anne Venner\textsuperscript{2,3}, Elda Arrigoni\textsuperscript{2,3}, Clifford B Saper\textsuperscript{2,3}, Patrick M Fuller\textsuperscript{2,3}

1. Comprehensive Epilepsy Clinic, Beth Israel Deaconess Medical Center
2. Department of Neurology, Beth Israel Deaconess Medical Center
3. Harvard Medical School

Since the first recording of EEG in the early 20\textsuperscript{th} century, there has been significant interest in the mechanisms of various EEG rhythms. Broadly, the effector of field potentials recorded in the EEG of humans and rodents is the cerebral cortex, in the latter case including the hippocampus. However, subcortical structures are fundamental to the control of cortical EEG activity, including the brainstem, diencephalon and basal forebrain. We will discuss recent work from our group, with particular focus on neuronal groups of the basal forebrain and diencephalon that promote fast EEG activity and wakefulness. Specifically, mostly using chemogenetic techniques, we have identified a novel population of wake-promoting neurons of the caudal hypothalamus that drive hippocampal theta and neocortical gamma activity, and have found potent wake- and gamma-promoting effects of GABAergic neurons of the basal forebrain. Cholinergic basal forebrain neurons did not drive wakefulness, but potently suppressed cortical slow activity. These findings and the techniques used will be discussed in relation to epilepsy.
The Role of Increased Branched-Chain Amino Acids in the Blood on Brain Extracellular Fluid Glutamate Concentrations in Naïve Rats

Authors: Shaun E. Gruenbaum, MD; Ronnie Dhaher, PhD, Tore Eid, MD, PhD

Introduction: Recent studies have demonstrated that branched-chain amino acids (BCAAs) may play an important role in neurotransmission, however the role of BCAAs on brain metabolism and seizure regulation is poorly understood. Preliminary in-vivo brain microdialysis studies have shown that in humans with mesial temporal lobe epilepsy (MTLE), basal concentrations of glutamate and BCAAs are elevated in the extracellular fluid (ECF) of the epileptogenic hippocampus. It is unknown whether the increased BCAAs contribute to the observed increased glutamate concentrations. The objective of this study was to determine whether increased concentrations of blood BCAAs leads to increased concentrations of BCAAs, glutamate, and glutamine in the ECF of the brain in naïve rats.

Methods: In four rats, a microdialysis guide cannula was surgically implanted in the left dentate gyrus. A microdialysis probe was inserted under brief isoflurane anesthesia, and flow was established through the probe by infusing 2 μL/min of artificial cerebral spinal fluid (aCSF). After baseline dialysate samples were collected for one hour, a 4% isotonic BCAA solution was injected (0.8cc/100g weight) intravenously, followed by a 30-minute intravenous infusion (0.8cc/100g weight).

Results: The results are shown in Figure 1. Compared with average baseline brain ECF concentrations, IV injection of BCAAs resulted in a transient increase in the brain ECF concentrations of valine (1.65 ± 0.78 to 12.8 ± 3.3, p<0.0005), leucine (1.77 ± 0.73 to 12.60 ± 4.70, p<0.0005), and isoleucine (1.26 ± 1.05 to 12.10 ± 5.99, p<0.005). There were no significant differences between the 3 BCAAs after injection. IV injection of BCAAs also resulted in a transient increase in the brain ECF concentrations of glutamate (1.19 ± 0.45 to 11.5 ± 7.8, p<0.0005) and glutamine (17.05 ± 1.56 to 25.34 ± 2.95, p<0.005).

Conclusions: This study demonstrated that increases in blood BCAA concentrations results in increased brain concentrations of BCAAs, glutamate, and glutamine in naïve rats. This study gives important insight into how changes in blood chemistry impact brain concentrations of glutamate, which may subsequently result in secondary brain damage. Although the role of BCAAs in seizure formation is unknown, BCAAs may play an important role in neurochemical modulation.
Figure 1.
Modeling and Understanding Focal Cortical Dysplasia

Authors: Angelique Bordey, Lawrence Hsieh, John Wen

Focal cortical dysplasia (FCD), a local malformation of cortical development, is the most common cause of pharmacoresistant epilepsy associated with life-long neurocognitive impairments in children. Understanding and treatment remain limited due to the lack of an experimental FCD. We developed a model of FCD-associated tonicclonic seizures that recapitulates the etiology and anatomical alterations of FCD type II, including dyslamination, white matter heterotopia, and neuronal dysmorphogenesis. FCDs were generated by increasing mTOR activity in selective cortical neuron populations using in utero electroporation and were associated with daily convulsive seizures occurring throughout life when targeted in the medial prefrontal cortex. Preventing all FCD-related defects with rapamycin treatments from birth eliminated seizures, but bypassing neuronal misplacement and heterotopia using inducible vectors did not prevent convulsive seizure incidence. Collectively, data obtained using our new experimental FCD-associated epilepsy suggest that life-long treatment to reduce neuronal dysmorphogenesis is required to suppress seizures in individuals with FCD.
Poster Session
Mechanisms of widespread cortical fMRI decreases in absence seizures

Authors: Albert Y. Chen, Steven Braun, Jennifer N. Guo, Hal Blumenfeld

The study of epilepsy can help to understand both normal and abnormal brain physiology. Generalized epileptic events such as absence seizures create neuronal activity changes across the brain which are characterized by spike-and-wave discharge (SWD). Typical large amplitude bilateral SWD are common in absence epilepsy, but are also found in other forms of epilepsy. It is hoped that an extensive understanding of the neuronal activity changes during SWD might lead to improved treatment for absence seizures. Blood oxygen-level dependent (BOLD) fMRI signal change alone cannot fully reveal neuronal activity in the imaged system. For example, absence seizures are associated with widespread cortical fMRI decreases that persist for up to 20 seconds after seizure termination, but the physiological basis for these sustained decreases remain unknown. A standard hemodynamic response function (HRF) is commonly used to relate electrical brain activity to the expected fMRI timecourse. An important question is whether the sustained fMRI decreases after absence seizures can be explained by any electrical activity pattern when using the standard HRF. We created a physiologically realistic model of electrical activity during SWD including 3-4 Hz peaks and troughs in activity. Convolving this function with the standard HRF did not lead to sustained fMRI decreases if the model of electrical activity ended at the time of seizure termination. In order to obtain the sustained fMRI decreases it was necessary to include a prolonged phase of depressed electrical activity which occurred after the time of electrographic seizure termination. These results suggest that if the canonical HRF is correct, then the decrease in BOLD fMRI signals seen following seizures can’t be explained by electrical activity during the seizure alone. Instead, either sustained electrical activity decreases must persist after seizures which drive the decrease in BOLD signals, or alternatively the canonical HRF may need to be modified to include uncoupling of electrical and fMRI signals in the postictal period. With further investigation it is hoped that the full pathophysiology of neuronal changes during and after SWD can be better understood to help guide future treatment.
First epilepsy case of in vivo imaging of synaptic vesicle glycoprotein 2A (SV2A) using a novel PET radiotracer

Authors: Kamil Detyniecki, Sjoerd J. Finnema, Nabeel Nabulsi, Tore Eid, Dennis Spencer, Anita Huttner, Richard E. Carson, Yiyun Huang

Respective surgery is most frequently the only alternative available to achieve seizure freedom in patients experiencing drug-resistant epilepsy. In patients where MRI shows no lesion, information obtained from functional imaging techniques is particularly important to plan the placement of subdural electrodes for invasive monitoring. Because $^{18}$F-FDG PET usually shows a large area of hypometabolism extending beyond the epileptogenic zone and the localization value in extra temporal lobe epilepsies is low, new PET radiotracers that could more accurately identify the epileptogenic zone are needed. Synaptic vesicle glycoprotein 2A (SV2A) is an essential vesicle membrane protein which is located ubiquitously in synapses in the central nervous system. Clinical and experimental data have suggested that SV2A is involved in epilepsy with decreased SV2A receptor density found in the epileptogenic zone. In addition, levetiracetam and its analogs appear to exert their anticonvulsant effect through specific binding at SV2A.

We recently developed $^{11}$C-UCB-J, a highly promising radioligand for quantitative measurement of SV2A with positron emission tomography (PET). Our first in human SV2A PET studies in healthy subjects have shown that $^{11}$C-UCB-J has high brain penetration, good plasma free fraction, and moderate peripheral metabolism. The kinetic profile produced extremely high-quality parametric images with excellent test/retest reliability making this a potentially excellent PET tracer for quantitative imaging of SV2A in the human brain.

Case JS: A 52 year old male with mild intellectual disability and intractable epilepsy since 11 months of age. He underwent Video EEG monitoring that captured seizures emanating from the right temporal region and MRI imaging that showed right mesial temporal sclerosis (MTS). PET imaging showed significant reduction of $^{11}$C-UCB-J binding in the right mesial temporal lobe colocalized with the MTS seen on MRI. He underwent a right anterior mesial temporal lobectomy. Immunohistochemistry showed decrease expression of SV2A in the surgically removed hippocampus compared to an autopsy control. He remains seizure free for the last 9 months since surgery.

We hypothesize that $^{11}$C-UCB-J has the potential to be more diagnostically useful than $^{18}$F-FDG (a measure of glucose metabolism and neuronal activation) for seizure focus determination in epilepsy patients, although further studies are needed.
Restoring consciousness during seizures with deep brain stimulation

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Abstract: Impaired consciousness during and following seizures from medically and surgically refractory epilepsy has a dramatic impact on morbidity, mortality, and overall quality of life. The ability to improve consciousness would be highly beneficial to patients. We have developed a partial limbic seizure rodent model which mimics the human electrophysiological and behavioral characteristics associated with the loss of consciousness in temporal lobe epilepsy. Additionally, we have shown EEG and fMRI suppression of multiple arousal structures including the brainstem cholinergic and thalamic nuclei. Herein, we investigate the effects of single-site pontine nucleus oralis (PnO) or central lateral intralaminar thalamic (CL) deep brain stimulation (DBS) as well as dual-site CL + PnO DBS on cortical arousal and behavior in our animal model. Electrodes were placed stereotactically and localization was confirmed via histologic staining. Seizures were induced with a brief 2 second hippocampal stimulation at 60 Hz. Stimulation of the bilateral intralaminar thalamic CL at 100 Hz and PnO at 50 Hz was then applied at varying current intensities during the ensuing seizure for up to 120 seconds while we synchronously recorded electrophysiology and behavior. We found that dual-site stimulation during seizures reduced cortical slow waves by greater than 85% while simultaneously eliciting robust behavioral arousal as measured by spontaneous exploratory behavior (n=6). This effect resembled that seen with stimulation during physiological sleep (n=6) and under anesthesia (n=6). In contrast, stimulation of just CL or PnO alone, was insufficient to produce reliable cortical desynchronization and behavioral improvement during seizures (n=12). We postulate that necessary dual, rather than single-site, stimulation provides further support for the network inhibition hypothesis, which itself describes how widespread subcortical inhibition during limbic seizure results in loss of consciousness. These data also suggest a novel therapeutic approach to improving consciousness during and after seizures. Finally, pairing this with responsive neurostimulation algorithms may lead to rapid implementation of a therapy for preventing impaired consciousness during and after seizures. Studying this model with expanded behavioral tasks will help to illuminate the degree of cognitive recovery in the ictal and postictal periods. Finally, other states of decreased consciousness may similarly benefit from multi-site stimulation.
Investigating the physiological basis of impaired consciousness during absence seizures in a rodent model

Authors: Cian McCafferty, Prince Antwi, Adam Kundishora, Petr Vitkovskiy, James Sampognaro, Emily Johnson, Wasif Islam, Lisa Zheng, Nicholas Smith, Yang Si, Adeolu Morawo, Eric Chen, Alex Kwan, Antoine Depaulis, Hal Blumenfeld

Absence seizures are a common symptom of many epilepsy syndromes, and the defining seizure type in childhood absence epilepsy (CAE) and juvenile absence epilepsy. CAE patients’ quality of life is significantly impaired by regular episodes of unconsciousness as well as learning difficulties, behavioral disorders and other psychiatric conditions. Current gold standard pharmacological monotherapies may not achieve freedom from seizures in a substantial proportion of patients, and attentional deficits can persist even when seizures are suppressed, with significant long-term psychosocial sequelae common. Despite such limitations, ethosuximide, the first line treatment, has been in use for over 50 years without being improved upon. This lack of therapeutic progress demands a better mechanistic understanding of AS pathophysiology.

Hitherto, in vivo studies on mechanisms of AS have primarily involved anesthetized or drugged animals. Differences in behavior, arousal level, and apparent hemodynamic activity between such preparations and clinical absence seizures limit their utility. Consequently, we aimed to develop a protocol by which AS could be studied in a fully awake, undrugged rat model, in a head-fixed arrangement to facilitate local and global neuronal and multi-modal hemodynamic recordings. These would provide insights into the basis of impaired consciousness during seizures, by comparing the neuronal and hemodynamic correlates of seizures with varying degrees of behavioral impairment.

Using body restraint and incremental habitation training, Genetic Absence Epilepsy Rats from Strasbourg (GAERS) were trained to accept periods of body and head restraint up to 90 minutes with minimal indicators of stress. GAERS expressed AS abundantly during these periods. Preliminary recordings suggest a decrease in local cortical blood flow during seizures, and provide the first data on the nature of neurovascular coupling during true absence seizures. Future experiments will correlate these neuronal and blood flow dynamics with behavioral impairment.
Modulation of thalamic neuronal activity during focal limbic seizures

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Rationale: Impaired consciousness in temporal lobe seizures is very common and has a major negative impact on quality of life. Previous work has demonstrated that the widespread cortical slow waves and reduced cerebral blood flow suggest depressed cortical activity, similar to other states such as coma and deep sleep. We have proposed that the mechanism for these cortical changes involves depressed activity in subcortical arousal systems. Our goal was to investigate activity changes in the intralaminar central lateral (CL) thalamus due to its known important role in modulation of consciousness.

Methods: We performed juxtacellular recordings of neurons in the CL in a rat model of focal limbic seizures. Seizures were induced by a single 2s, 60 Hz train of biphasic current pulses to the hippocampus in lightly anesthetized rats. Single unit activity was analyzed in CL at baseline, during seizures and in the postictal period. Combined DAB-nickel and Nissl co-stains help us identify the recorded neuron’s anatomical location.

Results: Single neurons in CL fired regularly prior to seizure initiation. During the hippocampal seizure, the cortical multiunit activity converted to up and down states, while cortical local field potential converted to prominent slow oscillations. CL neurons markedly decreased their firing almost immediately after the seizure began. Firing rates slowly recovered during the postictal period and resumed normal firing after variable intervals. Most neurons in CL fired with a burst pattern during seizures, especially at the beginning of the seizure, but fired single spikes during baseline and after recovery.

Conclusions: At a cellular level, we found reduced firing rates and a burst firing mode for identified CL neurons during focal limbic seizures. Burst firing has been previously described in thalamic neurons in states such as sleep or deep anesthesia. These results suggest depressed arousal function of the CL region of the thalamus, which may suppress the activity of the cortex. Further work is needed to characterize activity patterns in other major thalamic regions. Decreased subcortical arousal could be a critical mechanism for loss of consciousness in focal temporal lobe seizures.
Brain Site Specific Suppression of Glutamine Synthetase in Mice using an Adeno-associated Virus Knockout Approach

Authors: Maxwell Farina, Helen Wang, Ronnie Dhaher, Yun Zhou, Siu-Pok Yee, Niels Christian Danbolt, Tore Eid

The expression of astroglial glutamine synthetase (GS), a key enzyme in the glutamate/GABA-glutamine cycle, is perturbed in brain disorders such as Alzheimer’s disease, schizophrenia, depression, and mesial temporal lobe epilepsy (MTLE). In human MTLE, GS is lost from astrocytes in specific subfields of the hippocampal formation; however, the consequences of such a loss are not fully understood. Here, we used either hippocampal infusion of the GS inhibitor methionine sulfoximine (MSO) or adeno associated virus (AAV) to assess the consequences of GS suppression in C57Bl/6J mice.

Conditional knockouts for GS were generated in C57Bl/6J mice by insertion of loxP sites at the front of the 2nd and 7th exon in the GS gene. Delivery of Cre recombinase to floxed GS mice (10-12 weeks) was mediated by AAV5CreGFP delivered unilaterally into the hippocampus. In the contralateral hippocampus, control AAV5GFP virus was delivered. On both sides, a total of 0.5 μL of virus with a titer of ~1x10^{12} was delivered. As controls, wildtype mice (10-12 weeks) were injected following the same protocol. Separate groups of wild type mice (10-12 weeks) were implanted with an osmotic pump that infused either MSO or phosphate buffered saline (PBS) unilaterally into the hippocampus.

Videointracranial electroencephalogram (EEG) recording was performed immediately following placement of the pump, and 4 weeks after injection of virus, to monitor for seizures. Severity of seizures was characterized using a modified Racine Scale. Mice were perfusion fixed with 4% paraformaldehyde after 23 weeks of EEG monitoring. Brains were horizontally sectioned at 40 μm with a Vibratome. Virus injected sections were colabeled for GS and GFP to assess GS levels.

All of the MSO infused mice and none of the PBS infused mice developed spontaneous recurrent seizures including convulsive, behavioral seizures. In the ipsilateral hippocampus, mice exhibited glial proliferation and patterned loss of neurons, whereas minimal brain injury was present elsewhere. In the floxed GS mice, GS levels were decreased in the Creinjected side at 45 weeks after viral delivery whereas minimal reduction in GS was noted in the control injected side. These findings suggest a key role of GS suppression in the causation of MTLE and provide useful laboratory tools for further investigation on the role of GS in health and disease.
Effect of Glutamine Synthetase (GS) Inhibition in the Central Nucleus of the Amygdala (CeA) on Anhedonia in a Rat Model of Temporal Lobe Epilepsy (TLE)

Authors: Roni Dhaher, Shaun E. Gruenbaum, Helen Wang, Hitten P Zaveri, Tore Eid

Background: Depression is highly comorbid in TLE patients, and suicide prevalence is approximately 25 times higher in these patients than in the general population. Anhedonia, a symptom of depression that is predictive of suicide, is common in TLE patients. Studies have further demonstrated that GS, an astrocytic enzyme that converts glutamate to glutamine, is reduced in the amygdala in patients with epilepsy, depression, and in suicide victims. Here, we developed a novel model of anhedonia in TLE by microinfusion of GS inhibitor methionine sulfoximine (MSO) unilaterally into the CeA.

Methods: 14 Male Sprague Dawley rats were implanted with an osmotic pump injecting either MSO (n=7) or PBS (n=7) into the right CeA. Intracranial EEG activity and video recording was monitored for over 21 days after the onset of MSO infusion. Sucrose preference, a measure of anhedonia, was assessed following EEG recording.

Results: Rats exhibited recurrent non-convulsive seizures during the first 3 days of EEG recording, followed by convulsive seizures for the remainder of the recording period. MSO treated rats showed a decreased sucrose preference over days when compared to PBS control rats (p<0.01). H₂O consumption (mL) did not differ between PBS and MSO groups (2.0 ± 0.4 and 2.1 ± 0.6, respectively).

Conclusion: This study suggests that perturbations in GS activity in the CeA are implicated in the causation of anhedonia in TLE. We propose that the MSO CeA model can be used for mechanistic studies of comorbid depression in TLE and for testing novel therapies of this condition.
Inhibiting Striatal Enriched Phosphatase (STEP) during epileptogenesis suppresses seizures in mice with temporal lobe epilepsy


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Striatal-Enriched Protein Tyrosine Phosphatase (STEP) levels are elevated in several neurological disorders, including Alzheimer’s disease and schizophrenia. STEP deficiency caused by gene knockout or pharmacological inhibition of STEP with TC-2153, a STEP inhibitor, ameliorates cognitive deficits in these disorders. A role for STEP in epilepsy is implicated by prior studies showing that STEP knockout mice exhibit increased seizure thresholds in the pilocarpine model of temporal lobe epilepsy (TLE). The present study was conducted to determine whether STEP inactivation with TC-2153 prevents or attenuates seizures. Following pilocarpine induced status epilepticus (SE) in C57BL/6 mice (Harlan Laboratories,) TC-2153 was injected intraperitoneally every day for two weeks at doses of 0, 5, or 10 mg/kg. Seizure activity from 40 mice was monitored with continuous video-EEG (vEEG) for varying periods from 21 days to 85 days after SE. vEEG analyses were carried out on 27 mice from post SE days 40-60 to quantify seizure frequency, severity, and duration. Mice receiving TC-2153 injections showed significantly reduced seizure frequency and severity. Studies are underway to examine seizure-induced changes in STEP levels and the effects of TC-2153 on STEP substrate phosphorylation after SE. Our preliminary findings suggest a role for STEP in epileptogenesis and potential therapeutic benefits of STEP inhibition for the treatment of TLE.
Hypothermia Associated with Clobazam Use in Adult Epilepsy

Authors: Angela Gauthier, Imran Quraishi, Richard Mattson

Rationale: Benzodiazepines usually have only mild side effects, but they have been occasionally associated with hypothermia especially in the elderly or very young. Clobazam, a 1,5-benzodiazepine FDA approved in 2011, has never been associated with this adverse effect until very recently, in a case report involving two pediatric epileptic patients. This report describes a novel finding of hypothermia related to clobazam use in an adult patient.

Methods: Case history was obtained through clinical record review.

Results: The patient is a 58-year-old male with a history of developmental delay, left hemiparesis, dysphagia, hypertension, cyclothymia, urinary retention, and a convulsive seizure disorder since he was 3 years old. His seizures occur a few times per month, often in clusters. His medications include phenytoin (200 mg/day), levetiracetam (3000 mg/day), clonazepam (1 mg/day), fluoxetine (30 mg/day), quetiapine (100 mg/day), amlodipine (10 mg/day), and aspirin (81 mg/day). Although his seizures were initially partially controlled by oxcarbazepine, this drug caused hyponatremia and had to be discontinued. Soon after, clobazam was initiated at 5 mg/day and increased to 10 mg bid after a month. Seizures were initially controlled well, but it was unclear whether this was due to the actions of clobazam or the nature his intermittent attacks. A couple months after starting clobazam, the patient started developing episodes of hypothermia every several weeks, with temperatures ranging from 90 F – 95 F. Normothermia was achieved with Bair Hugger therapy. Urinary tract infections were initially suspected as the cause of hypothermia, but this suspicion could not be confirmed. TSH and cortisol levels were normal. After 8 episodes of hypothermia, clobazam was tapered to 5 mg bid for a week because its benefit was unclear and preliminary case report evidence linked the drug to hypothermia. The patient experienced 3 more episodes of hypothermia < 95 F during this time. Ever since clobazam was completely discontinued 5 months ago, there have been no more episodes of hypothermia.

Conclusions: This case report describes several episodes of hypothermia associated with clobazam use in an adult patient, which stopped after the drug was discontinued. No evidence of infection could be found in most incidences. Future studies of hypothermia with correlated drug levels are warranted to further explore this association, but this novel finding is important to keep in mind when prescribing clobazam to patients.
An Update on the Yale Seizure Cluster Study: Prevalence, Treatment, and Consequences

Authors: Chanthia Ma, Tenzin Choezom, Shiliang Zhang, Arpitha Komaragiri, Ben Weiss, Ariella Yazdani, Hitten Zaveri, Rasesh Joshi, Jennifer Bonito, Lawrence Hirsch, Kamil Detyniecki

There is currently no standardized definition for seizure clusters, yet the effects of clusters are profound, often leading to injuries and emergency room visits. As rapidly acting benzodiazepines are being developed for abortive treatment of seizure clustering, it is essential to properly define seizure clusters. The objectives of this study are to analyze patterns of clusters using the definition of two or more seizures within a 6-hour period as well as assess the adverse outcomes of clusters, current use and efficacy of rescue medication, incidence of clusters using other definitions, and identifying epilepsy localization and etiology of seizure clusters. This is an interim report on six month outcome from the first 200 patients in an ongoing prospective seizure diary study.

Three hundred subjects were enrolled according to their risk for developing clusters. The high-risk group included subjects reporting two or more seizures within 24 hours at some point in the prior year. The medium-risk group had at least one seizure in the past year, but never two or more seizures within a 24-hour period. The low-risk group had epilepsy, but had no seizures in the past year. Subjects recorded date, time, duration, use of rescue medications, occurrence of injuries, and emergency room visits in paper and/or online diaries and were contacted monthly.

Of the first two hundred subjects, 139 subjects reached the six month mark after excluding noncompliant and daily seizure patients. Of these 139, 33 were from the low risk group, 56 were from the medium risk group, and 50 were from the high risk group. Forty-eight percent of patients from the high risk group had clusters and 21% from the medium risk group had clusters. None of the patients in the low risk group reported clusters. Although there was no significant difference in emergency department visits between patients with clusters (n=36) and patients with seizures but no clusters (n=46), there was a significant difference in occurrence of injuries. The use of rescue medication was also not different between the two groups. Further analysis of prospective data will better identify risks and precipitants of seizure clusters for various definitions.
COMPARATIVE EFFICACY BY LOBE OF 13 ANTIETEPILEPTIC DRUGS IN ALMOST 2000 ADULTS WITH FOCAL EPILEPSY


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Rationale: Literature on antiepileptic drug (AED) efficacy by lobe is lacking. Understanding which lobe an AED is most effective in treat seizures from may help better achieve rational drug-therapy. In this retrospective study, we compared the efficacy of 13 AEDs within lobes for localization-related epilepsy (LRE) patients.

Methods: Outpatients (≥16-years) with LRE were included from the Columbia-Yale AED Database if they had physician-confirmed localization and attempted ≥2 unique regimens for ≥6 continuous months. Efficacy was gauged by ≥6 continuous seizure free months (SF6). We investigated 124 non-AED factors associated with SF6 and performed logistic regression to compare the SF6 rate of one lobe of a given AED to its aggregate efficacy of the other lobes and to each lobe individually. We evaluated frontal (FL), temporal with (TLmts) and without mesial-temporal-sclerosis (TL), occipital (OL), parietal (PL), and multi (ML) lobe epilepsy. We censored data following surgical resection and controlled for severity by dichotomizing into failed number of AEDs ≥2 (intractable) vs <2 (milder severity). We calculated median SF6 doses and levels. P-value for all analyses was P<0.05.

Results: 1,886 patients (median age 42±16 years, 863-male) were included. Milder severity was a significant non-AED predictor of SF6 (P<0.001, OR=2.793). Lobe-by-lobe analyses revealed:

- Clobazam had its highest SF6 rate in OL (71.4%), greater than its aggregate (40.4%, P=0.023, OR=3.964), greater than in FL (39.4%, P=0.036, OR=3.846) and TL (36.3%, P=0.015, OR=4.79). 
- Lamotrigine had its lowest SF6 rate in ML (38.0%), lower than its aggregate (56.3%, P=0.003, OR=0.483), lower than in FL (54.0%, P=0.026, OR=0.545), TLmts (54.0%, P=0.022, OR=0.511), TL (60.0%, P=0.002, OR=0.457), and OL (68.4%, P=0.035, OR=0.314).
- Oxcarbazepine had its highest SF6 rate in FL (46.7%), greater than its aggregate (31.5%, P=0.013, OR=2.352), greater than in TLmts (19.2%, P=0.028, OR=3.651) and TL (28.3%, P=0.014, OR=2.437).
- Zonisamide had its lowest SF6 rate in FL (18.2%), lower than its aggregate (30.6%, P=0.029, OR=0.438), lower than in TL (32.9%, P=0.045, OR=0.454), OL (66.7%, P=0.019, OR=0.111), and PL (53.3%, P=0.009, OR=0.194).

Conclusions: Compared to the same AED in other lobes, clobazam was most effective for OL, oxcarbazepine was most effective for FL, lamotrigine was least effective in ML, and zonisamide was least effective in FL. These findings must be replicated as this was an exploratory analysis.
A Novel Inherited SCN1A Mutation Associated with GEFS+ with Benign and Encephalopathic Epilepsy

Authors: Angela Gauthier, Louis Manganas, Candy Cardoza, Richard Mattson

Rationale: Generalized epilepsy with febrile seizures plus (GEFS+) is an inherited epileptic syndrome with a wide spectrum of clinical and genetic heterogeneity. It is characterized by febrile seizures that persist beyond 6 years of age and may present later as afebrile tonic-clonic, atonic, myoclonic, myoclonic-atonic or absence seizures. Genes commonly associated with GEFS+ include: SCN1A, SCN1B and GABRG2. SCN1A is a neuronal voltage gated sodium channel alpha-1 subunit. Mutations in the SCN1A gene are believed to reduce the rate of channel inactivation leading to increased sodium influx and increased excitability. Truncations or deletions within this gene typically lead to severe phenotypes while missense mutations can be associated with a wide range of phenotypes. Several mutations have been described in the past with the hope of not only gaining a better understanding for designing more effective therapeutics but also for prognostic purposes.

Methods: Analysis of SCN1A gene deletions and sequence analysis was performed by Athena Diagnostics.

Results: The case described here is an 8-year-old boy who developed febrile seizures at 10 months. After several months he developed non-febrile seizures at a rate of 1-2/month. Seizures have increased in number and severity over the years. He has failed every marketed antiepileptic drug including the ketogenic diet. He has declined cognitively with a recent FSIQ of 78. In addition, aggressive behaviors are now also apparent. Neurological exam, CT, MRI, PET have been normal. Prolonged Video/EEG monitoring has recorded focal seizures with secondary generalization arising independently from both hemispheres. Family history is significant for simple febrile seizures in his father, paternal aunt and paternal grandfather. All had simple febrile seizures as children, but none developed later epilepsy nor cognitive problems. Genetic studies of the patient and his father revealed a missense mutation in the very distal end of the first pore domain of the first alpha subunit of the tetramer. A tyrosine (Y) has been changed to Phenylalanine (F) at amino acid position 399 (just before the 6th transmembrane region). This is a result of a nucleotide change from A to T at nucleotide position 1196. This SCN1A mutation at this particular location has not been previously described. SCN1B sequencing revealed a C to T nucleotide change at position 300 without any amino acid change. GABRG2 sequencing showed no abnormalities.

Conclusions: This case report describes a novel inherited SCN1A mutation in a child with GEFS+ with benign and encephalopathic epilepsy. The patient’s father, who also had an identical mutation, only suffered simple febrile seizures. The missense mutation described here localizes to the distal portion of the first pore domain of the first SCN1A alpha subunit. Whether specific localization of these mutations and/or variable expressivity confers seizure severity is not clear.
Brief potentially ictal rhythmic discharges (BIRDs) on EEG have been described in neonates and recently in critically ill adults. They are most often consisted of very brief (1-3 seconds) runs of sharply contoured theta activity without obvious evolution, and they are highly associated with seizures (75%). Similar discharges (usually in alpha frequency) have been observed in patients who are not critically ill, and all patients with BIRDs were found to have epilepsy, majority of which were refractory to medications. Their location had high correlation with the seizure onset area. In patients who received intracranial monitoring, similar discharges (usually in beta and gamma frequency) were observed intracranially, and the electrodes which were maximally involved had good correlation with the seizure onset zone. We aim to examine the prevalence and characteristics of BIRDs in the intracranial EEG, and compare them to BIRDs on the scalp EEG and seizure onset pattern. We also aim to prospectively follow the patients for surgical outcome depending whether the area of the BIRDs were resected or not.
Changes in autonomic arousal elicited by human amygdala stimulation are parameter-dependent

Authors: Jon T Willie; Cory S. Inman; David I Bass; Robert E. Gross; Stephan Hamann

The amygdala, located within the medial temporal lobe, regulates emotional responses, motivation, and memory. However, few contemporary studies have used direct electrical stimulation of the amygdala in humans to examine stimulation-elicited physiological and emotional changes, and the nature of such effects remains unclear. To determine the effects of amygdala stimulation on acute autonomic physiology, we utilized epilepsy patients undergoing intracranial EEG monitoring in which depth electrodes were implanted surgically from a lateral temporal approach into unilateral or bilateral amygdala. Subjects underwent either sham or acute monopolar electrical stimulation at various parameters in electrode contacts located in either amygdala or within the lateral temporal cortex. Stimulation was applied at either 50 Hz (pulse width of 300 usec) or 130 Hz (pulse width of 90 usec), while amplitudes were increased from lower (4≤ mV) to higher (>4mV, 12 mV maximum) amplitudes in a stepwise fashion, with subjects blinded to stimulation condition. Varying pulse widths for each frequency were chosen to balance the charge density delivered across frequencies. Skin conductance responses (SCR), respiratory rate, heart rate, and electromyographic Hoffman-reflex amplitudes, and video images were recorded. At stimulation amplitudes well below patients’ subjective awareness of stimulation, and without eliciting any seizures, we found that increasing linear, does-responsive stimulation effects, with higher-amplitude amygdala stimulation (but not lateral control or sham stimulation) eliciting rapid and significant heart rate deceleration and increasing skin-conductance. This pattern of results parallels stimulation findings with stimuli. Notably, all the described physiological effects were observed below thresholds in which patients reported being conscious of stimulation or changes in mood. Such changes occurred only at higher stimulation amplitudes. In a subsequent experiment, ongoing emotional responses to emotional videos were also not interrupted by amygdala stimulation. More intense stimulation may be required to elicit subjective emotional responses such as fear that have been reported previously. In summary, these findings suggest that acute amygdala stimulation in humans is safe and can reliably elicit changes in emotion physiology without significant affecting subjective emotional experience providing a useful paradigm for investigation of amygdala-mediated modulatory effects.
Slide Session III:
Clinical/Electrophysiology
Effects of Deep Brain Stimulation of Amygdala upon Human Laughter-Induced Changes in Hoffman Reflex and Murine Cataplexy: Proof of Concept for Novel Therapy for Narcolepsy Type 1

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Cataplexy is sudden transient bilateral muscle weakness with preserved consciousness that is triggered by emotion. Cataplexy, often refractory to medications, is a debilitating symptom of the sleep-wake disorder narcolepsy with cataplexy. The amygdala, an integrator of emotional-motor networks with output to brain arousal circuits, is a potential target for intervention.

High frequency electrical stimulation of brain structures (deep brain stimulation; DBS) is increasingly recognized as a safe and effective therapy for many neuropsychiatric disorders. DBS may also illuminate functional anatomy of networks governing arousal systems. We propose to investigate the use of amygdala DBS for narcolepsy type 1 using human and animal models. The human Hoffman reflex (H-reflex) is attenuated during laughter and cataplexy and has been used as a neurophysiological surrogate for cataplexy. Utilizing epilepsy patients after surgical implantation of electrodes for seizure localization, we will test whether mirthful laughter elicited by watching comedic video recordings is associated with changes in amygdala local field potentials (LFP) and depression of the H-reflex. We will then test the hypothesis that electrical stimulation of the amygdala attenuates H-reflex suppression during laughter. Finally, using a murine model of narcolepsy type 1, orexin/ataxin 3 transgenic mice, we will directly test the hypothesis that amygdala DBS inhibits cataplexy episodes. This investigation has implications for use of DBS in a human sleep disorder, and will be a foundation for my broader research interests in developing DBS to target network disorders involving the sleep-wake system including narcolepsy, hypersomnias, Parkinson’s disease, restless legs syndrome, and post-traumatic stress disorder.
Introducing Automatic Responsiveness Testing in Epilepsy (ARTiE)

Authors: George Touloumes, Elliot Morse, William C. Chen, Leah Gober, Jennifer Dente, Rachel Lilienbaum, Emily Katzenstein, Ashley Pacelli, Emily Johnson, Yang Si, Adithya Sivaraju, Eric Grover, Rebecca Khozein, Courtney Cunningham, Lawrence J. Hirsch, Hal Blumenfeld

Determining the degree of behavioral impairment during seizures is critical for medical decision making. When evaluated properly and consistently, information regarding a patient’s level of impairment can affect diagnosis, presurgical evaluations and physician recommendations for driving. The quality of behavioral testing during inpatient video-EEG monitoring at Yale New Haven Hospital’s epilepsy center was investigated and a technical innovation that may improve clinical care was introduced through this study. We completed a retrospective review of 152 seizures in 33 adult or pediatric patients admitted for video-EEG monitoring. Results revealed that behavioral testing with questions or commands was performed in only 50% of seizures ictally and 73% of seizures postictally. Combined postictal or ictal testing was performed in 80% of all seizures. Additionally, the questions or commands given were highly inconsistent and performed by non-medical personal in about 25% of cases. In an effort to improve this situation and capitalize on the ease of behavioral testing analysis, we developed and introduced Automated Responsiveness Testing in Epilepsy (ARTiE), a series of video-recorded behavioral tasks triggered patient push-button events or by computerized seizure detections to play in a patient’s room. In initial technical testing using pre-recorded or live video-EEG data we showed that ARTiE can be reliably initiated by seizure detection software and push button events. We hope that with additional clinical testing, ARTiE will succeed in providing reliable and comprehensive behavioral testing for patients with epilepsy, leading to an improvement in their clinical care and an increased understanding of loss of consciousness during epileptic seizures.
The TRENdS trial: Intravenous lacosamide versus fosphenytoin for the treatment of frequent nonconvulsive seizures in critically ill patients


Rationale: The effectiveness of many antiepileptic drugs (AEDs) in treating nonconvulsive seizures (NCS) in critically ill patients has not been studied in prospective, randomized trials. In this study we compared the utility of lacosamide (LCM) with fosphenytoin (fPHT) in this patient population in the Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS) trial.

Methods: This was a prospective, multicenter, randomized, active-controlled, noninferiority, open-label trial with blinded electroencephalogram (EEG) review. Patients diagnosed with NCS by continuous EEG (cEEG) monitoring were enrolled. Treatment was randomized to IV LCM 400 mg bolus followed by LCM 200 mg every 12 hours or IV fPHT 20 mg PE/kg bolus followed by 2.5 mg PE/kg every 12 hours. A rebolus of LCM 200 mg or fPHT 5 mg PE/kg was administered if a breakthrough electrographic seizure occurred within 2-8 hours after bolus dose. The primary end point was no recurrence of electrographic seizures (with or without clinical correlate) for 24 hours following bolus (or rebolus, if administered) of study drug as determined by blinded EEG reviewers. The response rate (no further seizures) of the LCM arm was compared to the fPHT arm and the 90% confidence interval (CI) was determined. A modified intent to treat (mITT; those patients with at least 67% of cEEG monitoring completed) population was used for efficacy analysis. Noninferiority of LCM to fPHT was concluded if the lower bound of the CI for relative risk was above 0.8.

Results: The ITT population included 74 subjects (37 in both LCM and fPHT arms), whereas the mITT population included 62 subjects (30 in the LCM arm, 32 in the fPHT arm). The safety population (those that received at least one dose of study drug) included 72 subjects (35 in the LCM group, 37 in the fPHT group). The mean age (ITT population) was 63.6 years; 38 were women. The response rate (mITT population) was 19/30 (63.3%) for the LCM group and 16/32 (50.0%) for the fPHT group. The risk ratio was 1.27 (90% CI = 0.875, 1.833) and the p-value for establishing noninferiority for LCM was 0.021. Treatment emergent adverse events (AE) within 24 hours of study drug administration were noted in 9/35 (25.7%) of LCM and 9/37 (24.3%) of fPHT patients. Serious AE occurred in 5/35 (14.3%) of LCM and 4/37 (10.8%) of fPHT patients. Treatment was discontinued in 2 (5.7%) and 3 (8.1%) patients in the LCM and fPHT arms. The rates of specific AE for LCM and fPHT arms were as follows: arrhythmias (5.7% vs 8.1%), acute respiratory failure (2.9% vs 0) and hypotension (5.7% vs 5.4%).

Conclusions: LCM was noninferior compared to fPHT in controlling nonconvulsive seizures noted on cEEG. TEAE were comparable with both AEDs. LCM can be considered an alternative to fPHT in the treatment of NCS detected on cEEG monitoring in critically ill patients.
Effect of Ethnicity on the Pharmacokinetics of Anti-Epileptic Drugs

Authors: Qianyu Wang, Aman Ullah, Kamil Detyniecki, Lawrence J. Hirsch

Objective: To compare pharmacokinetics of 10 anti-epileptic drugs (AEDs) in adult epilepsy patients of different ethnicities.

Methods: Using the Yale-Columbia Antiepileptic Drug Database, the pharmacokinetics of the 10 most commonly used AEDs was retrospectively studied in patients ages 18-65 who had been seen as outpatients at either center during a 5-year period. The weight-adjusted hourly apparent clearance (CL) was calculated for each regimen using serum levels which were intended to represent steady-state trough serum concentrations and averaged for each patient. For each AED, the mean CL of each ethnic group was compared using one-way analysis of variance. Monotherapy and adjunctive therapy regimens were analyzed separately. Gender, age, weight, and concurrent use of enzyme inducing AEDs (EIAEDs) were controlled as variables that could potentially affect the CL of AEDs.

Results: Phenytoin (PHT) used in polytherapy was the only AED which exhibited a significant difference in mean CL between patients of different ethnicities ($p < 0.0005; n = 100$). Mean PHT CL differed significantly between Black (36.2 ml/h/kg; $n = 9$) and White (15.6 ml/h/kg; $n = 75$) patients ($p = 0.001$) as well as between Hispanic (27.5 ml/h/kg; $n = 14$) and White patients ($p = 0.033$). Gender, age, weight, and comedication with EIAEDs were not significantly associated with CL for patients taking PHT as polytherapy.

Conclusions: Black and Hispanic patients taking PHT as polytherapy have CLs approximately twice that of White patients. Neither gender, age, weight, nor comedication with EIAEDs were significantly associated with CL for PHT used in polytherapy.
Frontal lobe seizures and impaired consciousness: Intracranial EEG markers

Authors: Rahiwa Gebre, Leah Gober, Shamma Ahammad, Shivani Ghoshal, Dennis D. Spencer, Jason L. Gerrard, Hal Blumenfeld

Loss of consciousness is an important morbidity associated with epileptic seizures, and understanding how altered consciousness occurs could have impact on future therapies. Consciousness includes multiple levels of input and output that maintain alertness, attentiveness, and awareness of both self and the environment. Previous work from our laboratory using SPECT imaging and intracranial EEG analysis of temporal lobe seizures has supported the network inhibition hypothesis; this states that impaired consciousness in temporal lobe epilepsy involves activation of the temporal lobe leading to abnormal activity in the thalamus and brainstem portion of the subcortical arousal systems. These changes lead to the depressed function in the frontal and parietal association cortices and impaired consciousness. Research on the mechanisms of loss of consciousness in frontal lobe epilepsy isn’t as clear, and the purpose of this project is to understand the mechanisms involved. We currently have acquired data from 67 patients representing 70 admissions spanning from 1997 to 2012 from the Yale Epilepsy Surgery Database that have confirmed pathology involving the frontal lobe. From this data set, we will be looking at intracranial video-EEG recordings of patients with resections strictly involving the frontal lobe that have been seizure-free since surgery. We may also include patients who are not deemed candidates for resection (for example due to the lesion extending into the motor area) but for whom diagnostic studies and clinical history strongly suggest frontal lobe onset. Consciousness will be determined by whether patients appropriately respond to questions or commands that require a response. Loss of consciousness in frontal lobe seizures may occur in a similar mechanism to mesial temporal lobe epilepsy where the seizure focus propagates to the temporal lobes and subcortical regions leading to depressed function of the frontal and parietal cortices. However, given the diversity of frontal lobe epilepsy, there may be additional neural circuits to structures within the consciousness system that are impaired during complex partial frontal lobe seizures.
Slide Session IV: Electrophysiology
Identification of threshold concepts in EEG learning

Authors: Jeremy Moeller, MD and Tim Fawns, MSc

The electroencephalogram (EEG) is one of the central diagnostic tests in neurology, and basic proficiency in EEG interpretation is a requirement for specialty accreditation in neurology in the United States. Despite this requirement, EEG misinterpretation by neurologists has been identified as a major problem. There is very little research into how EEG is learned, or how an EEG curriculum might be designed to best support learning. Threshold concepts are defined as concepts that are necessary for progression to expertise in a particular field. They are often counter-intuitive or “troublesome,” but when learned, they transform a learner’s understanding of the field, and may show the inter-connectedness of different concepts within the field. Several research studies in higher education have suggested that threshold concepts may be used as a framework for enhancing learning of difficult material. In this study, I will identify possible threshold concepts in EEG interpretation, and explore how teachers and learners engage with these concepts. I will draw on data collected from individual semi-structured interviews involving both EEG experts and learners. Analysis of the data will be performed using a general thematic analysis approach. The aim of the study is to develop a working list of threshold concepts in EEG learning, and to explore how these threshold concepts could be used to enhance the EEG curriculum in residency and fellowship. In particular, I will explore how the threshold concepts can be applied to a previously designed “flipped” curriculum for EEG teaching. Preliminary findings and future research directions will be discussed.
Prognostication of Post-Cardiac Arrest Coma: Early Clinical and Electroencephalographic Predictors of Outcome

Authors: Adithya Sivaraju, Emily Gilmore, David Greer, Lawrence Hirsch & Nicolas Gaspard

We recently published our findings (Sivaraju et al., 2015 Intensive Care Med) using a data set of 100 consecutive post-anoxic patients receiving hypothermia and continuous EEG monitoring between May 2011 and June 2014 at Yale University. In addition to clinical variables, 5-minute EEG clips at 6, 12, 24, 48 and 72 hours after return of spontaneous circulation (ROSC) were reviewed. EEG background was classified according to the American Clinical Neurophysiological Society Critical Care EEG Terminology. Clinical outcome at discharge was dichotomized as good (Glasgow Outcome Scale [GOS] 4-5: low to moderate disability) vs. poor (GOS 1-3: severe disability to death). We found that non-ventricular fibrillation/tachycardia arrest, longer time to ROSC, absence of brainstem reflexes, extensor or no motor response, lower pH, higher lactate, hypotension requiring >2 vasopressors and absence of reactivity on EEG were all associated with poor outcome (all p-values ≤ 0.01). Suppression-burst at any time indicated a poor prognosis, with a 0% false positive rate (FPR) (95% confidence interval (CI): 0-10%). All patients (54/54) with suppression-burst or a low voltage (<20µV) EEG at 24 hours had a poor outcome, with a FPR of 0% (95% CI: 0-8%). Normal background voltage ≥20 µV without epileptiform discharges at any time interval carried a positive predictive value >70% for good outcome.

A multi-center study with similar methodology and approximately 600 post cardiac arrest comatose patients receiving hypothermia and continuous EEG monitoring is currently in progress. This has resulted in the compilation of a rich data set with extensive clinical and electrographic information, and we hope to discuss some potentially relevant research projects stemming from this data set.
A Real-Time EEG Sonification System and its Applications in Epilepsy

Authors: Psyche Loui, Matan Koplin-Green, Aaron Plave, Michael Massone, Keith Spencer, Wesleyan University

Reading human electroencephalography (EEG) data has been the prevalent method for diagnosing seizures for decades, but newer work on sonifying EEG data has opened up possibilities for diagnosing and managing seizures, as well as for potential biofeedback therapies. Here we present a pipeline for real-time EEG sonification. We begin with an introduction and review of existing systems in functional and aesthetic uses of EEG sonification. We then introduce a working system and the pipeline through which we are able to convert EEG data to sound in real time. Having demonstrated the use of our system with some examples, we show that listeners with no knowledge of seizures or abnormal brain activity can distinguish seizure activity from baseline activity by listening alone. Finally, we offer some future prospects and challenges facing the ongoing development of EEG sonification for neurofeedback and its therapeutic potential, with specific applications for patients with epilepsy.