Fifth Annual Yale Comprehensive Epilepsy Research Retreat
March 30 – 31, 2017

Old Saybrook Inn and Spa
Old Saybrook, 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.

DISCLOSURE POLICY

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. Design and interpret clinical research studies to improve epilepsy medical and surgical treatment
2. Discuss the biological mechanisms of epileptic seizure generation
3. Utilize the latest cutting-edge methods for epilepsy diagnosis and treatment
4. Interpret advanced neuroimaging and electrophysiology techniques used for mapping epilepsy
5. Understand and apply innovative treatments including neurostimulation and new medications
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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, Jaideep Kapur, MD, PhD, the Eugene Meyer III Professor of Neuroscience and Neurology at the University of Virginia School of Medicine will speak at the Retreat, provide feedback and guidance, and serve as an external Moderator and reviewer for the research program. Dr. Kapur is a world renowned epileptologist and neuroscientist, as well as recent president of the American Epilepsy Society. The Retreat will consist of investigator slide presentations, poster session, and discussions on new research approaches and collaborations.
Jaideep Kapur, M.B., B.S., PhD, is the Eugene Meyer III Professor of Neuroscience, Professor of Neurology at the University of Virginia School of Medicine. He is the Director of the University of Virginia Brain Institute.

Dr. Kapur provides care to epilepsy patients as a member of FE Dreifuss Comprehensive Epilepsy Program at the University of Virginia and serves as the Director of Neuroscience Center of Excellence. He has a long-standing interest in understanding the neurobiological mechanisms underlying prolonged self-sustaining seizures, called status epilepticus. He is a co-leader of the Established Status Epilepticus Treatment Trial (ESETT), a NIH funded multicenter clinical trial to determine the best second line treatment of benzodiazepine refractory status epilepticus. Another area of research is regulation of seizures by hormonal fluctuations. Grants from National Institutes of Health, Department of Defense, Epilepsy Foundation, CURE epilepsy foundation support his research.

He has served on numerous grant review panels for National Institutes of Health, CURE Epilepsy foundation, Epilepsy Foundation and Epilepsy Research Foundation. He served as the President of the American Epilepsy Society in 2010. He received the 2013 Epilepsy Research Recognition Award for Basic Science conferred by the American Epilepsy Society.
AGENDA
Thursday, March 30\textsuperscript{th}

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

10:40 – 12:20 p.m.  \textit{Slide Session I: Neuroimaging}

\textbf{Moderator: Hal Blumenfeld, MD, PhD}

10:40 – 11:00 a.m.  Reduced SV2A binding in the seizure onset zone in temporal lobe epilepsy patients – A PET study with \textsuperscript{11}C-UCB-J

Richard E. Carson

11:00 – 11:20 p.m.  Presurgical language fMRI: mapping of six critical regions

Christopher F.A. Benjamin

11:20 – 11:40 a.m.  Intracranial EEG in Evaluation of Dynamic Changes During Conscious Visual Perception

Wendy R Xiao

11:40 – 12:00 p.m.  How Does Biophysical Modeling Help Understand Neuroimaging Data in Epilepsy?

Jorge Riera

12:00 – 12:20 p.m.  Mechanisms of absence seizures investigated by relating hemodynamics, electrophysiology, and behavioral severity in an awake rodent model

Cian McCafferty

12:20 - 1:20 p.m.  \textit{Lunch and Annual Yale Comprehensive Epilepsy Center Clinical, Research, and Surgical Updates: Lawrence J. Hirsch, MD; Hal Blumenfeld, MD, PhD; Dennis Spencer, MD}
Thursday, March 30th
(continued)

1:20 – 3:00 p.m.  Slide Session II: Animal Models
Moderator: Tore Eid, PhD

1:20 - 1:40 p.m.  Computer Simulations and Rodent and Human Tests of Focal
Brain Cooling
Yong Jiang

1:40- 2:00 p.m.  Exploring limbic seizure pathways in vivo: Optogenetic and
neuroanatomical tracing approaches
Lim-Anna Sieu

2:00 – 2:20 p.m.  Whole-cell recordings from subcortical cholinergic arousal
nuclei in vivo during seizures
John P. Andrews

2:20 – 2:40 p.m.  IPSC and Mouse Models of Slack-Associated Epilepsy
Imran H. Quraishi

2:40 – 3:00 p.m.  Oral Administration of Branched-Chain Amino Acids Results in
Increased Seizure Threshold and Loss of Hippocampal Neurons
in a Rodent Model of Mesial Temporal Lobe Epilepsy
Shaun E. Gruenbaum

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 increases and
decreases in absence seizures
Jun Hwan Ryu

Developing standards in clinical language fMRI use in epilepsy
surgical planning
Christopher F.A. Benjamin
Behavioral assessment of bilateral neurostimulation of pontine and thalamic arousal systems to restore consciousness during and after limbic seizures.
Jingwen Xu

Modulation of Thalamic Neuronal Activity during Focal Limbic Seizures differs by Thalamocortical Network
Li Feng

Behavioral deficits in a genetic absence epilepsy animal model
Zongwei Yue

Medial Temporal Lobe Resection for Seizure Control: Long Term Seizure Outcome from a Single Center
John P. Andrews

Evaluating the Feasibility of Automated Responsiveness Testing in Epilepsy (ARTie)
Nehan Saleem

Circadian, AED Taper, and Seizure-Related Effects on the Intracranial EEG Second Spectrum
Rasekh B. Joshi

Frontal Lobe Seizures: Intracranial Markers of Loss of Consciousness
Rahiwa Gebre

Long-term Postoperative Outcomes in Patients with Focal Cortical Dysplasia: Predictive Factors and AED Withdrawal
Emily Stanford

5:00 – 5:30 p.m. General Discussion and Day 1 Summary Moderator: Jaideep Kapur, MBBS, PhD

5:45 – 6:30 p.m. Group Beach Run

7:00 – 11:00 p.m. Dinner and Social Event
Friday, March 31st

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

8:30 – 8:50 a.m. The Epidemiology of Psychogenic Seizures in Post 9/11 Veterans
Hamada Altalib

8:50 – 9:10 a.m. Recapitulating Malformations of Cortical Development Via Induced Pluripotent Stem Cell Technology
Anita Huttner

9:10 - 9:30 a.m. Post-seizure sleep and consolidation in human epilepsy
Mark R. Bower

9:30 – 9:50 a.m. GRDA: a potentially benign EEG finding in critically ill patients?
Emily Gilmore

9:50 – 10:10 a.m. Global and local sleep homeostasis in patients with focal epilepsy: a high-density EEG study
Melanie Boly

10:10 – 11:00 a.m. Coffee Break and Poster Session Revisit

11:00 – 12:20 p.m. Slide Session IV: Clinical/Electrophysiology Part 2
Moderator: Dennis Spencer, MD

11:00 – 11:20 a.m. Use of Intracranial Responsive Neurostimulator Detections as a Prognostic Factor for Medication Response
Michael Mercier

11:20 – 11:40 a.m. The Multiscale Structure of Human Seizures
Catherine Schevon
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| 11:40 – 12:00 p.m. | **Uncovering the subcortical neural mechanisms for visual consciousness**  
 Sharif I. Kronemer |
| 12:00-12:20 p.m.  | **Band Related Local Functional Connectivity of the Seizure Onset and Peri-Seizure Onset Area**  
 Hitten P. Zaveri |
| 12:20 – 1:20 p.m. | **Lunch Buffet and Final Discussion Moderated by Jaideep Kapur, MBBS, PhD and colleagues** |
Slide Session I: Neuroimaging
Reduced SV2A binding in the seizure onset zone in temporal lobe epilepsy patients – A PET study with \(^{11}\)C-UCB-J

Presenting Author: Richard E. Carson

Authors: Sjoerd J. Finnema\(^1\), Kamil Detyniecki\(^2\), Ming-Kai Chen\(^1\), Mark Dias\(^1\), Qianyu Wang\(^2\), Shu-fei Lin\(^1\), Nabeel B. Nabulsi\(^1\), Yiyun Huang\(^1\), Dennis D. Spencer\(^1\), Richard E. Carson\(^1\)

Affiliations: \(^1\)PET Center, Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT; \(^2\)Department of Neurology, Yale University, New Haven, CT; \(^3\)Department of Neurosurgery, Yale University, New Haven, CT

Objectives: We recently reported the development of \(^{11}\)C-UCB-J as a PET ligand for synaptic vesicle glycoprotein 2A (SV2A) in nonhuman primates and humans (Finnema et al., 2016; Nabulsi et al., 2016). SV2A is located on the membrane of synaptic vesicles, is decreased in resected brain tissue from epilepsy patients, and is the site of action of the antiepileptic drugs levetiracetam and brivaracetam (Löscher et al., 2016). Here we evaluated \(^{11}\)C-UCB-J binding in subjects with temporal lobe epilepsy (TLE) and compared the regional binding pattern to \(^{18}\)F-FDG.

Methods: Ten patients (6 males and 4 females, 39 ± 12 years of age) with TLE and mesial temporal sclerosis (MTS) were examined in the HRRT PET system with \(^{11}\)C-UCB-J. Regional BP\(_{ND}\) values were estimated with arterial input functions using the one-tissue compartment model (\(n = 9\)). In one subject, arterial data were not available and BP\(_{ND}\) values were obtained using SRTM2. The centrum semiovale was used as a reference region for non-displaceable binding. Subjects were evaluated with \(^{18}\)F-FDG on either the HRRT (\(n = 5\)), or a Discovery PET/CT system (\(n = 5\)). \(^{18}\)F-FDG uptake was quantified using mean radioactivity values corresponding to 30-60 min or 50-60 min post \(^{18}\)F-FDG injection in the HRRT or Discovery, respectively. Regional asymmetry indices were calculated as: 200% × [(ipsilateral - contralateral) / (ipsilateral + contralateral)].

Results: In all subjects, there was a clear reduction in \(^{11}\)C-UCB-J BP\(_{ND}\) values in the epileptogenic temporal lobe when compared to the contralateral side. The unilateral binding of \(^{11}\)C-UCB-J was region specific, with very limited asymmetry in other brain regions, e.g., 3 ± 6% in the fusiform gyrus. In nine of the subjects, the asymmetry was predominantly located in the hippocampus, with BP\(_{ND}\) asymmetry indices of -50 ± 39% (range: -143% to -12%). This regional asymmetry was much larger than that found in five control volunteers (11 ± 5%, 200% × [(right – left) / (right + left)]) (Finnema et al., 2016). The corresponding asymmetry in \(^{18}\)F-FDG uptake in the hippocampus of the TLE patients was -17 ± 6% (range: -29% to -11%) and the relative magnitude was consistent with \(^{11}\)C-UCB-J across subjects (Pearson’s correlation coefficient = 0.84). In one patient, hypometabolism of \(^{18}\)F-FDG was located predominantly in the lateral temporal lobe, which was consistent with lateral reductions in \(^{11}\)C-UCB-J binding.

Conclusions: \(^{11}\)C-UCB-J binding is reduced in the seizure onset zone of patients with TLE, and is consistent with previously reported SV2A loss in resected brain tissue of TLE patients. The reductions in \(^{11}\)C-UCB-J binding were 2.7-fold larger than for \(^{18}\)F-FDG. Thus, PET imaging of SV2A may be a promising biomarker approach in the presurgical selection and evaluation of TLE patients with MTS, and may improve the sensitivity of molecular imaging for seizure focus detection. References: Nabulsi et al., 2016, J Nucl Med, 57:5:777-84. Finnema et al., 2016, Sci Transl Med, 8:348:348ra96. Löscher et al., 2016, CNS Drugs, 30:11:1055-77.
Presurgical Language fMRI: Mapping of Six Critical Regions


OBJECTIVE: Language mapping is a key goal in neurosurgical planning. fMRI mapping typically proceeds with a focus on Broca's and Wernicke's areas, although multiple other language-critical areas are now well-known. We sought to determine whether clinicians could use a novel approach, including clinician-driven individualized thresholding, to reliably identify six language regions, including Broca’s Area, Wernicke’s Area (inferior, superior), Exner’s Area, Supplementary Speech Area, Angular Gyrus, and Basal Temporal Language Area.

METHODS: We studied 22 epilepsy and tumor patients who received Wada and fMRI (age 36.4[12.5]; Wada language left/right/mixed in 18/3/1). fMRI tasks (two sets of three tasks) were analyzed by two clinical neuropsychologists to identify these regions. The resulting maps were compared to fixed threshold language maps.

RESULTS: Clinicians generated maps that overlapped significantly, and were highly consistent, when at least one task came from the same set. Cases diverged when clinicians prioritized different language regions or addressed noise differently. Language laterality closely mirrored Wada dat. Activation consistent with all six language regions was consistently identified. In blind review, three external, independent clinicians rated the individualized fMRI language maps as superior in quality to fixed threshold maps; identified the majority of language regions significantly more frequently; and judged language laterality to mirror Wada lateralization more often.

SIGNIFICANCE: These data provide initial validation of a novel, non-invasive approach to localize language cortex in presurgical patients. With validation this method may guide and decrease the duration of direct brain stimulation, a method with relatively high morbidity and cost, and improve post-surgical language outcome in these patients.

This research was made possible by CTSA Grant Number KL2 TR001862 from the National Center for Advancing Translational Science (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH. The authors have no conflicts of interest.
Intracranial EEG in Evaluation of Dynamic Changes During Conscious Visual Perception

Authors: Wendy R Xiao¹, Rachel E Smith¹, Sharif I Kronemer¹, Rebecca E Watsky¹, William C Chen¹, Leah Gober¹, George J Touloumes¹, Meenakshi Khosla¹, Anusha Raja¹, Corey L Horien¹, Elliot Morse¹, Katherine Botta¹, Lawrence J. Hirsch¹, Rafeed Alkawadri³, Jason L Gerrard³, Dennis D Spencer³, and Hal Blumenfeld¹,²,³

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Introduction: Intracranial electroencephalographic monitoring of patients with intractable epilepsy provides a unique opportunity to study physiological changes in the brain both during seizures and during normal cognitive tasks. We wanted to study the entrance of external stimuli into the contents of conscious awareness by using a visual stimulus to probe conscious perception.

Methods: We recruited 9 patients from the Yale Epilepsy Surgery Program to perform a threshold visual perception task using a face stimulus titrated to each person’s 50% perception threshold. With the intracranial EEG recording, we were able to measure 40-115 Hz power as a measure of population neuronal activity within a 15-mm radius of the electrode center.

Results: Immediately after stimulus presentation, both perceived and not perceived visual stimuli produced increases within 100-200 ms post-stimulus in the primary visual cortex. However, a wave of activation at a speed of 149 mm/s passing through successive levels of association cortex and medial temporal cortex was only observed for perceived trials. At the same time, a decrease in activity was observed in visual cortex, higher association cortex, and the default mode network around 250-600 ms post-stimulus for trials that were perceived. This activity gradually transitioned to an increase >600 ms post-stimulus in the visual cortex and higher association cortex.

Conclusions: With these observations we propose a new “switch and wave” model of conscious visual perception involving sequential changes in networks used for stimulus detection, signal processing, memory encoding, and preparation for report.
How Does Biophysical Modeling Helps Understand Neuroimaging Data in Epilepsy?

Authors: Jorge Riera¹, Pedro Valdes Hernandez¹, Yinchen Song¹², Wei-Chiang Lin¹³, Byron Bernal¹; Fahmeed Hyder⁴, Basavaraju Sanganahalli⁴

Affiliations: ¹Department of Biomedical Engineering, Florida International University (FIU), Miami, FL; ²Department of Neurology, Geisel School of Medicine at Dartmouth, Hanover, NH; ³Department of Radiology, Nicklaus Children Hospital, Miami, FL; ⁴Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT

Objectives: Researchers use dipolar current source and canonical HRF models to analyze EEG/MEG and fMRI data, respectively. These empirical models might not be appropriate to represent such neuroimaging data if obtained from patients with epilepsy. In this talk, we will use both clinical and preclinical data to illustrate how important a characterizati

on of atypical mechanisms is while using biophysical modeling to evaluate neuroimaging data in epilepsy.

Methods: Human clinical data: Simultaneous HR-EEG (64 channels) and MEG (151-channel biomagnetometers) data were recorded from a 41-year-old right-handed woman with focal epilepsy (CTF system). This clinical study was approved by the IRB of the French Institute of Health (Dr. Christian Bénar, Gavaret et al., 2014). A realistic head model was constructed using the patient T1 MRI. Rat preclinical data: a “double-hit” FCD animal model was created with male Wistar rats (~130g, 4 weeks old). Single (Grass Data) and multiple (BrainAmpMR) channel EEG data were recorded concurrently with fMRI-BOLD signal (7T/9.4T Bruker Scanners). Intracranial electric potentials and optical data (IOS and LDF) were obtained from different epileptogenic ROIs (Song et al., 2016). These preclinical studies were approved by the IACUC of the FIU and Yale University. Interictal epileptiform discharges (IED) were detected and classified from both clinical and preclinical data. Brain imaging source analysis was performed on each IED. IED-evoked BOLD responses were used to define the epileptic network and its interactions with the resting-state fMRI network (Song et al., 2015). CSD analysis was performed on intracranial electric potentials.

Results: First, we demonstrated the importance of ion diffusion when performing brain source analysis using EEG and MEG data. We evaluated the physiological range for ion diffusion in the brain from such an extreme pathological to normal conditions. By introducing a diffusive component in the electrophysiological inverse problem, laminar profiles of the neuronal generators were extracted from combined EEG-MEG data. Second, we found particular dysfunctions in the neuro-vascular/metabolic coupling that impacted on the waveform of the HRF, which is crucial for any fMRI analysis. In particular, we proposed useful methods to separate HRF negativities caused by abnormal hyperemic/metabolic responses in epileptogenic cortical regions from those originated from vascular stealing/leaking effects. Finally, we provided evidence for the importance of modeling the epileptic network in the context of a dynamically evolving system.

Conclusions: We conclude that in order to improve neuroimaging protocols currently in use in many hospitals worldwide for defining epileptogenic networks inside the brain, diffusional brain current components and abnormalities in HRF models need to be incorporated. References: Gavaret et al., Brain Topogr 27, 192-196, 2014; Song et al., IEEE Trans Biomed Eng 63(1), 97-110, 2016; Song et al., PLoS ONE 10(7), e0134352, 2015.
Mechanisms of absence seizures investigated by relating hemodynamics, electrophysiology, and behavioral severity in an awake rodent model

Authors: Cian McCafferty; Zongwei Yue; Benjamin Gruenbaum; Jun Hwan Ryu; James Sampognaro; Emily Johnson; Wasif Islam; Petr Vitkovskiy; Adam Kundishora; Lovemore Makusha; Antoine Depaul; Peter Herman; Fahmeed Hyder; Hal Blumenfeld

Affiliations: Departments of Neurology, Neuroscience, Neurosurgery, Radiology, and Anesthesiology, Yale School of Medicine, New Haven, CT; INSERM, Grenoble, France

Rationale: Absence seizures are non-convulsive seizures that cause periods of inattention and unresponsiveness to mild external stimuli in patients, accompanied by generalized “spike-wave” discharges (SWDs). Syndromes characterized by these seizures significantly impair a patient’s quality of life. Treatment failure and persistence of symptoms is common, suggesting a need for more thorough understanding of the pathophysiology underlying ictal impairment of attention and behavior. Prior models have been limited by the use of anesthesia, which can alter arousal, blood flow, and neuronal activity during seizure. This project aims to overcome those limitations by relating absence seizure hemodynamics to neural activity in an awake, non-drugged rat model, and by investigating if and how any aspects of this relationship vary according to the behavioral severity of a seizure.

Methods: To study neural mechanisms and neurovascular relationships during seizures, Genetic Absence Epilepsy Rats from Strasbourg (GAERS), an established absence model, were trained to accept body and head restraint. Animals were incrementally introduced to greater degrees and durations of restriction of body and head movement over 4-5 weeks. Fronto-parietal EEG was recorded epidurally to detect SWDs, simultaneously with either local cerebral blood flow (CBF, via laser-Doppler flowmetry) and multi-unit activity (MUA), or with brain-wide BOLD fMRI signal. The latter echo-planar imaging signals were analyzed on a voxel-by-voxel basis, comparing seizure with non-seizure signal intensity, and on a region of interest basis, averaging signal intensity within an anatomically-determined volume around the start time of seizures. Freely-moving rats were also trained on a set of behavioral paradigms of varying complexity (task-free environmental interaction, sensory detection, and sensory discrimination) in order to detect variations in seizure severity.

Results: CBF and MUA (RMS voltage) in deep layers of multiple regions of the cortex showed increases from pre-seizure baseline for the first 2 seconds of seizure, and then decreased below baseline for the remaining seizure duration. This transient increase – prolonged decrease pattern matches that of BOLD fMRI from human AS, and contrasts with previous hemodynamics of anesthetized seizure models. The MUA increase appears to be dependent on seizure frequency rather than intensity of neuronal firing. Preliminary head-fixed BOLD fMRI results also agree with clinical data, displaying increases on seizure initiation in the thalamus and decreases in multiple cortical regions. Interestingly, larger CBF and MUA increases at seizure onset are associated with longer seizures, suggesting a
mechanistic basis of seizure severity. Further, initial behavioral experiments suggest that seizures impair task-free activity upon initiation to a degree related to eventual seizure duration.

**Discussion:** The hemodynamics of our non-anesthetized experimental absence seizures show qualitatively greater fidelity to human absence epilepsy than those of previous protocols employing anesthesia to prevent movement. This strongly suggests that neural mechanisms observed in this model may be relevant to clinical seizures, and indeed that it is imperative that any mechanistic investigations be carried out in similar anesthetic-free conditions. Further, the indications of severity-dependent variations in neuro- and hemodynamics are also in agreement with clinical studies. The rest of the study will include consolidation of the BOLD fMRI dataset as well as completion of the behavioral component, with the addition of single-neuron resolution electrophysiological recordings to fully characterize underlying mechanisms. These findings may help guide improved treatments for this common epilepsy syndrome in childhood.
Slide Session II: Animal Model
Computer Simulations and Rodent and Human Tests of Focal Brain Cooling

Authors: Yong Jiang¹, Mikhael Guy², Paul Crocco³, David Stokes⁴, Roni Dhaher⁵, Shaun Gruenbaum⁶, Tore Eid⁶, Lawrence J. Hirsch⁷, Dennis D. Spencer⁸, Hitten P. Zaveri⁹,¹⁰

Affiliations: Departments of ¹Physics, ³Laboratory Medicine, ⁶Anesthesiology, ⁷Neurology and ⁸Neurosurgery and the ⁹Computational Neurophysiology Laboratory and ²Science Research Software Core, Yale University, New Haven, CT; ³Laird Technology, Durham, NC; ⁴RTI International, Research Triangle Park, NC

Rationale. The long-term goal of this project is to build an implantable device to cool the human brain with an addressable array of cooling elements which are interspersed with icEEG and temperature sensors. We call this device a cooling, sensing, stimulating array (CSSA). There are three main applications for a CSSA:

1. Controlling Seizures. We seek to use cooling to stop seizures. The cooling function will be turned on when a seizure is detected, or when a seizure is anticipated, to interrupt the buildup of the seizure.
2. Mapping Brain Function. We seek to use cooling to reversibly disrupt function. By doing so we will be able to map brain function.
3. Reversible Functional Ablation. We seek to use cooling to reversibly turn off a part of the cortex which is being considered for surgical resection. By doing so we will be able to better understand the functional consequences of a planned surgery, and better plan the surgery.

Several technical and scientific aspects which will inform focal brain cooling and the CSSA design remain to be determined. The objective of this study was to determine the amount of cooling required to hold a volume of cortical matter at a lower steady state temperature for a given duration.

Methods: We designed and built two devices. First, a human brain sized device, and second a rat brain sized device. The human brain sized device was built with a single cooling element, wired power and a fluid based back-end. The cooling element was placed within a gold coated enclosure. Two thermocouples were placed next to the cooling element to provide temperature measurements. A study was performed during standard resective surgery for medically intractable epilepsy. The temporal pole was exposed. Subsequently during a 15-minute window, step the cooling device through several cooling levels, each for 30 seconds in duration and measured the resultant device interface temperature and temperature within white matter directly underlying the cooling element.

Results: Low steady state temperatures of ~12°C were observed in human brain and ~20°C in rat brain with 300 mA and 350 mA device current, respectively. Computer simulations were performed to replicate the focal brain cooling performed in the human study in silico, and project the number of cooling elements and inter-cooling element spacing which would be required to hold cortical tissue at a low steady state temperature, and simulate the changes in cortical temperature in response to focal cooling.

Conclusions: We have developed a powerful, small, thin-film thermoelectric cooler to control the temperature of a focal cortical area. Preliminary evaluations of this device and computer simulations demonstrate considerable potential for this technology.
Exploring limbic seizure pathways in vivo: Optogenetic and neuroanatomical tracing approaches

Authors: Lim-Anna Sieu, Li Feng, Chanthia Ma, Jessica Cardin and Hal Blumenfeld

Departments: Neurology, Neuroscience, Neurosurgery

Abstract:
Our work investigates brain networks including the cerebral cortex interacting with deeper structures to unveil how focal seizures impair consciousness. During temporal lobe seizures, intracranial EEG recordings show sleep-like activity in the cortex, accompanied by decreased cerebral blood flow. We have proposed a “network inhibition hypothesis” in which temporal lobe seizures inhibit subcortical arousal systems, causing depressed cortical function. Previous work from our lab has shown reduced cholinergic neurotransmission in both cortex and thalamus during partial seizures in a rodent model. In addition, focal hippocampal seizures in rats induce increased neuronal firing and cerebral blood flow in the lateral septal area. Electro-stimulation of the lateral septum (LS) in the absence of seizures resulted in cortical slow oscillations resembling deep sleep, suggesting that the LS might contribute to cortical deactivation via exerting an impact on subcortical networks. In this study, we explore possible pathways from LS to nucleus basalis (NB), a subcortical region that provides the most cholinergic input to cortex. By selectively using Cre-dependent expression of a light-activated channel Channelrhodopsin-2 (ChR2) in NB cholinergic neurons from ChAt-Cre transgenic rats, we found that photo-stimulation of cholinergic neurons in NB in vivo can convert slow-wave oscillations to fast awake-like activity in cortex, thus reinstating aspects of arousal during induced partial seizures. To identify anatomical circuitry between LS and NB, we use a combination of retrograde tracing from NB and anterograde tracing from LS. Our histology results reveal no direct anatomical connection between those two regions, suggesting that LS might innervate cholinergic neurons in NB via indirect polysynaptic pathways including other subcortical structures. Based on the tracing histology results available, hypothalamus, thalamus, Accumbens nucleus and claustrum might be the next targets for further investigation. Our hope is that by identifying the neural circuit responsible for impaired consciousness during focal seizures, new treatments can be devised to prevent this alteration of brain function and to thus improve patient quality of life.
Whole-cell recordings from subcortical cholinergic arousal nuclei in vivo during seizures

Authors: John P. Andrews,1 Garrett Neske,2 David A. McCormick,2 Hal Blumenfeld1,2,3

Affiliations: 1Yale School of Medicine Department of Neurology, 2Yale School of Medicine Department of Neuroscience, 3Yale School of Medicine Department of Neurosurgery

The mechanism of how seizures impair consciousness is not fully understood, but recent evidence suggests that ictal suppression of subcortical cholinergic arousal circuits, such as the nucleus basalis (NB) and pedunculopontine tegmental nucleus (PPTg), may play a role. Functional imaging and extracellular techniques show ictal suppression of activity in the NB and PPTg in a rat model of focal limbic seizures, but the postsynaptic signaling that leads to this depressed action potential firing rate is not known. The purpose of this investigation is to elucidate changes in postsynaptic currents and potentials in neurons of the subcortical cholinergic arousal system during seizures.

Whole-cell recording (WCR) from neurons in vivo is a powerful technique for characterizing postsynaptic neuronal signaling from intact physiologic circuits. Whole cell recording is commonly used to access cortical neurons in vivo, but the literature reporting whole-cell recording from deep brain structures in vivo is sparse. In this study, whole cell recordings in voltage-clamp and current clamp modes were obtained in neurons 6-8mm deep, measured from the cortex, in the brain of head-fixed, anesthetized rats.

Technical aspects limiting the depth of WCR include production of long, narrow glass pipets with sufficiently low resistance tips. A second obstacle to deep WCR is maintaining a viable pipet tip that can form a seal of >1GΩ with the target neuronal cell membrane (i.e., gigaseal) after passing through large amounts of tissue. To address the former problem, glass micropipettes were pulled using a multiline program to produce a 10 mm taper and 4-6 MΩ resistance. The problem of maintaining a viable tip during decent through over 6-8 mm of tissue was addressed in two ways. Firstly, intrapipette positive pressure was maintained at 500 mbar throughout the descent, and only dropped to <30 mbar upon reaching the target region. Secondly, the first pipette was lowered to the target region no and left in place for 30 - 60 minutes to allow the brain to form a narrow, minimally obstructed canal through which subsequent pipettes may pass. Subsequent pipettes were advanced no faster than 30 µm per second. In this way, brain architecture was minimally perturbed and pipettes could access deep subcortical structures.

Limited preliminary data in current clamp suggests that membrane potential of PPTg neurons is hyperpolarized during the ictal period, concomitant with decreased action potential firing, and returns to baseline postictally. Next steps include voltage clamp analysis of changes in postsynaptic currents during seizures. Ultimately these studies are aimed at identifying the synaptic mechanisms of depressed subcortical arousal during seizures, which may lead to new treatments aimed at preventing these changes and improving ictal and postictal cognition.
IPSC and Mouse Models of Slack-Associated Epilepsy

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Mutations in the potassium channel Slack (also called KCNT1 or KNa1.1) lead to various types of epilepsy including autosomal dominant frontal lobe epilepsy (ADNFLE) and epilepsy of infancy with migrating focal seizures (EIMFS). In the past couple of years, it has become clear that this is an important epilepsy gene, with over 20 epilepsy-causing mutations identified. Slack appears to be important in the synchrony of high frequency neuronal activity, survival from certain types of seizures, and in the regulation of neuronal protein translation. All of the mutations that we have tested to date in heterologous expression systems cause an increase in the sodium-activated potassium current. Using CRISPR-Cas9 we have now developed two new models of Slack-associated epilepsy. The first model is an engineered human IPSC line with the P924L mutation. By whole cell voltage clamp we confirmed for the first time a gain of function of the sodium-activated current in a human neuronal system. In addition, single unit multielectrode array recordings demonstrate an increase in bursting behavior. The second model is a transgenic mouse with the R455H mutation. These mice have spontaneous seizures by video-EEG monitoring and a decreased threshold for pentylenetetrazole-induced seizures. Finally, we have begun screening for selective modulators of the Slack channel as there are currently no specific drugs available. We identified a potent activator as well as the first state-dependent blocker of the channel. Taken together these results will form the framework for identifying the mechanisms of Slack-associated epilepsy and for targeted anti-epileptic drug discovery.
Oral Administration of Branched-Chain Amino Acids Results in Increased Seizure Threshold and Loss of Hippocampal Neurons in a Rodent Model of Mesial Temporal Lobe Epilepsy

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Introduction: The branched-chain amino acids (BCAAs) leucine, isoleucine and valine are commonly ingested in high doses by athletes to facilitate net muscle growth, improve performance and reduce fatigue. While studies have shown that all three BCAAs can enter the brain and influence neurotransmitter homeostasis, it is unknown whether high-dose chronic ingestion of BCAAs have beneficial or harmful effects on the brain. The objective of this study was to determine the effects of oral supplementation with BCAAs on seizures and neuronal viability in a rodent model of mesial temporal lobe epilepsy (MTLE), one of the most common forms of medication refractory focal epilepsies.

Methods: Sixteen rats were randomly divided into two groups: 8 rats drank a 4% aqueous solution of all three BCAAs (BCAA group) ad libitum for 31 days, and the other 8 rats drank regular water (control group) for the same period. After 10 days of drinking, a microinfusion cannula was surgically implanted in the right dentate gyrus to continuously infuse the glutamine synthetase inhibitor methionine sulfoximine (MSO) at a rate of 0.625 μg/hr for 28 days. The frequency of spontaneous seizures was analyzed via continuous video and electroencephalogram (EEG) monitoring for 21 days. To assess seizure threshold, all rats were then administered a single intraperitoneal injection of 40 mg/kg pentylenetetrazole (PTZ), a GABA antagonist. Rats were monitored for time to twitch, time to convulsions, and time interval between twitch and convulsions. After 31 days of drinking, rats were perfused transcardially with 0.9% NaCl followed by 4% formaldehyde in phosphate buffer. The brains were removed and fixed, sectioned on a Vibratome at 50-μm thickness, and were mounted on a gelatin-coated slides and stained with NeuN. Neuron counts in the hilar region were performed ipsilateral and contralateral to the infusion site using a stereological technique.

Results: There were no significant differences between BCAA rats and control rats with respect to the frequency or severity of spontaneous seizures in weeks 1, 2 or 3. After injection of PTZ, BCAA rats had an increased time to twitch (88.2 ± 20.9s vs. 44 ± 10.9s, p=0.07), convulsions (174.6 ± 17.26s vs. 51.9 ± 14.6s, p<0.05), and interval between twitch and convulsions (86.8 ± 42.8s vs. 7.9 ± 4.4s, p=0.05) compared with control rats. Rats in the BCAA group had 37% fewer neurons in the ipsilateral dentate hilus than the control group (5.8 x 10^{-4} ± 6.8 x 10^{-5} vs. 8.9 x 10^{-4} ± 5.6 x 10^{-5})
cells respectively, p<0.01), and 39% fewer neurons in the contralateral dentate hilus than the control group (5.0 \times 10^{-4} \pm 5.8 \times 10^{-5} \text{ vs. } 7.0 \times 10^{-4} \pm 3.4 \times 10^{-5} \text{ cells respectively, p=0.01}).

**Conclusions:** This study demonstrated for the first time the effects of chronic BCAA ingestion on spontaneous and induced seizures in a translationally-relevant rodent model of MTLE. Chronic BCAA ingestion was effective in increasing the seizure threshold to PTZ-induced seizures, but was ineffective in reducing the frequency or severity of spontaneous seizures in GS-inhibited, epileptic rats. Importantly, chronic BCAA ingestion aggravated the hilar neuron loss, which may have important implications for humans and should be further evaluated.
Poster Session
Mechanisms of widespread cortical fMRI increases and decreases in absence seizures

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Abstract

Childhood absence epilepsy (CAE) is a relative common disorder among children with epilepsy, characterized by 3-4hz spike and wave discharges (SWD) on EEG. The seizures vary in severity of behavioral impairment, ranging from a complete unconscious state and complete withdrawal from tasks to brief staring and relatively spared performance on tasks. Guo et al (2016) have shown three correlated networks during the absence seizures: the default mode network (DMN), task positive network (TPN) and the sensorimotor thalamus (SMT)1. Furthermore, they have shown a widespread larger fMRI amplitude in cortical and subcortical regions for seizures with impaired behavioral responsiveness compared to seizures with spared responsiveness. However, the mechanisms of absence seizures are still poorly understood, including the relationship between behavioral impairment and seizure duration, hemodynamic responses, and the neural activities during seizures. Bai et al. (2010) have shown that the boxcar approximation for the neural activity and the canonical hemodynamic response function (cHRF) are inadequate in predicting BOLD activity2. Using a large fMRI data from the Yale Childhood Epilepsy Project (1032 seizures in 39 patients), and holding the cHRF constant, we create a physiologically realistic model of the electrical activity before/during/after the SWD. The model reveals BOLD activity as long as 100 seconds before seizure onset in cortical and subcortical regions. The model also predicts different patterns in the core functional networks of the brain: that the DMN is mainly deactivated during the seizures and that the neural activity in the thalamus increases in linear proportion to seizure duration. This approach provides fundamental new insights into absence seizure pathophysiology which may help guide novel treatments for this disorder.

References:

Developing standards in clinical language fMRI use in epilepsy surgical planning

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Background: Clinical functional MRI is widely used for pre-surgical evaluation of language, and at many sites has largely replaced Wada testing for this purpose. In spite of this, relatively little is known about actual implementation of fMRI in the clinic, and anecdotally there is marked variation in fMRI methodology and patient outcomes between sites. The aim of this study was to document how epilepsy programs currently use fMRI in evaluating patients for epilepsy surgery.

Methods: Through email and phone, we contacted all level 3 and 4 epilepsy programs within the US via the membership directory of the National Association of Epilepsy Centers, and sites beyond the US via a snowball strategy. Measures included an online two-part survey: (i) fMRI use and relationship to surgical outcomes, and (ii) technical questions regarding language fMRI paradigms, processing and reporting procedures. 82 clinicians from epilepsy surgical programs responded.

Results: In mapping language presurgically, most sites use neuropsychological assessment (99% of responding sites, in 93% of patients) and fMRI (96%/58%) and Wada testing (76%/43%). Of those using fMRI routinely, 100% determine the dominant hemisphere, while 44% use fMRI to guide surgical margins. These sites focus almost exclusively on Wernicke's and Broca's Areas, rarely mapping other known language areas (e.g., 20-24%). With respect to outcomes, 13 sites (17% of respondents) reported at least one case who suffered persisting language deficits in spite of all fMRI-positive language sites being preserved. 14 sites (54%) reported cases where language deficits did not follow resection of fMRI-positive language cortex. None of these cases had been published.

Implications: fMRI is currently routinely used to lateralize but not localize language. When localizing cortex, fMRI inconsistently predicts outcome. This may relate to sites focus on historic models of the language system and reflect a need for clinicians to adopt more standardized analysis and contemporary models of the language system to improve surgical planning and neurosurgical outcomes.

This research was made possible by CTSA Grant Number KL2 TR001862 from the National Center for Advancing Translational Science (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.
Behavioral assessment of bilateral neurostimulation of pontine and thalamic arousal systems to restore consciousness during and after limbic seizures.


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Background: Impaired consciousness during the ictal and postictal states in epilepsy markedly increases the risk of mortality and social stigmatization. For patients who fail to respond to anti-epileptic drugs and surgery, the use of deep brain stimulation (DBS) to improve consciousness during and after seizures would represent an alternative therapeutic resource of significant impact on their quality of life. To explore this, our lab has developed and used a rodent model of limbic seizures that reproduces the human electrophysiological and behavioral manifestations associated with loss of consciousness in temporal lobe epilepsy. Some of our recent work in this rodent model has shown that dual-site stimulation of the thalamic intralaminar central lateral nucleus (CL) and pontine nucleus oralis (PnO) applied bilaterally during the ictal and postictal periods improved level of consciousness while restoring normal-appearing cortical electrophysiology. Here we focused on further investigating the behavioral effects of this dual site stimulation.

Method: We implement an operant behavioral task to assess performance during and after focal seizures and evaluate the cognitive improvements provided by DBS. During successive sessions, animals are trained to respond at an instrumental port (nose-poking) to activate an adjacent reward port, where they can collect sucrose water when signaled by a sound. After they complete training, electrodes are implanted bilaterally in CL and PnO, and unilaterally in the hippocampus and lateral orbitofrontal (LO) cortex. Animals are reevaluated in the task after recovering from surgery and retrained until they meet baseline performance criteria, at which point sessions with seizure trials begin. Seizures are induced by brief 2 second, 60 Hz hippocampal stimulation in some of the trials within a session. We then stimulate bilateral CL at 100 Hz and PnO at 50 Hz at varying current intensities during and after seizures while recording electrophysiology and behavior synchronously.

Results: In the training process, animals showed increased percentage of rewards collected, decreased response times, and increased selectivity in responding (n=12). Focal limbic seizures were accompanied by frontal cortical slow wave activity and impaired behavioral ability. Task performance was significantly impaired during seizures with cortical slow wave activity (p<0.05; n=21 seizures in 4 animals). In addition, CL+PnO stimulation was capable of restoring normal appearing cortical physiology during and following seizures.

Conclusion: We developed a behavioral paradigm using a rodent model that can quantitatively evaluate multi-step task performance during seizures. Further work is needed to determine the degree of improvement in performance obtained with the dual site stimulation during the ictal and postictal periods. We expect to obtain results that will provide additional necessary groundwork for the development of DBS as a therapeutic option to improve consciousness in patients with refractory epilepsy.
Modulation of thalamic neuronal activity during focal limbic seizures differs by thalamocortical network

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Rationale: Temporal lobe epilepsy has a major negative impact on quality of life, yet its epileptogenic mechanisms are not clear. Previous work has suggested that the thalamus, as a key region with connections to both subcortical structures and cortex, plays a critical role in thalamo-cortical network regulation and subcortical arousal maintenance. However, due to its complicated anatomic and functional organization, direct demonstration of seizure-associated neuronal activity changes in different thalamic nuclei has been lacking. Our goal was to identify the possible roles played by different thalamic nuclei in seizure propagation, cortical inhibition, or slow oscillation regulation during focal seizures, with the aim to guide the development of improved specific treatments.

Methods: Animals were anesthetized with ketamine/xylazine. Multi-unit recordings of different thalamic nuclei were performed in an anesthetized rat model of limbic seizures to study peri-ictal function of the intralaminar central lateral nucleus (CL), anterior nucleus (ANT), and ventral posteromedial nucleus of the thalamus (VPM). Furthermore, juxtacellular single neuron (SUA) recordings were also conducted in the CL of the thalamus to investigate single neuron activity changes during focal seizures. Neurons juxtacellularly recorded were labeled with DAB/ neurobiotin for histologic recovery and all the electrode tracts were identified by cresyl violet staining.

Results: We found that during focal limbic seizures, multiunit activity (MUA) in the CL region decreased while MUA in the ANT increased. In both regions, neuronal firing slowly recovered during the postictal period. The VPM was notable for an increase in spindle waves during partial seizures. Furthermore, we found that consistent with decreased MUA in the CL, SUA in the CL showed decreased firing after the seizure initiation and recovery during the postictal period. Interestingly, most neurons in CL fired with a burst pattern during seizures but fired tonically during baseline and after recovery.

Conclusions: Our findings suggest the modulation of thalamic neuronal activity during focal limbic seizures differs by thalamic subnuclei. The limbic ANT nucleus mirrors the ictal pattern of increased firing seen in the hippocampus, while thalamic CL and VPM both show patterns more consistent with slow wave sleep. These findings may guide our future precise treatments aimed at preventing specific abnormal activity patterns in different thalamocortical networks during focal limbic seizures.
Behavioral deficits in a genetic absence epilepsy animal model

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Rationale: Absence epilepsy is characterized by recurrent episodes of unconsciousness, which include behavioral deficits. However, the mechanism of how absence seizures impair cognition is unknown. It was recently found in a large patient sample that human absence seizures could cause different degrees of behavioral impairment, as shown by the bimodal distribution of performance in behavioral testing. The mechanisms underlying this differences could be key to understanding the relationship between absence seizures and impaired consciousness. In this study, we trained genetic absence epilepsy rats from Strasbourg (GAERS) in a variety of behavioral paradigms with simultaneous video-EEG to determine if variability of behavioral impairment also exists in an animal model of absence epilepsy and to lay the foundation for further study.

Methods: GAERS (Female, 8-12 weeks) were subjected to food restriction and sucrose introduction prior to behavioral training. Sensory detection, sensory discrimination and free licking tests are used in this study. For the former two tests, rats must lick at a Lickometer during a 10s reward window to receive a reward (20% sucrose water). In the sensory detection test, an 8Khz pure tone was used to signify reward availability (GO), while in the sensory discrimination test, a 2khz pure tone was added to signify 10s punishment window (NO-GO). No signal cues were given in the free licking paradigm, but rather a reward became available at varying intervals in order to investigate natural licking behavioral patterns. Frontoparietal epidural EEG electrodes were implanted after assessing rats’ training performance based on success rate and correct/incorrect ratio. Rats were given 5 days to recover before being subjected to food restriction and retraining. Video-EEG was recorded simultaneously when rats finished retraining.

Results: Rats can be trained to perform all three tasks, designed to show if inter-seizure variation of behavioral impairment exists. In the sensory detection test, the proportion of Go signals responded to can reach 90% within 7 sessions and remained high (>90%) after EEG implantation. Increased selectivity was showed by increasing the ratio of time allowed for correct (target period) vs. incorrect licks (from 3.64 to 8.36). In the sensory discrimination tests, rats can be trained to achieve 90% success rate for GO signals and 70% success rate for NO-GO signals.

Discussion: These initial findings demonstrate that epileptic GAERS can be successfully trained in three behavioral paradigms of varying difficulty, during simultaneous video/EEG. Our hope is that with further investigation we will be able to determine the cellular mechanisms for variable seizure severity in absence epilepsy, which may provide important mechanistic information to guide improved treatments.
Medial Temporal Lobe Resection for Seizure Control: Long Term Seizure Outcome from a Single Center

Authors: John P. Andrews; Abhijeet Gummadavelli; Pue Farooque; Jennifer Bonito; Dennis D. Spencer

Introduction: Temporal lobectomy is established as an effective intervention for seizures refractory to medical management, leading to freedom from disabling seizures for many patients. Seizure outcomes have been evaluated extensively in the years immediately following surgery for epilepsy, but the literature on outcomes at long-term follow-up is less robust.

Methods: Records of patients receiving an anterior medial temporal lobectomy by the senior author (DDS) from the years 2000 – 2015 were queried from the Yale Epilepsy Center database. Patients were excluded if surgery lacked medial temporal resection or if the surgery included extra-temporal resections. Engel outcomes were assigned based on chart review for 1, 2, 3, 4, 5 and ≥10 year follow-ups. Pathology was determined by postoperative pathology report. Freedom from disabling seizures was defined as Engel class I outcome.

Results: 114 patients met inclusion criteria. Pathologic diagnosis showed 74 patients with mesial temporal sclerosis (MTS), 25 neoplasms, 5 malformations of cortical development (MCD), 3 vascular malformations (VM), 1 infarct and 13 patients with gliosis as their only pathologic diagnosis. 7 patients had dual pathology (MTS/MCD/VM/neoplasm). Preliminary analysis shows Engel class I freedom from disabling seizures in ≥75% through 10 years follow-up. Of patients who had recurrent disabling seizures after surgery, over 50% recurred during post-operative year 1, and 85% by year 3. Of the 18 patients who had a disabling seizure during their first post-operative year, 5 were of the group showing only gliosis on pathology. Kaplan-Meyer analysis of time to first disabling seizure shows a significant difference between patients lacking a defined lesion on pathology (i.e. only gliosis in path report) compared to those with a pathologically confirmed defined lesion (MTS, neoplasm, MCD, VM, or infarct).

Conclusions: In this retrospective, single-center, single surgeon consecutive series, the most common pathology treated with anterior medial temporal lobectomy for seizures was mesial temporal sclerosis. Preliminary analysis suggests that the majority of patients treated with anterior medial temporal lobectomy will achieve stable freedom from disabling seizures through 10 years follow-up. Rate of seizure recurrence was highest in the first 3 postoperative years. Patients lacking pathologic evidence of a defined lesion appear to have shorter time to first seizure than lesional pathologies. Next steps will include analysis of how seizure outcome correlates with preoperative localization of seizure foci and postoperative AED regimen.
Evaluating the Feasibility of Automated Responsiveness Testing in Epilepsy (ARTiE)

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Behavioral evaluation of patients during seizures is crucial for clinical decision-making. Information about patient responsiveness during seizures guides decisions about accurate diagnosis, driving safety, seizure localization, and assessment of the severity of seizures for presurgical evaluation. Thus, objective evaluation of behavior during seizures is important and can be obtained through inpatient or outpatient video/EEG monitoring. However, this presents limitations because testing of responsiveness during seizures relies on bedside availability of trained hospital personnel or family members. In our most recent analysis of this type of behavioral testing in the Yale Comprehensive Epilepsy Center Inpatient Monitoring Unit, we found that questions or commands asked during seizures were highly inconsistent, with testing being performed only 50% of the time during seizures, and often by nonmedical personnel. Our lab has built an efficient prototype “Automatic Responsiveness Testing in Epilepsy” (ARTiE) system to improve the reliability and consistency of behavioral testing during seizures. ARTiE consists of a series of video-recorded behavioral tasks that is automatically triggered in the patient’s room upon computerized seizure detection or by event button press. Thus, ARTiE represents a more reliable and standardized testing procedure that may ultimately improve clinical care for people with epilepsy. We have recently introduced ARTiE into routine clinical use on the Yale inpatient epilepsy monitoring unit and initial experience has demonstrated useful clinical evaluation during seizures which has augmented the testing normally performed by human personnel. With continued clinical testing using ARTiE, we hope to further gather more valuable information for clinical decision-making and on the response of patients to ARTiE in the epilepsy monitoring unit, and ultimately to improve the clinical evaluation of these patients.
Circadian, AED Taper, and Seizure-Related Effects on the Intracranial EEG Second Spectrum

Presenting Author: Rasesh B. Joshi

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Rationale: In previous work, we examined correlations in slow amplitude modulations of the intracranial EEG (icEEG) band power time-series (i.e., the second spectrum), for evidence of spatial relationships between different parts of the brain and their correspondence with fMRI-defined resting state networks. Although we reported a lack of support for the fMRI-defined default mode network (DMN) in the icEEG second spectrum, our results and a number of other studies suggest that these envelope correlations may form the basis for distant spatial coupling in the brain that could exist independently of networks defined by fMRI. Briefly, in our prior analysis of resting data, we found that second spectrum relationship decreased with greater intercontact distance, and that relationships were highest in the delta band and decreased with increasing frequency. We also found relatively stronger relationship in the frontal lobes in the delta and theta bands, and in the occipital lobes in the alpha and beta bands [1]. The objective of this study was to determine how these second spectrum relationships are affected by day/night cycles, AED taper, and seizures.

Methods: We analyzed the full icEEG record of 13 medically refractory epilepsy patients who underwent icEEG monitoring and seizure localization at Yale-New Haven Hospital. We estimated magnitude-squared coherence (MSC) below 0.15 Hz of the running power in the delta, theta, alpha, beta, and gamma bands in order to quantify slow envelope correlations of these bands. First, we calculated second spectrum MSC on hour-long background icEEG segments before and after AED taper when patients appeared to be resting quietly with eyes open. We then calculated second spectrum MSC over the entire record for each patient in order to examine any variations related to time of day. Finally, for each patient, we reviewed the clinical record to find any seizures which were at least 6 hours removed from any other seizure. We then examined the icEEG before and after these seizures using our second spectrum measures.

Results: The second spectrum MSC, evaluated over the course of monitoring, increases on average during the night and decreases during the day. There was a small, but significant increase in second spectrum MSC with AED taper. In our seizure-related analysis, we analyzed data from 61 seizures, of which 28 occurred during the day and 33 occurred at night. The second spectrum MSC was significantly increased in all frequency bands except theta around
the time of seizure, and these changes occurred for both daytime and nighttime seizures.

**Conclusions:** Our analysis of the second spectrum MSC shows periodic changes related to day/night cycles, an increase with AED taper, and consistently higher estimates around the time of seizure. These changes indicate that the second spectrum MSC faithfully captures essential changes to the icEEG during monitoring and could aid understanding the processes underlying seizure generation.

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 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 is not yet as well defined. We initially examined the intracranial EEG in 9 focal frontal lobe seizures from 6 patients that had impaired consciousness and noted that there was a common ictal pattern of widespread low voltage fast activity. We hypothesized that widespread low voltage fast activity may play a role in loss of consciousness in patients with frontal lobe seizures. To further investigate this hypothesis, we obtained a larger cohort of 91 patients from the Yale epilepsy surgery program. We then included patients that had intracranial studies that found a frontal lobe onset, and excluded seizures with no meaningful behavioral interaction and also eliminated seizures that secondarily generalized. This led to a final cohort of 14 patients who were recorded from 2004-2015 and 26 seizures. Based on our data analysis, we found that there is an increase of low voltage fast activity associated with frontal lobe seizures exhibiting loss of consciousness. In addition, seizures with impaired consciousness exhibited higher amounts of epileptic activity based on EEG ictal patterns, and more post ictal slowing than seizures with maintained consciousness. These findings suggest a novel mechanism for loss of consciousness during frontal lobe seizures which may differ from temporal lobe seizures, and could guide improved treatments for frontal lobe epilepsy.
Long-term Postoperative Outcomes in Patients with Focal Cortical Dysplasia: Predictive Factors and AED Withdrawal

Authors: Emily Stanford, Alma Rechnitzer, Katie Bandt, Dennis Spencer, Jennifer Bonito, Pue Farooque, Lawrence Hirsch

Objective: Identify predictive factors of success for resective neurosurgery in treating epilepsy associated with focal cortical dysplasia (FCD); analyze long-term outcomes and results of attempts to reduce antiepileptic drugs (AEDs) postoperatively.

Background: FCD associated epilepsy is often medically refractory; therefore, surgery is often considered as a treatment. In this study, 45 FCD patients (median age: 26 years; median duration of epilepsy: 15 years) who underwent epilepsy surgery at Yale New Haven Hospital between 1986 and 2015 were analyzed regarding several demarcations of postoperative success.

Design/Methods: The medical records of 45 patients 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.

Results: 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), and was 62% at latest follow-up. At latest follow-up, 89% of patients saw at least a 50% improvement in seizure frequency (ILAE 1, 1a, 2, 3, 4). No predictive factors of surgical success (age at time of surgery and duration of epilepsy before surgery) were statistically significant. 41/45 patients were able to reduce the number or dosage of medications; only 15% of the seizure-free patients ceased AED treatment completely. Seizure-relapse occurred in 4/6 patients who attempted medication withdrawal; after reestablishing AEDs, seizures persisted in 2/4 patients.

Conclusions: Regarding seizure frequency, long-term outcomes were favorable with 62% seizure-free at the last follow-up, and 91% (41/45) reducing number of AEDs. However, most patients remained on one or more medications.
Slide Session III: Clinical/Electrophysiology
Communicating Diagnostic Certainty of Psychogenic Nonepileptic Seizures: A National Study of Provider Documentation

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Funding: This work was supported by the Department of Veterans Affairs, Veterans Health Administration (VHA), VISN 1 Career Development Award to Hamada Hamid Altalib and a VHA Health Services Research and Development Service Center of Innovation award (CIN 13-047).

Introduction. Management of psychogenic nonepileptic seizures (PNES) requires collaboration among and between health care professionals. Although criteria are established for diagnosis of PNES, miscommunication between neurologists, primary care providers, and mental health professionals may occur if the clinical impression is not clearly articulated.

Methods. Data from Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans, which includes 749,036 Veterans, were included in this analysis. Only Veterans with a history of seizure disorders or epilepsy (ICD-9 code of 345 or 780.39) from 2001 to 2014 were included. Since there is no ICD-9 code to identify Veterans with PNES in the VA national database and the ICD-9 code for conversion disorder (300.11) was and is not readily used by neurologists to label PNES, an EHR mining tool called Voogo was used to identify patients with PNES in neurologists’ progress notes\textsuperscript{(10, 11)}. Voogo allows users to conduct keyword searches within text and retrieve texts of 20 words before and after each PNES keyword (snippets of texts). Keywords to search for PNES included: “non-epileptic seizure”, “nonepileptic seizure”, “PNES”, and “psychogenic”. The above filtering criteria yielded 750 unique patients and 1645 neurology service progress notes.

Results. Of the 750 patients being worked up for PNES, the majority of patients did not meet criteria for PNES (64.6%). Of those who were thought to suffer from PNES, 147 (19.6%) met International League Against Epilepsy (ILAE) criteria for documented PNES, 14 (1.9%) for clinically established PNES, and 104 (13.9%) for probable or possible PNES.
**Conclusion** Neurologists tended to use ambiguous language, such as “thought to be” or “suggestive of” to describe their impressions of patients overall, even those with definitive PNES. Ambiguous language may lead to miscommunication across providers and inappropriate health care.

Future research will explore the change in prevalence of newly diagnosed post-traumatic (PTPNES) and non-traumatic PNES in the Post 9/11 Veterans receiving VA healthcare. Second, we will describe the risk factors, including gender, PTSD, depression, anxiety, military sexual trauma, chronic pain, and TBI for PNES including PNES subsequent to TBI (PTPNES). Finally, we will evaluate whether prior psychotropic and psychotherapeutic treatments for PTSD, mood and anxiety disorders decrease the risk of developing PNES, decrease the severity of PNES (number of monthly psychogenic seizures), and increase the likelihood of recovery (seizure-free for six months).
RECAPITULATING MALFORMATIONS OF CORTICAL DEVELOPMENT VIA
INDUCED PLURIPOTENT STEM CELL TECHNOLOGY

Author: Anita Huttner, MD, PhD.

Background: Progress in our understanding of somatic cell reprogramming, particularly the isolation and characterization of human induced pluripotent stem cells (iPSCs) opened new avenues for modeling human disease. iPSCs allow the generation of large numbers of genetically modifiable cells specific to the underlying human genetic background, and form an unparalleled opportunity to gain new insight into disease pathophysiology. This will further lay the foundation for the development of patient specific pharmacological assays and/or stem cell based therapies. We focused on Walker Warburg Syndrome (WWS), a rare and severe form of lissencephaly paired with congenital muscular dystrophy. Most children die before the age of three years. Several genes have been implicated in the etiology of this syndrome, however, to this date the pathogenesis is poorly understood. In addition, none of the animal models appears to faithfully reflect the human condition. Patient derived iPSCs, however, allow the targeted differentiation of cells into tissue specific phenotypes of brain and muscle, and thus provide an assay for the recapitulation of disease specific pathophysiology.

Design: iPSC lines were derived from skin biopsy specimens of patients with WWS and normal age matched controls. The generation of iPSCs followed established protocols using nucleofection (Amaxa system) of episomal plasmids expressing OCT3/4, SHp53, SOX2, KLF4, LIN28, and MYC. The cells were grown in culture and differentiated into all lineages of the human brain. Furthermore, since one of the hallmark features of lissencephaly is altered neuronal activity, this system form a unique opportunity to monitor electrical activity of iPSC derived neurons.

Result: Directed differentiation of iPSCs into neuronal precursors was demonstrated in vitro with antibodies for CNS phenotypes, like GFAP, TUJ1, Tbr1/2. Furthermore, neuronal activity was monitored with ultrasensitive fluorescent protein calcium sensors (GCaMP6) and showed altered neuronal activity in neurons derived from patients versus normal controls.

Conclusion: This model allows the phenotypic recapitulation of complex neurogenetic traits, and provides insights into the pathophysiology of human forms of malformations of cortical development. The combination of technologies offers a unique opportunity to model human neurological disease and hold promise for the development of new treatment strategies.
**Post-seizure Sleep and Consolidation in Human Epilepsy**

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**Objectives:** An elegant chain of events at the behavioral, circuit and cellular level has been described for how experiences are translated into memories through cellular plasticity mechanisms known as Cellular Consolidation that occurs specifically during sleep. Seizures are associated with long-term memory deficits and are known to activate many of the same gene pathways associated with sleep-dependent learning. While epilepsy and sleep are known to be related (e.g., seizures often occur at sleep-wake transitions), relatively little is known about what persistent changes occur during sleep following a seizure. Cellular Consolidation is known to involve reactivation of correlated neural activity during slow-wave sleep (SWS), specifically during sharp-wave/ripple complexes (SWR). Recently, we have shown that reactivation of seizure-related activity occurs after seizures in humans (which we have termed seizure-related consolidation, or SRC), both in terms of action potentials (Bower et al., 2015) and inter-ictal spikes (Bower et al., 2017). This suggests that the same mechanisms observed in task-related learning paradigms may apply to human seizures and opens a new area of study in regards to epilepsy.

**Methods:** Continuous, high-frequency (32 kHz) scalp EEG and intracranial data were obtained from patients undergoing monitoring for intractable epilepsy in the EMU at Mayo Clinic. Scalp EEG was used to stage sleep by expert review. Intracranial recordings were used to identify single-neuron action potentials (AP) and inter-ictal spikes (IIS). Correlation coefficients were computed for pairs of neuron AP and IIS recorded from different electrodes and grouped according to slow-wave sleep (SWS) and wake before and after seizures, as well as for the 30 min preceding seizure onset. Partial regression was used to determine whether changes in pairwise correlation preceding seizure onset correlated with changes observed post-seizure, given correlations that already existed in the pre-seizure period.

**Results:** In nine seizures from six EMU patients, pre-seizure changes in AP correlation coefficients were reactivated selectively during SWS ($p = 0.0424$), but not during wakefulness ($p = 0.9430$). Pre-seizure changes in IIS were also reactivated selectively during SWS ($p=0.0486$), but not during wakefulness ($p=0.559$). These changes were observed for electrodes located both within and outside the seizure onset zone, but was greatest in IIS when at least one electrode was located within the SOZ.

**Conclusions:** Neural activity patterns and IIS synchrony changes that occur in the minutes preceding seizures are selectively reactivated during post-seizure sleep. Observations relating reactivation to the seizure onset zone suggest that reactivation occurs broadly, and that it might be associated with the expansion of the seizure onset zone. These results are consistent with consolidation theory as described for behavioral learning and suggest that post-seizure
reactivation may activate learning-related cellular machinery as occurs following learned behaviors. This novel approach could help address current debates regarding whether ictal neuronal activity is organized as variable neural assemblies or fixed, repeated motifs; whether SRC arises from neuronal activity organized by inter-ictal epileptiform discharges (similar to physiological learning) or from generalized hyper-activation of neurons; and whether these effects can be disrupted or enhanced by interference with sleep.

References:
GRDA: a potentially benign EEG finding in critically ill patients?

Authors: Galluzzo D; Pereira S; Hirsch LJ; Sheth KN; Gilmore EJ

Generalized rhythmic delta activity (GRDA) is an abnormal, transient, EEG pattern most commonly found in patients affected by metabolic derangements and in those that have deep midline structural pathologies of the brain. Its pathophysiological impact is unknown. In a prospective cohort of 365 patients monitored with continuous EEG (cEEG) between November 2015 and December 2016, we reviewed the charts of 69 patients who displayed GRDA without any other periodic or rhythmic patterns. The median age of these patients was 53 years old (range 19-82 years old), with 54% of these patients being male. Fifty-two of the 69 patients were evaluated with cEEG to rule out the presence of non-convulsive seizures/status. Fifty-three of the 69 patients had altered mental status during EEG monitoring. GRDA was most commonly frontally predominant, at a frequency of 1Hz without +F or +S modifiers, and an occasional to abundant prevalence with a very brief duration. Forty-nine of the 69 patients (69%) were admitted for neurologic conditions, including; hemorrhagic and ischemic stroke (14%), seizure (13%), and traumatic brain injury (11%). Metabolic derangements were present in 7 patients (10%). At presentation 16 (23%) patients had normal neurological examinations, 16 (23%) had altered mental status with an absence of focal neurological deficits, and 7 (10%) had focal neurologic deficits consisting of cranial neuropathies or cortical spinal tract dysfunction.

Neuroimaging, in the form of CT and MRI, was performed in 64 (93%) patients. For 16 patients, imaging was normal. For 23 patients, (48%), the abnormalities were either diffuse or multifocal. In 11 patients (23%) the abnormalities were predominantly hemispheric involving the frontal or temporal lobes. The appearance of GRDA alone on cEEG did not warrant treatment. Forty of the 69 patients either did not receive antiepileptic drugs or their home dose was not adjusted during their hospitalization; at follow up 83% of these patients were not on AEDs, 17% were lost to follow up. Nine patients received prophylactic dosing of an AED. Of the 20 patients who received therapeutic AEDs, 3 had brief electrographic seizures (provoked by an acute brain injury), 7 had known epilepsy and experienced breakthrough seizures, and 10 presented with “seizures” in the emergency room and were continued on therapy at discharge.

Although in the proper clinical scenario ictal-interictal patterns warrant treatment as they may represent a focus of epileptogenic potential or cortical hyperexcitability, we propose that generalized rhythmic delta activity does not. GRDA may instead represent a benign, self-limited finding during times of metabolic derangement or structural brain pathologies. It is possible that GRDA may be associated with the post-ictal state, perhaps as a protective slow state following excitatory activity, although further studies are warranted to confirm this.
Global and local sleep homeostasis in patients with focal epilepsy: a high-density EEG study

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Introduction: In animal studies, both seizures and interictal spikes induce synaptic potentiation. Recent evidence suggests that electroencephalogram (EEG) slow wave activity (SWA) during sleep reflects synaptic potentiation during wake, and that its homeostatic decrease during the night is associated with synaptic renormalization and its beneficial effects. Here we asked whether epileptic activity induces plastic changes that can be revealed by high-density EEG recordings during sleep.

Methods: 15 drug-refractory focal epilepsy patients (mean age 43 ± SD 14, 9 females) were recruited at the Epilepsy Monitoring Unit of the University of Wisconsin. Individual patients presented variable seizure focus localization on 10-20 EEG clinical readings: left temporal (n=4), left frontal (n=4), right temporal (n=2), bilateral temporal (n=2), bilateral frontal (n=1), right parietal (n=1), or right extra-temporal (n=1). 256 electrodes high-density EEG overnight recordings were performed in patients and compared to those performed in 15 age and gender matched healthy volunteers (mean age 43 ± SD 14, 10 females). Epochs of steady non rapid eye movement (NREM) sleep and REM sleep were then extracted from the recordings for further preprocessing. EEG data were filtered from 1 to 40 Hz, and semi-automated artifact rejection was used to further select clean epochs and channels. Individual NREM slow waves were also detected and the overnight decrease in slow wave up-slope was computed as described in previous work. Topographic values of SWA (delta) and spindle power as well as the overnight decrease in the negative slope of slow waves for each EEG channel were converted to 2D images and analyses were performed using Statistical Parametric Mapping. All results were thresholded at family-wise error corrected p<0.05.

Results: Compared to controls, patients with epilepsy displayed increased NREM sleep SWA over widespread, bilateral scalp regions (Figure 1). This increase in SWA was only present during NREM sleep and was positively correlated with the frequency of generalized seizures in the 3-5 days preceding the recordings. Individual patients also showed local increases in NREM sleep SWA at scalp locations matching their seizure focus. This local SWA increase was positively correlated with the frequency of interictal spikes during the last hour of wakefulness preceding sleep (Figure 2). By contrast, frequent interictal spikes during NREM sleep predicted a reduced homeostatic decrease in the slope of sleep slow waves during the night, which in turn predicted reduced daytime learning. Patients also showed an increase in sleep spindles, which was negatively correlated with IQ.

Conclusions: Altogether, these findings suggest that both seizures and interictal spikes can induce plastic changes in the human brain that can be sensitively detected by EEG markers of sleep homeostasis. Furthermore, abnormalities in sleep EEG markers are correlated with cognitive impairment, suggesting that not only seizures, but also interictal spikes can have negative consequences.
Slide Session IV: Electrophysiology
Use of Intracranial Responsive Neurostimulator Detections as a Prognostic Factor for Medication Response

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Objective: To determine whether the efficacy of a newly started anti-seizure drug (ASD) can be predicted in a clinically meaningful amount of time using detection outputs from an intracranial responsive neurostimulator (RNS).

Background: Determining the clinical efficacy of a new ASD being added to a patient’s regimen is often a lengthy and risky process. Currently, there are no metrics available to accurately predict ASD response in a relatively short amount of time following its initiation.

Design/Methods: Patients implanted with an intracranial responsive neurostimulator (RNS; Neuropace, Inc) device and receiving care at a single center were identified for analysis. Medical records were reviewed to identify all ASD changes patients had undergone since device implantation. Daily detection outputs in the form of “episode starts” and “long episodes” were averaged and compared at varying time points before and after ASD initiation. Ratios of detection counts before and after the medication change were then compared with medication response outcomes. Medication success or failure was retrospectively determined on an individual basis based on provider documentation of improvement in seizures, whether or not the provider and patient chose to continue the medication long term, and patient-reported clinical efficacy (seizure diaries).

Results: 22 ASD changes identified from 20 patients met inclusion criteria for a clinically relevant time-point analysis in which detection counts were averaged three months before and one week after initiation of a new ASD. A significant difference between long episode ratios was found between medication successes and failures (p=0.0031). If long episodes decreased by 40% in the first week on a new medication (seen in 11 instances), medication was effective in all but one instance (ppv=91%). Similarly, if long episodes increased by 40% (seen in 4 instances), medication failed in 3 instances (NPV=75%).

Conclusions: In this small cohort of patients with an RNS, changes in long episode detections within the first week following start of a new ASD accurately predicted clinically relevant ASD responses.
The Multiscale Structure of Human Seizures

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The need to define the spatial structure of seizures is driven by epilepsy surgery procedures, in which limited brain regions are resected or ablated in order to prevent recurrent seizures. Surprisingly, there has been little advancement in this area since current surgery techniques were pioneered in the early to mid 20th century. By studying epilepsy patients undergoing invasive EEG studies using continuous recordings from microelectrode arrays implanted in the seizure onset zone, our group has developed a useful mesoscale characterization of focal seizures. Specifically, focal seizures are composed of a small, slowly expanding core with unrestrained intense bursting activity, triggering an enhanced inhibitory response in the surrounding regions. We now describe how this structure can drive the large-scale, coordinated EEG activity that is typically seen during seizures. Using a combination of computational modeling and human EEG data analysis in three patients recorded with microelectrode arrays placed into the seizure core, we demonstrate that the ictal wavefront seeds epileptiform discharges that form traveling waves of activity directed backward into the core, and forward into the surrounding brain regions. The ictal wavefront, which is generally invisible to clinical EEG recordings, thus drives the large-scale structure of seizures. Its localized dynamics are sufficient to explain clinically observed features of seizures such as simultaneous seizure termination.
Uncovering the subcortical neural mechanisms for visual consciousness.

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Keywords: Consciousness, fMRI, intracranial EEG, epilepsy

The neural mechanisms of consciousness remain a fundamental scientific question. To investigate cortical activity that drives conscious perception, we recruited epilepsy patients to complete a visual perception task while undergoing seizure monitoring with intracranial EEG. These results found a global posterior to anterior 150 mm/second wave of broadband gamma (40-100 Hz) activity in frontal-parietal networks for visual conscious events. In addition, network switching was observed, including the deactivation of the default mode network and activation-deactivation-reactivation of gamma power in the visual cortex for conscious perception. These results offer key insights into the cortical mechanisms of consciousness, but neglect to explain the role of subcortical structures. Indeed, the network switching observed in the intracranial EEG study suggests that subcortical arousal networks are assisting in cortical network modulations linked to conscious perception. We utilized functional magnetic resonance imaging (fMRI) as an alternative to intracranial EEG to investigate the cooperation between cortical and subcortical networks (e.g., the thalamus and brainstem) in visual conscious perception. Correspondingly, 37 healthy controls were recruited to complete a behavioral task that distinguishes visual conscious and unconscious events while recording blood-oxygen-level-dependent (BOLD) signal. Preliminary analyses of the BOLD signal accords with our EEG findings, revealing prominent bilateral signal increases in frontal-parietal networks and signal decreases in the default mode networks for consciously perceived visual targets. If confirmed, these results support the assumption that the EEG data collected from epilepsy patients during cognitive testing is generalized to healthy controls. Ongoing analyses are underway to fully explicate the role of subcortical structures in visual conscious perception. Understanding these pathways may have important practical implications for both the mechanisms of normal consciousness and disorders of consciousness, including epilepsy.
Band Related Local Functional Connectivity of the Seizure Onset and Peri-Seizure Onset Area

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Rationale: To determine the band-related local functional connectivity (BRLFC) of the seizure onset area or areas (SOA) and the peri-SOA, and the relationship between BRLFC and outcome to surgery.

Methods: This study was conducted on 18 unselected adult patients with intractable epilepsy undergoing icEEG monitoring for surgery. Intracranial EEG electrode contacts were located from post-implantation CT and MR images and registered to the MRI of a standard brain to allow interpretation of results from all patients in the same space. A 1 hr icEEG epoch, recorded during wake and removed in time from seizure occurrence, was studied. Coherence was estimated for all pairs of electrode contacts ipsilateral to the SOA in delta, theta, alpha, beta, gamma and a high frequency band. The BRLFC of each electrode contact was estimated as the average band-related coherence between it and all electrode contacts within a specified spatial window.

Results: A graded relationship was observed between BRLFC and distance to the SOA such that electrode contacts with the greatest connectivity were closest to the SOA and those with the lowest connectivity were at a distance of several cm from the SOA. This relationship between distance to the SOA and connectivity was present primarily in the alpha, beta, gamma and high frequency bands, and was preserved over multiple days of intracranial monitoring. This spatial structure could be exploited to identify the region of seizure onset using an automated search algorithm. Further, BRLFC in the SOA and peri-SOA, for the delta and gamma frequency bands was greater in patients who were seizure free after surgery in comparison to those who were not seizure free. These observations could be used to construct a classifier to correctly predict surgical outcome in nearly all patients who proceeded to surgery.

Conclusions: There is altered BRLFC, in the SOA, and peri-SOA, expressed in the background icEEG of patients with medically intractable epilepsy. This altered BRLFC may be a marker of medically intractable epilepsy and can be used to both locate the seizure onset area and predict outcome to epilepsy surgery.