Sixth International Workshop on Seizure Prediction

Bahia Resort Hotel
San Diego, California

November 6-7, 2013

IWSP6 hosted by Alliance For Epilepsy Research

Sixth International Workshop on Seizure Prediction

Bahia Resort Hotel
San Diego, California – November 5-6-7, 2013

Schedule

Tuesday, November 5, 2013

18:00-21:00	Registration, Welcome Reception

Wednesday, November 6, 2013

07:30-08:30	Registration and continental breakfast
08:30-09:40	Themes, Goals and Benchmarks
09:40-10:00	Break
10:00-12:00	Session
12:00-13:00	Lunch (provided)
13:00-15:00	Session
15:00-15:30	Break
15:30-17:40	Session
17:40-19:00	Dinner (on own)
19:00-21:30	Poster session

Thursday, November 7, 2013

07:30-08:30	Continental breakfast
08:30-10:30	Session
10:30-10:50	Break
10:50-12:30	Session
12:30-13:30	Lunch (provided)
13:30-15:30	Session
15:30-16:00	Break
16:00-16:30	Session
16:30-17:10	Discussion and wrap-up
18:00-21:30	Dinner cruise

Welcome

It is our great honor to host the sixth International Workshop on Seizure Prediction (IWSP). The IWSPs are a forum that brings together an international interdisciplinary group of epileptologists, engineers, physicists, mathematicians, neurosurgeons and neuroscientists with the goal of developing engineering-based “closed-loop” epilepsy treatments.

This meeting continues the series’ goal of reporting progress in seizure prediction, but also seeks to focus attention on the basic seizure mechanisms that are key roadblocks to our clinical treatment goals. There remain large gaps in theoretical knowledge of seizure origin, spread, and termination, and we need to address the subtleties of how to observe such phenomena using physiological measurements. Through these questions we hope to arrive at new approaches to understand epileptic seizure generation mechanisms across all scales of brain from neuron to organism, and to close the gap between models of seizure generation and physiological/clinical observations.

Historically, this community's strength has been the willingness of participants to find a common language, and an understanding that expertise from many disciplines are needed for success. To build on this tradition, we have built in ample time for discussion and informal interaction throughout the meeting, including two discussion sessions articulating themes, goals and benchmarks for the community, and we have invited younger investigators to introduce the speakers.

We would like to express our deep appreciation to the Alliance for Epilepsy Research for once again hosting an IWSP meeting and to the many sponsors and donors that have made this workshop possible. We hope you will enjoy the workshop and take the opportunity to interact with other members of the seizure prediction community during your visit to San Diego.

The Organizing Committee
Bruce J. Gluckman
Björn Schelter
Catherine Schevon
Susan Arthurs

General Information

Numerous brochures about San Diego, the immediate area, and public transportation are available in the lobby of the Bahia Resort Hotel. The hotel concierge or those at the front desk can help you with questions.

Emergency Information

In case of emergency, the phone number for police or ambulance is 911.

Contents

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We especially appreciate CURE's support of selected young investigators.

This conference is supported in part by a grant from the National Institute Of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R13NS083314. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily represent the official views of the National Institutes of Health.

Program

All events are held in the Mission Bay Ballroom ABC unless otherwise noted.

Tuesday, November 5, 2013

18:00-21:00 – Welcome Reception and Registration, Mission Bay Ballroom Foyer

Wednesday, November 6, 2013

07:30-08:30 – Registration, Mission Bay Ballroom Foyer

07:30–08:30 – Continental Breakfast

08:30-09:40 – Themes, Goals and Benchmarks

Session Moderator: Bruce Gluckman, Penn State Univ.

Introductory Remarks 08:30
Bruce Gluckman, Organizing Committee

Seizure mechanisms and prediction: Finding a benchmark for success 08:40
William Stacey, Univ. of Michigan (CURE supported)

Panel positions:
Steven J. Schiff, Penn State Univ. 09:10
Brian Litt, Univ. of Pennsylvania 09:20
Andreas Schulze-Bonhage, Univ. Hospital Freiburg 09:30

09:40-10:00 – Break

10:00-12:00 – Basic Mechanisms

Session Moderator: Anatol Bragin, Univ. of California Los Angeles

Activation of epileptic networks 10:00
Kevin Staley, Harvard Univ.
Introduced by Josha Dian, University of Toronto

Interictal spikes generate bursts of inactivated action potentials in human epileptogenic neocortex: relationship to high-frequency oscillations 10:40
Ed Dudek, Univ. of Utah
Introduced by Yun Sang Park, Brown Univ.

Decoding the EEG: an electrographic Rosetta Stone 11:20
Andrew Trevelyan, Newcastle Univ.
Introduced by Yilin Song, Polytechnic Institute of NYU

12:00-13:00 – Lunch provided

13:00-15:00 – Sleep, SUDEP and Autonomic Effects

Session Moderator: Steve Weinstein, Children's National

Neurostimulation to Increase Consciousness in Complex Partial Seizures 13:00
Hal Blumenfeld, Yale School of Medicine
Introduced by Diana Cogan, Univ. of Texas at Dallas

Diagnostic implications of chrono-epileptology 13:40
Tobias Loddenkemper, Boston Children's Hospital (CURE supported)
Introduced by Madineh Sedigh-Sarvestani, Univ. of Pennsylvania

Seizures, Autonomic Dysfunction and Sudden Death 14:20
Lisa Bateman, Columbia Univ.
Introduced by Ehsan Negahbani, Univ. of Waikato

15:00-15:30 – Break

15:30-17:40 – Human Studies in Seizure Forecasting & Control

Session Moderator: Gregory Worrell, Mayo Clinic

The RNS System: What can a chronically implanted responsive neurostimulator teach us about epilepsy? 15:30
Felice Sun, NeuroPace
Introduced by Vanessa Senger, Technische Universität Dresden

Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study 16:10
Kent Leyde, NeuroVista
Mark Cook, Univ. of Melbourne
Introduced by Michelle Chong

Discussion Panel 17:10
Bjoern Schelter, Univ. of Aberdeen
Catherine Schevon, Columbia Univ.
Theoden Netoff, Univ. of Minnesota

17:40-19:00 – Dinner on your own

19:00-21:30 – Poster Session

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Thursday, November 7, 2013

07:30-08:30 – Continental Breakfast

08:30-10:30 – Epilepsy Connectome

Session Moderator: Catherine Schevon, Columbia Univ.

Functional network analysis of seizure activity in humans 8:30
Mark Kramer, Boston Univ.
Introduced by Sridevi Sarma, Johns Hopkins Univ.

Resting connectivity and the ictal onset zone 9:10
Ashesh Mehta, Hofstra North Shore LIJ
Introduced by Prashanth Selvaraj, Univ. of California Berkeley

Classification of the Preictal State in Naturally Occurring Canine Epilepsy 9:50
Benjamin Brinkman, Mayo Clinic

Factors affecting early automated epileptic seizure detection for online evaluation 10:10
Matthias Dümpelmann, Univ. Medical Center Freiburg

10:30-10:50 – Break

10:50-12:30 – Active Manipulation

Session Moderator: Hitten Zaveri, Yale Univ.

On-demand optogenetics for temporal lobe seizure control 10:50
Esther Krook-Magnuson, Univ. of California Irvine (CURE supported)
Introduced by Malenka Mader, Univ. of Freiburg

Towards a wireless, closed-loop optogenetic stimulator for seizure modulation 11:30
Steven Lee, Purdue Univ.

A Standardized Dosing System for Vagus Nerve Stimulation Therapy 11:50
Matthew Ward, Purdue Univ.

Assessment of excitability in neuronal populations based on selective activation of interneurons 12:10
Pascal Benquet, Univ. Rennes

12:30-13:30 – Lunch provided

13:30-15:30 – Slice Physiology and HFOs

Session Moderator: Levin Kuhlmann, Univ. of Melbourne

Macro- vs micro-level synchronization in the epileptic hippocampus: imaging in vitro and in vivo 13:30
Sarah Feldt-Muldoon, INSERM Marseille (CURE supported)
Introduced by Nirnith Sah, Indian Institute of Science

Tracking Neural Dynamics: A Method to Elucidate Mechanisms Involved in Seizure Generation and Termination 14:10
Richard Balson, Univ. of Melbourne

Cellular and synaptic rules of hippocampal high-frequency ripples in temporal lobe epilepsy 14:30
Lisette Menendez de la Prida, Instituto Cajal CSIC
Introduced by Dominique Duncan, Stanford Univ.

Analysis of single unit firing patterns preceding human seizures 15:10
Edward Merricks, Newcastle Univ.

15:30-16:00 – Break

16:00-16:20 – Database Updates

EU Database
Andreas Schulze-Bonhage, Univ. Hospital Freiburg

US Database
Brian Litt, Univ. of Pennsylvania

16:20-17:10 – Outcomes and targets for the ISPG

Moderators: IWSP6 Organizers

Participants:
Fabrice Wendling, Univ. of Rennes
Levin Kuhlmann, Univ. of Melbourne
William Stacey, Univ. of Michigan (CURE supported)

17:10 – Closing remarks

The IWSP6 Organizing Committee

18:00-21:30 – Dinner and cruise on Mission Bay on the sternwheeler, William D. Evans

Organizing Committee

Email: OrganizingCommittee@IWSP6.org

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Scientific Advisory Board

Speaker Abstracts

Seizure mechanisms and prediction: Finding a benchmark for success

Speaker: Stacey, William, MD PhD, Assistant Professor, Department of Neurology, Department of Biomedical Engineering, University of Michigan

Since 2000, the NIH has been soliciting input from clinicians, basic scientists, and the public regarding specific goals to strive for in the search for a cure of epilepsy. These Epilepsy Research Benchmarks have become a primary metric to justify clinical importance in NIH grants and to demonstrate successful research to government and the public. Our community of "quantitative" epilepsy researchers has a great opportunity both to achieve some of these Benchmarks and to guide the formation of new ones, reinforcing the importance of our research to the epilepsy community.

Activation of epileptic networks

Speaker: Staley, Kevin, Harvard University, Cambridge, MA
Lillis, Kyle
Swiercz, Waldemar

Understanding the anatomy of activation of epileptic networks during interictal spikes and seizures may illuminate aspects of ictogenesis that facilitate seizure prediction. We have studied the sequence of activation of neurons in epileptic foci using electrocortigraphic patient data, ex vivo recordings from resected epileptic foci, and multiphoton calcium imaging in chronically epileptic organotypic hippocampal slice cultures. We found a surprising degree of variance in the “ignition pathways” of epileptic foci in the electrophysiological data as well as in data sets from high-speed, targeted path scanning calcium imaging experiments. The number of ignition pathways collapsed in the presence of convulsant GABAA receptor antagonists, indicating that synaptic inhibition was necessary for pathway variance. Variance in the patterns of Ictal onset was greatest early in the course of epilepsy, and declined as seizure probability increased. Our results to date suggest that the sequence by which neurons join in the synchronous activation of epileptic foci reflect both the integrity of the inhibitory network and stage of epilepsy. We have not yet investigated intriguing implications such as whether the variance in spike activation patterns reflect an evolution of inhibition that might help predict subsequent ictal onsets.

Interictal spikes generate bursts of inactivated action potentials in human epileptogenic neocortex: relationship to high-frequency oscillations

Speaker: Dudek, F. E.

B Greger[1*], SS Kellis[2*], TS Davis[1], PA House[3], L Shao[4], CA Schevon[5], RG Emerson[5], G McKhann[6], RR Goodman[6], FE Dudek[3,4]

Departments of Bioengineering[1], Electrical and Computer Engineering[2], Neurosurgery[3], and Physiology[4] University of Utah, Salt Lake City, UT
and Departments of Neurology[5] and Neurosurgery[6]
Columbia University, New York, NY

These authors contributed equally to the project[*]

Both interictal spikes - brief electrical events that occur between epileptic seizures - and high-frequency oscillations (HFOs; 250-600 Hz) have been used to diagnose epilepsy and localize seizure onsets. Although interictal spikes are thought to arise primarily from large excitatory postsynaptic potentials (EPSPs), the mechanism responsible for HFOs and their role in epilepsy remain unclear. The hypothetical contribution of EPSPs and action potentials to these events was studied *in vivo* with simultaneous intra-cranial electrocorticography and extracellular recordings from 96-microelectrode arrays in patients undergoing surgical treatment for intractable epilepsy. Bursts of full-amplitude action potentials, and action potentials that had undergone variable degrees of depolarization-induced inactivation, were recorded with the microelectrode array during HFOs. The HFOs were superimposed on slower local field potentials (LFPs), which occurred synchronously with interictal spikes recorded with electrocorticography. Both the slower LFPs and the HFOs propagated across neocortex in a direction-specific manner. Simultaneous extracellular and intracellular recordings in neocortical slices - obtained from resected tissue adjacent to a micro-electrode array - confirmed that (1) the slow LFPs were EPSPs and equivalent to interictal spikes, and (2) superimposed HFOs coincided with bursts of action potentials that experienced variable degrees of depolarization-induced inactivation. These data, recorded from patients with intractable epilepsy, strongly suggest that the 250-to-600 Hz oscillatory band characteristic of HFOs arises from a mixture of full-amplitude and depolarization-inactivated action potentials, rather than complex patterns of asynchronous EPSPs. Furthermore, these data suggest that interictal spikes with superimposed HFOs represent action potentials superimposed on large EPSPs and thus serve is potential markers of the epileptogenic zone; interictal spikes without HFOs, on the other hand, hypothetically have smaller EPSPs and few if any action potentials, and thus hypothetically represent surrounding non-epileptogenic areas that receive propagated input from nearby epileptogenic areas.

Acknowledgments: This work was supported by the University of Utah Research Foundation, NIH grants NS16683 and NS048871, and NSF ERC grant EEC-9986866.

Decoding the EEG: an electrographic Rosetta Stone

Speaker: Trevelyan, Andrew, Newcastle University, UK
Hannah Alfonsa, Newcastle University, UK
Edward Merricks, Newcastle University, UK
Shennan Weiss, Columbia University, NY
Ron Emerson, Cornell University, NY
Catherine Schevon, Columbia University, NY

Progress in epilepsy has been hindered by the complexity and diversity of seizure activity, and the abstract nature of our primary clinical tool, the EEG. These electrophysiological recordings underpin most of our knowledge of human epilepsy, and are considered a cornerstone of clinical epilepsy managment, for diagnosis, seizure localization and, potentially, seizure prediction. However, evidence suggests that analyses of iEEG currently perform poorly for both seizure prediction and seizure localization. Seizure localization is essential for all surgical treatments, and relies heavily on iEEG, which logically should be the gold standard for discerning the pathological location. Yet analysis of surgical outcomes shows that this is not so. In cases where iEEG is the only means to guide the neurosurgeon to a seizure focus, epilepsy often persists after surgery. This contrasts with better outcomes in “lesional cases”, where there is a visible abnormality on MRI scanning, and which is therefore usually included in

any resection. In each case, one could argue that the iEEG adds little to the clinical management at all. This should not be so, because there is clearly a vast amount of information latent in EEG recordings; the challenge is to distinguish what is important from other, confounding factors.

Animal studies provide opportunities to explore the basic patho-physiology of epilepsy in ways that are not available in the clinic. I will discuss how these studies can then be related to human recordings, even when the mode of recordings is not exactly equivalent. We have been helped significantly in this by the recent development of microelectrode arrays. I will present examples where animal recordings suggest testable hypotheses about the location and nature of human epileptic recordings, and will discuss how this may advance clinical practice.

Neurostimulation to Increase Consciousness in Complex Partial Seizures

Speaker: Blumenfeld, Hal, Departments of Neurology, Neurobiology and Neurosurgery, Yale School of Medicine, New Haven, CT
Motelow, Joshua E., Dept of Neurology, Yale School of Medicine, New Haven, CT USA,
Gummadavdelli, Abhijeet, Dept of Neurology, Yale School of Medicine, New Haven, CT USA
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Sanganahalli, Basavaraju, Dept of Diagnostic Radiology, Yale School of Medicine, New Haven, CT USA
Hyder, Fahmeed, Dept of Diagnostic Radiology, Yale School of Medicine, New Haven, CT USA

Impaired consciousness in complex partial seizures has a devastating impact on quality of life for people living with epilepsy. In some patients complex partial seizures cannot be controlled by medications or by surgery. For these patients, a treatment which increases the level of consciousness during and following seizures would provide a dramatic improvement. Prior work from our group has provided a rodent model of complex partial seizures which mimics the human behavioral arrest and cortical EEG signature of ictal neocortical slow waves. We found in this model that seizures suppress the subcortical arousal systems including the brainstem cholinergic and intralaminar thalamic nuclei. In patients with other disorders of consciousness such as minimally conscious state, stimulation of the intralaminar thalamic nuclei has markedly improved the level of consciousness. Therefore, our goal is to restore consciousness during complex partial seizures by stimulating the intralaminar thalamic nuclei in an animal model. We found that stimulation of the intralaminar centrolateral nucleus under anesthesia while recording blood oxygen level dependent (BOLD) fMRI allowed titration of optimal stimulus parameters, and produced widespread BOLD increases in the thalamus, cingulate and frontal cortex. Electrophysiological recordings under anesthesia (ketamine/xylazine 90/15 mg/kg) demonstrated that stimulation of the thalamus converted cortical slow oscillations to low voltage high frequency activity resembling the awake state. Finally, intralaminar thalamic stimulation during complex partial seizures converted ictal neocortical slow waves as well as post-ictal slow waves into normal-appearing fast activity. Our results suggest a novel therapeutic approach for restoring consciousness during complex partial seizures involving thalamic stimulation during both the ictal and post-ictal periods. Our initial findings suggest this approach can restore

normal cortical EEG and may therefore improve level of consciousness. In future experiments we will stimulate the thalamus in awake animals in an effort to restore normal behavior during seizures. If successful in the animal model, intralaminar thalamic stimulation may ultimately provide a novel therapy for preventing impaired consciousness during complex partial seizures in human patients.

Diagnostic implications of chrono-epileptology

Speaker: Loddenkemper, Tobias, Boston Children's Hospital

The combination of chronobiology and epilepsy offers novel diagnostic options. Knowledge of the interactions between circadian patterns, entrainment, sleep patterns, as well as biomarkers of the sympathetic and parasympathetic nervous system and epilepsy may provide additional diagnostic options for modeling seizure occurrence patterns. It may also provide novel insights into the regulation processes of epilepsy and relationships to clock-genes, ultimately rendering new treatment options. Temporal fluctuations of seizure susceptibility based on sleep homeostasis and circadian phase in selected epilepsies may provide predictability based on mathematical models. This offers opportunities for individualized treatment paradigms based on chrono-pharmacology, differential medication dosing, chrono-drug delivery systems, and utilization of 'zeitgebers' such as chronobiotics, light-therapy and desynchronization strategies, as well as biomarkers for sudden death in epilepsy.

Seizures, Autonomic Dysfunction and Sudden Death

Speaker: Bateman, Lisa, Columbia Comprehensive Epilepsy Center, Columbia University, NY

The autonomic nervous system is frequently involved in seizures. While the most profound autonomic disturbances have been described in association with generalized tonic-clonic seizures, focal seizures may also present with distinct symptoms and signs of autonomic dysfunction. These changes likely result from direct excitation or inhibition of central autonomic centers during seizures. In some settings, autonomic symptomatology may suggest specific seizure onset localization, while in others this more likely reflects seizure spread to autonomic areas. Multimodality cardiorespiratory monitoring performed in conjunction with video-EEG recordings, direct brain stimulation and studies in animal models of epilepsy have helped to define cardiac and respiratory autonomic dysfunction associated with seizures and identify the brain regions involved with its occurrence.

Restoration of baseline autonomic function may be delayed by minutes to several hours following seizure termination. In some individuals with epilepsy, there is additional evidence of interictal autonomic dysfunction, suggesting baseline functional and/or structural abnormalities in brain regions involved in autonomic control related to epilepsy. These deficits may impair the ability of the autonomic system to respond to and recover from severe seizures.

In its most extreme form, inter-ictal and peri-ictal autonomic dysfunction may contribute to sudden unexpected death in epilepsy (SUDEP), the leading cause of seizure-associated death in patients with epilepsy. The precise physiological mechanisms of SUDEP are unknown and likely there are several potential contributing factors. Further

study of peri-ictal cardiorespiratory physiology and betterunderstanding of the influences of seizures on central autonomic systems are needed to define thepathophysiology of SUDEP and develop clinically relevant methods of risk assessment and reduction.

The RNS System: What can a chronically implanted responsive neurostimulator teach us about epilepsy?

Speaker: Sun, Felice, NeuroPace, Inc.
Morrell, Martha, NeuroPace, Mountain View, CA
Skarpaas, Tara, NeuroPace, Mountain View, CA

Responsive (closed-loop) stimulation is an emerging treatment for epilepsy. The RNS® System (NeuroPace, Inc.) is an investigational device that is the first closed-loop responsive neurostimulation system for the treatment of partial onset seizures. The system includes a cranially implanted neurostimulator that is connected to 1 or 2 recording and stimulating depth and/or subdural cortical strip leads, which are implanted at the seizure focus. The neurostimulator continually senses electrocorticographic (ECoG) activity through the leads and is programmed by the physician to detect specific electrographic abnormalities and then to provide short bursts of electrical stimulation to the seizure focus. The neurostimulator stores the time and type of ECoG detections as well as ECoG samples. These can be transmitted securely over the internet for later physician review.

A 2-year multicenter randomized double-blinded controlled pivotal study of the RNS System as an adjunctive treatment for adults with partial onset seizures demonstrated a significant reduction in seizures and safety comparable to alternative treatments and procedures. Additional safety data was collected in an earlier 2-year feasibility study, and a multi-center prospective open-label 7-year longterm treatment study is being conducted to follow those subjects who completed the feasibility or pivotal study in order to provide a total of 9 years of prospective data on safety and effectiveness.

In total, 256 subjects have been implanted with the RNS Neurostimulator and Leads and followed for an average of 4.5 years (ranging from 5 weeks to over 8.5 years). Seizure frequency data from the studies show a significantly greater reduction in seizures in the Treatment group (receiving responsive stimulation) compared to the Sham stimulation group (receiving no stimulation) during the blinded period. Open-label data show a reduction in seizures that improves over the first 2 years of treatment and is sustained in the following years. Safety data indicate that stimulation is well tolerated; during the blinded periods, there were no adverse events that were reported with significantly greater frequency in the Treatment group compared to the Sham group, and there was no deterioration in cognition or mood during the blinded period or the open-label period. Adverse events were consistent with the risks associated with epilepsy and the risks of alternative treatments and procedures.

The neurostimulator data collected during the RNS System clinical trials provides the first longitudinal ambulatory ECoG data recorded from a chronically implanted neurostimulator. The data may provide insights into the long-term patterns and dynamics of the epileptic brain.

This presentation first reviews the results of the clinical studies and then presents initial observations from neurostimulator data, including the types of electrographic patterns

detected by the neurostimulator, the circadian and ultradian patterns associated with these detections, and electrocorticographic changes concomitant with seizure reduction over time.

Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study
Speakers: Kent Leyde, Mark Cook, Univ. of Melbourne

Objectives
An implantable seizure prediction system could be clinically useful to patients with epilepsy and could improve independence, safety, and enable new forms of treatment. We developed an implantable seizure prediction system, and conducted a multicentre clinical feasibility trial to assess the safety, accuracy, and efficacy of the system in adults with drug-resistant focal seizures.
Methods
We enrolled patients at three centres in Melbourne, Australia, between March 24, 2010, and June 21, 2011. Eligible patients had between two and 12 disabling partial-onset seizures per month, a lateralised epileptogenic zone, and no history of psychogenic seizures. After devices were surgically implanted, patients entered a data collection phase, during which an algorithm for identification of periods of high, moderate, and low seizure likelihood was established. If the algorithm met performance criteria (i.e., sensitivity of high-likelihood warnings greater than 65% and performance better than expected through chance prediction of randomly occurring events), patients then entered an advisory phase and received information about seizure likelihood. The primary endpoint was the number of device-related adverse events at 4 months after implantation. Our secondary endpoints were algorithm performance at the end of the data collection phase, clinical effectiveness (measures of anxiety, depression, seizure severity, and quality of life) 4 months after initiation of the advisory phase, and longer-term adverse events. We also measured seizure prediction performance attained during the advisory phase.
Results
We implanted 15 patients with the advisory system. 11 device-related adverse events were noted within four months of implantation, two of which were serious (device migration, seroma); an additional two serious adverse events occurred during the first year after implantation (device-related infection, device site reaction), but were resolved without further complication. The device met enabling criteria in 11 patients upon completion of the data collection phase, with high likelihood performance estimate sensitivities ranging from 65% to 100%. Three patients' algorithms did not meet performance criteria and one patient required device removal because of an adverse event before sufficient training data were acquired. We detected no significant changes in clinical effectiveness measures between baseline and 4 months after implantation.
Conclusions
This study showed that seizure prediction based on long term intracranial monitoring is feasible in ambulatory patients with drug-resistant epilepsy. If these findings are replicated in larger, longer studies, the improved understanding of preictal electrical activity and seizure generation may lead to improved seizure prediction methods and new management strategies.

Functional network analysis of seizure activity in humans

Speaker: Kramer, Mark, Department of Mathematics and Statistics, Boston University, Boston, MA
Cash, Sydney, Mass General Hospital, Boston, MA
Eden, Uri, Boston University, Boston, MA
Kolaczyk, Eric, Boston University, Boston, MA

The notion of an "epilepsy connectome" is a powerful concept with a variety of potential manifestations. In this presentation, we will focus on one possible aspect of this connectome: functional networks, and more specifically the application of functional network analysis to seizure dynamics in humans. We will outline methodological aspects related to functional network inference, techniques to characterize functional networks, and the application of these techniques to brain voltage recording from human patients during seizure. We will also discuss the insights into seizure activity deduced from functional network analysis, and suggest how these techniques may motivate new treatment strategies, and possibly techniques to anticipate seizure. We will conclude with a discussion of how functional organization manifests at different spatial scales of brain voltage activity.

Intraindividual, multimodal mapping of functional and epileptic networks

Speaker: Mehta, Ashesh, MD, PhD, Assistant Investigator, Center for Neuroscience, Feinstein Institute for Medical Research, North Shore LIJ Health System, Manhasset, NY. Assistant Professor. Department of Neurosurgery. Hofstra University School of Medicine.

The idea of epilepsy as a large-scale network disease as opposed to focal and discrete has been discussed for many years. Recent interest and development of analytical tools to measure and analyze large scale brain networks has provided us with unprecedented methodology to test this hypothesis. In this talk, I will review what is known about resting networks and their neurophysiological basis and present evidence that epileptogenic regions do indeed form networks that can be mapped in an individual's resting brain via interictal measures of activity using functional magnetic resonance imaging, electrocorticography and direct cortical stimulation. Resting-state and task-based functional MRI and intracranial EEG are used to assess the functional connectivity of the individual brain and define pathological networks involved in epilepsy as well functional networks involved in motor control, language and perception. Direct cortical stimulation confirms and extends this mapping by introducing effective connectivity, i.e. how activity in one brain region influences activity in other areas. We combine information from these different network measures into connectivity maps that are unique to the individual patient under scrutiny. Our analysis suggests that both local and global connectivity measures should be considered and that they carry different implications about function and pathology. We believe that, generally speaking, the network hypothesis is correct, and that patterns of interictal connectivity should guide where to place electrodes to monitor seizure activity and how to intervene to stop seizures. In order to accomplish this, we advocate for the development of inter-institutional normative databases of multimodal connectivity measures.

Classification of the Preictal State in Naturally Occurring Canine Epilepsy

Speaker: Brinkman, Benjamin, Mayo Systems Electrophysiology Laboratory, Mayo Clinic, Rochester, MN 55905
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Management of medically resistant partial epilepsy would be greatly assisted by a reliable and practical seizure warning system capable of alerting patients prior to seizures. Such a system requires successful identification and classification of a preictal, or seizure-prone state adequately in advance of a seizure to allow the patient to adjust activities or medication. This abstract reports successful identification of preictal states in continuous long-duration intracranial electroencephalographic (iEEG) recordings of dogs (1 deceased, 4 living) with naturally occurring epilepsy using a support vector machine (SVM) algorithm. The five dogs studied were implanted with a 16-channel mobile iEEG recording device with average channel reference for a mean (st. dev.) of 380.4 (87.5) days producing 220.2 (104.1) days of intracranial EEG recorded at 400 Hz for analysis. The iEEG records had mean (st. dev.) 51.6 (52.8) seizures identified, of which 35.8 (30.4) seizures were preceded by more than 4 hours of seizure-free data. Recorded iEEG data were stratified into 11 contiguous, non-overlapping frequency bands between 0.6 Hz and 154 Hz, and were Hilbert transformed to obtain amplitude and variance measures in one minute blocks. These measures, along with an accumulating time metric since the last seizure to account for periodicity, served as input features for the classifier. Performance of the SVM classifier was assessed using a 5-fold cross validation approach, where preictal training data were taken from 90 minute windows with a 5 minute preseizure offset, and interictal training data were taken from data segments more than 100 hours distant from any seizure and decimated by a factor of 40 to improve training speed. A 90 minute seizure warning was triggered if SVM classifications in a 90 minute lagging window exceeded a tunable threshold, and true positive detections were counted only if the seizure warning was active 5 minutes prior to a lead seizure. Results are significantly better than a random chance predictor ($p<0.05$) for all dogs studied, and this approach achieves clinically useful sensitivity (78.89% (13.35) of lead seizures) and specificity (30.57% (0.81) time in warning). Analysis of the optimal preictal training time was performed by repeating the cross validation over a range of preictal windows and comparing results.

Factors affecting early automated epileptic seizure detection for online evaluation

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Dümpelmann, Matthias, Epilepsy Center, University of Freiburg, Germany

Seizure detection is increasingly discussed as a basis for closed-loop neuromodulation systems in the treatment of epilepsy. Whereas a number of algorithms have claimed high sensitivity, the tradeoff regarding latency until detection, specificity, and computational demand poses problems for polymorphic patterns in long-term EEG recordings.

We will report a comparison of computationally simple seizure detection algorithms applied on intracranial recordings from the European EEG database in the framework of the cluster of excellence BrainLinks-Braintooks. Analyses performed a total of 3633 hours of continuous intracranial EEG from 18 patients will compare latencies until detection in a pseudo-online analysis. The aim to early identify electrographic seizure patterns at a low computational demand poses limitations on bandwidth, channel numbers to be analyzed, and referential baseline periods.

We will show that depending on seizure morphology, more complex algorithms my outperform simple measures. Patient-specific selection of seizure onset channels for online analysis can decrease computational demands, but poses limitations to both, sensitivity and specificity. This is based on analyses using energy, linelength, maximum, minimum, mean, median, variance, mobility, complexity, mobility/complexity, number of inflexions, number of zero-crossings and number of zero-crossings of the first derivative.

On-demand optogenetics for temporal lobe seizure control

Speaker: Krook-Magnuson, Esther, UC Irvine
Caren Armstrong
Mikko Oijala
Ivan Soltesz

Through the selective expression of light-sensitive proteins called opsins, optogenetics provides the opportunity to modulate specific cell-types at specific times. Optogenetics is therefore a powerful tool to study mechanisms in epilepsy, and potentially provide new therapeutic approaches. Temporal lobe epilepsy is the most common form of epilepsy in adults. In over 40% of patients, seizures are not controlled with current treatment

options and current treatment options can have major negative side effects. Because temporal lobe seizures tend to arise from discrete regions prior to overt clinical behavior, it may be possible to design a treatment option which would overcome these problems by providing temporal and spatial specificity. By combining optogenetic techniques with novel, tunable, custom-designed seizure detection software, we have demonstrated successful inhibition of spontaneous temporal lobe seizures in a mouse model of temporal lobe epilepsy through on-demand modulation of select cell populations in the hippocampus. Seizures were detected in real-time, early during seizures and prior to overt behavioral manifestations. Detection was tuned to the specific EEG signature for each chronically epileptic animal, and could utilize combinations of spike features, signal power, and frequency properties. Detected seizures triggered light delivery to the hippocampus and activated opsins. Strong and immediate inhibition of spontaneous seizures was achieved when the inhibitory opsin halorhodopsin was selectively expressed in excitatory principal cells (57±12% of seizures stopped within 1s of light delivery). Remarkably, an alternative approach which directly targeted less than 5% of neurons in the hippocampus also produced significant inhibition of seizures. Specifically, the excitatory opsin channelrhodopsin was targeted to interneurons expressing parvalbumin. Detecting seizures early, prior to overt behavioral manifestations, and providing on-demand optogenetic intervention reduced the frequency of seizures progressing to behavioral seizures (29.6% reduction in behavioral seizures, defined as minimally stage 3-4 on a modified Racine scale, with forelimb clonus plus rearing). These results demonstrate not only that spontaneous temporal lobe seizures can be detected and stopped, but also that this control can be achieved while directly affecting only specific cell populations in a spatially restricted manner. A clinical approach built on these principles (affecting a minimum number of cells and only at the time of a seizure) may overcome many of the side-effects of currently available treatment options. Future on-demand optogenetic studies will provide additional important insight into mechanisms of epilepsy and seizure control.

Funding: US National Institutes of Health grant NS074702 (to IS), the Epilepsy Foundation (to CA), and the George E. Hewitt Foundation for Medical Research (to EKM)

Towards a wireless, closed-loop optogenetic stimulator for seizure modulation

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A wireless, closed-looped device that delivers seizure suppression in vivo is an actively sought goal in the epilepsy community. Using optogenetic tools, promoter-specific neuronal modulation can be achieved. Excitatory drivers of seizures could be directly suppressed with inhibitory opsins or indirectly suppressed with excitatory opsins expressed in interneurons. Wireless technology would allow researchers to monitor large

cohorts of animals in parallel without a tethered artifact. We aim to design and implement a robust and programmable wireless, closed-loop stimulator. To achieve this, we first developed a wireless, deep-brain optogenetic stimulator (OGS). An LED acts as the light source and is controlled by a microcontroller (MCU) and a constant current driver. Greater than 30 mW/mm2 are produced with 64 mW input power. The MCU allows user defined stimulation protocols power management. During periods of no stimulation, the device consumes < 26 uWs. We validated the OGS in vivo with a 3-chamber conditioned place aversion (CPA) behavioral paradigm. We generated mice expressing ChR2-H134R and tdTomato in interneurons under the control of Gad2-cre. Optical fibers were targeted at the right ventral tegemental area (VTA) to activate interneurons suppressing dopamine release. Results show a significant decrease in place preference for mice treated with sufficient stimulation. For applications in epilepsy, a seizure event triggers the stimulation. We are actively developing an FPGA based single channel recording system that will be expandable for multichannel data collection. Seizure detection is provided by a previously published custom application specific integrated circuit (ASIC) and is used to trigger the MCU for stimulation and data transmission. Integration of the OGS, recording system, and seizure detection ASIC into a singular device for animal studies is pursued.

A Standardized Dosing System for Vagus Nerve Stimulation Therapy

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Vagus nerve stimulation (VNS) is an effective treatment alternative for many epileptic and depressed patients whose symptoms are not well managed with pharmaceutical therapy. In all nerve stimulation-based therapies, the therapeutic effects are mediated by neural activation or inhibition in response to stimulation, not necessarily by the parameters of stimulation. The fixed stimulus paradigm in use today is therefore suboptimal due to inter-patient response variability at the nerve-electrode interface and the intra-patient risk of acclimating to an unchanging stimulus. Real-time feedback control of nerve activation is necessary to improve efficacy and reduce side effects, as this will allow for a dosing system based on the biological conduits of the therapy: The type, proportion and pattern of nerve fiber activation.

We present Autonomous Neural Control (ANC), a nerve activation control system designed to eliminate patient response variability and adverse effects of the foreign-body response at the device-tissue interface. ANC personalizes the electrical stimulus to each patient, nerve, neuron type and disorder. In rats, ANC rapidly learns how to most efficiently activate any proportion of vagal A, B, and/or C fibers over time. It provides a new dosing mechanism based on neural activation – the biological conduit of the therapy – rather than the strength of a stimulus, which has variable effects across patients. In real time, evoked compound nerve action potential (CAP) responses are systematically decoded and used to construct a patient-specific Nerve Activation Profile (NAP), which describes how each neuron population in the nerve will respond to any strength of stimulation. As VNS therapy is provided, ANC continuously refines the NAP to improve its prediction accuracy and adapt to circadian, drug-induced, or immune-mediated changes at the device-tissue interface.

For investigators, ANC can be used to design and perform experiments that systematically delineate the therapeutic and non-therapeutic mechanisms of VNS. Furthermore, suspected or known biological markers of treatment response can be measured and classified with respect to the NAP, simplifying the development of fully-personalized, closed-loop control systems for epilepsy and depression. For physicians, ANC will 1) establish an objective, standardized dosing system based on the level of nerve/neuron activation (expressed as a % of maximal nerve/neuron activation), 2) eliminate the complicated, time-consuming stimulus parameter tuning process, 3) provide a simple mechanism to adjust the relative ratios of A, B and C fiber activation, and 4) ensure that therapeutic nerve/neuron activation is maintained over time. For patients, ANC will 1) enhance the overall quality of VNS therapy, 2) reduce the number of doctor visits, and 3) help extend device lifetime by reducing energy waste from excessive stimulation.

Assessment of excitability in neuronal populations based on selective activation of interneurons

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GABAergic interneurons are crucial in maintaining stable levels of activity in the brain. Impaired interneuron function is implicated in diverse pathological states, including fragile X syndrome, autism spectrum disorder, Down syndrome, schizophrenia, affective disorders, and epilepsy. Impaired GABAergic inhibition can result from a decrease of GABAA receptor density, a shift in the chloride reversal potential toward more positive values, a decrease in synapse number, or even selective cell death of interneurons. In the epileptic brain, abnormal behavior of interneurons contributes to both interictal and ictal activities. Inadequate inhibitory tone promotes the propagation of focal ictal discharges across the cortex. A simple method allowing the selective assessment of inhibitory synaptic function within healthy or pathological brain tissue would therefore be very useful for clinicians treating patients with these disorders.

Electrical bipolar stimulation with depth-EEG electrodes is routinely used during pre-surgical evaluation of drug-resistant epileptic patients. We have recently developed a new stimulation paradigm consisting of bipolar supra-threshold low-frequency pulses, which was optimized using a translational approach combining computational modeling, patch clamp/field recordings in brain slices, and field recordings in vivo.

First, we reproduced and analyzed the effects of stimulation with a lumped-parameter computational model. Then, we validated the results and predictions from the model with patch-clamp recordings obtained from pyramidal cells and putative interneurons in

organotypic hippocampal slices, and in vivo in a mouse model of epilepsy (kainate injected into the hippocampus). We found that direct bipolar stimulation can selectively evoke GABAergic inhibitory post-synaptic potentials (IPSPs) in pyramidal cells if the stimulation intensity is appropriately tuned, i.e. just above the excitability threshold. The optimal stimulation frequency was around 8 Hz. This protocol leads to the selective emergence of interneuron responses in both healthy and pathological brain tissue.

We propose that this approach could be implemented to quantify excitability in neuronal networks to distinguish between healthy and epileptogenic brain areas in humans. A clinical study is now being conducted to evaluate this method in epileptic patients undergoing pre-surgical evaluation at the University Hospital of Rennes.

Macro- vs micro-level synchronization in the epileptic hippocampus: imaging in vitro and in vivo

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Epilepsy is characterized by synchronous network activity in the form of both interictal events and seizures. While these macro-level events are often studied using electrophysiological approaches such as EEG and LFP, less is understood about the micro-level dynamics of how spatially distributed cells contribute to this large-scale activity. I will present data obtained from both in vitro and in vivo two-photon calcium imaging of the simultaneous activity of individual neurons from chronically epileptic mice. In both cases, we observe a highly variable pattern of cell participation during interictal-like activity. In vitro imaging of epileptic slices reveals that, during interictal-like events, dentate granule cells are organized into functional clusters whose varying co-activation comprises the overall network events. Additionally, in vivo imaging of the CA1 region shows that during spontaneous interictal spiking, interneurons play a large role, again displaying a diverse and variable pattern of activation.

Tracking Neural Dynamics: A Method to Elucidate Mechanisms Involved in Seizure Generation and Termination

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Epilepsy is a debilitating disorder that affects approximately 1% of the world's populace. To date, the mechanisms behind the generation of seizures are not fully understood. We discuss a model-based approach to provide further insights into physiological changes occurring in the brain prior to and during seizures. In particular, we show that a neural mass model can be fit to data using an unscented Kalman filter, and that this procedure can be used to observe physiological changes in recorded EEG that are not elucidated by standard EEG evaluation techniques. To demonstrate this method, we have used an in vivo model of focal temporal lobe epilepsy, where tetanus toxin is injected into the rat hippocampus. Two depth electrodes are inserted into the hippocampus to record local field potentials, which are used as the observations for the estimation procedure. We make use of a neural mass model (Wendling et al. 2002) that has been shown to provide a good phenomenological description of hippocampal EEG.

Preliminary results from the estimation of 10 seizures from two different animals demonstrate decreases in the excitatory and slow inhibitory synaptic gains at the transition from background to seizures. Furthermore, the fast inhibitory synaptic gain increases at the transition to seizure. The results also demonstrate an increase in the excitatory synaptic gain at seizure termination, while both inhibitory synaptic gains remain constant. The estimation results showed that the mean of the input firing rate increases at seizure onset, and remains constant post-ictal.

In this tetanus toxin model of temporal lobe epilepsy, the similarity in estimation results across different animals and different seizures indicates that seizures could lead to a depression in both excitatory and slow inhibitory mechanisms (in this neural mass model), while peri-somatic, or fast inhibitory populations, are hyper-active. Considering these results, this method might allow for improvements in EEG evaluation techniques, and provide insights into mechanisms involved in both seizure initiation and termination.

Reference: Wendling, F., Bartolomei, F., Bellanger, J., and Chauvel, P. (2002). Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. European Journal of Neuroscience, 15(9):1499–1508.

Cellular and synaptic rules of hippocampal high-frequency ripples in temporal lobe epilepsy

Speaker: Menendez de la Prida, Liset, Instituto Cajal CSIC, Madrid, Spain

Transient high-frequency ripples (250–800 Hz) are recorded locally from the epileptogenic regions of the hippocampus and the temporal cortex of epileptic humans and rodents and at larger neuronal territories in the epileptogenic neocortex. High-frequency ripples have particular clinical significance due to their association with the onset of seizures and with interictal events. Here, I will discuss on our recent data aimed to identify the rules governing high-frequency ripple dynamics in the epileptic hippocampus. We will examine different TLE animal models and human data obtained with a combination of techniques including multi-site recordings and single-cell electrophysiology. We will mainly focus on the diverse sources of extracellular signals and the contribution of different neuronal actors to this rhythmopathy.

Analysis of single unit firing patterns preceding human seizures

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Information processing in cortical networks is likely to arise from dynamical shifts in the balance between inhibitory and excitatory neuronal firing. Similar dynamic interplays are also likely to both underlie ictogenesis and be of critical importance in regulating the spread of pathological activity once seizures have started. These dynamics are, however, poorly understood.

To understand whether there are characteristic trajectories into seizures, we therefore analyzed the spiking patterns of single units recorded using multielectrode arrays (MEAs) implanted close to the ictal focus in 4 human patients prior to epilepsy surgery. This MEA data was band pass filtered between 300 and 3000 Hz, from which spike events were extracted using a dynamic threshold based on the standard deviation of the signal. Key characteristics were extracted from each spike, with the inspection of minimum and maximum amplitudes versus spike duration, to yield distinct putative single unit clusters. These clusters created characteristic and distinct distributions for individual electrodes, which were highly reproducible in separate time epochs, indicative of stable single units recorded over prolonged periods (>24 hours) using MEAs in humans. Notably, though, the distributions of spike shapes were altered dramatically when the local territory was recruited to the seizure.

Previous analyses of spiking patterns in animals suggest that interneurons and pyramidal cells may be separated by their spike shape, but also, more accurately, by characteristic temporal spiking patterns (Csicsvari et al, Neuron 1998). Following these analyses, we analyzed single units recorded from baseline (non-ictal) activity using the spike kinetics, their firing rates, and the median lag of the autocorrelation of their spike timings, in order to segregate putative pyramidal cells and interneurons. This cluster analysis was then used to examine the activity of these same cells in the immediate period preceding seizure recruitment; a period which corresponds to the time when the MEA is within the penumbral territory, prior to being incorporated into the ictal core territory (Schevon et al, Nat. Commun. 2012). We will present our analyses of the activity profiles of different identified neurons prior to seizure onset.

Sixth International Workshop on Seizure Prediction

IWSP6

Poster Session

Bahia Resort Hotel
San Diego, California
Mission Bay Ballroom A
November 6, 2013 – 7:00 to 9:30 p.m.

Poster Session Judges

Anatol Bragin *(University of California, Los Angeles, CA US)*

David Grayden *(University of Melbourne, Melbourne, Australia)*

Levin Kuhlmann *(University of Melbourne, Melbourne, Australia)*

Steven Schiff *(Pennsylvania State University, University Park, PA US)*

Andreas Schulze-Bonhage *(University Hospital of Freiburg, Freiburg, Germany)*

Gregory Worrell *(Mayo Clinic, Rochester, MN US)*

Hitten Zaveri *(Yale University, New Haven, CT US)*

Poster Abstracts

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Seizure Detection and Prediction

1. A case study demonstrating the pitfalls during evaluation of a predictive seizure detector

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Introduction: Epilepsy is a neurological disorder characterized by recurring epileptic seizures that can occur at any given time. A system predicting these seizures could give a patient sufficient time to bring himself to safety and to apply a fast-working anti-epileptic treatment to suppress the upcoming seizure. Many seizure detection techniques claim to be able to detect seizures before the marked seizure onset on the EEG. In this work we study the predictions of such a seizure detection system.

Materials: For the experiments the MIT Scalp EEG dataset was used, which contains at least 20 hours of EEG and 3 seizures for 24 pediatric patients [1].

Methods: The data is preprocessed using a filter-bank of 8 Butterworth filters of 3 Hz wide between 0.5 and 24.5 Hz [1]. Next the energy is determined for windows of 2 seconds wide with 1 second overlap. This data is presented as input for the machine learning component based on Reservoir Computing (RC) [1]. RC uses a randomly created recurrent artificial neural network, the reservoir, to map the input to a higher dimensional space. The system is trained using a linear readout of the reservoir. After this readout a simple thresholding technique is applied for classification [1].

Experiments and results: For each patient, the system is trained on the data of the 23 other patients. During training, the 2 minutes of EEG prior or following a seizure is not used. Next the system is evaluated on the data of the considered patient. Detections which occurred 10 minutes before the marked seizure onset were considered as true positives. This resulted in a system that was able to detect 75% of the seizures with about 6 false positives per correctly detected seizure. For 11 out of 24 patients some seizures were detected before the marked seizure onset. Furthermore, in 4 of these patients at least half of the seizures were detected before the marked onset, and in a single patient all seizures were detected before the marked onset.

Discussion: However, in retrospect, 65% of the early detections are caused by EEG artifacts. Most others can be attributed to inter-ictal spike and wave discharges in the EEG preceding the seizure. Only 3% of the early detections have currently an unknown cause and could be actual early detections. Although nearly all early detections can be considered as false positives. However such false positives have a significantly greater occurrence right before marked seizure onsets, but further research is needed to analyze the cause of this correlation. It might be that these artifacts contain predictive information or for example that the selection criteria for adding EEG sections to the dataset were less strict for EEG sections containing a seizure. These pitfalls call for common guidelines and datasets to evaluate early seizure detection methods.

References: [1] Buteneers, P. (2012). Detection of epileptic seizures: the reservoir computing approach (Doctoral dissertation, Ghent University).

2. An analysis of temporal separability of spectral power features in the FSPEEG database

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The purpose of this study is to explore our hypothesis that the separability of Kalman filtered classifier confidences from nine spectral power features/channel in rest and 30 minute pre-seizure periods of the FSPEEG database is due, not to the presence of a desired underlying pre-seizure state, but rather to temporal separation between data files. After replicating the results presented by Park et. al. [1], we observed an inverse relationship between false alarm rate and minimum time between pre-seizure and rest data. In order to determine the effect of temporal separation on the discriminability of features, we established a two-step test that focused only on discontinuous rest files within the database. Six patients had seizures at short time intervals, preventing Friedburg practitioners from obtaining continuous 24 hr measurements of rest data as desired. For these patients, rest data surrounding seizures were provided in temporally separate blocks of data. Since seizure files occurred between rest files, the time gaps between rest files were greater than the time gaps between rest and seizure files. In the first step of our test, for each of these patients, we naively labeled N-1 of N rest files as H0 and one rest file as H1, where N is the number of rest files for a given patient. Using N-fold cross validation, we show that classification, using methodology similar to that in [1], obtains higher sensitivity and specificity for rest file prediction than it does for rest vs. pre-seizure state prediction. The high discriminability between rest files provides strong evidence for our hypothesis.

Park alluded to the poor generalization of a spectral feature-based classifier when features from rest periods within the seizure files were included in the H0 observation pool. We provided further evidence for this conclusion by comparing the area under Receiver Operating Characteristic (ROC) curves for two conditions: one in which filtered classifier confidences from rest periods within seizure files were included in the H0 observation pool and one in which only features from separate rest files were included in H0. The area under the curve (AUC) resulting from including both types of rest features was substantially lower than the AUC resulting from limiting H0 to include features from separate rest files alone. This result lends credence to our hypothesis that prediction algorithms, as used in this study, exploit a temporal difference, rather than a state difference to distinguish between pre-seizure and rest features. While these results suggest that the prediction algorithm as implemented may not provide a robust method of online seizure prediction, potential improvements from modifying the normalization and cross-validation methods, and modeling the impact of time on the H0 and H1 features will be discussed.

References [1]Y. Park, L. Luo, K. K. Parhi, and T. Netoff, “Seizure prediction with spectral power of EEG using cost-sensitive support vector machines.,” Epilepsia, vol. 52, no. 10, pp. 1761–70, Oct. 2011.

3. Assessing seizure susceptibility using visual psychophysical tests

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There would be great benefits arising from a non-invasive assay of seizure risk. This may help monitor disease progression in people with epilepsy, and could also help lifestyle management by alleviating the inherent unpredictability of seizures. One theory suggests that the timing of seizures reflects fluctuations in the quality of cortical inhibition, which may be assayed using visual psychophysics tests. Some support for this view comes from similar studies showing

altered visual psychophysics performance in various neurological conditions, including schizophrenia (Tadin et al. J.Neurosci, 2006), autism (Koldewyn et al. Brain, 2010) and major depression (Golomb et al., J.Neurosci., 2009). We therefore investigated the possibility of measuring a person`s cortical inhibitory restraint by comparing assays of visual surround suppression, in subjects with epilepsy and in control subjects.

We have currently recruited 135 volunteer control subjects with no history of neurological disorder and 26 patients with a clinically confirmed diagnosis of epilepsy. The control subjects ranged in age from 17.3 to 69.0 (mean 37.4 +/- 16.0years); patients range, 17.0 to 72.5, (mean 42.2 +/- 19.1 years). Some patients were tested soon after diagnosis before anti-epileptic medication was started. Others have long standing epilepsy, and medication was maintained. The duration of epilepsy ranged from a few months to 34 years.

The motion stimulus was a standard Gabor patch, a drifting vertical sine grating windowed by a Gaussian spatial envelope (MatLab, psychophysics toolbox). The duration of observing a patch was controlled by a temporal Gaussian envelope and was defined as 2 SDs of the temporal Gaussian. The spatial frequency was 1 cycle per degree and the speed was 2°/s. Observers discriminated the perceived direction by pressing right or left on a controller. The duration thresholds (82%) for distinguishing stimulus direction were assessed in each block of trials by three QUEST staircases. The stimulus duration was adjusted according to the performance of observers, gradually converging, over the course of 150 trials, on the threshold duration. Data were pooled by measuring the “surround suppression index, SSI”: log10 (threshold for large stimulus) – log10 (threshold for small stimulus). Regression analysis indicated a clear reduction in SSI with increasing age, in both control and patient groups. Based on the currently limited sampling, there is a small but non-significant difference between control and patient groups. New subjects continue to be recruited and we will present a more complete analysis at the meeting.

4. Cardiac-based Seizure Detection Algorithm

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Cyberonics has developed a cardiac-based seizure detection algorithm (CBSDA) intended for the detection of heart rate changes associated with epileptic seizures (ictal tachycardia). A review of the literature indicates that there is a high prevalence of ictal tachycardia among patients with epilepsy, with the percentage of patients experiencing seizure-related heart rate changes ranging from 33-100% (Marshall, Westmoreland et al. 1983, Blumhardt, Smith et al. 1986, Smith, Howell et al. 1989, Epstein, Sperling et al. 1992, Vaughn, Quint et al. 1996, Massetani, Strata et al. 1997, Nei, Ho et al. 2000, Wilder-Smith and Lim 2001, Zijlmans, Flanagan et al. 2002, Mayer, Benninger et al. 2004, Rugg-Gunn, Simister et al. 2004, Kerem and Geva 2005, Oliveira, Gondim et al. 2007, Jeppesen, Beniczky et al. 2010, Moseley, Nickels et al. 2010, Işik, Ayabakan et al. 2012). Compared with electroencephalography (EEG), it is easier and more cost-effective to acquire and process electrocardiographic (ECG) signals, and thus ECG-based systems are generally easier to use, making cardiac-based seizure detection more practical to implement.

Cyberonics’ CBSDA is based on detection of ictal tachycardia events and utilizes ECG sensing and R-wave detection to calculate instantaneous heart rate. A short-window moving average applied to the instantaneous heart rate produces a foreground heart rate (or HRFG) and a long-window moving average produces a background heart rate (or HRBG), which are both obtained beat-by-beat. The relative heart rate—defined by HRFG/HRBG — is then calculated beat-by-beat and compared to a preset threshold. If the relative heart rate is greater than the threshold for a

certain period of time, a tachycardia event is detected and the CBSDA can trigger a responsive VNS stimulation.

Cyberonics' CBSDA has shown promising performance when tested against existing validation database of epilepsy monitoring unit (EMU) data from patients who exhibit heart rate increases associated with their seizures. A device implemented with the CBSDA is currently undergoing testing in European and US clinical studies, NCT01325623 and NCT01846741, respectively. In the clinical application of the CBSDA where latency of detection is important, the sensitivity of seizure detection of the CBSDA has been shown to be as high as 98% for seizures associated with a HR increase of at least 55% or 35bpm and exhibiting an ictal heart rate greater than or equal to 100bpm. Cardiac based seizure detection coupled to the VNS Therapy System shows promise as a closed-loop system, and as a means of automatically triggering VNS stimulation.

5. Detecting preseizure state in intracranial EEG data using diffusion kernels

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Rationale: We studied the variability of the statistics of the icEEG data of patients with epilepsy over time to distinguish between different states of a patient. In icEEG data, we assume that the measurements are controlled by underlying processes that represent brain activity. We would like to recover these underlying brain processes to distinguish different brain states, such as interictal and preseizure states. Diffusion mapping, which is one of the leading manifold learning methods, provides dimensionality reduction of the data as well as pattern recognition that can be used to distinguish different states of a patient. Since diffusion mapping may detect abnormal behavior in the data, it can be used to determine changes in brain states. However, diffusion maps assume access to the underlying process that it aims to reveal. In icEEG data, the relationship between samples of the data and the underlying activity may be stochastic, and the data are assumed to be noisy. Hence diffusion mapping is not the most suitable approach to use with our icEEG data. A new algorithm, which is an adaptation of diffusion maps, may be more applicable in our case and is developed to construct coordinates that generate efficient geometric representations of the complex structures in the icEEG data. The new algorithm assumes a stochastic mapping between the underlying processes and the measurements; the mapping is inverted and a kernel is used to recover the underlying activity. Furthermore, the combination of local covariance matrices and the Mahalanobis distance in the algorithm is used to remove the noise from the data to extract the underlying brain activity.

Methods: icEEG data were collected from a patient with localization related epilepsy who was undergoing presurgical evaluation at the Yale-New Haven Hospital. The seizure onset area was located on the right occipital lobe. We focus on the 3 electrode contacts that overlaid the seizure onset area and use our algorithm to distinguish interictal and preseizure states from 6 icEEG epochs, each of which corresponds to a seizure experienced by the patient over the course of the icEEG monitoring.

Results: Numerical results show that the proposed approach provides a distinction between interictal and preseizure states by constructing a mapping that separates data along these two classes. Once we have learned the mapping, it can quickly be applied to new data for classification in real time.

Conclusions: Based on the variability of the statistics of the data, we were able to show a distinction between interictal and preseizure states. The combination of the local statistics and the Mahalanobis distance is shown to be beneficial for such noisy data. Our goal is to define a

threshold that separates the interictal state from the preseizure state in a wide range of cases and develop an automatic method to predict seizures.

6. Early Detection of Human Focal Seizures Based on Neocortical Microelectrode-Array LFPs

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A robust early seizure detection approach could improve significantly the autonomy and quality of life of people suffering from pharmacologically intractable epilepsy. Despite promising approaches based on scalp electroencephalogram (EEG) and intracranial electroencephalogram (iEEG) signals, the reliability of early seizure detection algorithms still remains an important issue. Here, we provide preliminary analyses of a new approach based on local field potentials (LFPs) recorded from a 96-microelectrode array (96-MEA; 4x4-mm2 platform; Blackrock Microsystems, Salt Lake City, UT USA) implanted in the neocortex of a person with focal epilepsy. The examined framework consists of: (1) sampling of broadband LFPs (0.3 Hz – 7.5 kHz, sampled at 30 kHz); (2) LFP preprocessing with Kalman-filter denoising and artifact removal; (3) spectral power estimation in patient-specific frequency bands in 1-sec moving time windows; (4) extraction of statistical features across MEA channels: mean, variance and Fano factor of spectral power calculated in each of the frequency bands; and (5) binary classification of interictal and ictal spectral features with cost-sensitive support vector machines (SVMs) in a leave-one-seizure-out cross-validation scheme. In this preliminary report, we tested the framework on a total of 169-min interictal segments and 4 seizure events from one participant. The participant was 52 years old female with complex partial seizures. The 96-MEA was implanted in the left temporal middle gyrus and standard electrocorticogram (ECoG) grid recordings were simultaneously performed. Seizure onsets were determined based on ECoG visual inspection and video monitoring. In this participant, spectral power in 0.3-10 Hz, 20-55 Hz, and 125-250 Hz frequency bands changed significantly between interictal and ictal periods. These three frequency bands were selected for early seizure detection. In the evaluation of the framework's performance, we considered both event-wise and sample-wise early detection. In the event-wise, where a full time segment containing a seizure occurrence is considered as one single event, the framework showed 100% sensitivity (4/4) and one approximately 20-sec-long false positive (likely an ECoG-detectable subclinical seizure event according to a follow-up visual inspection). The detection latency was 4.35 ± 2.21 sec (mean ± std). In the sample-wise analysis, where a feature in a single 1-sec time window was classified as an interictal or ictal event, the framework achieved a sensitivity of 93.8% and specificity of 99.8%. These results did not involve any postprocessing of SVM outputs, which could further improve the detection performance. These preliminary analyses indicate that LFPs recorded from neocortical MEAs may carry important information for reliable early detection of human epileptic seizures.

7. Eigenvalue based EEG signal analysis for seizure prediction

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Several studies of signal prediction methods in seizure prediction have shown that a prediction of EEG signals not only leads to a surprisingly low prediction error but also that the prediction error may be used as a feature for seizure prediction [1]. Further investigations suggested that the EEG-signal is dominated by strong linear signal components. Therefore, it can be useful to apply a Principal Component Analysis (PCA) to the signals in order to study signal signal components with lower eigenvalues.
PCA has been applied to signals both in frequency and time domain and is widely used as a preprocessing step for dimension reduction of the signal space [2]. In this contribution, nonlinear prediction of PCA components will be addressed.
Cellular Neural Networks (CNN) were introduced by Chua and Yang in 1988 and have been considered for the feature extraction problem within the seizure prediction research community. Due to their inherently massive parallel processing power they form an attractive basis for the realization of a miniaturized seizure warning device. Here, we propose a new feature extraction method in order to analyze different PCA components with regard to seizure precursor detection.
First, PCA is applied to multichannel recordings of several patients and then a CNN based signal prediction algorithm is carried out taking into account different polynomial orders of the coupling weights. Results obtained so far indicate that the proposed method might not only be able to improve existing seizure prediction features but also be used to identify nonlinear components of the EEG signal otherwise hidden by strong linear signal effects. In particular, our new findings may explain prediction results for EEG recordings in previous investigations.

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8. Fast and robust offline epileptic seizure detection using Rossler oscillators

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We present a novel seizure detection method for efficient and robust offline detection of epileptic seizures. Our method results in high sensitivity and a low false positive rate, while being computationally efficient. We propose a multivariate synchronization measure that is derived from the dynamics of a network of coupled Rossler oscillators. The network receives input from the EEG channels of the standard 10/20 EEG system. In addition, we use the fraction of signal energy in the 2-25 Hz range to improve the robustness of our detector to EEG artifacts. Signal pre-processing was performed using simple schemes such as filtering and scaling. The extracted measures are used to train an approximate extreme points support vector machine (AESVM), a computationally efficient classification algorithm. By virtue of the low-dimensional nature of the proposed multivariate measure, the computational requirements for training AESVM and using it for offline seizure detection are minimized. We used the extensive CHB-MIT public database of pediatric EEG in our experiments to validate our method. Upon performing leave-one-record-out cross validation, our method resulted in an exemplary seizure detection performance of 100% sensitivity and a false positive rate less than 3 per 24 hours.

9. Identification of pre-ictal states based on an EEG-ECG multi-feature clustering approach

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Different seizure prediction methods have suggested the existence of a pre-ictal state or a time-interval preceding the seizure onset; in this interval the seizure occurrence probability is higher than during other inter-ictal state. Although non-linear and statistical methods utilize a threshold-based strategy to differentiate inter-ictal from pre-ictal periods, others have adopted a machine-learning strategy based on a prior selection of inter-ictal and pre-ictal states. In general, most of the existing methods need to stablish, for their operation, different a priori assumptions about the time periods that will be tagged as inter-ictal or pre-ictal states, not always corroborating if a basic difference exists between them. For this reason, we analyzed if time epochs preceding seizures tend to spontaneously differentiate between them into inter-ictal epochs and those that are close in time to seizures (pre-ictal ones), without making any assumptions about their time distribution related to the seizure onset. For that, we applied several clustering methods, particularly hierarchical top-down and bottom-up, k-means and spectral clustering, to investigate if several measurements taking from physiological electroencephalogram (EEG) and electrocardiogram (ECG) data can be grouped into different epileptic states. Thus, we analyzed 50 seizures selected from 10 epileptic patients recorded with intracranial (iEEG) and scalp EEG as well as ECG, following an invasive brain exploration related to their epilepsy. We selected only seizures preceded of at least 8 hours of inter-ictal activity (seizure-free activity) and calculated different features for all of the 3-seconds, non-overlapping sliding windows belonging to the 8-hours inter-ictal state prior to the seizure onset. All seizures were annotated by experts. Beside classical features in time and spectral spaces, we included some relatively new reported ones such as slow-phase-fast-amplitude modulation and high frequency activities that have been investigated in different physiological and pathological contexts and in particular in epilepsy. In total, we computed 64 and 12 features for each EEG and ECG channel respectively. Through different testing strategies, including for instance the use of only electrodes associated with the seizure onset or selected EEG electrodes plus ECG ones, we could identify, particularly for the hierarchical top-down algorithm with a deep of 20 clustering levels, that samples can be differentiated in two main temporal windows associated with inter-ictal and pre-ictal states. It was found that, for some patients, the time interval previous to seizure lasts up to 4 hours. Some clusters however grouped a few number of samples (~ 10%) that were distributed without presenting a consistent evolution in time and that could be related to a high presence of artifacts or non-specific epileptic activity. In conclusion, our study shows that inter-ictal states can be spontaneously differentiated from pre-ictal ones through different clustering algorithms based on a multi-feature strategy calculated from iEEG, EEG and ECG data.

10. New modified Heart Rate Variability analyses as detector of epileptic seizures

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Tachycardia is often seen during epileptic seizures, but it is also a characteristic result of physical exercise. In order to uncover if focal epileptic seizures can be detected by short term moving window Heart Rate Variability (HRV) analysis, we modified the geometric HRV method, Lorenzplot, to consist of only 50 R-R intervals pr. analyzed window. From each window we calculated the Cardiac Sympathetic Index (CSI) and compared the maximum CSI of the patient's epileptic seizures with that of the patient's own exercise and non-seizure sessions as control. The 11 patients analyzed all had complex partial seizures (CPS) (30 temporal, 1 frontal) during their 1-5 days Video/EEG long term monitoring. All CPS with electroencephalographic correlation were selected for the HRV analysis. The CSI was correspondently calculated after each heart beat depicting the prior 50 R-R intervals at the time. CSI showed a higher maximum peak during seizures than exercise/non-seizure (103-256%) for 7 of 11 patients within 2 seconds before till 86 seconds after seizure onset time even though exercise maximum HR exceeded that of the seizures. The 7 patients with higher CSI maximum during seizures vs. exercise/non-seizure had a tendency of higher maximum HR during seizures than the remaining 4 patients. The results indicate a sudden and inordinate sympathetic shift in the sympathovagal balance of the autonomic nervous system just around seizure-onset for certain patients. This new modified moving window Lorenzplot-method seems promising as an easy and inexpensive way of constructing a portable ECG-based epilepsy alarm for certain patients with epilepsy who needs aid during seizure.

11. Noise and stimulus-induced leading indicators of state transitions

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When a dynamical system approaches a state transition, the system loses resilience, and critically slowed temporal and spatial patterns can appear. These patterns can be observed in single-neuron and neural population models. Here we examine a simplified mean-field model of cortex, and demonstrate critical fluctuations prior to four distinct classes of bifurcation, including (a) saddle-node, (b) Hopf, (c) Turing, and (d) Turing-Hopf interactions.

Our model is a Wilson-Cowan interlinked network of 1500 excitatory (E) and 1500 inhibitory (I) neurons, forming a 3mm-length 1D rod. Neurons have all-to-all connections, with synaptic weights being exponentially-decaying functions of distance. External inputs to the cortical network (such as subcortical drive, gap-junction mediated currents and any applied stimulus) are presented as control parameter P. We use linear stability analysis to extract the Jacobian matrix for the linearized system, locate steady states as a function of P, and identify the stability of the equilibria.

We find that the cortical rod supports up to three steady states. The midbranch is always an unstable saddle, and the bottom branch is always a stable node. These two states collide and annihilate via a saddle-node bifurcation, pushing the system to an alternative state on the upper branch. The upper branch consists of stable or unstable spiral points separated by a Hopf bifurcation. If the range of inhibitory connections is made longer than that for excitatory connections, spatial waves can form on the rod through a Turing mechanism.

By adjusting the external input to the E neurons and the synaptic range of inhibitory connections, we are able to sweep the system toward temporal (saddle-node, Hopf), spatial (Turing), and spatio-temporal (Turing-Hopf) instabilities without actually crossing the transition threshold. We study critical fluctuations in the firing rate of E neurons in response to white-noise or stepped excitatory stimulus. We use autocorrelation functions in time and space to quantify our analysis.
All four classes of bifurcation investigated here show clear evidence of critically-slowed fluctuations on close approach to state transition. Leading indicators show themselves in the form of prolonged correlation time and correlation distance, as well as a profound increase in fluctuation variance, regardless of the type of bifurcation.
If the transition from quiescent neural activity to active seizure can be described as a state transition, then we hypothesize that leading indicators in time and space should accompany the state of the neural system prior to this transition. As a model for cortical probing experiments, we also demonstrate spatio-temporal prolongation of excitatory firing rates in response to externally induced excitatory current before emergence of Turing patterns. Our results provide modelling support for experimental attempts to capture pre-seizure leading indicators.

12. Physiological Response to Stress: Analysis and Classification

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Motivation: Although most seizure detection and prediction research is focused on EEG analysis, the required monitoring is inconvenient for the patient and unsuitable for home use. Consequently, more effort is needed in the search for a set of physiological metrics that will lead to a comfortable, non-stigmatizing, wearable device capable of warning patient and caregiver of an imminent seizure.

Prior Work: To date, the major focus on extra-cranial physiological metrics has been to find one or two metrics that will detect a seizure. For example, I. Osorio and S. Schachter [1], looked at the effects of seizures on heart rate. They found that heart rate changes associated with seizures are much greater than those produced by typical physical stresses. Ming-Zher Poh [2] looked at the effects of seizures on electrodermal activity, temperature and movement. He found that EDA responses caused by generalized tonic-clonic seizures are much greater than those caused by typical cognitive, emotional, and physical stresses.

Key Vision: In order to recognize a physiological seizure/pre-seizure response, we must first know what non-seizure responses to various stresses look like. Consequently, we have designed a "Healthy Response to Stress" test in order to study our chosen metrics in non-seizure situations. The two goals of our test are to: 1)Determine clear patterns of what physiological changes (rate and magnitude) are created by typical physical, cognitive and emotional stresses so we will be able to differentiate them from seizure responses. 2)Demonstrate that the use of multiple metrics allows us to distinguish various types of stresses with higher reliability than the use of only one or two metrics (as in the Osorio and Poh studies). We have designed a system to monitor five metrics associated with seizures and detectable by a wrist worn device: heart rate, arterial oxygenation, electrodermal activity, temperature and wrist movement. Testing is being done using two wrist-worn sensors that measure our selected metrics.

Experimentation: Our "Healthy Response to Stress" test asks volunteers to alternately relax and perform three pre-designed tasks. During the four relaxation sessions the subject is asked to sit quietly and listen to soothing music. The objective of these sessions is to establish a baseline for the physiological metrics we are measuring. That way we can see how each metric changes during the three tasks and what the sensitivity and specificity of each metric is. Our preliminary

test results show physiological differences among the three types of stress. We are confident that once we have collected sufficient data to apply machine learning we will be able to distinguish the three types of stresses with a high degree of confidence, since the computer will be able to see patterns that are not obvious upon visual inspection. These results will, in turn, allow us to compare the response of these five metrics to seizure data to be collected in the near future. The results will allow us to use machine learning to recognize seizures in a patient worn device.

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13. Seizure Prediction using Ratio of Spectral Power from Single EEG Electrode

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This paper presents a novel approach to patient-specific seizure prediction based on a ratio of spectral power between two different bands. This ratio is then thresholded to predict a seizure. The threshold is chosen by a receiver operating characteristic (ROC) analysis. The algorithm when applied to scalp EEG data from 17 pediatric patients from the MIT database collected at Children's Hospital Boston [1] predicts 70/78 seizures from 17 patients, with an average false positive of 0.17/hour.

Seizure prediction, thought to be a difficult problem, is shown to have a surprisingly simple solution. While the predictability of seizures has already been established, predicting seizures in a computationally simple manner remains a difficult task. To this end, this paper shows that a single ratio of spectral power from a single electrode is a discriminatory feature, and can predict seizures with a sensitivity of about 90%. Thus, the algorithm only requires two filtering operations, a division, and a thresholding operation. This algorithm does not require any sophisticated classifiers such as support vector machine or Adaboost. In addition, only one electrode is analyzed as opposed many electrodes. The computation complexity of the algorithm is 2-3 orders of magnitude smaller than any known algorithm with similar sensitivity and false positive rate.

The seizure prediction horizon varies from patient to patient. For 13 out of 17 patients, the minimum prediction time ranges from 10 to 60 minutes, while the maximum prediction horizon ranges from 15 to 90 minutes. For the remaining 4 patients, the minimum prediction horizon ranges from 1 to 6 minutes, while the maximum prediction horizon ranges from 60 to 90 minutes.

Various ratios of spectral ratio were tried as features. The bands considered include theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), Gamma1 (30-47 Hz), Gamma2 (53-64 Hz), Gamma3 (64-97 Hz), and Gamma4 (103-128 Hz). The gamma band was divided to four bands. The maximum frequency content is 128 Hz, since the sample rate is 256 Hz. It is shown that the band power ratio between Gamma4 and the sum of the low frequency bands theta, alpha and beta seems to have the maximum predictability for most patients, although not for all. The spectral bands are selected in a patient-specific manner.

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14. State of Vigilance Based Seizure Prediction in the Tetanus Toxin Model of Temporal Lobe Epilepsy

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There is an established relationship between sleep and seizure states in animal and human models of epilepsy. Utilizing this relationship may lead to novel therapeutic options (Loddenkemper 2011). There has been a significant effort to develop seizure prediction algorithms both as a warning tool for patients (Cook 2013) and as part of closed-loop control systems. Although it has been noted that false-prediction rates follow a diurnal variation (Schelter 2006), the state of vigilance (SOV) has not been formally used as a seizure prediction feature. We therefore examined the likelihood of seizure onset as a function of SOV in the chronic tetanus toxin model of temporal lobe epilepsy.

We perform long-term ECoG, LFP and head acceleration recordings from adult rodents in the Tetanus Toxin (TeTX) model of spontaneous limbic epilepsy (Jefferys 1995). We use an automated system to accurately classify sleep-state (Sunderam 2007). We analyzed 28 days of recording from 9 rodents with 486 spontaneous seizures to investigate the likelihood of SOV prior to seizure onset. We used survival analysis to study the related distributions of state bout duration and transition probabilities. We developed a probabilistic prediction algorithm conditioned on SOV and compared its performance, using the Brier score (Jachan 2009), to the performance of an unconditioned predictor. We considered the prediction formalism presented in (Schelter 2006b), and optimized performance with respect to seizure prediction horizon and seizure onset period.

We found that a disproportionate number of seizures (46%) initiated in rapid-eye-movement (REM) sleep. In addition, we found that a notable fraction of seizures initiated in exploratory wake (34%), another state of vigilance characterized by hippocampal theta oscillations. Our simple SOV conditioned prediction algorithm outperformed the unconditioned predictor for self-trained and cross-trained testing schemes. However, the addition of time-of-day to the SOV conditioned predictor did not provide additional performance improvement. Using survival analysis, we found a significant difference between the duration of preseizure and interseizure REM bouts. Our findings are important for three reasons: First, they provide strong counter-evidence to the growing consensus that REM sleep is always anti-epileptic. Second, our survival analysis results provide support for the existence of a unique preseizure state in the TeTX model of TLE. Third, our methodology serves as a template for inclusion of SOV in experimental seizure prediction efforts.

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15. Statistical validation of forecast mechanisms

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Forecasts of extreme, but rare events, such as epileptic seizures, render interventions and precautions possible. In order to statistically validate the performance of a prediction system, the performance must be compared to the one of a predictor randomly raising alarms. We propose a statistical framework of validating both sensitivity and specificity of a prediction system, independently. Other than conventional methods, our method accounts for both an extended period, in which an event is expected to occur after a prediction, and an independent assessment of sensitivity and specificity.

16. Temporal Epilepsy Seizures Monitoring and Prediction using Cross-Correlation and Chaos Theory

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Temporal seizures due to Hippocampal origins are very common amongst epileptic patients. This article presents a novel seizure prediction approach employing Correlation and Chaos theory. The early identification of seizure signature allows for various preventive measures to be undertaken. EEG (Electro-Encephalography) signals are spectrally broken down into the following sub-bands: Delta, Theta, Alpha, Beta and Gamma. The proposed non-linear approach consists of observing a high correlation level between any pair of electrodes for the lower frequencies and a decrease in the Lyapunov index (chaos or entropy) for the higher frequencies. The PSD (Power Spectral Density) and statistical analysis tools were used to determine threshold levels for the lower frequencies. After studying all 5 sub-bands, the analysis has revealed that the seizure signature can be extracted from the Delta band and the high frequencies. High frequencies are defined as both the Gamma band and the ripples occurring within the 60Hz-120Hz sub-band. In order to validate the proposed approach, five patients from both sexes and various age groups with temporal epilepsies originating from the hippocampal area were studied using the Freiburg Database. An average seizure prediction of 26 minutes, a detection accuracy of 75%, and a false positive rate of 0% were accomplished throughout 164 hours of recording time.

Neural Models and Mechanisms

17. Assessment of excitability in neuronal populations based on selective activation of interneurons

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GABAergic interneurons are crucial in maintaining stable levels of activity in the brain. Impaired interneuron function is implicated in diverse pathological states, including fragile X syndrome, autism spectrum disorder, Down syndrome, schizophrenia, affective disorders, and epilepsy. Impaired GABAergic inhibition can result from a decrease of GABAA receptor density, a shift in the chloride reversal potential toward more positive values, a decrease in synapse number, or even selective cell death of interneurons. In the epileptic brain, abnormal behavior of interneurons contributes to both interictal and ictal activities. Inadequate inhibitory tone promotes the propagation of focal ictal discharges across the cortex. A simple method allowing the selective assessment of inhibitory synaptic function within healthy or pathological brain tissue would therefore be very useful for clinicians treating patients with these disorders.

Electrical bipolar stimulation with depth-EEG electrodes is routinely used during pre-surgical evaluation of drug-resistant epileptic patients. We have recently developed a new stimulation paradigm consisting of bipolar supra-threshold low-frequency pulses, which was optimized using a translational approach combining computational modeling, patch clamp/field recordings in brain slices, and field recordings in vivo.

First, we reproduced and analyzed the effects of stimulation with a lumped-parameter computational model. Then, we validated the results and predictions from the model with patch-clamp recordings obtained from pyramidal cells and putative interneurons in organotypic hippocampal slices, and in vivo in a mouse model of epilepsy (kainate injected into the hippocampus). We found that direct bipolar stimulation can selectively evoke GABAergic inhibitory post-synaptic potentials (IPSPs) in pyramidal cells if the stimulation intensity is appropriately tuned, i.e. just above the excitability threshold. The optimal stimulation frequency was around 8 Hz. This protocol leads to the selective emergence of interneuron responses in both healthy and pathological brain tissue.

We propose that this approach could be implemented to quantify excitability in neuronal networks to distinguish between healthy and epileptogenic brain areas in humans. A clinical study is now being conducted to evaluate this method in epileptic patients undergoing pre-surgical evaluation at the University Hospital of Rennes.

18. Characterization of in vitro human neocortical seizures

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The precise relationship between electrographic seizures recorded in vitro from animal models and those that spontaneously occur in humans remains ambiguous. Pharmacological convulsants and electrical stimulation precipitate ictal activity in in vitro animal models yet neither appears to

play a role in the generation of human seizures. Here we employ human neocortical brain slices excised during epilepsy surgery from a region distant from the seizure focus. We conducted electrophysiological recordings in the deep and superficial layers using either glass electrodes or microelectrode arrays.

We observe that in a subset of tissues undergoing physiological activation using low concentration Kainic Acid and Carbachol, spontaneous ictal events emerged. These ictal events differed from spontaneous oscillatory activity observed in the slices and allowed classification of activity using temporal and spectral features. We applied time-frequency and coherence analysis to characterize the spontaneous ictal events and their relationship to established pharmacological seizure models. This methodology can help to validate the efficacy of animal models to study human seizures.

19. Computational Model of Dravet syndrome

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Dravet syndrome (DS) is a rare pediatric epilepsy syndrome (incidence <1/40,000) characterized by hemi- or generalized (tonic-)clonic seizures appearing from the first year of life and often triggered by fever. SCN1A gene mutations (which encodes the voltage-gated sodium channel α1 subunit) have been found in about 85% children with DS. A mouse model of DS with SCN1A mutation has shown a selective failure of excitability of GABAergic interneurons resulting in epilepsy.

Conventional treatments have been disappointing. However, a newer antiepileptic drug, Stiripentol, used in association with the benzodiazepine clobazam, has produced a significant (though incomplete) reduction in seizure rate. This drug is known to increase the duration of GABAA receptors opening time and potentiate the antiepileptic action of clobazam.

We developed a physiology-based computational model in order to investigate some possible pathophysiological causes of DS. This model starts from the reproduction of typical EEG patterns recorded in DS patients and introduces a number of neurobiological hypotheses.

Methods: Advanced signal processing methods were used to quantitatively analyze EEG recordings of 5 patients with DS. A lumped-parameter approach lying at the level of cortical neuronal population was used to represent the generation of spontaneous EEG activity. The model includes one sub-population of pyramidal cells and two sub-populations of interacting interneurons: somatic-projecting interneurons (basket-like) with fast synaptic kinetics GABAA (fast, I1) and dendritic-projecting interneurons with slow synaptic kinetics GABAA (slow). Basket-like cells were interconnected to produce mutual inhibition (I1->I1). Parameters of the sigmoid function (representing the firing rate of interneurons) were adapted to mimic the genetic alteration found in DS.

In addition, the model accounts for a number of neurobiological hypotheses. First, we implemented the mechanism referred to as “depolarizing GABAA” mediated post-synaptic potential in the model, as a number of studies reported that the chloride reversal potential can switch from negative value to more positive value depending on interneuronal activity. Second, “shunting inhibition” promoted by GABAA receptor activation and slow astrocytic impact on neuronal population was also modeled. Finally, the dose dependent effect of Stiripentol on the generated field potential was also considered.

Results: Quantitative analysis of real EEG showed pronounced (1) slow delta wave on background activity (2) epileptic spikes (3) several electrophysiological patterns of seizure activity and (4) fast onset activity which was found in some patients’ EEG.
For fixed parameter configurations of the computational model, the slow increase of the proportion of depolarizing GABAA mediated IPSP (I1->I1 and I1->P) is sufficient to switch the activity from background to interictal epileptic spikes, to fast onset activity with decreasing frequency with time (shirp-like), seizure like activity and seizure termination. Different morphologies of interictal spikes and patterns of seizures observed in patients were reproduced in the model by tuning the amount of depolarizing GABAA postsynaptic potential. Finally, stiripentol by increasing the shunting inhibition reduced seizure-like activity in a dose dependent manner.

20. Estimating brain activity, state and connectivity changes using neural mass models and control theoretic methods

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Intracranial electroencephalography (iEEG) holds a significant place in quantifying important brain changes that are relevant for epileptic seizure detection, prediction and control; however, iEEG provides only limited measurements of the changes in brain activity, state and connectivity. Improved observation of these changes will lead to improvements in seizure detection, prediction and control. Here, a method for inferring underlying changes in brain activity, state and connectivity from limited EEG measurements is presented. In this method, neural mass models are considered as models of the iEEG, and an adaptive observer, an estimation algorithm derived using control theoretic concepts, reads in the simulated iEEG from the model (or in practice, real iEEG data) to estimate changes in the states (i.e. unmeasured variables) and parameters of the neural mass model. If the neural mass model is an adequate description of the brain regions considered, then when the adaptive observer is applied to real iEEG data, the inferences made about brain activity, state and connectivity changes should be accurate.

Specifically, here an adaptive observer is derived and applied to single and multiple inter-connected neural mass models in order to estimate the states and parameters of the neural mass models. The states represent the activity of different neural populations (e.g. excitatory and inhibitory), while the parameters reflect the brain state (e.g. interictal and ictal) and connectivity between different brain areas. The derived adaptive observer applies to a class of inter-connected neural mass models including the models of Stam et al. (1999) Clin. Neurophysiol. 110 1801–13 as well as Jansen and Rit (1995) Biol. Cybern. 73 357–66. Therefore the adaptive observer should have general applicability in several neuroscience problems. To demonstrate the efficacy of the adaptive observer, it is applied to simulated data of a neural mass model composed of two interconnected Jansen and Rit (1995) models. Simulations show that the

adaptive observer provides reliable estimates in the presence of iEEG measurement noise. Only a few frameworks, such as dynamic causal modelling, can estimate the states and parameters (including connectivity) of neural mass models. Contrary to dynamic causal modeling, our framework provides online state and parameter estimates with guaranteed convergence to the true states and parameters of the neural mass model. Future work will seek to apply the adaptive observer to real iEEG data to address the challenges of epileptic seizure detection, prediction and control.

21. Feasibility of Recovering Mesoscopic Neural Models from Electrophysiological Data

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This research describes a method for evaluating the feasibility of fitting neural mass models using Bayesian estimation methods to electrophysiological data. The method, namely the Bayesian Cramer-Rao bound [1], can also be used for benchmarking the statistical performance of estimation algorithms against the optimal, highlighting the opportunity for reducing uncertainty in the recovered models.

Mesoscopic mathematical models of the brain are becoming increasingly popular as tools for generating hypotheses on the physical principals that govern neurodynamics. Forward models have led to theory on the emergence of the brains rhythms, the mechanisms of anaesthetic agents, the brain's response to sensory stimuli, short-term memory formation, visual hallucinations and epileptic seizures. Most recently, advances in engineering methods and computing resources have expanded the utility of these models to estimate of system and parametric states that cannot be directly measured using electrophysiology. An established framework to reliably estimate physical properties underlying brain dynamics has the potential to revolutionise how we observe, diagnose, treat and cure neurological disorders. For example, in epilepsy the dynamics of hidden system and parametric states are thought to be highly patient-specific and unknown. Thus the ability to estimate these quantities will enable a greater understanding of individuals' pathologies, leading to more tailored therapies and better patient outcomes. Furthermore, subject-specific models will enable the application of control theory to the neurosciences, a technology traditionally limited to man-made systems.

The Bayesian Cramer-Rao bound [1] was used to examine the inherent uncertainty in neural mass models with varying complexity [2,3,4] and the expected performance of the extended Kalman filter (EKF) was assessed against this bound. Estimation performance was also evaluated and compared between different types of activity within models, alpha and seizure, and across different models of increasing complexity.

The results show that is the uncertainty bounds for three levels of vary complexity in the neural mass models are comparable, indicating that all models are feasible given a good estimation scheme. The results from extended Kalman filtering do not achieve these bounds, motivating the need to investigate alternative methods.

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22. From transient LFP events to hyperexcitability mechanisms in epileptogenic systems

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In partial epilepsies, two types of interictal transient events are commonly observed in depth-EEG signals or in local field potentials (LFPs).

One the one hand, sporadic epileptic spikes (ESs) consists in brief events characterized by a fast component (spike) followed by a more or less pronounced slower component of opposite polarity (wave). ESs have been extensively studied over the past decades.

On the other hand, high frequency oscillations (HFOs) have been also observed during interictal periods. HFOs in general and fast ripples (FRs, 250-500 Hz) in particluar have been a topic of increasing interest since the end of the nineties.

In order to relate these typical transient events to specific pathophysiological mechanisms occuring in epileptogenic neuronal systems, we have developed two computational modeling approaches.

The first approach is often referred to as the ‘detailed’ approach. It starts from the explicit representation of cells using multi-compartment neuron models which are then interconnected (via glutamatergic and GABAergic synapses) to form neural networks. Here, a forward problem must be solved to simulate a local field potential. Using this model, we found that FRs are generated by small clusters of hyperexcitable and slightly asynchronous bursting pyramidal cells. The origin of the hyperexcitability was found to be due to a moderate increase of glutamatergic conductances (AMPA and NMDA), to a slight decreased conductances associated with GABAergic currents, and to a shift of the GABA reversal potential toward more depolarized values. The low number of hyperexcitable neurons, the degree of synchronicity and the network topology (clustered) was found to be critical to produce FRs around 250 Hz and up to 500 Hz. Interestingly, experiments performed on hippocampal slices brought some elements of validation for computationally-generated hypotheses.

The second approach is macroscopic and is based on the description of the “average activity” of a population of neurons consisting of interconnected sub-populations of main cells and interneurons. Here, the model output reflects a local field potential that approximates the LFP as recorded by extracellular electrodes.

We used this approach to study the morphological changes occurring in ESs during epileptogenesis (defined as the progressive pathological process which leads to the chronic epileptic condition, after initial brain insult) in an in vivo experimental model of epilepsy (mouse, kainate). In brief, we developed signal processing methods to automatically detect and characterize ESs over long duration periods (30 days). We characterized the shape changes of these spikes as a function of time. The computational model was then used to explain actually observed changes. We first showed that realistic epileptic spikes could be simulated. We then identified some key parameters that impact the morphology of simulated epileptic spikes. Results

showed that hyperexcitability stems from the progressive diminution of GABAergic inhibition. This model-based hypothesis was experimentally verified, both in vivo and in an in vitro. Based on these results, we derived a novel electrophysiological marker which provides information about the progress of the disease from LFPs.

23. Improved clustering of spike patterns through video segmentation and motion analysis of micro Electrocorticographic data

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We have recently developed flexible, active, multiplexed recording devices for high resolution recording over large, clinically relevant areas in the brain. While this technology has enabled a much higher-resolution view of the electrical activity of the brain, the analytical methods to process, categorize and respond to the huge volumes of seizure data produced by these devices have not yet been developed.

This paper exams a series of new measurements of vivo animal seizure recording based automatic spike segmentation, feature extraction, unsupervised clustering algorithm and quantitative evaluation for spike segmentation and clustering. We found significant improvement in spike classification accuracy by examining not only the pattern of individual channel but also the spatial temporal pattern variation over all adjacent channels.

In this paper, we first applied advanced video analysis techniques (particularly region and motion analysis) for spike segmentation and feature extraction. Then we explored recent advances in machine learning for discovering useful features for clustering spike patterns and identifying natural clusters. After comparison base on evaluation matrices including Adjusted Random Index, Mutual Information Scores, we found the best combination of feature set and clustering algorithm to be applying Dirichlet Mixture Model on raw video segmentation correlation matrix.

The research is expected to yield new insights regarding how seizures initiate, progress and terminate, as well as subsequently significant improvement in seizure detection and prediction.

24. Interactive dynamics of HCN channels and α5βγ GABA-A receptors alters resonance properties of subicular pyramidal neurons

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GABA release from presynaptic nerve endings activates postsynaptic GABA-A receptors, which evoke transient phasic inhibitory postsynaptic currents (IPSCs) and non-inactivating inhibitory tonic current, mediated through extrasynaptic GABA-A receptors. These receptors are heteropentameric GABA-gated channels assembled from 19 possible subunits (α1-6, β1-3, γ1-3, δ, π, ρ1-3, θ, and ε). The 2 major subunits involved in tonic GABA-A currents in the hippocampus are α5 and δ subunits. Tonic GABA-A receptor mediated inhibitory current plays an important role in neuronal physiology as well as pathophysiology such as mood disorders, insomnia, epilepsy, autism spectrum disorders and schizophrenia. While the alterations of various electrical properties due to tonic inhibition have been studied in neurons from different regions, its influence on intrinsic subthreshold resonance in pyramidal excitatory neurons having hyperpolarization-activated cyclic nucleotide-gated (HCN) channels is not known. We explored different aspects of tonic inhibition in subiculum, which has been implicated in novelty detection, spatial navigation and several neurological disorders. In the present study, we show the involvement of α5βγ

GABA-A receptors in mediating picrotoxin sensitive tonic current in subicular pyramidal neurons using known pharmacological agents that target specific GABA-A receptor subunits. We further investigated the contribution of tonic conductance in regulating subthreshold electrophysiological properties using current clamp experiments. These experiments showed a significant decrease in input resistance, sag and resonance strength upon enhanced tonic inhibition. We verified these results with dynamic clamp experiments, where we modeled tonic current and observed its effect on subthreshold properties. Dynamic clamp studies with mathematical models of tonic inhibitory current and HCN current showed a concerted influence on the subthreshold properties. Our experiments suggest that subicular pyramidal neurons can sense ambient GABA depending upon the inhibitory neuronal activity and act as an adaptive filter for distinct synaptic inputs by modulating subthreshold properties of subicular pyramidal neurons (including resonance due to HCN channels) that may potentially alter the response dynamics in an oscillating neuronal network.

25. Tracking Neural Dynamics: A Method to Elucidate Mechanisms Involved in Seizure Generation and Termination

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Epilepsy is a debilitating disorder that affects approximately 1% of the world's populace. To date, the mechanisms behind the generation of seizures are not fully understood. We discuss a model-based approach to provide further insights into physiological changes occurring in the brain prior to and during seizures. In particular, we show that a neural mass model can be fit to data using an unscented Kalman filter, and that this procedure can be used to observe physiological changes in recorded EEG that are not elucidated by standard EEG evaluation techniques. To demonstrate this method, we have used an in vivo model of focal temporal lobe epilepsy, where tetanus toxin is injected into the rat hippocampus. Two depth electrodes are inserted into the hippocampus to record local field potentials, which are used as the observations for the estimation procedure. We make use of a neural mass model (Wendling et al. 2002) that has been shown to provide a good phenomenological description of hippocampal EEG.

Preliminary results from the estimation of 10 seizures from two different animals demonstrate decreases in the excitatory and slow inhibitory synaptic gains at the transition from background to seizures. Furthermore, the fast inhibitory synaptic gain increases at the transition to seizure. The results also demonstrate an increase in the excitatory synaptic gain at seizure termination, while both inhibitory synaptic gains remain constant. The estimation results showed that the mean of the input firing rate increases at seizure onset, and remains constant post-ictal.

In this tetanus toxin model of temporal lobe epilepsy, the similarity in estimation results across different animals and different seizures indicates that seizures could lead to a depression in both excitatory and slow inhibitory mechanisms (in this neural mass model), while peri-somatic, or fast inhibitory populations, are hyper-active. Considering these results, this method might allow for improvements in EEG evaluation techniques, and provide insights into mechanisms involved in both seizure initiation and termination.

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26. Two different mechanisms contribute to high-frequency oscillations (200 Hz) in the human epileptic subiculum in vitro

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Human hippocampal tissue resected for treatment of pharmacoresistant epilepsy was investigated. In slices of the subiculum prepared from this tissue, high-frequency oscillations around 200 Hz were found in extracellular field potentials during spontaneous interictal discharges (IID) and also during preictal discharges (PID) preceding ictal-like events. These oscillations were very similar in their spectral properties, also to those reported in the hippocampus in vivo. With combined intra- or juxta-cellular and extracellular recordings, we showed that, despite the overlap in their spectral components, IID and PID oscillations are generated by two different cellular/synaptic mechanisms. On one hand, IID-o appeared to be mediated by a GABAergic mechanism, since the associated synaptic inputs were predominantly inhibitory and a majority of cells were inhibited. On the other hand, PID-o were more homogeneously associated with excitatory synaptic inputs reaching the threshold of action potential generation and bursting neurons. Altogether, our data support the idea that high-frequency oscillations in epileptic human subicular circuits are generated by two different forms of synchronization mechanisms.

Epilepsy Connectome

27. Failure of adaptive self-organized criticality during epileptic seizure attacks

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Over the recent years it has become apparent that the concept of phase transitions is not only applicable to the systems classically considered in physics. It applies to a much wider class of complex systems exhibiting phases, characterized by qualitatively different types of long-term behavior. In the critical states, which are located directly at the transition, small changes can have a large effect on the system. This and other properties of critical states prove to be advantageous for computation and memory. It is therefore suspected that also cerebral neural networks operate close to criticality. This is supported by the in vitro and in vivo measurements of power-laws of certain scaling relationships that are the hallmarks of phase transitions. While critical dynamics is arguably an attractive mode of normal brain functioning, its relation to pathological brain conditions is still unresolved. Here we show that brain dynamics deviates from a critical state during epileptic seizure attacks in vivo. Furthermore, insights from a computational model suggest seizures to be caused by the failure of adaptive self-organized criticality, a mechanism of self-organization to criticality based on the interplay between network dynamics and topology.

28. Gamma wavelets as a tool for analysis of functional connectivity in the brain

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There are several publications indicating that gamma activity is generated by local networks. In this study we investigated functional connectivity between brain areas by analysis of temporal relations between gamma wavelets. The temporal relationship between gamma events generated in different brain areas was estimated by calculation of perievent histograms. The strength of the peak in the histogram was measured using Shannon entropy followed by calculation of the connectivity index, which reflects the strength of functional connectivity between recorded brain areas. The spatial pattern of functional connectivity is represented by color coded matrices and connectivity graphs. We have shown that gamma wavelets recorded between electrodes 1.5mm apart in the majority of cases, are generated by different neuronal modules interfering with each other. The spatial pattern of functional connectivity during the resting state, to a certain degree, reflects morphologically defined connections between brain areas, but is unique for each individual animal. This spatial pattern is stable in a given behavioral state, but changes when animals move from one behavioral state to another. Pharmacological manipulation of different types of synaptic transmission changes the spatial pattern of functional connections. Our data suggest that functional connectivity between interhemispheric areas depends on GABAergic transmission, while intrahemispheric functional connectivity is kainate receptor dependent. This approach opens a new horizon for investigation of brain functional connectomics and may be applied for merging fMRI and electrographic data in investigation of functional properties of neuronal networks.

29. Network Fragility in the Epileptic Brain: Linking Structure to Function

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Epilepsy is characterized by atypical cortical activity at the neuronal and population levels during seizures, including tonic spiking, increased heterogeneity in spiking rates and synchronization.

The etiology of epilepsy is unclear but a common theme among possible mechanisms is that the effective coupling between neurons is altered. For this reason, epilepsy is understood to be a network phenomenon and network models are often used to study the relationship between structural connections and functional activity.

Neural network models consist of a set of nodes (neurons or neuronal populations) with internal dynamics, connected by weighted edges (synapses) that define the nature of nodal interactions. Two possible mechanisms of seizure which operate at the level of cortical columns, chandelier cell loss and abnormal axonal sprouting from Layer V pyramidal cells, can be modeled by altering specific edge weights in the network. For example, abnormal axonal sprouting of an excitatory cell can be modeled in two ways: (i) by increasing its outbound edge weights and/or its recurrent loop edge weight (structural features), which increases the firing activity (a functional feature) of its downstream targets; or (ii) by decreasing inbound inhibitory edge weights and/or increasing inbound excitatory edges weights, which increases the cell's excitatory influence on its targets. Linking such structural changes to corresponding functional activity is non-trivial and contingent on the dynamics and topology of the network. In this study we link changes in synaptic weights between neurons (structure) to network stability (function).

It is hypothesized that aberrant functional activity observed during seizures does not arise from random changes in network structure, but from the disruption of the most fragile nodal connections in the network. Fragility of a node is defined as the minimum energy perturbation required to destabilize the network.

To test this hypothesis, the minimum energy perturbation on functional connectivity required to destabilize linear networks is derived for two classes of perturbations that affect different subnetwork topologies. Perturbation results are then applied to a probabilistic nonlinear neural network model that operates at a stable fixed point. That is, if a small stimulus is applied to the network, the activation probabilities of each neuron respond transiently but eventually return to the fixed point. When the perturbed network is destabilized, the activation probabilities shift to larger or smaller values or oscillate when a small stimulus is applied. Finally, the structural modifications in the neural network that achieve the functional perturbation are derived.

The findings suggest that the most fragile nodes in the neural network are either excitatory neurons that become more active or inhibitory neurons that become less active. This is consistent with abnormal axonal sprouting of Pyramidal neurons and loss of chandelier cells observed in epileptic tissue. Furthermore, simulation of the unperturbed and perturbed network reflect neuronal activity observed in epilepsy patients implanted with electrodes before and during seizure, respectively. The qualitative changes in network dynamics due to destabilizing perturbations, including the emergence of an unstable manifold or a stable limit cycle, may be indicative of neuronal or population dynamics during seizure.

30. State Dynamics of the Epileptic Brain and the Influence of Seizure Focus

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Communication between specialized regions of the brain is a dynamic process that allows for multifarious transient connections to accomplish different tasks. Neurological disorders result in disturbed connectivity that may shed insight into the nature of these dysfunctions. In focal epilepsy, this disruption is clinically observed as seizures, which originate from discrete

epileptogenic regions (foci) before spreading to wider areas of the brain. In resection-eligible medically refractory epilepsy (MRE) patients, the foci are localized by visually inspecting electrocorticographic recordings (ECoG) acquired through subdural and depth electrodes at the onset of seizure events, where seizures are marked by a variety of signatures, such as fast rhythmic activity, electrodecremental activity, or spike-wave-complex followed by rhythmic activity. Although the ECoG-based identification of the focus is challenging (~40% of surgically-treated patients have seizure recurrence within 6 months post-surgery, the richness of ECoG signals gives a unique opportunity to study brain connectivity and gain insight into how epilepsy affects neural communication.

To date, studies evaluating functional brain connectivity using ECoG have been confined to brief sections of data (few to several hundreds of seconds) across many patients during inter-ictal or seizure periods, and only a handful have examined the role of the annotated focus. It remains unknown whether a consistent functional network structure emerges over time, where the brain transitions through a finite set of networks in a predictive manner, or whether connectivity changes continuously without repetition. Furthermore, the role of the focus in network connectivity dynamics remains an open question.

We applied a network-based analysis to ECoG recordings from 12 MRE patients undergoing pre-surgical evaluation (130.7±40.9 hours of recordings per patient [mean±S.D.]) and measured brain connectivity continuously (every second) during inter-ictal, peri-ictal, and seizure periods. For each patient, we then used unsupervised clustering to group all the networks computed over time into a finite set of distinct networks, and if a robust set of clusters emerged, we examined how the brain transitions between each distinct network, i.e. brain state. For each brain state, we also investigated the role of the annotated focus. We found that across all patients, inter-ictal activity enters only 2-5 distinct states, while there are 2-11 states during seizure. Furthermore, seizure states had a significantly consistent progression of transitions in time with characteristic onset and suppression states. Finally, we found across several patients that there is a specific seizure state that consistently occurs shortly after onset in which the focus is significantly isolated from the rest of the network. Our findings suggest that brain connectivity may be described in a lower dimensional state-space, and that the isolated focus seizure state may be used to assist in focus localization.

Seizure Intervention

31. A control architecture for co-adaptive closed-loop neuromodulation in epilepsy

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Closed-loop neuromodulation systems for seizure treatment can be classified into two main categories. The first category includes detection-based systems in which certain patterns of neural activity will trigger a predefined stimulation. The second category contains reference-based systems in which the controller will monitor a certain variable and applies stimulation to keep the target variable in a certain pre-defined range. In both of these approaches, static selection of the neuromodulation parameters overlooks the dynamic nature of the disease and brain plasticity, which create a nonstationry environment for the controller. Developing intelligent neuroprosthetic systems which are able to learn the optimal control policy and co-adapt with the brain autonomously may improve the effectiveness of neuromodulation interventions for epilepsies.

Here we formulated the closed-loop neuromodulation problem as the interaction between two adaptive systems, the brain and an intelligent agent, and developed a framework for co-adaptive neuromodulation. This framework is designed based on the hierarchical Actor-Critic learning architecture. The Actor is a reinforcement learning agent that implements an adaptive control policy based on the input neural state. The Critic provides an evaluative feedback for the Actor based on monitoring the changes in a brain driven objective function in response to actions of the Actor. In the co-adaptive neuromodulation framework, the output stimulation is a function of the input neural activity. The goal of the Actor is learning to maximize the positive reinforcement from the Critic.

The system design philosophy of the co-adaptive framework is to enable the brain modulating the stimulation and using the neuroprosthetic system as an auxiliary information pathway. The Actor-Critic architecture provides a flexible yet powerful framework for the implementation of multiple-input multiple-output control policies by simultaneous neural recording from several brain areas and distributed stimulation of multiple brain targets. The Critic can implement a multi-dimensional objective function by monitoring multiple physiological variables and combine them into a single evaluative feedback, through a data fusion process. The detection-based and reference-based control strategies can be viewed as special cases of the Actor-Critic architecture.

32. A Neural Mass Model of Spontaneous Epileptic Seizures with Closed-Loop Control

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The goal of this research is to establish a link between system properties that modulate neural activity and the fast changing dynamics, such as membrane potentials and firing rates that can be manipulated using electrical stimulation. Establishing this link is likely to be a necessary component of a closed-loop system for feedback control of pathological neural activity.

We present a neural mass model that is capable of simulating the transition to and from various forms of paroxysmal activity such as epileptic seizure-like waveforms [1]. These transitions

between events occur without changing parameters in the model. The model is based on an existing neural mass model [2], with the addition of slow states that represent parameters, which evolve through feedback of the fast dynamics.

Using the new model, we have designed a stimulation strategy to control the simulated paroxysmal events. The stimulation strategy utilizes charged-balanced bi-phasic pulses, which is a requirement for practical clinical application.

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33. Improving the Efficiency and Selectivity of Electrical Stimulation with Burst-Modulated Pulse Waveforms and Response-Based Stimulus Design

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Electrical stimulation of neural tissue is an effective treatment for patients living with epilepsy, especially for those who respond poorly to pharmaceuticals. Vagus nerve stimulation (VNS) has experienced more than a decade of success, and deep brain stimulation (DBS) has been shown to be very promising as well. The stimulus waveforms typically used in VNS and DBS consist of a train of short rectangular pulses that have somewhat arbitrary parameters. As a different approach, we propose to replace these rectangular pulses with bursts of smaller pulses, which are referred to here as “pulsons”. In addition, we developed a neural stimulation system that, instead of simply generating rectangular pulses of arbitrarily defined parameters (the conventional role of a stimulator), allows the user to map different waveforms to the response profile of target neural tissue and select waveforms based on the desired type of response.

Using the burst-modulated pulse waveforms and the stimulation system, we were able to dramatically increase the efficiency of stimulation (the amount of electrical charge needed to elicit the same level of response) as well as manipulate the selectivity (preferential activation of a certain group of neurons). Conventional rectangular pulses preferentially activate fast-conducting axons—axon fibers with larger diameter and more myelin are activated more easily. This feature is not always desirable and can pose a challenge to therapy as well as research. Using burst-modulated pulses, it is possible to alter the selectivity of electrical stimulation to target the slower fibers.

For example, in Long-Evans rats, using burst-modulated pulses and response-based stimulus design, we were able to maintain the same level of C fiber activation, and at the same time, the amount of A fiber activation was adjustable by tuning the pulse waveforms. In addition, the charge needed to achieve those activation levels was much lower than that when using rectangular pulses (as much as 30% lower). This stimulation system provides control over the neural response to electrical stimulation in ways not possible with conventional stimulus waveforms. Our findings have important implications for studying the mechanism of VNS and DBS systems, and this technology has the potential for immediate clinical impact in treating epilepsy, as well as other neuropsychiatric disorders.

34. Open loop optogenetic control of epileptiform activity in a model two dimensional cortex

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The high temporal and spatial resolution optogenetics offers in the stimulation of neurons makes it a versatile tool for the treatment of cortical disorders such as epileptic seizures. Using the meso scale cortical model first developed by Liley et al. (Phys. Rev. E, 2005) extended to two dimensions, we study the nature of seizure waves and demonstrate that optogenetic control can be used to suppress epileptiform activity. The inhibitory population, which in the mathematical model is modified to express optogenetic ion channels in the cell membrane, is targeted with pulsed or constant illumination to suppress seizure waves. The method is shown to be robust.

35. Towards a wireless, closed-loop optogenetic stimulator for seizure modulation

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A wireless, closed-looped device that delivers seizure suppression in vivo is an actively sought goal in the epilepsy community. Using optogenetic tools, promoter-specific neuronal modulation can be achieved. Excitatory drivers of seizures could be directly suppressed with inhibitory opsins or indirectly suppressed with excitatory opsins expressed in interneurons. Wireless technology would allow researchers to monitor large cohorts of animals in parallel without a tethered artifact. We aim to design and implement a robust and programmable wireless, closed-loop stimulator. To achieve this, we first developed a wireless, deep-brain optogenetic stimulator (OGS). An LED acts as the light source and is controlled by a microcontroller (MCU) and a constant current driver. Greater than 30 mW/mm2 are produced with 64 mW input power. The MCU allows user defined stimulation protocols power management. During periods of no stimulation, the device consumes < 26 uWs. We validated the OGS in vivo with a 3-chamber conditioned place aversion (CPA) behavioral paradigm. We generated mice expressing ChR2-H134R and tdTomato in interneurons under the control of Gad2-cre. Optical fibers were targeted at the right ventral tegemental area (VTA) to activate interneurons suppressing dopamine release. Results show a significant decrease in place preference for mice treated with sufficient stimulation. For applications in epilepsy, a seizure event triggers the stimulation. We are actively developing an FPGA based single channel recording system that will be expandable for multichannel data collection. Seizure detection is provided by a previously published custom application specific integrated circuit (ASIC) and is used to trigger the MCU for stimulation and data transmission. Integration of the OGS, recording system, and seizure detection ASIC into a singular device for animal studies is pursued.

Systemic Interactions

36. Effect of Vigilance State on Clinical Seizure Predictability: A Pilot Analysis

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Rationale: The ability to anticipate or predict seizures with reasonable accuracy would benefit patients with intractable epilepsy as well as their caregivers. Many of the seizure prediction algorithms (SPAs) proposed to date extract dynamical features ("prediction variables") of the electrocorticogram (ECoG) and consider abnormal trends in advance of seizures as evidence of a preictal state (i.e., an abnormal state especially conducive to seizures) [Brain 2007; 130:314-33]. But changes in sleep-wake state have been found to limit the performance of some SPAs [Epilepsia 2006; 47:2058-70]. Vigilance state (REM or R, NREM or N, Wake or W) is already known to bias seizure likelihood [Epilepsia 1997; 38:56-62] in addition to circadian phase, sleep debt and stress, but a detailed investigation of its effects on seizure predictability is lacking. One limitation is that polysomnography (PSG) is needed to determine vigilance state, but PSG is not commonly performed in conjunction with ECoG [Sleep 2000; 23:231-4], which is the source of most (if not all) data used to develop and test SPAs. The purpose of this study is to determine how prediction variables derived from ECoG are influenced by vigilance state. This is addressed by analyzing ECoG and PSG data recorded simultaneously from patients with refractory epilepsy.

Methods: We analyzed prospectively acquired ECoG and PSG (C3-O1 or C4-O2, EOG, submental EMG) data from two patients undergoing intracranial monitoring as part of presurgical evaluation at UTSW. Electrodes for PSG were placed contralateral to the craniotomy. Vigilance state was scored from overnight recordings using a hidden Markov model (HMM) that labeled each 30 s epoch as W, N1/2, N3, or R. Signal features used in the model were delta/theta and (alpha+beta)/(delta+theta) power ratios of the EEG respectively and root-mean-squared EMG and EOG. This algorithm gave moderate to high agreement (Cohen's kappa of 0.6-0.8) with expert scores on a PSG database [IEEE-BME 2000; 47:1185-94, Circulation 2000; 101:e215-e220] for six normal subjects. Next, three prediction variables—linear cross-correlation peak, mean phase coherence, and sample entropy—were computed from differential ECoG in the vicinity of the seizure focus. Mean values of these prediction variables for the four HMM-scored vigilance states were compared using analysis of variance.

Results: Each of the prediction variables derived from ECoG was found to vary significantly with vigilance state ($p < 0.001$). Although post hoc pair-wise comparisons showed no consistent patterns of difference between vigilance states across prediction variables or patients, there appeared to be some differentiation between sleep and wake states.

Conclusions: Univariate and bivariate ECoG features typical of those incorporated in SPAs were found to vary significantly with vigilance state as determined by PSG. Our preliminary analysis of simultaneous ECoG/PSG recordings from two patients suggests that such algorithms should correct for normal changes in vigilance state in order to minimize false predictions. Collection and analysis of ECoG-PSG recordings from more patients undergoing intracranial evaluation is ongoing and expected to yield more definitive ways of correcting for state and improving SPA performance.

37. Markov Modeling of Sleep-Wake Dynamics Following Acute Neural Injury

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Rationale: Traumatic brain injury (TBI) usually disrupts circadian rhythms and sleep. The ability to track changes in the microstructure of sleep in the post-traumatic period could help assess the effect of intervention and perhaps provide clues about the likelihood of epileptogenesis. However, convenient metrics that track sleep-wake dynamics over time—beyond simplistic measures such as the percent time spent in each state (Wake, REM sleep, and non-REM sleep) or mean bout duration—are lacking. Here, a methodology based on hidden Markov models (HMMs), estimated from physiological measurements in mice, is proposed for characterizing transient sleep-wake dynamics.

Methods: With IACUC approval, adult C57BL/6J mice were implanted with EEG/EMG preamplifiers and monitored round-the-clock within hours of surgery for 3-4 weeks with brief weekly interruptions for cage cleaning. The HMM, an unsupervised probabilistic model, was used to sequence time series of EEG/EMG features in 4s epochs into REM, non-REM, and Wake states. The features supplied to the HMM were the delta/theta power ratio of the EEG and the root-mean-squared EMG. The HMM is parameterized by a 3x3 state transition matrix (STM) representing the probabilities of different Markov state transitions. HMMs were re-estimated from EEG/EMG feature sets every four hours. The output of the HMM was validated for sample recordings against manual scores. Trends in HMM properties were inspected to characterize progressive changes in behavior following surgery.

Results: HMMs were found to track instantaneous sleep-wake state with over 90% accuracy from continuous EEG/EMG measurements (92% sensitivity and 95% specificity; n = 4 mice) when compared to manual scores. Two parameters extracted from the HMM, the probability of Wake (Pw) and the trace (Tr) of the STM, were used as measures of sleep quality and the persistence of any ongoing state respectively. Immediately after implantation, Pw was abnormally low, as expected after general anesthesia and mild head trauma associated with the EEG surgery. Although low Pw indicates increased somnolence, Tr was low as well, which suggests more fragmented sleep. Pw and Tr took 7-10 days to reach stable levels consistent with full recovery, with patterns characteristic of normal sleep-wake cycles and circadian rhythms.

Conclusions: Preliminary results suggest that HMMs estimated from physiological measurements could provide quantitative markers of transient behavior and recovery from brain injury. We intend to use this approach to track physiological and behavioral changes in a model of post-traumatic epilepsy.

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Seizure Localization

38. Evaluation of the epileptogenic zone based on computer assisted network analysis of electrical stimulations during intracranial stereo-EEG recordings

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Purpose: Approximately one third of patients with pharmacoresistant epilepsy are potential candidates for epilepsy surgery. Successful surgery may substantially reduce or eliminate seizures and the associated disability. In 30-40% of cases the cerebral area responsible for seizure generation can be defined only by intracranial EEG recordings. For precise pre-surgical evaluation of the epileptogenic network the low-frequency bipolar stimulation (up to 2-5mA, 1ms pulses at 1 Hz for 30s) is performed at each recording site. This generate a huge amount of electrophysiological data analyzed by time consuming visual inspection. We propose a novel computational approach to study epileptogenic brain areas based on the evoked response analysis of intracranial EEG recordings.
Method: We developed an original computer assisted algorithm to analyze evoked responses based on LabView and connectivity network analysis; mono or bipolar responses of each tested couple of contacts were averaged and reliability assessed. Averaged responses selected on the basis of their amplitude/area and features (peak amplitude, delay and area) were computed and stored. 3D-plot representation of parameters was available for quantitative measures. Group probabilistic maps datasets of the evoked responses were created and analyzed exploiting supervised data mining algorithms. Structural connectivity and epileptogenic area were further explored with descriptive network analysis using clustering with overlapping neighborhood expansion algorithm.
Results: Different phases of evoked responses were identified. Based on activation pattern physiological and pathological connectivity between epileptogenic zone and surrounding tissue were evaluated. Network clustering analysis based on evoked responses was performed individually for every patients SEEG data set. Cluster size, internal weight and connection directions were identified as a significant attributes of the epileptogenic contacts clusters.
Conclusions: Our analysis approach has proved to be useful to assist the evaluation of the epileptic zone borders and the functional connections in epileptic patients. Specific reproducible interactions between epileptic contacts were identified by complex network analysis algorithms. Application of a novel workflow for intracranial EEG stimulation protocol will lead to more precise definition of the EZ, helping to understand basic mechanisms of ictogenesis and will improve post-surgical outcome in terms of seizure control and neuropsychological performance.

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39. Measuring seizure propagation speed in humans with ictal high frequency oscillations

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Recordings of multi-unit activity during spontaneous human seizures have clearly distinguished between neuronal territories fully recruited into the seizure (characterized by high level and synchronized neuronal firing) and territories on the periphery of this core recruited area (characterized by low level and desynchronized firing). We use the terms “ictal core” and “ictal penumbra” for these two regions. Using multi-unit activity as a gold standard, we recently validated ictal high gamma activity recorded with subdural electrodes as a proxy of the ictal core. We hypothesized that the propagation speed of the ictal core, as defined by the spread of high gamma activity, would fall into a relatively narrow range of values across pathologic substrates. We performed a retrospective comparison of seizure propagation speeds in 16 seizures across six patients using ictal high gamma as a proxy for the ictal core. High gamma activity was identified by visual inspection. The raw EEG tracing was displayed adjacent to a 80 to 150 band pass filtered tracing obtained by forward and reverse filtering with a 500th order finite impulse response filter. Channels were considered recruited into a seizure (ictal core) when they demonstrated a low frequency ictal rhythm in which greater than 50% of the low frequency waveforms were associated with high gamma bursts at least 3 times the amplitude of the pre-ictal baseline. Once all recruited channels were identified the earliest changes from the pre-ictal baseline in the raw and 80-150 Hz band-pass filtered tracings were defined as the onset times in the low frequency and high gamma bands, respectively. Adjacent recruited channels (10 mm spacing) were then identified and the speed of low frequency and high gamma spread was measured between channels. To address the problem of spurious oscillations in high pass filtered data, raw EEG was inspected for the presence of “rippling” concomitant with high gamma activity; when uncertainty remained after examination of the raw EEG data wavelet transformations were examined. Reports of pathologic examination were available for all patients. Pathologies included mesial temporal sclerosis with normal surrounding neocortex, mesial temporal sclerosis in association with a neocortical temporal cavernous angioma, non-specific neocortical gliosis in the right frontal lobe, left neocortical temporal malignant glioma, cortical dysplasia in the right insular cortex, and normal parietal and temporal cortex surrounding a previous infarction. Across all patients and seizures, the mean spread of ictal high gamma was 0.86 mm s-1 (+/- 0.7 mm s-1), similar to the 0.83 mm s-1 propagation speed previously measured in spontaneous human seizures. The mean spread of the wideband ictal rhythm was 2.68 m s-1, significantly faster than the spread of the ictal core ($p < 0.01$, Welch’s t-test). Ictal high gamma spread at speeds between 0.47 and 1.53 mm s-1 irrespective of the underlying pathology. This work supports the hypothesis that propagation of the ictal core, as measured by ictal high gamma activity, occurs at a relatively narrow range of values across different pathological substrates and more slowly than spread of the low frequency ictal rhythm.

40. RIPPLELAB: A user interface for detection and analysis of high frequency oscillations

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Studies in intracranial macroelectrode electroencephalogram recordings suggest that pathologic high frequency oscillations (HFO) can be considered as an electrophysiological biomarker of the epileptic brain. Despite of this, no conclusive results have been obtained yet due to, among other reasons, the difficulty in the detection of this type of events in large databases. In order to overcome this obstacle, some methods for automatic detection of HFO have been developed. Each one of them has been nevertheless improved for specific databases and all have been designed according to particular HFO criteria, which difficults quantitative comparisons between

them. In addition, it is important to optimize a detector for a particular type of data instead of using a standard global configuration. Equally important is the possibility to perform a visual validation in order to corroborate the quality of detected events.

For all these reasons, a MATLAB-based user interface, RIPPLELAB, has been developed to ensure an efficient use of available data and to provide a powerful and versatile HFO analysis tool. In addition to visual marking, the interface offers the possibility to use, test and evaluate four of the most known published methods for detection and analysis of high frequency oscillations. The interface allows users to visually confirm, classify and save detected events for further evaluation. Additionally, different temporal and frequency characteristics of selected events can be inspected through time-frequency plots and power spectral analysis. To demonstrate RIPPLELAB's capabilities, we performed an analysis over 16 patients of the EPILEPSIAE database over a total of 229 electrodes applying three of the automatic detection methods with a further visual validation over a selection of the detected events, which allowed us to evaluate the type of HFO events identified through the interface. This software tool will be registered under GNU license facilitating thus the use in academic, research and clinical contexts.

41. Specific HOC Features Correlate with Seizure Onset Zone in Human EEG

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Rationale: High frequency oscillations (HFOs), encompassing ripples (frequencies between about 50 Hz to 200 Hz) and fast ripples (frequencies greater than 200 Hz), have been shown to be have some correlation with seizures both temporally and spatially, though the specificity and sensitivity are not yet high enough for clinical applications. Most work in the field has focused on very limited features of HFOs, usually either the peak frequency or rate of the HFOs. We seek to improve the specificity and sensitivity of HFOs for determining the seizure onset zone through detailed analysis of HFO features and more advanced classification algorithms.

Methods: Human iEEG data was recorded at 32 kHz in eight refractory seizure patients. Over 100,000 HFOs were identified by automated analysis, and the raw signals were used to extract several signal features in both the time and frequency domain such as peak and median frequency, interquartile distance, and the standard deviation of the peak voltages per oscillation. These features were used in several different classification algorithms such as support vector machines and boosted decision trees to determine a feature set unique to the seizure onset zone. Classification was performed first on individual, single channel HFOs, then each channel is classified, and finally clustering algorithms are used to determine the final estimate of the seizure onset zone. The Matthew's Correlation Coefficient (MCC) was used to measure accuracy, and the results were also benchmarked against the common methods of HFO rate and peak frequency. The algorithms were tested by both cross validation and hold out methods on each patient, as well as training on various subsets of patients and testing on others subsets of patients.

Results: The MCC score was a reliable indicator of clinical accuracy. Large disparity existed between results from different patients, both in accuracy and in the specific features that predicted the seizure onset zone. Some feature sets were found which resulted in an improved MCC score compared with the traditional rate and frequency algorithms, while some subsets preformed more poorly. There was no algorithm that performed well across multiple patients. A novel class of HFOs with broad spectral power was identified that did not appear to have any relationship with seizure onset zone.

Conclusions: HFOs are complex dynamic phenomena that are only partially described by rate and peak frequency. By analyzing more sophisticated features, the specificity and sensitivity of identifying the seizure onset zone is improved. Further work is needed to identify features and algorithms of HFOs that can be used in a prospective fashion to localize epileptic networks.

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Bahia Resort Hotel
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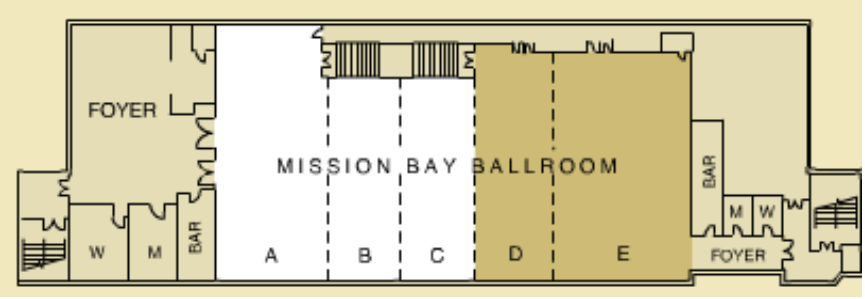

Registration and Welcome Reception in the Foyer (on the A side)

Posters in Mission Bay Ballroom A

Continental breakfasts, lunches, breaks in Mission Bay Ballroom A

Sessions in Mission Bay Ballroom B & C