ICTALS2019

The Epilepsy Journey

2-5 September

In partnership with

Abstract book

This conference is supported by a grant from the American Epilepsy Society

UNIVERSITY OF EXETER

ICTALS2019
The Epilepsy Journey

Foreword

The International Conference for Technology and Analysis of Seizures, 2019 (ICTALS2019) aims to bring together neurologists, neuroscientists, researchers from quantitative disciplines and people with lived experience of epilepsy in order to work as a community to advance our understanding of epilepsy and develop practical ways to improve diagnosis and treatment.

The theme for this year's conference is: The Epilepsy Journey: from first seizure to treatment and beyond. We will emphasise how advances in our understanding of the dynamics of brain networks can be used to make a difference to people with epilepsy at all points of their journey: from elucidating the causes of the first seizure to diagnosing epilepsy, understanding how ictogenic networks give rise to recurrent seizures and how this insight can inform personalised treatment.

To encourage this focus on the whole epilepsy journey we seek to include all relevant communities. In addition to discussions on current scientific, clinical and technological advances, we will take steps to increase accessibility for people with lived experience of epilepsy.

Dates: Monday 2 September 2019 - Thursday 5 September 2019

Venue: University of Exeter, Streatham Campus, Xfi Building

Conference website: http://ex.ac.uk/ictals2019

Contact the organisers: ictals2019@exeter.ac.uk

ICTALS2019

The Epilepsy Journey

Partners

We are partnering with charities Epilepsy Research UK and Epilepsy Action and Alliance for Epilepsy Research.

Sponsors

This event would not be possible without the generous contributions from our generous sponsors UCB, the Epilepsy Foundation, NeuraLynx, and Liva Nova. This conference is supported by a grant from the American Epilepsy Society

Inspired by patients. Driven by science.

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Wifi information

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3. You will be asked to provide the following details: **Your name and email address**
4. Please tick the terms of use box
5. Click register, you will receive a confirmation receipt

Program

Monday 2nd Sept	Tuesday 3rd Sept	Wednesday 4th Sept	Thursday 5th Sept
Education	**Epileptogenesis and ictogenesis**	**Ictogenisis and Treatment**	**Ictogenisis and Treatment**
ICTALS 2019 will take place at the XFi building, University of Exeter. Refreshments will be served in the Atrium. Talks will be held in the Henderson lecture theatre. Posters will be located in the conference rooms. The Epilepsy Action coffee and chat space will be located in the seminar room.	8:30 – 9:30 **Profs. Paddy Ssentongo and Bruce Gluckman** From cerebral malaria to epilepsy in human and in animal models.	8:30 – 9:30 **Prof. Mark Richardson** Brain network trait and dynamic states in genetic generalized epilepsy and My Seizure Gauge: a new multicentre project	8:30 – 9:30 **Prof. Kathryn Davis** Localizing seizure "hotspots" with quantitative neuroimaging
	9:30 – 10:30 **Prof. Mark Cook** Slave To The Rhythm - Cycles and memory in epilepsy (with apologies to Grace Jones)	9.30 - 10.30 Contributed talks: **Dr. Thorsten Rings** **Dr. Dean Freestone**	9.30 - 11.00 Contributed talks: **Drs. Miao Cao and Daniel Galvis** **Dr. Gerold Baier** **Dr. John Bernabei**
	10:30 – 11:00 Refreshments	10:30 – 11:00 Refreshments	
11:30 – 12:45 Arrival Lunch and registration	11:00 – 12:30 **Discussion session:** What are ictogenic networks?	11:00 – 12:30 **Discussion session:** Evolving networks: resilliance and control	11:00 – 11:30 Refreshments
			11:30 - 12:30 **Prof. Cathy Schevon** Epilepsy networks across spatial scales
12:45 - 13:00 Welcome	12:30 – 13:30 Lunch **Poster Session**	12:30 – 13:30 Lunch **Poster Session**	12:30 – 14:00 Lunch **Poster Session**
13:00 – 14:00 **Prof. Khalid Hamandi** Clinical pathways for epilepsy			
	13:30 – 14:30 **Prof. Fabrice Wendling** What can micro- and macro-scale computational models reveal about epileptogenesis and ictogenesis?	13:30 – 14:30 **Prof. Viktor Jirsa** Translational Neuroscience: from bifurcations to personalized medicine	
14:00 – 14:30 Refreshments			14:00 – 15:00 Contributed talks: **Dr. Rasesh Joshi** **Dr. Gabrielle Schroeder**
14:30 – 16:00 Tutorial: Network methods for understanding epilepsy **Dr. Piotr Slowinski** **Dr. Jen Creaser**	14.30 - 15.30 Contributed talks: **Dr. Beth Lopour** **Dr. Maxime Baud**	14:30 Social until late: Depart for Topsham, ferry to Turf Hotel and BBQ	15:00 – 15:30 Refreshments
16:00 – 16:30 Refreshments	15:30 – 16:00 Refreshments		15:30 – 16:30 Contributed talks: **Prof. Bill Stacey** **Prof. Premysl Jiruska**
16:30 – 18:30 Testimony from people with lived experience of epilepsy and discussion session: **Mrs. Lottie Pagram:** My Epilepsy and Me **Mr. Neil and Mrs. Hannah Parker:** Diagnosis and caring **Mr. Simon Privett:** My Epilepsy Journey - Can Epilepsy be a Positive? **Miss Torie Robinson:** The impact of temporal lobectomy on cognitive function, mood regulation and mental health	16:00 – 18:00 Large-scale clinical data session (chaired by Prof. Mark Richardson) **Dr. Jonas Duun-Henriksen** **Dr. Sharanya Desai** **Dr. Levin Kuhlmann** **Prof. Jacqueline French and Sonya Dumanis (EFA)**		16.30 Closing remarks
	18:00 – 19:00 **Poster Session**		
18:30 - 19:30 Mentoring session	19:00 Coach to conference dinner		

Contributed talk titles

Dr. Beth Lopour	Dynamics of EEG-based functional connectivity in infantile spasms and healthy infants
Dr. Maxime Baud	Multidien Chronotypes in Human Focal Epilepsy
Dr. Jonas Duun-Henriksen	Objective treatment optimization and what to learn from 11,774 hours of ultra long-term subcutaneous EEG from nine patients
Dr. Sharanya Desai	Therapy proposer and evaluation tools developed from mining big epilepsy data
Dr. Levin Kuhlmann	Epilepsyecosystem.org update: Searching for Seizure Prediction Solutions
Dr. Thorsten Rings	Seizure prediction and seizure control: cautionary tales from measuring resilience of the brain
Dr. Dean Freestone	Critical slowing as a biomarker for seizure susceptibility
Drs. Miao Cao and Daniel Galvis	Reducing the need for invasive intra-cranial monitoring for epilepsy surgery.
Dr. Gerold Baier	Implementing Horsley's dream: Stimulation-responses to uncover the epileptogenic network prior to epilepsy surgery
Dr. John Bernabei	Virtual resection predicts surgical outcome for drug resistant epilepsy
Dr. Rasesh Joshi	Seizure-related spatiotemporal fluctuations in infraslow networks in intracranial EEG and MEG
Dr. Gabrielle Schroeder	Slow shifts in seizure pathways in individual patients with focal epilepsy
Prof. Bill Stacey	Seeing the big picture: expanding the scope of electrical and biochemical biomarker research
Prof. Premysl Jiruska	Decrease in neuronal network resilience precedes seizures at multiple temporal scales.

Venue

The conference will be held in the Xfi building at the University of Exeter.

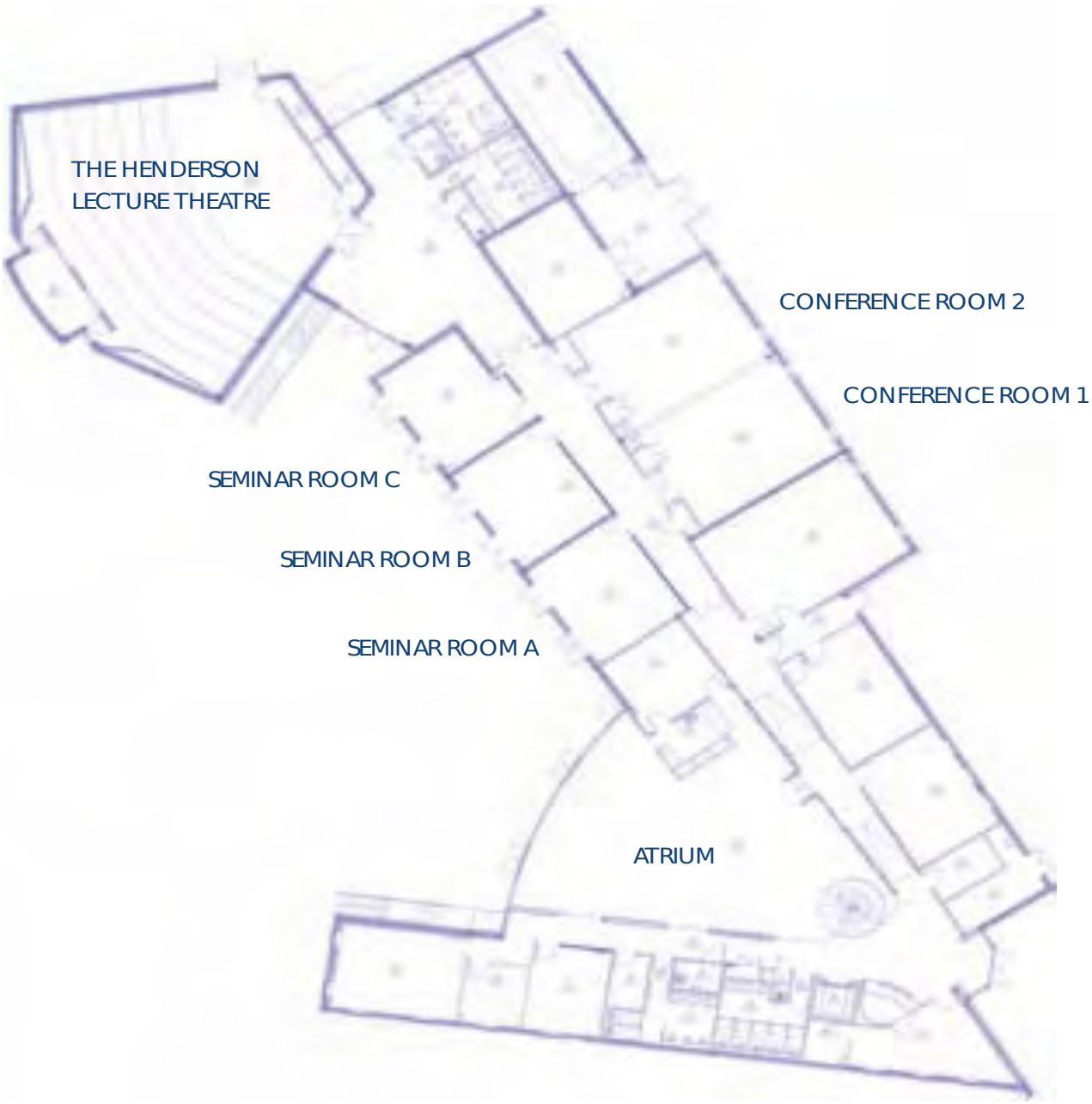
Conference dinner

The conference dinner is at Puerto Lounge on **Tuesday 7pm**, September 5th. There will be coaches from and back to the University.

Social event

The social event is a free ferry trip (weather permitting!) to the Turf Hotel followed by BBQ and drinks on **Wednesday evening**, September 4th.The BBQ will be at your own expense, but some drinks will be subsidised. There will be coaches from and back to the University.

Map of Xfi building



Talks: The Henderson Lecture Theatre
Posters: Conference rooms 1 and 2
Lunch and coffee breaks: Atrium
Epilepsy action coffee and chat space: Seminar room C

ICTALS 2019: The Network Debates

Organized by: Klaus Lehnertz, Björn Schelter and Hitten Zaveri

Session 1: What is an epileptic network?

1. Debate: From pathologic to physiologic: is the epileptic network part of an existing large-scale brain network?
   Debaters: Yes: Hitten Zaveri vs No: Cathy Schevon
   Discussant: Fabrice Wendling

2. Debate: Are micro scale recordings pertinent for defining the epileptic network?
   Debaters: Yes: Premysl Jiruska vs No: John Jefferys
   Discussant: Mark Cook

3. Debate: From seconds to years: do we need all temporal scales to define an epileptic network?
   Debaters: Yes: Greg Worrell vs No: Andreas Schulze-Bonhage
   Discussant: Mark Richardson

Session 2: How can we control an epileptic network?

4. Debate: Is it necessary to fully define the epileptic network to control it?
   Debaters: Yes: Rasesh Joshi vs No: Björn Schelter
   Discussant: Thorsten Rings

5. Debate: Is controlling seizures sufficient to control the epileptic network?
   Debaters: Yes: Viktor Jirsa vs No: Marc Goodfellow
   Discussant: Klaus Lehnertz

6. Debate: Does the epileptic network want to be controlled?
   Debaters: Yes: Christian Meisel vs No: Klaus Lehnertz
   Discussant: Piotr Suffczynski

Guidelines: Each debate will be conducted over 30 minutes. There will be 6 minutes for each position (pro and con). This will be followed by brief comments by a discussant for up to 3 minutes. Following the comments by the discussant we will open to the floor for up to 15 minutes of discussion.

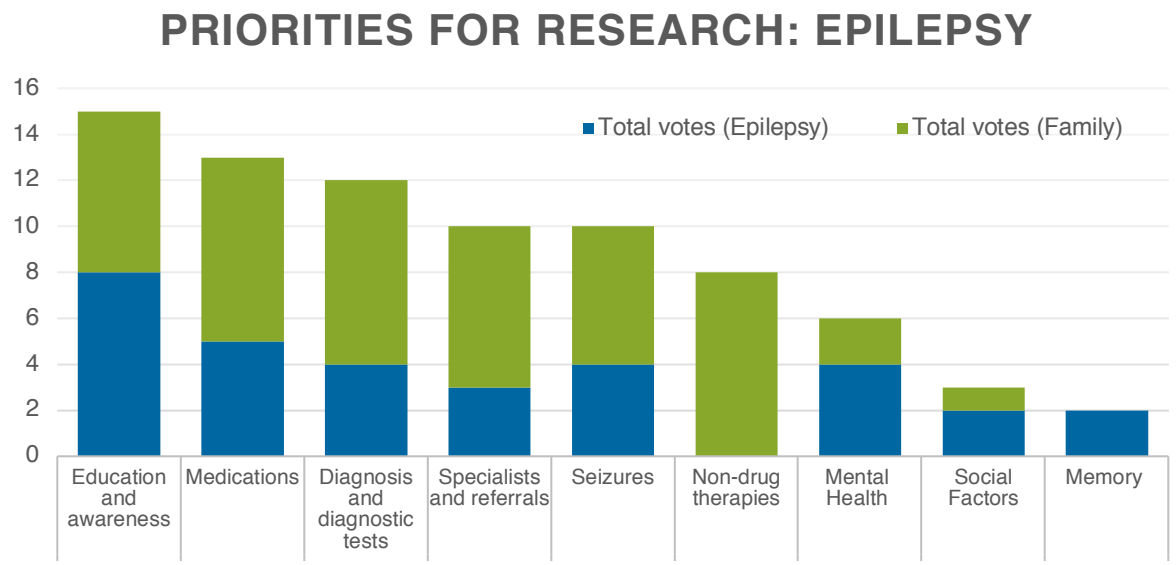
Not only for scientists

ICTALS 2019 is partnering with charities Epilepsy Research UK, Epilepsy Alliance and Epilepsy Action to bring together people with lived experience of epilepsy and scientists. The first day of the conference will be an educational day in which introductory talks will be given to build a bridge between the scientific community and the public. Then people with lived experience of epilepsy will share their testimonies.

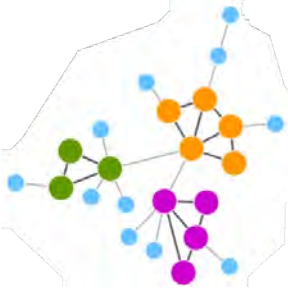
To aid in making the science accessible to the general public, there will be a **buddy system**, where appointed researchers from the University of Exeter will be available to answer any questions that may arise. Epilepsy Action will have a **coffee and chat space** where everyone will be welcome to talk and rest away from the main sessions of the conference.

The Quantitative Biology and Mathematics @ Exeter contains a growing group of epilepsy researchers. We want to ensure that our research is anchored in the real-life experiences of people with epilepsy. To establish a conversation between people with a lived experience of epilepsy and our researchers we set up the Experts in Epilepsy public involvement group. We held a priority setting workshop in which fourteen people took part. Six people had a diagnosis of epilepsy and 8 people were family members (supporters and carers) for people with epilepsy.

The themes discussed at the workshop were voted on by the participants. The votes were used to rank priorities.



Education Day



The afternoon of Monday 2nd September is an education day for conference participants. This will consist of a tutorial followed by testimonies from people with a lived experience of epilepsy.
Everyone is encouraged to attend.

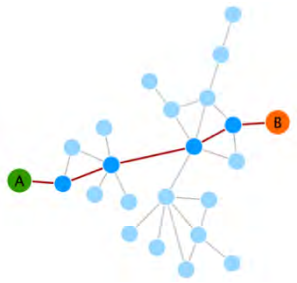
Prof. Khalid Hamandi will provide a tutorial on some specific aspects of epilepsy from the clinical perspective. He will introduce notions of classification and semiology of seizures and talk about different aspects of the patient journey from new diagnosis (classification, treatment decisions and prognosis) through to the effects of treatment (including drug resistance and co-morbidities). He will also give a perspective on the need for novel treatments.

There will be a tutorial on **Network Methods for Understanding Epilepsy**. This tutorial is aimed at people with a non-mathematical background who are interested in how tools from mathematics and data science are used to research epilepsy. It will cover the key themes of the conference in an accessible way.

The first part of the tutorial will focus on why we use networks to study the brain and epilepsy. Then how we can use different sorts of data to create networks. We look both at physical networks extracted from data showing anatomical connections in the brain, and functional networks extracted from the signals of brain activity.

The second part of the tutorial will focus on mathematical modelling of epilepsy. This talk will look at what we mean by a mathematical model and cover some of the key types of models used to study epilepsy. We will show some specific examples of how seizures can be reproduced and studied. Finally, we will look at how *network models* can produce the wide variety of seizure patterns observed in different epilepsy syndromes using networks that have been extracted from the data

The tutorial will be followed by a **series of short talks presented by people with a lived experience of epilepsy**, this includes people with a diagnosis of epilepsy and carers. The profiles of the speakers can be found on the following pages.



Public Speakers

Lottie Pagram

Diagnosed in 1990 aged 14 with 'absence seizures' gradually developing into Idiopathic Generalise Tonic Clonic Seizures, Lottie struggled to control the seizures with medications. In 2012 the seizures worsened following a blood clot to the brain having suffered a major seizure. Brain surgery was deemed inappropriate and the VNS (Vagal Nerve Stimulator) was suggested and duly inserted in August 2014.
Lottie currently works as a Medical Administrator for the Oncology Department of the Royal Devon & Exeter Hospital. She is also an Accredited Volunteer for Epilepsy Action. She is married and has a teenage daughter.

Neil and Hannah Parker

Neil was possibly misdiagnosed with only epileptic seizures at 9 years old. While suffering from psychogenic and epileptic seizures Neil has studied, worked and raised a family with his wife and carer Hannah. It has taken 41 years for them to obtain a confirmed diagnosis. Seizures and medication have significantly impacted Neil's education, work, career, family, friendships and mobility. The condition has seriously affected the physical and mental health of both Neil and Hannah. They will tell you their story which they hope will strike a chord with sufferers and carers and will enlighten medical professionals and researchers to the realities of living with psychogenic and epileptic seizures.

Simon Privett

Diagnosed with Idiopathic generalised seizures aged 14, Simon has spent much of the last 23 years fighting to control his epilepsy. Various changes of meds have seen him stable for periods, most recently for almost three years until an attack in March. Simon has worked with epilepsy charities and University departments to keep epilepsy research engaged with those with lived experience, whilst also running support groups for people with epilepsy. Simon's full time employment is as a caterer but believes his true calling is helping others to overcome their diagnosis.

Torie Robinson
Epilepsy Sparks

Torie Robinson is a Public Speaker regarding Epilepsy & Mental Health, and the CEO & Founder of Epilepsy Sparks. Bridging the communication gap between neurologists, scientists, researchers, neuropsychologists, patients, families, friends and employers; Torie's purpose is to empower those affected by epilepsy through education.
Torie speaks at hospital and university conferences, at charity events, in UK Parliament and at corporates such as Google and CBSi. Torie also writes for blogs including Epilepsy Sparks, Medium, Illinois Science and more.
A Trustee for the charity known as Epilepsy Action, on the Scientific Advisory Board for Epilepsy Research UK, and Advocate for the EU EpiCARE, Torie provides patient perspective for key decisions made.
Diagnosed with epilepsy aged 10, Torie's seizures and mental health worsened over the years. As the result of her refractory epilepsy and with a decreasing quality of life and an increasing risk of SUDEP, Torie had a temporal lobectomy in 2013. Now on reduced dosages of AEDs and with an increased life expectancy, Torie devotes her life and career to bettering the lives of others affected by epilepsy and mental health comorbidities.

Plenary Speakers

Mark Cook
University of Melbourne

Khalid Hamandi
Cardiff University Brain Imaging Research Centre and University Hospital of Wales

Catherine Schevon
Columbia University

Kathryn Davis
University of Pennsylvania

Viktor Jirsa
Aix-Marseille université

Paddy Ssetnongo
Penn State University

Bruce Gluckman
Penn State University

Mark Richardson
King's College London

Fabrice Wendling
Université de Rennes

Profiles of the plenary speakers can be found here.

Plenary Talk Abstracts

Localizing seizure "hotspots" with quantitative neuroimaging

Kathryn Davis
Center for Neuroengineering & Therapeutics, University of Pennsylvania
Department of Neurology, Hospital of the University of Pennsylvania

The Davis Lab focuses on the evaluation and clinical translation of novel methods for localizing and characterizing seizure foci. Dr. Davis' work utilizes both the advancing fields of multimodality neuroimaging in addition to electrophysiology with an ultimate goal of improving the treatment of epilepsy patients. Dr. Davis will review current qualitative clinical treatment paradigms for drug resistant epilepsy. There remains an unmet clinical need for reliable quantitative tools to localize seizure networks noninvasively. She will present her lab's ongoing work incorporating quantitative analysis of structural and functional imaging modalities in the drug resistant epilepsy patient population. Recent and ongoing work connecting intracranial EEG functional networks to underlying structural networks holds promise for predicting seizure spread and the impact of surgical approach using noninvasive imaging.

Translational Neuroscience: from bifurcations to personalised medicine

Viktor Jirsa
Institut de Neurosciences des Systèmes, Inserm UMR1106, Aix-Marseille Université, Faculté de Médecine, Marseille, France

Over the past decade we have demonstrated that the fusion of subject-specific structural information of the human brain with mathematical dynamic models allows building biologically realistic brain network models, which have a predictive value, beyond the explanatory power of each approach independently. The network nodes hold neural population models, which are derived using mean field techniques from statistical physics expressing ensemble activity via collective variables. Our hybrid approach fuses data-driven with forward-modeling-based techniques and has been successfully applied to explain healthy brain function and clinical translation including stroke and epilepsy. Here we illustrate the workflow along the example of epilepsy: we reconstruct personalized connectivity matrices

of human epileptic patients using Diffusion Tensor weighted Imaging (DTI). Subsets of brain regions generating seizures in patients with refractory partial epilepsy are referred to as the epileptogenic zone (EZ). During a seizure, paroxysmal activity is not restricted to the EZ, but may recruit other brain regions and propagate activity through large brain networks, which comprise brain regions that are not necessarily epileptogenic. The identification of the EZ is crucial for candidates for neurosurgery and requires unambiguous criteria that evaluate the degree of epileptogenicity of brain regions. Stability analyses of propagating waves provide a set of indices quantifying the degree of epileptogenicity and predict conditions, under which seizures propagate to non-epileptogenic brain regions, explaining the responses to intracerebral electric stimulation in epileptogenic and non-epileptogenic areas. These results provide guidance in the presurgical evaluation of epileptogenicity based on electrographic signatures in intracerebral electroencephalograms and have been validated in small-scale clinical trials. The example of epilepsy nicely underwrites the predictive value of personalized large-scale brain network models.

Brain network trait and dynamic states in genetic generalised epilepsy and My Seizure Gauge: a new multicentre project

Mark Richardson
Institute of Psychiatry, Psychology & Neuroscience, King's College London

Background: Noninvasive wearable biosensors may be capable of forecasting the probability of seizures. However, rigorous testing with EEG-based seizure records is needed to develop and validate such a system.

Materials and Methods: This three-year project is organized into three phases. In year 1, commercially available wearable sensors are evaluated for signal quality, patient acceptability, and potential to detect and predict seizures in patients undergoing invasive EEG, ambulatory scalp EEG, or hospital scalp EEG. Biosignals are correlated with confirmed clinical and electrographic seizure events. In year two, patients trialing sub-scalp EEG monitoring devices (UNEEG SubQ, or Epi-Mynder subscalp) or an ambulatory intracranial EEG device (Medtronic RC+S) will wear sensors for multiple months to correlate biosignal records with EEG seizure annotations. In year three, a machine learning competition to develop forecasting algorithms on biosignals will be conducted. Biosignals evaluated in year 1 include photoplethysmography (PPG), accelerometry (ACC), electrodermal activity (EDA), electromyography (EMG), scalp EEG, heart rate (HR), and Biosensors under evaluation in year 1 include the Empatica E4 watch, the GeneActiv actigraphy watch, the EpiTel EpiLog scalp EEG sensor, ByteFlies sensor dots, the Biovotion Everion armband, and the Equivital TnR vest. In addition, surveys of mood and premonitory symptoms (Haut, 2012) will be evaluated as possible seizure predictors in years 1 and 2 of the project.

Results and Conclusions: To date, we have enrolled 55 patients and recorded 115 seizures over a total of 296 days. The enrolled patient group is 53% female with a median age of 32 years. Sixteen patients (29%) were undergoing stereotactic EEG, 29 (53%) ambulatory scalp EEG, 1 (2%) subdural invasive EEG, and 9 (16%) scalp EEG. Seven patients enrolled (13%) were pediatric. Subjects' seizure localizations were wide ranging, including left temporal (4, 7%), right temporal (3, 5%), right frontal (1, 2%), right occipital (2, 4%), and generalized or non-localized (8, 15%). Twenty six patients (47%) did not have seizures with a clear EEG correlate during monitoring, but may have had behavioral spells or other events. In total 16 seizures have been recorded with EMG, 9 with wireless scalp EEG, 30 with wrist PPG, 37 with chest PPG, 58 with wrist ACC, 53 with chest ACC, and 30 with EDA.

Epilepsy networks across spatial scales

Cathy Schevon
Dept of Neurology, Columbia University

The clinical practice of epilepsy surgery is founded on the idea that seizures arise from a definable seizure source that is restricted to a small neocortical or mesial temporal brain region. However, the appearance of EEG recordings often belies this simple model, and has led to an alternative proposal that seizures originate from distributed, potentially large-area networks. Previously, our group demonstrated that small seizure foci can be present despite apparent large-area EEG signatures, using a combination of animal studies and microelectrode recordings of human seizures. The key observation is that synaptically transmitted, excitatory barrages travel outward from the locus of seizing brain, triggering a powerful inhibitory response and creating an EEG signature that may be indistinguishable from that recorded from the seizing brain territory. We now extend this model to explore the long-range dynamics of seizure propagation in human and animal recordings, and discuss implications for epilepsy surgery approaches and outcome prediction.

From cerebral malaria to epilepsy in human and in animal models

Paddy Ssetnongo and Bruce Gluckman
Department of Engineering Science and Mechanics, Penn State University, University Park, Pennsylvania 16802
Center for Neural Engineering, Penn State University, University Park, Pennsylvania 16802

Cerebral malaria (CM) is arguably the leading cause of epilepsy worldwide. Survivors of CM have at least a 6-fold higher incidence rate of epilepsy than those who never had malaria; and population rates epilepsy rates in regions where malaria is endemic are of order 3-4 times that in places without. We'll discuss epidemiological, clinical and experimental malaria research that highlight new dynamics of acute brain infection and cerebral vasculature pathology, how those link to likely processes involved in epileptogenesis and epilepsy. We will include discussion of our own work developing a murine model of post-CM epilepsy, findings related to detection of epileptogenesis, and some novel findings related to seizure dynamics from this and related models.

What can micro- and macro-scale computational models reveal about epileptogenesis and ictogenesis?

Fabrice Wendling
INSERM U1099, LTSI, Rennes, France

The processes of epileptogenesis (development of epilepsy) and ictogenesis (transition from interictal activity to seizure) remain unclear. In both cases, pathological mechanisms occur at the level of neurons, neuronal assemblies and large-scale networks leading to electrophysiological markers of

epileptic activity: epileptic spikes, high frequency oscillations (HFOs) and seizures. These mechanisms are not mutually exclusive, they act in synergy resulting in the hyperexcitability in underlying epileptogenic systems. In this presentation, I will show how neurophysiologically-plausible models of epileptic activity can be used to investigate these mechanisms. With a special emphasis on the hippocampal activity recorded in various experimental models (in vivo and in vitro) as well as in epileptic patients, I will describe some results and insights that are gained from computational models, at two different levels of description: microscopic (detailed network of neurons) and macroscopic (neural mass). At each level, it will be shown how HFOs, spikes and seizures can be generated depending on the model features. The replication of observed signals, the prediction of possible mechanisms as well as their experimental validation will be presented and discussed; as are the advantages and limitations of the two modeling approaches.

Contributed Talk Abstracts

Implementing Horsley's dream: Stimulation-responses to uncover the epileptogenic network prior to epilepsy surgery

Gerold Baier
University College London

Liyuan Zhang[α]
[α]Beihang University, Beijing, China

"The exact localization [of area to be removed] could be ascertained by the use of the induction current" was how Victor Horsley described the use of electrical stimulation to inform epilepsy surgery [1].

The details of the observations leading to the localisation are not known but Penfield and Jasper elaborated that one important aspect is the observation of abnormal responses to electrical stimulation, the so-called afterdischarges (ADs). ADs can vary from a few isolated spikes in only one location to full clinical seizures. However, their intended use to contribute to surgical decision has led to inconclusive results and therefore abnormal stimulation-responses are in general not used in this context.

We conjecture that reasons for this failure are naive assumptions about the dynamical constellation underlying epileptic seizures. It is now established that the transitions to epileptic seizure rhythms stem from an interplay of global and local excitability as well as short and long-range connectivity in conjunction with (brain-)internal and external perturbations. A large number of sophisticated analysis and computational modelling of clinical data is available for adaptation to the situation of an individual surgical candidate.

We will outline how the analysis of invasive recordings that contain spontaneous epileptic activity and responses to electrical stimulation can be used to tailor a computational model with data-based assumptions about local and global heterogeneities, connectivities and irritabilities. A stimulation-based sensitivity analysis can be performed to select optimal stimulation protocols [2]. These may be used to complement structural and functional criteria to infer the presumed epileptogenic network and thereby help "ascertain" the location and extent of area to be resected prior to surgery.

[1] V. Horsley, Brain-Surgery. Brit Med J 1886; 2:670–5.

[2] G. Baier, P.N. Taylor, Y. Wang, Understanding epileptiform after-discharges as self-terminating transients. Front. Comput. Neurosci., 18 April 2017. https://doi.org/10.3389/ fncom.2017.00025

Multidien Chronotypes in Human Focal Epilepsy

Maxime O. Baud[a,b]
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[b]Wyss Center for Bio- and Neuro-technology, Geneva, Switzerland

Marc Grau Leguia[a,b], Thomas K. Tcheng[c], Vikram R. Rao[d], Maxime O. Baud[a,b]
[a]Sleep-Wake-Epilepsy Center and Center for Experimental Neurology, Neurology Department, Inselspital University Hospital, University of Bern, Switzerland
[b]Wyss Center for Bio- and Neuro-technology, Geneva, Switzerland
[c]NeuroPace, Inc., Mountain View, California, United States
[d]Neurology Department and Weill Institute for Neurosciences, University of California, San Francisco, California, United States

Epilepsy, one of the most common neurological disorders, is characterized by spontaneous, seemingly random seizures interleaved with seizure-free periods. Personalized treatments for seizure prevention may be possible but depend critically on the ability to anticipate seizure timing. In a recent analysis of 37 patients with epilepsy implanted with a device that provides chronic electrocorticography (ECoG; RNS®System, NeuroPace, Inc.), we uncovered multidien (multi-day) rhythms of interictal epileptiform activity (IEA) that are biomarkers for seizure risk (Baud et al., 2018). Here, using similar methodology, we extend these findings to a larger cohort of RNS System patients (N=199) who charted their seizures on a daily basis over years (median: 9.5 years). First, we characterized multidien rhythms of IEA in chronic ECoG. Using a measure of spectral entropy against surrogate time-series, we found that more than 80% of patients had multidien rhythms of IEA for at least 70% of the recording duration. Second, we classified patients by their multidien IEA periodicity and found five clusters, centered around 7 days, 9–10 days, 14–15 days, 25–30 days, and 35 days. Third, we found that the timing of clinical seizures reported by patients depended on multidien IEA phase (phase-locking values: 0.2–0.8). The high prevalence of multidien IEA rhythms in this large cohort suggests that seizure risk estimation using these biomarkers may have broad applicability. Our findings underscore the power of chronic recordings of brain activity to reveal patterns that influence seizure timing.

Virtual resection predicts surgical outcome for drug resistant epilepsy

John Bernabei
Department of Bioengineering, University of Pennsylvania

Lohith G. Kini[a,b], John M. Bernabei[a,b], Thomas Campbell Arnold[a,b], Fadi Mikhail[b,c], Peter Hadar[b,c], Preya Shah[a,b], Ankit N. Khambhati[d], Kelly Oechsel[b,c], Ryan Archer[b,c], Jacqueline Boccanfuso[b,c], Erin Conrad[c], Joel Stein[e], Sandhitsu Das[e], Ammar Kheder[c], Timothy H. Lucas[f], Kathryn A. Davis[b,c], Danielle S. Bassett[a,g,h,i], Brian Litt[a,b,c,f].
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[c]Department of Neurology, Hospital of the University of Pennsylvania.
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[g]Department of Electrical & Systems Engineering, University of Pennsylvania.

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Patients with drug-resistant epilepsy often require surgery to become seizure-free. While laser ablation and implantable stimulation devices have lowered the morbidity of these procedures, seizure-free rates have not dramatically improved, particularly for patients without focal lesions. This is in part because it is often unclear where to intervene in these cases. To address this clinical need, several research groups have published methods to map epileptic networks, but applying them to improve patient care remains a challenge. In this study we advance clinical translation of these methods by: (1) presenting and sharing a robust pipeline to rigorously quantify the boundaries of the resection zone and determining which intracranial EEG electrodes lie within it, (2) validating a brain network model on a retrospective cohort of 28 patients with drug-resistant epilepsy implanted with intracranial electrodes prior to surgical resection, and (3) sharing all neuroimaging, annotated electrophysiology, and clinical metadata to facilitate future collaboration. Our network methods accurately forecast whether patients are likely to benefit from surgical intervention based on synchronizability of intracranial EEG (area under the ROC curve of 0.89). We further report that removing synchronizing brain regions is associated with improved clinical outcome, and postulate that sparing desynchronizing regions may further be beneficial. Our findings suggest that data-driven network-based methods can identify patients likely to benefit from resective or ablative therapy, and perhaps prevent invasive interventions in those unlikely to do so.

Reducing the need for invasive intra-cranial monitoring for epilepsy surgery.

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The current pre-surgical workup for epilepsy surgery requires invasive intracranial electroencephalography (iEEG) to identify the epileptogenic zone (EZ). However, a major limitation of this approach is that it assumes the implanted grid captures the entirety of the seizure generating network. At present it is unclear for which cases this assumption is valid. Recent advances in sophisticated time-series analysis, network analysis, and dynamic modelling have demonstrated feasibility for objectively and systematically identifying whether or not the EZ is appropriately captured by the iEEG grid placement as well as identifying the optimal resection site (Proix et al., 2017).

High-density EEG (hd-EEG) and MEG coupled with source reconstruction algorithms are non-invasive recording techniques that can reveal properties of the seizure generating network, without the spatial constraints associated with iEEG recordings. In this study, we have captured 35 seizures simultaneously with hd-EEG and MEG from 13 patient studies with focal epilepsy (Plummer et al., 2019). With this dataset, we create "virtual grids" in multiple brain regions in reconstructed source space and apply time-series analyses and dynamic modelling to (1) identify the grid that best overlaps with the EZ and (2) predict the optimal resection site within that grid. Our study aims to examine the translatability of these computational techniques from iEEG to non-invasive EEG and MEG, which would lead to the development of novel approaches for identifying the EZ safely and non-invasively during the pre-surgical workup. The successful implementation of such methods would lead to significant benefits for people with intractable seizures: making surgery more available, minimising invasive recordings and therefore mitigation of risks, as well as improved surgical outcomes.

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Therapy proposer and evaluation tools developed from mining big epilepsy data

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Assessing patient outcomes in epilepsy is an enduring challenge. Daily reports of seizure counts can be unreliable, and seizures that occur during the night often go unreported. Another challenge is to expedite the process of finding optimal neurostimulator settings and anti-epileptic drugs. Often this is an iterative and time-consuming process, requiring months after a therapy adjustment to assess effectiveness before making subsequent adjustments. In addition to providing responsive neurostimulation to epilepsy patients, the NeuroPace®RNS®System also captures short electrocorticographic recordings of brain activity (ECoGs). These recordings are typically 90 seconds long, have 4-channels of data sampled at 250 Hz, and may be captured at specific times of day (scheduled) or when long abnormal epileptiform events (typically electrographic seizures) are detected. Over 3 million ECoG records from over 2,500 patients have been captured with the RNS System to date. Statistical data analysis and deep learning methods were applied to scheduled ECoG records to identify electrographic correlates of clinical outcomes in patients with mesiotemporal and neocortical onset epilepsies. Machine and deep learning algorithms trained with these electrographic features can assess clinical outcomes in new patients with over 75% accuracy. Such therapy evaluator tools trained solely on scheduled ECoG records can be used to help physicians assess patients' outcomes more quickly – within days and weeks instead of months. A prototype therapy proposer tool based on unsupervised clustering of deep learning features was built for finding RNS clinical trial patients with good clinical outcomes who are similar (i.e., with similar clinical, demographic and electrographic features) to a given new patient. Therapy settings (i.e., neurostimulator detection and stimulation settings and anti-epileptic medications) from the clinical

trial patients can be used to propose potential options for the new patient to expedite the process of searching through the vast therapy parameter space.

Objective treatment optimization and what to learn from 11,774 hours of ultra long-term subcutaneous EEG from nine patients

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In epilepsy, the treating physician has a blind spot when it comes to the effect of the treatment. Patients are known to underreport seizure frequencies and sometimes fill in seizure diaries in the waiting room of the clinician. We tested a minimally invasive device developed for ultra long-term subcutaneous EEG monitoring of epilepsy patients over periods of months in the patient's everyday life.

We present the first data ever recorded on epilepsy patients based on nine subjects with temporal lobe epilepsy. An impressive 11,774 hours of EEG were recorded from merely nine subjects in a discrete and unobtrusive way. Four of the subjects had furthermore a 2-5 days simultaneous recording in the epilepsy monitoring unit (EMU).

We investigate the correlation between EMU recorded scalp EEG and simultaneously subcutaneous EEG by time-frequency analysis across an array of clinically relevant waveforms and patterns. We also explore the correlation between the reported number of seizures in the diary with the actual number measured with the continuous recorder and the impact of changing the anti-epileptic drug dosing on seizure frequency.

Finally, we discuss how this extensive amount of data can lead to optimized treatment for the patients, how understanding the temporal pattern of seizure occurrence can lead to better personalised treatment and why reliable algorithms for detection of seizures is necessary before clinicians are able to use this kind of devices.

Critical slowing as a biomarker for seizure susceptibility

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Epilepsy is characterised by seemingly random and unexpected seizures. Long term intracranial EEG (iEEG) studies have recently discovered that seizures in fact follow cyclic rhythms lasting days to months [1]. While the underlying cause of these rhythms remain unknown, computational models describing the brain as a dynamical system suggest that seizures are preceded by critical slowing – a theory describing a system's progressive loss in resilience as it approaches a tipping point (i.e. seizure). As such, tracking markers in the EEG related to critical slowing can serve as a biomarker for seizure susceptibility and could lead to the development of improved seizure forecasting algorithms.

In this study, we tracked two markers of critical slowing – autocorrelation and variance – in 14 patients with focal epilepsy. Critical slowing suggests that seizures occur on the rising phase of these two signals. Recordings were obtained using an implanted device that captured continuous iEEG signals over an average of 1.5 years per patient [2]. The autocorrelation and variance of the iEEG were computed at 2 minute intervals over the duration of the recordings.

Our results demonstrate that seizures are indeed governed by patient specific rhythms in the autocorrelation and variance signals and that these rhythms underlie seizure susceptibility. Seizures were linked to increases in the two signals, as expected from a critically slowing process. Seizure forecasting using the autocorrelation and variance signals produced the best pseudoprospective forecasting yet obtained on this dataset, demonstrating the utility of tracking these markers for seizure susceptibility. This work provides much needed evidence for a dynamical systems approach underlying seizure susceptibility. Furthermore, our work demonstrates the clinical utility of using critical slowing and its potential for the titration of therapies to treat the disease.

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Decrease in neuronal network resilience precedes seizures at multiple temporal scales.

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Introduction: The transition to epileptic seizure represents a sudden and abrupt shift between distinct dynamic regimes of the brain. In some complex systems, the transition between contrasting states can be preceded by detectable changes in their dynamics. These changes manifest as early warning signals, which mark the approach of the critical threshold. This study aimed to examine whether seizures are preceded by detectable changes in the brain's resilience.

Methods: Spontaneous seizure-like events were induced by perfusing the rat hippocampal slices with artificial cerebrospinal fluid containing 8 mM potassium. In vivo, chronic epilepsy and seizures were induced by intrahippocampal injection of tetanus toxin. In both preparations, spontaneous local field potentials were recorded, and properties of early warning signals of critical slowing were extracted from the signals.

Results: In vitro, seizures were preceded by a progressive increase in lag-1 autocorrelation and variance of preictal data when compared with surrogates. These changes ran in parallel with the spatial expansion of preictal activity. Using active perturbation, we have demonstrated progressively increasing recovery time from the perturbation and weakening of resilience ahead of seizures. In vivo, no preictal changes in early warning signals were observed. However, the loss of resilience was present during the period of seizure quiescence, which separated periods of high seizure probability (seizure clusters).

Conclusions: In this study, we bring experimental evidence that the loss of the neural network's resilience via critical slowing precedes the onset of seizures or seizure clusters. It suggests that this dynamical phenomenon can occur at multiple temporal scales and be involved in different aspects of ictogenesis. The lowest resilience was observed immediately before the onset of a seizure or seizure cluster, when weak internal or external perturbations could tip the network dynamics to seizure.

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Seizure-related spatiotemporal fluctuations in infraslow networks in intracranial EEG and MEG

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We have recently reported that infraslow (<0.15 Hz) coherence in intracranial EEG (icEEG) changed significantly in states when patients were more susceptible to seizure [1]. Here, we sought to determine, with icEEG and magnetoencephalography (MEG), how infraslow envelope correlations change spatially in relation to seizure onset area (SOA) both around the time of seizure and in resting data.

We studied multi-day icEEG data collected from 13 medically refractory adult epilepsy patients who underwent monitoring and SOA localization at Yale-New Haven Hospital. The resting, hour-long MEG scans came from 31 medically refractory epilepsy patients seen at Wake Forest Baptist Medical Center. For both modalities, we estimated the average magnitude-squared coherence (MSC) below 0.15 Hz of traditional EEG/MEG frequency band power time-series for all contact pairs. For the icEEG data, we separated contacts into the clinically-defined SOA, peri-SOA (any contacts within 5 cm of, but not including, SOA contacts), and distant areas (contacts more than 5 cm from all SOA contacts). For the MEG data, we considered SOA sensors as those overlying the lobe of seizure onset. All other sensors were non-SOA.

Overall, there was a significant increase in average infraslow envelope MSC between 3 hours pre-seizure and 1 hour post-seizure relative to resting data. Interestingly, infraslow envelope MSC in contact pairs involving SOA peaked at 3 hours pre-seizure, then decreased monotonically until 1 hour post-seizure (though still remaining above baseline levels). For resting icEEG data, we found that infraslow MSC was decreased in SOA relative to other areas in all frequency bands except gamma, both before and after AED taper. In our resting MEG analysis, we found that infraslow MSC was decreased in SOA compared to non-SOA in all frequency bands.

Our icEEG and MEG results demonstrate that the architecture of the epileptogenic network in medically refractory patients is altered to the point that changes can be identified in resting data removed in time from seizure. The seizure-related, SOA-specific decreasing trend in MSC we observed in icEEG may reflect progressive pre-seizure disengagement of ictogenic circuitry from overlying infraslow modulatory activity.

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Epilepsyecosystem.org update: Searching for Seizure Prediction Solutions

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Epilepsyecosystem.org was launched in 2018 as an online platform to crowdsource solutions to seizure prediction over the long term. The platform leverages intracranial EEG data from the first-in-human seizure advisory system device trial. The ecosystem currently has 200+ registrants, 100+ members in its Github organisation where people can share code and discuss issues, and 60+ people are working with the data. Here we report progress with the ecosystem to date with a focus on the top 3 team algorithms applied to the problem of classifying interictal and preictal data. Algorithm 1: For features, power is calculated for 8 frequency bands. Then the data is standardised for every patient separately. A Convolutional Neural Network with weight shared convolutional layers is applied to every time step using the Adam optimiser and the class weights are adjusted to combat the imbalance. After initial training with all the subjects, the network is fine tuned for every patient separately. Algorithm 2: Numerous features were first calculated including (non-exclusively) absolute mean value, mean value, standard deviation, skewness, kurtosis, Hjorth parameters, spectral edge, correlation, power and Shannon's entropy across energies in each frequency band (0.1-4 Hz, 4-8 Hz, 8-14 Hz, 14-32 Hz, 32-70 Hz), and correlation of the powers between channels. These features are then used to train an ensemble of models consisting of linear regression, multiple decision tree models and support vector classifier for each patient. The mean ensemble output is used for classification. Algorithm 3: A Convolutional Neural Network is applied to raw EEG time-series in a patient specific manner with no spatial information included. Out-of-sample average AUC testing performance for Algorithms 1, 2 and 3 was 0.84, 0.83 and 0.77, respectively as compared to 0.72 for the previous benchmark. Future work will assess performance of these and more methods on the full trial dataset.

Dynamics of EEG-based functional connectivity in infantile spasms and healthy infants

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Infantile spasms (IS) is associated with many underlying etiologies, yet the brain activity of children with this disease, measured with electroencephalography (EEG), tends to exhibit certain shared characteristics. Our work has focused on elucidating the common underlying networks that mediate this activity. We first present results from a retrospective study of EEGs from 21 IS subjects and 21 normal controls. We show that IS patients exhibit stronger functional connections compared to controls; these networks are highly individualized, and they are more stable than those of control subjects. Successful treatment is associated with a reduction in strength and stability to control levels, and strong pre-treatment functional connectivity is predictive of favorable treatment response. This demonstrates the value of functional connectivity as a marker of IS and treatment response. To evaluate the temporal dynamics of this marker during treatment initiation, we prospectively obtained 24-hour EEG recordings for 27 normal control subjects as well as 48-72 hour recordings for 13 IS subjects immediately upon

steroid treatment initiation. For each subject, functional connectivity was measured in 5-minute windows with 90% overlap to assess temporal network changes. We show that wakefulness and sleep are associated with distinct networks, and these two states can be reliably classified using principle components analysis. Consistent with the prior analysis, these networks are subject-specific and stable over many hours for both groups. Sleep and IS are associated with stronger connectivity, and we show that network strength is significantly modulated by circadian rhythm. We are currently working to correlate changes in functional connectivity in IS subjects to clinically-evaluated treatment response, and at the completion of the study we will also be able to evaluate their relationship to long-term epilepsy and neurocognitive outcomes.

Seizure prediction and seizure control: cautionary tales from measuring resilience of the human epileptic brain

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Efficient seizure-control techniques based on seizure-prediction profits from knowledge about how the epileptic brain's resilience changes over time. There are many approaches to estimate resilience, however these approaches require perturbing the system or full knowledge of the system's dynamics. Here, we present a novel data-driven, non-perturbative approach to estimate brain resilience [1]. Using our approach, we investigate time-dependent changes of resilience in 43 subjects with epilepsy. Unexpectedly, we observe resilience to increase during the pre-ictal phase in the majority of the 112 evaluated seizures. This increase even exceeded physiologically-induced changes (e.g., due to circadian rhythms). We discuss the possible impact of our findings with respect to developing novel seizure-control techniques.

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Slow shifts in seizure pathways in individual patients with focal epilepsy

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Seizures form pathways through the space of possible neural dynamics. Although these pathways are often described as stereotyped in a given patient, distinct and different populations of seizures can co-exist in the same individual. Little is known about the prevalence, characteristics, or implications of within-subject seizure variability. Here we quantitatively compare within-subject seizure network dynamics using intracranial recordings of 700 seizures from 31 patients with focal epilepsy (mean 16.5 seizures/subject) and three canines with focal-onset seizures (mean 62.3 seizures/subject). In all subjects, we find variability in seizure onset, progression, and termination, leading to either a spectrum or clusters of different seizure dynamics. Seizures with more similar state progressions tend to occur closer together in time, but do not necessarily have similar durations or circadian profiles. These results suggest that slow modulatory processes shape within-subject seizure dynamics, leading to variable seizure pathways that may require tailored treatment approaches.

Seeing the big picture: expanding the scope of electrical and biochemical biomarker research

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Rationale: Tremendous effort has been placed in identifying ictogenic or epileptogenic biomarkers. Research has identified potential EEG targets such as HFOs as well as biochemical targets such as alterations in molecules such as glutamate and GABA. However, the precision necessary for such work has limited the research scope: HFOs are typically analyzed only during brief epochs, and microdialysis experiments typically analyze only a few chosen molecules. We sought to analyze these biomarkers on a broader scale to identify multivariate effects.

Methods: For HFOs in humans with epilepsy, we utilized a validated, automated detector that was capable of recording all intracranial HFOs for the entire hospitalization (mean=7 days). We then identified all 10-minute epochs of slow wave sleep and compared the HFO distribution in each of them using blind source localization. For microdialysis in pilocarpine rats, we collected serial samples from the hippocampus of awake behaving animals and processed 24 molecules simultaneously with high performance liquid chromatography. The animals were placed into a controlled pro-ictal state by adjusting the random synaptic input to the hippocampus. Results were analyzed using univariate and multivariate techniques.

Results: While short time windows or individual molecules yielded significant results similar to previous work, expanding the scope demonstrated more complex behaviors: 1) the location of peak HFO counts changed depending on the epoch sampled; 2) several less-recognized molecules had more significant effects than GABA and glutamate; 3) proictal changes varied between different animals

and different seizures in the same animal ; 4) multivariate techniques demonstrated several novel relationships that have not been accounted for in previous biomarker research.

Conclusions: When looking with limited scope, both HFOs and microdialysis yield significant, yet incomplete, results. Future work should include multivariate analyses that evaluate the “big picture”.

Poster abstracts

Automatic Epileptic Tendency Screening using Statistical Features of MEG Data and SVM

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In this paper, a novel Magnetoencephalography (MEG) signal classification method based on statistical features for classifying multi-channel MEG signals into epileptic and healthy subjects is proposed. The method is composed of two phases: statistical feature extraction and classification. After segmenting the multi-channel signal into 1-minute non-overlapping segments, eight statistical features are extracted from each segment of each brain region to form the feature vector. The features are max, min, standard deviation, skewness, kurtosis, mean, median, and interquartile range. The feature vectors are used for training a support vector machine (SVM) classifier, which is then employed in the testing phase. A four-fold cross-validation strategy is adopted in the experiment. The proposed method is evaluated using real MEG data obtained from 32 healthy subjects and 32 epileptic patients and achieved a sensitivity of 99.35%, a specificity of 95.47%, and an accuracy of 97.41%. The obtained results show good promise of the proposed method as a screening tool for epilepsy diagnosis.

Beyond the intervention: long-term morphological changes after surgical resection

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The brain is characterized as a network of interdependent regions that carry out complex tasks. In epilepsy it is believed that seizure generating tissues utilize network structure for the pathological spread of synchronous electrical activity. The primary treatment for refractory epilepsy is surgical excision of brain regions containing epileptogenic tissue. Given the complex connectivity between brain regions, we anticipate that resective surgery will cause long-term restructuring of the brain network. Loss of functional input and compensatory neuroplasticity are expected to result in morphological changes for regions that are associated with resected tissues. Here we characterize alterations in brain morphology that result from the most common surgical procedure, a temporal lobectomy. Using image processing pipelines provided by Advanced Normalization Tools (ANTs), we compare cortical thickness and regional volumetric between presurgical MRI and 1-5 years post-operative imaging. We demonstrate that in the temporal lobe contralateral to surgical excision, there are decreases in cortical thickness. Additionally, we find that cortical thickness increases in regions outside the temporal lobe that are associated with the limbic system. Our findings suggest that brain networks adapt to tissue removal. The decrease in contralateral temporal lobe volume could result from the loss of functional input from the symmetric hemisphere, while the increase in remote task associated regions is likely a compensatory response. Establishing morphological changes is an important step towards understanding patient outcomes, including seizure-freedom and cognitive deficits. Furthermore, the methodology we developed may be adapted to study long-term morphological alteration in other lesional diseases, such as stroke and brain tumors.

Identification of sinusoidal electrical stimulation parameters able to abort epileptic activity based on co-dimension 2 bifurcation analysis

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Neurostimulation and neuromodulation have long been identified as promising procedures to impede seizures that dramatically impair the quality of life of patients suffering from epilepsy. However, despite recognized applicability, acknowledged effects, safety and encouraging results, brain stimulation cannot be routinely indicated as a treatment for focal epilepsies. From a clinical viewpoint, stimulation parameters are chosen empirically and a rational definition of stimulation protocols is still missing. From a theoretical viewpoint, predicting and understanding brain network response to electrical stimulation is a difficult and open issue. In this study, we started from the biologically-inspired Wendling's neural mass model to simulate neuronal assembly response to local electrical stimulation applied at seizure onset. We investigated the model's response to sinusoidal stimulation using numerical bifurcation analysis. First, we studied the model output (local field potentials, LFP) as a function of the stimulation amplitude at fixed frequency (>90Hz) based on previous studies. Two types of bifurcation points denoting changes in stability were identified; limit points and Neimark-Sacker (torus) bifurcation. The latter represents a critical point, since it enabled us to determine effective parameters capable to abolish epileptic activity. Second, we conducted a novel co-dimension 2 bifurcation analysis in amplitude and frequency starting from this point. We concluded that brain stimulation effectiveness depends on both amplitude and frequency. Furthermore, the 2D-parameter space (amplitude, frequency) can be divided into two regions: effective and ineffective in aborting epileptic activity. Interestingly, the system dynamics becomes frequency-independent, once a limit value is reached. In conclusion, this model-guided approach brings further support for the identification of optimal stimulation parameters to switch from epileptiform to background activity patterns.

Long-term changes in response to neurostimulation and synaptic dynamics in the epileptic brain

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Responsive neurostimulation (RNS) is emerging as an important potential treatment for pharmacoresistant epilepsy. RNS implanted devices provide only intermittent, discrete instances of stimulation, yet have been shown to have a cumulative effect on seizure burden in at least some patients over several months or even years. Thus RNS may induce two types of changes in the system: An immediate change in local brain activity in response to individual stimulation events, but also slower changes in micro-circuitry coupling that accumulate over time in a way that affects seizure propensity. Here we investigate these effects using neural mass models of cortical microcircuitry. We parameterize a hierarchical Bayesian model of changes in synaptic coupling in these cortical microcircuits based on very long-term recording of 12 patients with implanted responsive neurostimulation devices. Our results

demonstrate that responsive neurostimulation cause both very short- (seconds) and very long-term (months) changes in the spectral profile of the iEEG recordings across a wide range of frequencies (10-50 Hz). Moreover we identify a minimum set of synaptic parameters that explains spectral changes induced by neurostimulation. Together, the results presented here provide insight into possible the synaptic mechanisms that shape the effect of responsive neurostimulation at the clinically relevant time scales.

Identification of Epileptic Neuronal Networks using Effective Connectivity

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Rationale: The rate of brain surgery failures in patients with refractory epilepsy remains significant. One possible explanation is the inaccurate localization of the seizure onset zone of ictal electroencephalography (EEG) recordings. Indeed, visual analysis of such recordings may be arduous especially if the ictal discharge appears widespread and/or propagates rapidly. Recent work suggest that modern techniques to analyze brain networks using quantitative connectivity approaches can be used to complement visual assessment of EEG recordings. In this work, we study the value of the spectrum-weighted adaptive directed transfer function (swADTF), an effective connectivity measure based on an adaptive multivariate autoregressive model [1], to identify epileptic neuronal networks in patients with drug-resistant epilepsies.

Methods: The swADTF was tested on 3 datasets of intracranial EEG (iEEG) recordings namely: 1) synthetic recordings consisting of a 9-node (3x3) connectivity pattern to which we added a white Gaussian noise [-12dB, 12dB], 2) recordings of 7 patients (21 seizures) with operculo-insular epilepsy admitted for surgical evaluation at our epilepsy monitoring unit, and 3) recordings of 12 patients (2694 seizures) implanted with the NeuroVista ambulatory monitoring device [2]. The relatively high number of seizures allowed investigating the reproducibility of results.

Findings: 1) Synthetic recordings: results demonstrated the ability of the swADTF to identify the generator of seizure activity in the presence of high noise levels; 2) Patients with operculo-insular epilepsy: swADTF-identified generators were within the resected volume for patients with good post-surgical outcomes (5 patients) while different or additional seizure foci were identified in patients with bad post-surgical outcomes; 3) Melbourne NeuroVista seizure prediction database: on average, for each patient, the same generator appeared during 82.87% of seizures.

Significance: Although more work is necessary, our preliminary findings suggest that the swADTF effective connectivity measure is a promising tool to provide quantitative identification of the epileptic network.

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Sub-lobar EEG source localization during seizures

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The value of EEG source localization of interictal epileptiform discharges (IEDs) to localize the epileptogenic focus has been shown repeatedly. However, the irritative zone does not necessarily correspond with the brain regions where the seizures originate from, i.e. the seizure onset zone (SOZ). For treating epilepsy the localization of the seizure onset zone is of utmost importance. In this study we analyze the value of ictal EEG source localization. 22 seizures of 4 extra temporal lobe epilepsy patients (1 cortectomies, 3 disconnections) have been localized and were compared to the resection or disconnection that rendered the patient seizure free. The seizure epochs were marked by an expert electrophysiologist who indicated the electrophysiological onset and band of rhythmic discharges. From the marker an epoch of 1s before to 3s after was segmented. EEG source localization was performed at each time point to estimate the activity of 50 sub-lobes. The sub-lobe with the highest activity in the provided frequency band was identified as SOZ. In (16/22)73% of seizures the localization corresponded with the resection/disconnection that rendered the patient seizure free. This indicates that ictal EEG source localization has potential to be used during the presurgical evaluation.

Do important vertices and edges in evolving epileptic networks carry predictive information of seizures?

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Dynamical aspects of spatially extended complex systems are captured in edge properties, such as their weight. Hence, understanding "importance" as a characteristic of edges may lead to a better comprehension, control, or manipulation of spatially extended complex systems such as the brain.

Analyzing evolving epileptic networks derived from the long-lasting invasive EEG recordings of 43 subjects with drug resistant epilepsy, we address the question which constituents are important for the network's dynamics. We present novel edge centrality concepts as well as a decomposition method to identify edges/groups of edges that are important between other pairs/groups of vertices. Eventually, we investigate whether time-variant changes of importance of vertices and edges allow reliable identification of pre-seizure states.

Detecting focal seizures in multimodal biosignal data from wearables

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Background:

In Epilepsy research, wearables have been considered to detect and log seizures of patients with epilepsy (PwE) in their day-to-day environment. These are most commonly smartwatch-like devices or fitness trackers recording biosignals such as accelerometry (ACC), electrodermal activity (EDA), and blood pulse via photoplethysmography (PPG). These biosignals have been shown to give sufficient indication towards epileptic seizures, with research focusing on monomodal and multimodal detection of generalized tonic-clonic seizures (GTCS) [1,2].

Materials and Methods:

Here, a first look is offered into one possible multimodal approach to detect focal seizures (FS), which is a relatively new and unexplored avenue in epileptic seizure detection. A new and extensive data set of biosignal data from wearables worn by PwE during video-EEG monitoring was recorded. A multimodal seizure detection pipeline for variable types of seizures was implemented, and a large feature set was calculated from biosignals like ACC, EDA and PPG. The feature set specifically mixes features from all biosignal modalities, and at multiple feature window lengths. This allows for a comprehensive feature selection particularly for different types of FS.

Results and Conclusions:

Preliminary tests of the detection pipeline on individual patients that have multiple FS with motor components recorded show promising results. For example, in an event-based leave-one-seizure-out cross-validation on three select patients with varying levels of motor components in FS, a simple Random Forest model could detect 100%, 78%, and 57% of seizures respectively. While one patient had multiple characteristic FS with tonic and clonic components that were robustly detectable, the patient with the worst detection rate showed mainly pedal, manual and oral automatisms. In the future, the cross-patient behavior of such a system needs to be evaluated, as well as the performance on different types of seizures like autonomic or dyscognitive FS.

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High-Frequency Oscillations in Long-Term Intracranial EEG

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High-Frequency Oscillations (HFOs) have been proposed as promising new biomarkers in epilepsy [1]. They have been shown to localize in epileptic brain tissue and are believed to arise from seizure generation networks. However, most existing findings have so far been obtained from group analyses with small intracranial EEG (iEEG) datasets recorded over short durations. Limited evidence is available on the long-term spatiotemporal dynamics of HFOs within individual patients. This study aims to investigate how HFO rates change over time in long-term iEEG recordings, how their temporal patterns are associated with seizures and how these properties differ from spikes. Information on these might provide insight into the dynamics of epileptic networks and new personalized strategies for seizure management.

In this study, HFOs were automatically labelled from over a total of 7795 days of iEEG data recorded continuously from fifteen drug-resistant epilepsy patients [2]. The changing patterns of HFO rates were investigated for periodicity using autocorrelation and wavelet scalograms. The circadian phases of HFO rates were analysed and compared with seizures using circular statistics. Similar analyses were conducted for spike rates.

We observed that HFO and spike rates have high inter-patient variability and high temporal variability over the long durations of recording. Both measures showed clear evidence of repeated circadian variation patterns. For some patients, different channels showed different circadian variation patterns. In some patients, the circadian phases of HFO rates better aligned to the circadian phases of seizures compared to spike rates. In some other patients, the converse was true. Our findings suggest that the use of HFOs should be customized in a patient-specific manner and the temporal dynamics of HFO rates are likely to provide additional useful information for seizure prognosis.

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A simple biophysical model of ictal and interictal discharges: spatially homogeneous and 2D extended Epileptor-2

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A simple but biophysically sound model of interictal and ictal discharges (IDs) "Epileptor-2" [1; http://www.ioffe.ru/CompPhysLab/Epileptor-2.html] is described by ordinary differential equations for four variables: extracellular potassium concentration, intracellu-lar sodium concentration, membrane

potential and synaptic resource. Population activity is reflected in a single representative neuron and well compared to 4-AP-in-vitro model of epilepsy. The accumulation of potassium in the extracellular space predetermines the spontaneous occurrence of IDs. Each ID consists of a cluster of interictal-like events, which correspond to bursts of spikes in the single neuron. During an ID, sodium accu-mulates inside cells and activates the sodium-potassium pump, which then terminates the ID by restoring the potassium gradient and repolarizing neurons. Mathematically, the interictal-like events are stochastic high-amplitude oscillations, which in the case of ictal discharge generation are modulated by slow fluc-tuations in ionic concentrations. The transition to IDs with increasing bath potassium concentration is a non-smooth saddle-node-on-invariant-circle-like bifurcation. ID propagation due to potassium diffusion in the extracellular space is compared to its propagation by means of axo-dendritic con-nections. Ex-perimental data testify in favor of the second hypothesis. Providing a mini-mal biophysical description of ionic dynamics and network interactions, the proposed model "Epileptor-2" reproduces the epileptic discharges and may serve as a basis for more detailed models of epilepsy.

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The organization and resilience of epileptic network determine the ictogenetic nature of interictal epileptiform activity

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Introduction: The role of interictal discharges (IEDs) in the transition to seizure is still a matter of intense debate and available theories appear mutually exclusive. Studies demonstrate that IEDs can be either a seizure preventing, seizure facilitating or without impact of ictogenesis. In this study we aimed to explain the existing dichotomy from a dynamical perspective.

Methods: Isolated CA1 slices were perfused with artificial CSF containing high potassium (>8 mM). Field potentials from the hippocampal CA1 were recorded using extracellular electrodes. Interictal perturbations mimicking IEDs were delivered by stimulation of Schaffer collaterals.

Results: The CA1 network was perturbed with 1 Hz to mimic spontaneous IEDs. Stimuli that initiated after the end of the seizure delayed seizure onset by increasing the duration of the interictal period (>50% increase, n=41/7 stimulations/slices). To evaluate the observation that pro-seizure effect of IED occurs when the neural network is unstable, we have delivered a single stimulus either early after previous seizure or just before the next seizure. Only 38 % of early stimulations with the intensity of 300 μA were able to induce seizure (n=3/8 stimulations). In contrary, preictal stimulation with the intensity of 200 μA and 300 μA induced seizure in all cases (6/6 and 4/4 stimulations respectively).

Conclusion: We demonstrated that the complex effect of IEDs depends on when they occur, how often they occur and how strong the perturbations are in respect to the instantaneous dynamical state of the seizure-generating network. Recent results also suggest that ictogenic potential of IEDs is also

determined by the spatiotemporal relationship between IED generating and seizure onset zones. Obtained results may have implications for design and optimization of brain stimulation therapy. Supported by grants AZV 17-28427A, 15-33115A and GACR 18-07908S.

Computational model explains acute and lasting effects of tDCS on epileptic activity

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Transcranial direct current stimulation (tDCS) is a widely used neuromodulation technique based on the use of weak electric currents (typically up to 2 mA, producing an electric field around 1 V/m on the cortex) delivered through scalp electrodes. tDCS has commonly been used to modulate cortical networks activity in a large panel of clinical conditions. Notably, cathodal stimulation have been shown to decrease cortical excitability in the context of epilepsy. Despite highly variable clinical results, some studies have shown a reduction of seizure frequency and/or a decrease of interictal epileptic activity just after or even several hours after cathodal tDCS.

However cellular mechanisms responsible for both acute and long-lasting effects of tDCS remain unclear. Indeed most in vitro studies investigating cellular mechanisms are biased as the electric fields intensity is 10 to 100 times higher than in actual tCS. While the impact of such low magnitude tDCS-induced electric fields might be almost negligible (0.12 mV depolarization of the cell bodies for each 1 V/m) at the level of a single neuron, the situation might be different at the level of local cortical networks when several thousand neurons are involved.

To tackle this question and generate mechanistic assumptions on acute and long-lasting effects of tDCS, we developed an innovative computational modeling approach, combining key features of both cellular and neural mass models. This model comprises 10 000 individual neurons connected by 5.106 plastic synapses, individually affected by tDCS, including pyramidal cells and 3 types of GABAergic cells (VIP-, Basket, and SOM+). The model integrates realistic information regarding the cortical layers, projection, connectivity and neurites orientation.

Simulating realistic electric fields in term of intensity, main results showed that 1) tDCS are best explained by an impact on presynaptic probability of release 2) long-lasting effects depend on glutamatergic synaptic plasticity 3) tDCS effects on plasticity increase with the size and connectivity of the network.

Unified dynamics of interictal events and absence seizures

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The dynamics of interictal events between absence seizures and their relationship to seizures themselves are investigated by employing a neural field model of the corticothalamic system. Interictal events are modeled as being due to transient parameter excursions towards the seizure threshold, in the present case by sufficiently temporally varying the connection strength between the cerebral cortex and thalamus. Increasing connection strength drives the system into 3 Hz seizure oscillations via a supercritical Hopf bifurcation once the linear instability threshold is passed. Depending on the time course of the excursion above threshold, different interictal activity event dynamics are seen in the time series of corticothalamic fields. These resemble experimental interictal time series observed via electroencephalography.

It is found that the morphology of these events depends on the magnitude and duration of the excursion above threshold. For a large-amplitude excursion of short duration, events resemble interictal spikes, where one large spike is seen, followed by small damped oscillations. For a short excursion with long duration, events like observed interictal periodic sharp waves are seen. When both amplitude and duration above threshold are large, seizure oscillations are seen. Using these outcomes, proximity to seizure can be estimated and tracked.

Sleep and Seizures- how everyday variations in sleep can influence seizure likelihood

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The relationship between sleep and seizures is complex and bidirectional. Deviations from regular sleep patterns can influence seizure likelihood and in turn the occurrence of seizures can alter sleep. Numerous studies have shown that total sleep deprivation, for periods of 24 hours or longer, promotes seizure occurrence even in individuals that don't have epilepsy. However, the effects of small day-to-day deviations in sleep duration and quality on seizure likelihood have scarcely been addressed. Gaining a better understanding of the bidirectional relationship between sleep and seizures will likely improve seizure management.

A total of 4340 days of sleep-wake data were analysed across 10 patients with refractory epilepsy. Continuous intracranial electroencephalography data was sleep scored using a semi-automated machine learning approach. Data was categorised into wake, stages 1, 2 and 3 non-rapid eye movement (NREM) sleep and rapid eye movement sleep (REM) states.

Across the population the rate of seizures was highest during stage 1 NREM sleep. The occurrence of a seizure increased the duration of sleep and reduced sleep quality by increasing the degree of sleep fragmentation and the percentage of stage 1 NREM sleep at the expense of REM and deep (stage 3

NREM) sleep. These effects were more pronounced when the seizure occurred during sleep. Seizure likelihood was influenced by small variations in sleep duration and quality. For most, but not all, patients, both a decrease and an increase in sleep duration relative to the mean resulted in a higher likelihood of a seizure in the following 24 hours. We observed similar patient specificity in the effects of variation in sleep quality on seizure propensity.

Our results demonstrate that small deviations from regular sleep duration and quality can influence seizure likelihood, ultimately emphasising the importance of regular sleep patterns in reducing the occurrence of seizures in patients with epilepsy.

Mathematical analysis of seizure initiation and abortion in a neural mass model of the entorhinal cortex

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A large body of evidence shows that the closed-loop hippocampus-entorhinal (HIP-EC) circuit plays a crucial role in temporal lobe epilepsy (TLE). In this large-scale network, the EC has been identified as one of the critical structures involved in seizure generation. Experimental studies have shown that the EC can generate epileptiform activity independent of HIP inputs, and has been pointed out as a key structure in the interictal/ictal transition in TLE. Therefore, understanding the characteristics of this dynamical system is essential for designing methods to abort epileptic seizures [Sobayo and Mogul, Epilepsia 2016].

Here, we focused on a neural mass model of the EC which reproduces the local field potentials measured during background activity and during different stages of seizures, namely pre-ictal, fast onset, ictal-burst and termination [Labyt et al., J. Neurophysiol. 2006]. In accordance with anatomical descriptions, this model subdivides the EC in superficial and deep layers, and considers the synaptic interactions between principal neurons and interneurons. We first analyzed each layer separately to understand intrinsic dynamics, and discovered that bifurcations in the EC deep layer depending on the amplitude of average postsynaptic potentials lead to different behaviors, notably, epileptic activity. In particular, fast GABAergic interneurons determine the characteristics of ictal onset, while slow GABAergic interneurons are responsible for the seizure development. Contrary to the dynamic variability in the deep layer, the superficial layer possesses only equilibria in the parameter space under consideration and behaves as a “follower” of the deep layer activity. Finally, we derived parameter settings for two different stimulation strategies that mimic the effects of either optogenetics light source or bi-phasic electrical pulses on neuronal assemblies. Results show that targeting GABAergic interactions of the deep layer can induce a switch from ictal to background activity. These results contribute to the optimization of active, perturbation-based seizure abortion procedures.

Comparative evaluation of two study protocols for treatment studies in epilepsy and head tremor

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Episodic head tremor (HT) is a paroxysmal idiopathic movement disorder in dogs. The unpredictable occurrence of HT episodes resembles the clinical course of epilepsy with recurrent seizures. In general, episodic HT is a benign disorder which may spontaneously remit, yet treatment may be warranted in some severely affected dogs. In this study we used canine episodic HT with frequent episodes as a model to compare and evaluate two different epilepsy study protocols in a prospective blinded manner.

Material and methods: 24 dogs with frequent episodic HT were randomly and blinded assigned to treatment with either study drug or placebo for up to 3 months. Responder rates were assessed with two different methods: method 1, prolongation of HT free period by factor 3; method 2, $\geq$ 50% reduction of monthly seizure frequency. All dogs were offered to exit the study after the third HT episode following titration, but dogs were also free to continue treatment for up to 3 months. For all dogs, which continued the treatment, responder rates were calculated by the two different methods (method 1, method 2).

Results: Only dogs treated with the study drug were classified as responders when evaluated with method 1. The same dogs treated with the study drug and additional dogs treated with placebo appeared as responders when evaluated with method 2.

Conclusion: Method 1 appears more specific than method 2 for recognition of responders. In addition, method 1 offers early study exit points to the participants and thus avoids unnecessary exposure of participants to prolonged treatment with ineffective drugs. Future use of this approach in treatment studies for epilepsy is warranted.

Can we classify focal epileptic seizures?

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To date, there is no objective classification scheme for focal epileptic seizures. A classification of this type of epileptic seizures could not only provide insights into the onset and dynamics of such events but also suggest optimal therapeutic procedures.

In this study we propose a prototype of a classification scheme that consists of evaluating multifractal properties of ictal segments recorded from 12 patients undergoing evaluation for epilepsy surgery, with a total of 137 epileptic seizures. Once the multifractal metrics are obtained, we look at the spectral width and apply Principal Component Analysis to reduce the dimensionality of the data. A Dynamic

Time Warping (DTW) was applied as a measure of dissimilarity between the different seizures. The dissimilarity measure was used to obtain a dendrogram of the epileptic seizures with a complete-linkage hierarchical clustering method.

Our analysis shows that machine learning techniques are capable of finding similarities in different seizures that could be exploited for future classification schemes for focal epileptic seizures. Such a scheme could, in future, provide new ways of assessing potential treatments for patients.

Bispectrum analysis of iEEG: A new biomarker for seizure activity

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Background: While the field of seizure prediction and detection has made tremendous progress using intracranial electroencephalography (iEEG) classification algorithms in recent years, spectral band power remains the most commonly used feature for epileptic seizure analysis. Although band power can quantify phase changes, more complex measures related to the concept of cross-frequency coupling are required to track interactions between different frequency components of a signal. Our group has recently reported promising performances of bispectrum, a measure of nonlinear cross-frequency coupling, for seizure prediction in canine epilepsy [1]. In this work, we investigated the feasibility of distinguishing between preictal and ictal recordings based solely on bispectrum-extracted features in human iEEG.

Methods: Three quantitative bispectrum features were extracted from 30-sec windows of long-term human iEEG recordings from the Melbourne database acquired using the NeuroVista ambulatory monitoring device in 12 patients (1181 seizures) [2]. The data includes the ictal period and 60 seconds of preictal activity from 16 channels and only seizures lasting at least 30 seconds were selected. A t-test assessed the existence of statistically significant differences in each feature between preictal and ictal samples for each patient. Features were subsequently used as input to support vector machine (SVM) classifiers in a subject specific manner. Data were split on a seizure-per-seizure basis where 70% of seizures were used for training and 30% for testing.

Results: Statistical Analysis: t-tests showed significant changes ($p < 0.01$) in at least 2 bispectrum-extracted features between preictal and ictal periods for all patients. SVM Classification: Feature inputs to the SVM classifier, normalized and squared normalized entropy, and mean magnitude achieved respective average held-out accuracies of 86%, 81%, and 84% (lowest: 66%, highest: 100%). Furthermore, 8/12 patients achieved >90% test accuracy for at least one feature.

Significance: The bispectrum shows promise as a biomarker for different epileptic brain states.

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Subcutaneous sleep monitoring of epilepsy patients

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A good night's sleep is essential for the well-being of all people, but especially in people with epilepsy. One reason is because poor sleep quality increases the risk of seizures. Possible reasons for poor sleep are insufficient sleep, inadequate sleep hygiene, and anticonvulsants known to disrupt sleep. Gaining insight into the daily sleep structure of an epilepsy patient can aid individualized treatment of both the epilepsy, sleep and the interaction between the two. As the first, we show a proof-of-concept for sleep monitoring using a subcutaneous implant measuring the EEG in epilepsy patients.

Four patients with confirmed or suspected temporal lobe epilepsy was enrolled in the Epilepsy Monitoring Unit at the Zealand University Hospital, and were monitored with both routine scalp EEG and a novel device for subcutaneous EEG recording (24/7 EEG™ SubQ, UNEEG medical A/S , Lynge, Denmark) . In total, 11 nights were recorded. The scalp EEG was scored by a trained expert according to the AASM guidelines, and the resulting scalp-hypnograms together with the subcutaneous EEG were used to train and evaluate an automatic sleep scoring algorithm.

By training person specific models, we achieved a mean Cohen's Kappa value of 0.74 across recordings. This is comparable to the interrater agreement one would expect between two human raters from different sleep labs, as reported by Danker-Hopf et al [1]. When detecting sleep vs. wake, we achieved a sensitivity of 95.5 % and a specificity of 94.5 %, which is an improvement over the widely used actigraphy.

In conclusion, the results show that sleep monitoring epileptic patients using subcutaneous EEG is possible, even with a performance on pair with clinically acceptable standards. With the subcutaneous EEG recorder and our sleep detection algorithm, we believe we are one step closer to empowering the patient by offering objective sleep quality data.

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Quantitative metrics of background EEG data are associated with the seizure onset zone

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Objective. Methods to identify the epiletogenic zone, used to help guide resective surgery planning, are nearly all based on analysis of isolated discrete events: seizures, spikes, high frequency oscillations (HFOs), etc. However, computational models suggest that quantitative features of the interictal background EEG signal is a potential biomarker of seizure onset zone. Our goal is to test that hypothesis in a cohort of subjects with good (ILAE Class I) surgery outcomes.

Methods. Data were acquired from 15 patients, each with multiple days of intracranial EEG recording, sampled at over 4 kHz. Using only interictal data, we evaluated 40 features that were suggested by computational modeling to be indicative of the epileptogenic zone. HFOs and sharp transient artifacts were redacted using previously published automated detectors. Features were then calculated in mid- (30-80 Hz) and high- (80-500 Hz) frequency bands (20 features per each band) for every 5 minute time interval of interictal patient data. Features were normalized per time window, and the median of each feature over the full recording was computed, resulting in a single value for each channel. Logistic regression was used to assess association with the clinically-determined seizure onset zone (SOZ).

Results. A total of 8 features were found to be associated with the SOZ, including the skewness (p=0.001) and kurtosis (p=0.038) in the mid-frequency band and the mean (p=0.002) and kurtosis (p=0.002) of the curvature in the high-frequency band.

Conclusion. The interictal background (i.e. non-HFO) EEG contains information that can be used to localize the SOZ. Further work is needed to determine the best way to utilize this information to prospectively identify the epileptogenic zone.

Significance. Background EEG activity is altered in the epileptogenic zone, a potential biomarker independent of HFOs or epileptic spikes.

Seizure Prediction, Localisation, and Control with Graph Neural Networks

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Several works in recent literature have focused on applying machine learning techniques to graph-structured data. Indeed, exploiting the inherent relational dependencies between the elements of a system can provide an important inductive bias for explaining the behaviour of the system itself.

This is particularly true in neuroscience, where modelling the functional or structural connectivity among brain regions can highlight the dynamics of neurological phenomena and provide insights on the underlying causes. However, most works at the intersection of machine learning and neuroscience fail to take into account this networked structure in the inference process.

Graph neural networks (GNNs) constitute a recently proposed family of models that apply deep learning techniques to arbitrarily-structured graph data. Here we propose a machine learning framework for characterising and controlling epileptic seizures, using GNNs to learn from functional connectivity (FC) networks derived from intracranial electroencephalogram (iEEG) data. In particular, we

discuss three main subjects of research. First, we propose to use GNN-based methods for detecting and predicting epileptic seizures from sequences of FC networks. This was partly covered in [1], where we developed an unsupervised learning method for detecting arbitrary changes in graph streams, with applications in seizure detection. Second, we propose to localise the brain regions involved in seizure generation, using GNNs augmented with an attention mechanism [2]. This allows us to identify not only the relevant brain regions, but also how the connections among them might influence the seizure. Finally, we propose to combine reinforcement learning and GNNs, in order to learn a control strategy for preventing or mitigating seizures. Such method would exploit the networked structure of the brain to take into account how a control action might propagate in the brain network.

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Single EEG channel blink artifact removal via deep learning

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In recent years, it has become clear that "ultra-long term" (i.e., multi-month) electroencephalogram (EEG) recordings via wearable or implanted EEG devices can improve epilepsy diagnosis and trigger therapeutic interventions. However, analyzing such data comes with novel challenges. In particular, the conventional spatial filtering techniques used to remove EEG artifacts with conventional 20+ channel montages will not work well with the limited number of sensors typical of these devices. Here we explore an alternative approach, temporal filtering via deep neural networks (DNNs). DNNs are capable of learning very complicated filters and should be able to learn to remove the waveforms typical of EEG artifacts. As a proof-of-concept, we have attempted to correct for blink potentials in EEG data from eight neuronormal undergraduates at 30 electrodes. Conventional spatial filters were used to estimate blink artifacts in these data and an equal number of blink-contaminated and blink-free one second clips of data were sampled from the data. Subsequently, a DNN was trained to remove blink artifacts from data at a channel in the center of the forehead using the spatial filter output as a teaching signal. The DNN's performance was then compared with that of the spatial filter using held out data. On average, the power spectrum density (PSD) of the blink contaminated EEG data show a dramatic 8.1 dB increase relative to the spatially filtered EEG data from 0-12 Hz. The PSD of the DNN filtered data very closely matches that of the spatially filtered data (mean absolute deviation of 0.45 dB and 0.27 dB in the 0-50 Hz band for blink-contaminated and blink-free trials respectively). Our results demonstrate the feasibility of DNN temporal filters for EEG artifact removal, which could potentially improve the utility of data acquired from limited channel count EEG devices.

Automatic Seizure Detection in Scalp and Intracranial Recordings through Convolutional Neural Networks

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The monitoring of brain activity through the electroencephalogram (EEG) is one of the standard techniques to diagnose epilepsy. For this, the physician needs to visually detect the presence of epileptic seizures in long-lasting EEG recordings, which is usually a laborious and time-consuming task. To facilitate this process, automatic algorithms for seizure detection have been proposed. Most of them operate in the signal domain through feature extraction and classification strategies. In this work, we developed an automatic method for seizure detection based on high-level algorithms currently used for recognition tasks in Computer Vision.

In detail, we selected EEG recordings from 11 patients of the EPILEPSIAE database [1], comprising both scalp and intracranial electrodes with at least 5 days of continuous recording. In total, we analyzed 1,497 EEG hours, including 111 seizures. Our approach consisted on a binary classification of brain activity into ictal and interictal states, and we evaluated our results in terms of precision and sensitivity. We trained cross-patient (for scalp channels) and patient-specific (for scalp and intracranial channels) models in which we selected ictal and interictal instances from the first 80% of recordings with seizures, and evaluated on the remaining ones. We balanced the number of instances between two classes by doing an oversampling and subsampling of ictal and interictal epochs, respectively. Our results in the cross-patient model presented a broad variation among patients: for the two patients with the largest number of seizure episodes, the model achieved a precision of 79.7% and 40.7%, and sensitivity of 56.9% and 38.1%. We chose the 4 patients with the highest number of seizures for training patient-specific models. When comparing to models with only scalp data, experiments with intracranial and both electrode types consistently improved the performance of the algorithm, obtaining precision values above 90% and sensitivity higher than 80%.

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Kernel Methods and Slow-Fast Neural Mass Models for Seizure Detection

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Seizure detection algorithm can potentially improve monitoring the condition of patients with epilepsy-for example to avoid self-injury or to alert recurring of epileptic seizures. In this paper, we build on the recent work in [1,2] to detect epileptic seizures in multi-scale dynamical systems developed in [3,4].

A Slow-fast neural mass model [3,4] that emulates transition into and out of seizures due to the slow evolution of internal model parameters is employed to generate simulated EEG recording with paroxysmal transitions into and out of epileptic seizures. The model provides means to replicate large scale electrophysiological recording while it also gives insights into underlying generators of epileptic seizures. Then, we use the maximum mean discrepancy (MMD) as a metric between probability measures embedded in reproducing kernel Hilbert spaces (RKHSs) to classify seizures from apparently normal activity.

The results show that our proposed algorithm can accurately detect the onsets and ongoing recurrent of epileptic seizures, thereby pave the way for development of biologically informed seizure detection method.

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Can naive stability quantification help localization of epileptic dynamics?

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Introduction:

The emergence of epileptic seizures can be conceptualized as loss of stability of the ongoing healthy brain state. While seizures typically occur abruptly, gradual loss of stability may be accompanied by markers of transition, or alternatively the vulnerable nodes may be close to unstable dynamics in long-term. Such weakened stability should be reflected in relatively high values of autocorrelation. In this study we aim to test the utility of this theoretical approximation by assessing its relevance to detection of epileptogenic area.

Methods:

We analyse a sample of intracortical electroencephalography signals from seizure initiation segments of 10 second duration obtained in a group of N=22 subjects with focal cortical dysplasia. To assess the stability of signal observed at each electrode we approximate suitably down-sampled data

(20Hz) by an autoregressive process of order one; the strength of the self-coupling then determines the local process stability.

Results:

To assess the relation between the node stability and relation to seizure activity, for each subject we have assessed the agreement of the contacts included in resection and the same amount of most instable contacts according to signal autocorrelation by the Jaccard index. The agreement was increased in the group of subjects that had successful treatment outcome (Engel I vs II-IV): mean(std)=0.23(0.17) in Engel I group, 0.12(0.21) in Engel II-IV group, $p<0.05$,Wilcoxon rank test.

Conclusion:

The concept of local process instability has proved promising in detection of key areas (signals) related to the seizure-onset zone, with promising predictive performance with respect to surgery outcome.On the other side, while the agreement was increased in the good outcome group, it was still relatively low. Of course, the current model represents an extreme simplification in several directions and validation of the concept on larger datasets and experimental models is required. Ties to other recently used indices that call for theoretical explanation.

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Changes in functional connectivity networks during interictal spikes in infantile spasms

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Objective: Infantile spasms (IS) is an epileptic encephalopathy that is characterized by seizures called epileptic spasms. Although the electroencephalogram (EEG) of IS subjects is often chaotic with multifocal interictal spikes, this activity is characterized by strong, stable functional connectivity networks (FCNs) [1]. Here we investigate the impact of interictal spikes on the strength and structure of FCNs in IS.

Methods: We analyzed the interictal FCNs in sleep EEG in eight IS subjects by computing the cross-correlation in one-second epochs. For each subject, we generated networks by selecting three groups of epochs: (1) all epochs, (2) epochs containing focal spikes, and (3) epochs without spikes. Changes in an individual's network structure and connection strength across all three networks were quantified using graph theory. We compared these network changes to FCNs generated in eight healthy controls, in which simulated spikes were added to sleep EEG.

Results: For IS subjects, we found that epileptic spikes did not change the structure of the connectivity network, but they were associated with increased connection strength. Non-spiking FCNs exhibited similar network structures to the FCN generated with all epochs, but with decreased connection strength. In contrast, the inclusion of simulated, physiologically-realistic spike waveforms in control subject data did not increase the connection strength. At very high amplitudes, we saw a change in the network structure, followed by an increase in connection strength.

Conclusions: The differences in FCNs between IS subjects and healthy controls with simulated spikes suggest that underlying pathological neural mechanisms strengthen the network during spikes, supporting hypotheses of subcortical driving in IS [2]. Moreover, our simulations using healthy subjects

suggest that this increase in strength is not an artifact generated purely by the presence of the spike waveform.

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3,3',4',7-Tetrahydroxyflavone modulates neuroinflammation by activating CREB-BDNF pathway in animal model of epilepsy

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Epilepsy is a chronic neurological disease, introduced as the fourth most common neurological disorder and affects about 65 million people worldwide. About 30% of the patients receiving current antiepileptic drugs remains refractory to the disease with epilepsy and are prone to comorbities like psychiatric and cognitive impairment. This urges the need to find a molecule which interacts at cellular and molecular levels, thereby inhibiting the process of epileptogenesis. Therefore, present study was designed to assess the effects of the 3,3',4',7-tetrahydroxyflavone in pentylenetetrazole (PTZ)-induced kindling model of epilepsy in mice, a model for temporal lobe epilepsy. Oxidative stress is among the mechanisms involved in epileptogenesis. It causes generation of reactive oxygen species that leads to neuroinflammation and neuronal plasticity. In our study, we have observed that PTZ-induced kindling induced significant rise in oxidative biomarkers as evident by enhancement of lipid peroxidation and protein carbonyl levels. Altered histoarchitecture of hippocampal region was observed in PTZ group. Proinflammatory cytokine and HMGB1 (high mobility group box-1) were found to be overexpressed in PTZ group. Furthermore, brain cyclic adenosine monophosphate response element binding protein (CREB) and brain derived neurotrophic factor (BDNF) levels were studied at genetic level. Decreased seizure threshold was observed in PTZ group evident from generalized tonic–clonic seizure score on alternate days. Administration of flavonoid increased the seizure threshold significantly in a dose dependent manner. Transfer latency of PTZ kindled group was increased significantly and step down latency was decreased indicating impaired cognition. However, decrease of transfer latency and increase in step down latency was observed in flavonoid treated animals indicating improvement in cognition. Oxidative stress and altered histology was ameliorated by the flavonoid. Moreover, our findings demonstrates modulatory role of flavonoid by activation of CREB-BDNF signaling pathway and suppression of aforementioned inflammatory markers.

When is a responder not a responder? Using multi-day seizure cycles to improve assessment of treatment response in epilepsy.

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Individuals' seizure rates are highly volatile, with large fluctuations from month-to-month, as well as slow, multi-day cycles that modulate seizure rates (Karoly et al., 2018). Nevertheless, changes in individuals' mean seizure rates are used to measure whether or not trial participants successfully respond to treatment. This study quantifies challenges in identifying treatment responders in epilepsy and demonstrates a novel approach to evaluate drug efficacy based on knowledge of individual's epileptic rhythms.

A power calculation was performed to determine the trial duration required to detect a significant 50% decrease in seizure rates ($p < 0.05$). Seizure rate simulations were also performed to determine the number of people who would appear to be 50% responders by chance. We show how chance responder detection can be governed by seizure cycles. Seizure rate statistics were derived from long-term seizure counts recorded during a previous clinical trial for an implantable seizure monitoring device (Cook et al., 2013), as well as from long-term mobile seizure diaries. We showed that individual variance in monthly seizure rates can lead to an unacceptably high false positive rate in the detection of individual treatment responders. This error rate cannot be reduced by increasing the trial population; however, it can be reduced by increasing the duration of clinical trials. We also show that alternative metrics to assess changes in seizure rates, which consider known multi-day cycles that govern baseline rates, can provide a more robust measure of treatment efficacy.

Our findings suggest some drugs may be incorrectly evaluated as effective; or, conversely, helpful drugs could be rejected based on 50% response rates. It is important to pursue more nuanced approaches to measuring individual's treatment response, which consider patient-specific cycles of seizure rates.

Seizure clustering in tetanus toxin model of epilepsy

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Introduction: The long-term fluctuations in seizure probability and seizure clustering were multiple times reported in both patients and animal models of epilepsy including the tetanus toxin model in rats. The aim of this study was to explore the mechanisms which govern cluster progression and cluster onset.

Methods: Epilepsy was induced in adult rats (n=6) by injection of 10 ng of tetanus toxin into the right dorsal hippocampus. Electrodes were implanted bilaterally into dorsal hippocampus and motor cortex. Animals were continuously video-EEG monitored for >2 weeks. Seizures were identified and classified as convulsive or non-convulsive. Signal power during seizures was analyzed in each studied brain area. Apart from that, we analyzed long-term evolution of epileptic bursts – few second long series of EEG spikes. We analyzed their rate, duration, power and channel cross-correlation.

Results: We analyzed one seizure cluster in each animal. Clusters lasted 2.3$\pm$0.2 days and contained 90$\pm$15 seizures. All clusters were characterized by progressive increase of ISI. The percentage of convulsive seizures progressively increased in all clusters (p=0.008) and so did the signal power in the motor cortices (p=0.008) whereas in the hippocampi a non-significant decrease of power was observed (p=0.74). Between the clusters, we observed increasing rate, power and spread of epileptic bursts whereas the duration produced a U-shape.

Conclusion: We have shown that during and between the clusters, the brain undergoes complex changes. We hypothesize that early non-convulsive seizures facilitate spreading of later seizures. In contrast, later generalized seizures have inhibitory effect which leads to reduction of seizure rate and finally to the cluster termination. Between the clusters, changes of the epileptic burst can be interpreted as increase of excitability and delayed recovery from internal perturbations which may serve as an early warning signal of impending transition to the next seizure cluster [1].

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High-Frequency-Oscillations help detect seizures at the group level but not for the specific seizures

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High-frequency-oscillations (HFO) are known to be spatial biomarkers of epileptic tissue, their value as temporal biomarkers of seizures is however much less explored; despite this, some evidence has been found for characteristic changes in the HFO activity during the brain's transition from the pre- to the ictal-state [1], [2]. We automatically detected the HFO-rate per second on the intracranial Electro-Encephalogram (iEEG) of 8 patients. The iEEG segments analyzed were 4 hours long (i.e. 2 hours before and after a seizure) and the total number of seizures was 129. At the patient-group level (i.e average HFO-rate across all patients and all seizures.), a small increase in the HFO-rate was observed immediately prior to seizures. At the seizure-group level (i.e. average HFO-rate across the individual patients' seizures) some patients showed again an increase in the HFO-rate prior to the seizures while other patients showed a strong decrease in the HFO-rate 10 to 15 seconds prior to seizures. At the individual seizure level, both an increase as well as a decrease in the HFO-rate was observed across seizures. The results obtained show the need to further classify seizures in order to understand the changes in the HFO-rate when transitioning into the brain's ictal-state. Additionaly, the results show how a simple feature of the HFO activity, namely the occurrence-rate, does show clear variations when transitioning from the pre-ictal to the ictal-stage, these changes are however not consistent across patients nor seizures. A multivariate characterization of the HFO activity could then allow an improved detection of seizures.

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Heart Rate Variability Analysis in Drug-resistant Epilepsy Patients Towards Seizure-specific Preictal Time Assessment

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Changes in electrocardiographic (ECG) recordings have been observed simultaneously with the electroencephalographic (EEG) brain alterations occurring as consequence of an upcoming epileptic seizure. In fact, alterations of the cardiovascular status, triggered by the intervention of the autonomic nervous system, have been widely explored in the context of seizure prediction. Similarly to the EEG, it is possible to identify differences in ECG recordings seconds to hours before the occurrence of a seizure [1]. Such behaviour may evidence the existence of a preictal interval following a normal ECG trace (interictal interval) and preceding the ictal interval during which seizure clinically manifests. The preictal state, however, has not yet been defined by medical experts in the area, not even in the extensively analysed EEG signal. Such interval was found to differ among patients and also among seizures occurring in the same patient [2].

A heart rate variability (HRV) study was performed to investigate the discriminative power of HRV features in the identification of the preictal interval for a given seizure. A dataset comprising 20 drug-resistant epilepsy patients stored in EPILEPSIAE database was inspected. Discrimination of interictal and preictal intervals was performed in a total of 238 temporal seizures. Time and frequency domain features (linear and non-linear) were extracted from 5-min nonoverlapped segments contained in the 240 min of ECG signal present before a given seizure event.

A total of 4960 three-dimensional feature combinations were inspected using three clustering methods. The results indicate the existence of similar clustering solutions among seizures occurring in the same patient for 15 out of the 20 patients, specifically when considering a two-cluster solution. In these cases, one of the clusters was considerably smaller, occurred in between the other and was also continuous in time (resembling a small Dirac comb), which might suggest the existence of a preictal interval.

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SAM(g2) localizes to where spikes propagate in MEG imaging of focal epilepsy patients

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Background: In patients with focal epilepsy, the irritative zone is normally more extensive than the epileptogenic zone (EZ), which is defined as the minimum amount of cortex that must be resected to obtain seizure freedom. Some studies have shown the propagation of interictal spikes within the brain and associate the location of the earliest phase of the spike with the EZ [1]. SAM(g2) is a source reconstruction method used with MEG imaging; it has been shown that interictal spikes reconstructed by SAM(g2) are associated with interictal spikes on ECoG channels [2]. However, studies on the association of SAM(g2) results with EZs are still very limited.

Method: We retrospectively applied SAM(g2) to 13 focal epilepsy patients imaged using MEG and manually selected virtual sources (VSs) that related to interictal spikes. Since each patient has multiple g2-maps, we selected the brain voxels with consistent interictal spikes as our solutions. The validation reference used in this study is the clinical EEG/MEG source localisation, which prospectively delineated the onset and propagation of interictal spikes as part of the EZ characterisation in all 13 patients [1].

Results: Regions localized by SAM(g2) coincided with spike onset in one patient, coincided with spike propagation regions in seven patients, and co-localized with both spike onset and propagation

regions in two patients. One patient had independent bilateral temporal lobe epilepsy and SAM(g2) localized to the right side. Two out of thirteen patients did not show consistent localized areas between SAM(g2) and clinical localization.

Conclusion: SAM(g2) localizes the propagation areas of interictal spikes more often than spike onset regions and so may not be a good indicator of the EZ.

Data-driven analysis of high frequency oscillations to improve seizure localization

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High frequency oscillations (HFOs) have garnered considerable excitement in the epilepsy community for their potential as a biomarker of the seizure onset zone (SOZ) and tool for surgical planning. The rate of HFOs (number per minute) is higher in the SOZ, and the surgical removal of brain regions exhibiting HFOs has been correlated with improved seizure outcomes. However, there are significant barriers to their broad clinical implementation. Detection of HFOs relies on an empirical definition based on visual observation, rather than one derived from physiology. Moreover, the measurement of HFO rate using this definition is not robust, as relative rates between individual electrodes change over time. We are addressing these barriers through the development of new computational tools for detection and modeling of HFO activity. First, we present a machine learning approach to the identification of unique high frequency events that is based on anomaly detection. This method does not require selection of an amplitude threshold nor assumptions about HFO morphology, enabling us to objectively identify HFOs and measure their characteristics. We show, using intracranial EEG (iEEG) data collected from 10 patients undergoing evaluation for epilepsy surgery, that HFO characteristics measured in this way provide better classification between electrodes inside versus outside the SOZ. Second, to address the challenge of HFO rates fluctuating over time, we show that a hierarchical Bayesian model with two states can be fit to measurements of HFO rate in iEEG recorded over periods of 24 hours. The model automatically identifies sleep and wake periods, verified by comparison to concurrent scalp EEG, and it provides stable measurements of rate that can be used to reliably classify electrodes inside and outside the SOZ. Both tools enhance the single-subject reliability of HFOs as a biomarker of the SOZ, thus facilitating translation to clinical practice.

Optimization of Individualized Seizure Detector using Random Forest Classifier for Closed-loop Applications

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About 30 percent of epilepsy patients are resistant to antiepileptic drugs. A novel treatment approach for this group of patients with focal epilepsy is the application of electrical stimulation. We here report optimization of features in combination with classifier optimization for patient specific and energy-efficient seizure detection based on Random Forest classification.

The seizure detector optimization was performed on intracranial long-term recordings of 27 patients (471 seizures). For each patient, four channels from the seizure onset zone were selected. Random forest based classification was performed on 10 selected EEG-features.

Optimization of the patient specific automatic seizure detector was performed on two levels. First, the classifier was optimized by cross-validated (3 fold) random search on hyperparameters. Second, an automatic feature selection procedure (based on recursive feature elimination) was implemented. The feature selector used the optimized classifier (as calculated in the previous step) to extract the optimal number of features required for this classifier by performing a 5-fold cross-validation.

The results showed 18.8% reduction in the number of features (from 40 to 32) on average. The most often selected features were in turn line length, beta-band power and gamma-band power. Classifier optimization combined with feature selection resulted in an increase of the area under the ROC curve (AUC) about 1.4% (from 91.4% to 92.8%).

The results suggest that patient specific optimization of random forest classifiers can play an important role in improving performance of the seizure detector while saving energy for application in implantable devices.

Effects of Electrical Stimulation on Cortical Phase Synchronization as a Measure of Excitability

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Introduction:

One emerging treatment modality for drug-resistant epilepsy patients is direct electrical stimulation of the epileptogenic zone. Knowledge about the level of excitability and its modulation has the potential to improve the efficacy of closed loop neurostimulation devices. Mean of phase synchronization dynamics was suggested as a potential intrinsic excitability measure (IEM) in human cortex. Objective of this study was to assess the effect of low-frequency electric cortical stimulation on the excitability levels and phase synchronization dynamics of epileptic focus.

Methods:

Biphasic electric current (250 μs/phase) was delivered to two adjacent electrodes in the seizure onset zone in four patients with a stimulation frequency of 1Hz. Stimulation was divided into three stimulation blocks of 10 minutes with 10 minutes pause in between. The peak-to-peak (P-P) amplitude of the averaged evoked potential was taken as a measure of excitability and compared between the first and last stimulation blocks. Mean phase synchronization was estimated in the frequency bands 1-50 Hz, 50-100 Hz and 100-200 Hz. To evaluate synchrony changes, a 10 min data segment before stimulation was compared to a 10 min block after the stimulation.

Results:

Our results showed that excitability on average decreased for all the patients (about 6.5%). Phase synchrony increased on average over all the patients in the 50-100 Hz (about 8%) and 100-200 Hz (about 7%) frequency bands. However, Phase synchrony changes in the 1-50 Hz were negligible.

Discussion:

We showed modulation of cortical excitability by low frequency electrical stimulation and a negative relation between phase synchrony and excitability levels in the 50-100 Hz and 100-200 Hz frequency bands. Additional patients are required to systematically assess the seen effects, taking also anatomical regions of stimulation, the underlying etiology and disease progress into account. Comprehensive results may lead to improved treatment options for patients with medically refractory patients.

A unifying dynamical model for seizure susceptibility in epilepsy

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Epileptic seizures are characterised by abrupt, seemingly random changes in brain state. These changes can have a catastrophic effect, resulting in loss of consciousness and even death. Critical slowing is a theory that describes the increasing time that a complex system takes to recover from disturbances as it approaches a state change (i.e. seizure). We previously demonstrated that on a fast dynamical scale (minutes to few hours), recorded brain signals show signs of critical slowing prior to seizures [1]. Further to this, we recently demonstrated that seizure susceptibility is modulated by patient specific combinations of fast and slow rhythms in the metrics used to track critical slowing. However, the patient specific dynamics observed led to ambiguities which were difficult to explain with current models of seizure dynamics. In some patients, the long rhythms were implicated in seizure clusters. In others, seizures unexpectedly occurred during periods of low susceptibility.

Here, we propose a dynamical systems model with two state variables that separate the slow and fast dynamics of seizures. The slow parameter modulates seizure susceptibility, while the fast parameter describes the dynamics of the seizure event. Through this model, we explore the parameter combinations of the model that help explain three observations in our data: (1) how seizures can occur during periods of high resilience, (2) how seizures cluster and (3) how seizure termination can also

be described by a critical transition. This model provides a unifying description of seizure dynamics that help explain the patient specific dynamics observed across more than 3000 seizures in fourteen patients [2]. Our results provide a conceptual advance in our understanding of how seizures are generated, and may lead to novel interventions to help prevent seizures.

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Establishing a safety margin to seizure runaway activity: Antiepileptic drugs induce subcritical dynamics in human cortical networks

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Cortical network functioning critically depends on a finely tuned level of excitability, the transient or steady-state response in which the brain reacts to a stimulus. On the one side, excitability must be small enough to prevent explosive growth of neuronal activity cascades. On the other side, it must be large enough to allow for activity propagation over long distances to afford neuronal communication across sites far apart. The importance of finely tuned cortical excitability levels is highlighted by the pathological consequences and impairments resulting from aberrant network excitability in neurological and psychiatric diseases. In epilepsy, changes in cortical network excitability are believed to be an important cause underlying the initiation and spread of seizures, pharmacological reduction of excitability consequently constitutes a main treatment approach to control and avert seizures.

Theory and experiment suggest that the control of activity propagation by network interactions can be adequately described by a branching process. This hypothesis is partially supported by strong evidence for balanced spatiotemporal dynamics observed in the cerebral cortex, however, evidence of a causal relationship between network interactions and cortex activity, as predicted by a branching process, is missing in humans.

Here we test this cause-effect relationship by monitoring cortex activity under systematic pharmacological reduction of cortical network interactions with antiepileptic drugs in 17 epilepsy patients undergoing presurgical monitoring. We report that cortical activity cascades, presented by the propagating patterns of epileptic spikes, as well as temporal correlations decline precisely as predicted for a branching process. Our results provide a missing link to the branching process theory of cortical network function with implications for understanding the foundations of cortical excitability, its monitoring in epilepsy and establishing resilience to seizures associated with runaway excitation.

Action potential alterations and cell-type specific activity through ictal recruitment in humans

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Much recent debate has focused on cell-type-specific patterns of activation at seizure onset. However, action potential waveform changes during seizures can confound detection and classification of single units. We developed template-matching-based methods to identify single neurons in ictal microelectrode recordings from 27 patients with intractable focal epilepsy. Neuronal identities were defined as spikes occurring within the convex hull in feature space of cluster-sorted neurons in the peri-ictal period, discarding those with < 1% probability in a χ2-distribution of Mahalanobis distances. Spike-match likelihood was calculated using the Gaussian distribution of voltages in the original neuron, from which probabilistic firing rates were calculated. Neurons were then subclassified by cell type.

We identified two distinct neuronal activity patterns at seizure onset. Type 1, found in 8 patients, was characterized by tonic firing, reduced spike amplitude, and increased half-width. Type 2 showed burst firing with no waveform change. All neurons returned to their pre-ictal waveforms after seizure termination. We interpret Type 1 as consistent with recruited tissue, as defined in prior animal studies, and Type 2 as a downstream effect of recruited tissue. Of 413 neurons, 48 (11%) were identified as interneurons. Of these, 35 (73%) showed significantly increased firing during seizures, 1 (2%) showed a decrease. While interneuron firing was maintained throughout the seizure, there was out-of-phase firing and a prominent, transient increase in interneuronal firing just prior to the onset of Type 1 activity. We conclude that the distinction between tissue that has been recruited versus penumbra is maintained at the level of single neurons. Novel template-matching methods enabled us to demonstrate continued firing of the inhibitory population following ictal invasion. Interneuron activity patterns during the ictal transition suggest multiple mechanisms are involved, including altered inhibitory effects and depolarization block. Our data do not appear to corroborate an interneuronal triggering mechanism.

Interictal network integration-segregation and recruitment in the identification of the seizure onset zone

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Changes in brain connectivity dynamics preceding and leading up to the time of seizure onset are poorly understood. Conventionally we consider the pertinent pre-ictal changes to be seconds to minutes prior to seizure onset, but there is evidence of detectable changes hours before seizure onset. While these studies have focused on changes in interictal activity, energy or used predictive analysis without considering the neurophysiological basis, little has been done in the way of using a network approach to study these changes. In this study, we analyze hours of interictal EEG data recorded from intracranial electrodes implantation from patients with intractable epilepsy. We study the temporal-spatial dynamic changes of the functional community structure. We investigate the nodal flexibility over time, a measure of the frequency of a brain region of switching allegiance between different modules, and find that the seizure onset zone (SOZ) can show higher flexibility than non-SOZ regions. This is in contrast to the nodal promiscuity, the total fraction of modules in which a node participates, which does not show a significant difference. An analysis of nodal recruitment, the probability that a node remains within the community of its own functional system, robustly showed that the SOZ regions have higher recruitment than non-SOZ regions. Finally, we analyzed nodal integration, the nodal probability of being part of communities that belong to other systems, and the intra-module variability in nodal connectivity. We found significant differences between SOZ and non-SOZ regions in their participation coefficient (a measure of nodal integration). In summary, our findings show that the SOZ regions have distinct temporal dynamic connectivity and community membership compared to other brain regions. This can lead to better prediction of the SOZ, even only based on interictal data without the need to induce seizures during surgical implantation.

On Handling of Datasets for Seizure Prediction

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Recently, numerous publications emerged using state-of-the-art machine learning methods for epileptic seizure prediction (counting far more than 100 publications on “seizure prediction” at Google Scholar in the last two years). However, in our perception the published results are very often strongly distorted due to an inconsistent handling of datasets, making an objective comparison of the methods impossible.

Most studies are conducted on one of the following datasets: The Freiburg EEG database, the CHB-MIT EEG database (both containing short-term data only), and two long-term datasets that have been acquired with the NeuroVista seizure advisory system and were published to the community in two Kaggle competitions. Typically, the methods require a separation into training and test data, and occasionally validation data. Since one of the main problems in seizure prediction is the long-term instationarity of the iEEG data for model evaluation (i.e. test data) has to be temporally separated from data used for model estimation (i.e. training data, validation data) to avoid an adaption to these instationarities that is not feasible in a real-world scenario. This means that training and test sets must not contain randomly chosen clips from different recording times but have to be strictly separated in time.

In an experimental set-up we will demonstrate how performance estimates can be overly optimistic in case of inappropriate data handling. For this purpose, we implemented a recently proposed deep learning method for seizure forecasting for three different scenarios: 1) choosing temporally shuffled

segments of training and test data; 2) choosing training data temporally separated from validation and test data; 3) choosing a strict separation of training, validation, and test data. For all scenarios, we compare the performances by evaluating the receiver-operating characteristic and the precision-recall area und curve.

Non-invasive seizure forecasting

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Epileptic seizures may be governed by a range of environmental and physiological factors, such as stress, sleep, medication and other variables. An individual's seizure triggers are thought to be highly patient-specific. However, it has recently become clear that there are some generalisable patterns that modulate seizure onset. For instance, a majority of people show a circadian rhythm in their seizure times. Most people (over 50%) also show a slower, multi day rhythm of one week or longer (Karoly et al. 2018). These seizure cycles can be captured from a range of recording modalities, including continuous intracranial EEG, implanted deep-brain stimulation and recording electrodes and self-reported seizure diaries. The ability to capture seizure cycles non-invasively via mobile diaries is particularly exciting, because it suggests that a measure of seizure likelihood could be provided to patients via a mobile app. Other factors known to modulate seizure times can also be measured non-invasively, such as weather conditions, sleep quality, stress/mood, medication and physiological data such as heart rate, skin conductance and oxygen saturation. This study presents a mobile app and web-based framework to generate real-time forecasts that combine data recorded from wearable devices and user inputs from a mobile app. We provide a proof-of-concept for the performance accuracy of non-invasive seizure forecasting using an existing database of long-term, individual seizure records (Cook et al. 2013). Seizure forecasts were also tested in a pseudo-prospective manner using data recorded from a mobile app. Our results show that non-invasive measures can be combined to provide an accurate forecast of seizure likelihood. In particular, we demonstrate that non-invasive measures of seizure likelihood provide a useful indication of times of safety, when seizures are unlikely to occur. This information can provide people with epilepsy more confidence to go about their everyday lives.

The spread of gap-junction mediated activity in neocortex is modulated by extracellular potassium

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Parvalbumin-expressing interneurons in cortical networks are coupled by gap-junctions, thus forming a syncytium that supports propagating epileptiform discharges in vitro, induced by blocking voltage-gated K+ channels using 4-aminopyridine (4-AP). It remains unclear, however, whether these interneurons can sustain propagating events under more natural states, without pharmacological blockade. In particular, we investigated whether such propagation occurs when extracellular K+ rises, as is known to occur following intense network activity, such as during seizures. We examined how increasing [K+]o affects the likelihood of propagating activity away from a site of focal (200-600μm), optogenetic activation of PV-interneurons. Activity was recorded using a linear 16-electrode array placed along layer 5 of primary visual cortex. At baseline levels of [K+]o (3.5mM), induced activity was recorded only within the illumination area. However, when [K+]o was increased above a threshold level of 7.9mM, time-locked activity was also recorded outside the illumination area, propagating at approximately 55 mm/s. Blockade of glutamatergic synaptic transmission reduced the efficacy of propagation, but did not fully prevent it. In contrast, propagation was prevented by pharmacological blockade of gap-junctions, achieved by any of three different drugs, quinine, mefloquine or carbenoxolone. Wash-out of quinine rapidly re-established the pattern of propagating activity. Propagation is qualitatively different in high [K+]o and 4-AP, and we show using computer simulations that this arises from differences in the electrotonic effects of these two manipulations. We conclude that interneuronal syncytial interactions are likely to affect the complex electrographic dynamics of seizures, once [K+]o is raised above this threshold level.

Seizure forecasting with deep learning and external factors on long-term data

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Deep learning has become a huge benefit for many industries due in part to the large amount of data that is now available across many domains. In epilepsy, and the medical industry in general, big data is harder to acquire due to privacy issues and the complexity of data recording. For this reason, deep learning algorithms have not been extensively explored as a tool to forecast seizures. The NeuroVista dataset (Cook et. al. 2013) has years of data for each patient with which to train forecasting algorithms and so presents a unique opportunity to explore deep learning techniques. Additional information about external factors such as sleep, weather and time of day has been shown to influence seizure frequency and so may compliment deep learning algorithms that use internal EEG factors.

Data were analysed from eight NeuroVista patients with an average of 248 seizures each across an average of 1.5 years of continuous recording. A long short-term memory (LSTM) algorithm was trained on the first 50% of seizures samples (and corresponding interictal samples). The design of the LSTM was based on previous work on a smaller data set that showed promising results (Tsiouris et. al., 2018). Sleep stage and time of day was calculated from the EEG data. Weather data was provided by the Australian Bureau of Meteorology. Using external factors alone, forecasts performed better than chance in six of eight patients. Performance is expected to improve dramatically with the addition of the LSTM forecasting on EEG data. This study shows the potential of deep learning and external factors as tools in seizure forecasting. These tools may hold the key to bringing forecasting out of academia and into widespread clinical use, alleviating the uncertainty that people with epilepsy must contend with every day.

A novel brain state analysis for determining epilepsy surgery outcome

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Successful methods that quantify epilepsy surgery outcome start computing single brain region dynamics from invasive EEG recordings (iEEG) in order to define brain region epileptogenity. We introduce a new method that rely on functional connectivity alone to classify real and virtual resections between favorable and unfavorable outcomes.

We chronologically selected 10 patients who underwent stereoelectroencephalography evaluation (SEEG, a type of iEEG) and epilepsy surgery, 5 with favorable (Engel I) and 5 with unfavorable (Engel III-IV) outcome at 1 year of follow up, in pairs involving: the mesial temporal, the neocortical temporal, the occipital, the parietal and frontal lobes. Using prediction error connectivity (PEC), a recently published method used to analyse transitions between interictal and preictal states, we determined brain region connectivity around 60 seconds before and 15 after the seizure onset (least seizure duration). Through a machine learning algorithm, we calculated the participation of regions in brain connectivity transitions of one second. Using real resections, we computed an index that represented surgery impact on the transition efficiency between preictal to ictal state. We repeated calculations using several frequential methods instead of PEC.

The patients had an average of 18 years of epilepsy and 9 seizures per week, due to different etiologies (focal cortical dysplasia, hippocampal sclerosis and heterotopia). Using PEC we classified patients in two clear-cut groups: favorable vs. unfavorable (0.86 ± 0.07 vs. 0.38 ± 0.06, $p<0.00001$). With frequential methods we obtained mixed results. This preliminary study introduces a connectivity index that might be useful to design epilepsy surgeries. While previous studies showed brain region participation over ictal time, our results suggest that the resectable epileptogenic zone is determinant for the transition between preictal and ictal state. Extending this study, this algorithm could generate different resection hypothesis and calculate the possible outcomes before entering the surgery room.

Forecasting Seizure Risk at a 24-hour horizon

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The seemingly random occurrence of seizures creates constant uncertainty, a source of suffering for patients with epilepsy. A pioneering prospective study predicting the preictal state, minutes ahead of impending seizures, demonstrated the feasibility of seizure prediction in some patients [1]. Recently, using chronic EEG recordings (NeuroPace RNS®System), we showed that proictal states of heightened seizure risk recur cyclically at longer time-scales. Indeed, circadian and multidien (multi-day) rhythms of interictal epileptiform activity (IEA) strongly correlate with the likelihood of seizure occurrence [2], suggesting that seizure forecasting may be achievable at unprecedented horizon lengths.

In this study, we hypothesized that the phase of IEA rhythms at different time-scales (hours – days) can inform seizure likelihood modeled as a point-process. Using recordings of hourly counts of IEA and seizures over several months in 17 patients, we trained point process generalized linear models that included circadian and multidien rhythms as covariates. Optimal history length was first selected using the validation dataset. Model performance at horizons of one and 24 hours was evaluated on a held-out test dataset (40% of data) using the area under the sensitivity versus proportion of time in warning curve. In both cases, the phase of the multidien rhythms significantly improved the prediction scores compared to when only the recent history of seizures and IEA was used. In a subset of patients, it was possible to forecast days of heightened seizure risk 24 hours in advance, and sensitivity greater than 80% was achievable with time in warning under 30%.

These results show that the inclusion of IEA rhythms at multidien time-scales can improve seizure prediction algorithms. Forecasting proictal states with a 24-hour horizon represents a paradigm shift in the field of seizure prediction that has so far mostly focused on the preictal state.

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Carbogen inhalation during Non-Convulsive Status Epilepticus: A quantitative analysis of EEG recordings

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Objective: To quantify the effect of inhaled 5% carbon-dioxide/95% oxygen on EEG recordings from patients in non-convulsive status epilepticus (NCSE).

Methods: Five children of mixed aetiology in NCSE were given high flow of inhaled 5% carbon dioxide/95% oxygen using a face mask for maximum 120s. EEG was recorded concurrently in all patients. The effects of inhaled carbogen on patient EEG recordings were investigated using band power, functional connectivity and graph theory measures. Carbogen effect was quantified by measuring effect size (Cohen's d) between "before", "during" and "after" carbogen delivery states.

Results: Carbogen's apparent effect on EEG band power and network metrics across all patients for "before-during" and "before-after" inhalation states was inconsistent across the five patients.

Conclusion: The changes of different measures suggest a potentially heterogeneous effect of carbogen on the patients' EEG measurements. Different aetiology and duration of the inhalation may underlie these heterogeneous effects. Tuning the carbogen parameters (such as ratio between CO2 and O2, duration of inhalation) on a personalised basis may improve seizure suppression in future.

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Localizing Seizure Foci in Intractable Epilepsy using Structure and Function Correlation

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Precisely localizing seizures is vital to evaluating drug-resistant epilepsy patients for invasive treatment. Such patients may be candidates for invasive treatment, such as focal resection, ablation or responsive neurostimulation. However, 30-50% of these patients continue to have seizures, perhaps because the seizure onset zone (SOZ) was mis-localized, or perhaps because the seizures are a result of a difficult to localize network of excitatory and inhibitory regions [1]. Current localization methods

are constrained, in part, by sampling error due to limited electrode placement. We attempt to address this problem by combining electrophysiology, measured by stereoelectroencephalography (SEEG) to capture seizure activity, with structural imaging methods, measured by diffusion tensor imaging (DTI) to map the tracts through which seizures propagate. By coupling these metrics, we demonstrate that the underlying structural scaffold of the brain constrains functional connectivity derived from SEEG. This expands upon prior work using more cortically focused grid and strip electrode recordings, which do not capture longer range network connections. Our findings suggest that noninvasive measures of structural connectivity have the potential to guide intracranial electrode placement to more accurately localize networks responsible for seizure generation and propagation. Further studies are underway to determine if this approach of using imaging in a quantitative manner – in contrast to the qualitative manner used in clinical practice currently – can improve outcomes in patients undergoing invasive therapy for drug-resistant epilepsy

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Dynamical functional connectivity in the epileptic brain: insights from the rat model and human data.

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The dynamical processes that bring a brain network to an epileptic state are still unclear. For instance, the transition from a normal brain to a brain able to generate seizures, named epileptogenesis, is not well understood. Furthermore, the transition from an interictal state to an ictal state, the ictogenesis, also needs further research. For this reason, we have explored the brain connectivity before and after a lesion with kainic acid in the rat brain, which causes the development of epilepsy within the following months. More specifically, we have explored the functional connectivity of the brain network before, one day and seven days after the lesion in 13 rats. Two different methods of functional connectivity from EEG recordings were compared: correlation coefficient and phase synchronization of gamma activity. We have observed a decrease of connectivity at a global scale, as well as increased connectivity within the epileptogenic zone. On the other side, we have extended the same analysis to intracranial EEG recordings of epileptic patients. In this case, we have analyzed the functional connectivity 8 hours before the seizure onset in 10 patients from the EPILEPSIAE Database. For some patients, we have observed dynamical changes in the network around 1.5 hours before the seizure onset. We have calculated measures from graph theory to characterize the networks (path length, small-worldness index, and node degree). These preliminary results suggest that a more connected network in specific regions could certainly conduce to the seizure generation. We believe that combining our results could lead to some insights about the dynamical processes before the generation of an epileptic event or epilepsy itself.

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Epileptic seizures lead to a loss of near-critical brain organisation in the zebrafish brain

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Zebrafish have emerged as an important new model for epilepsy. In part, its utility lies in the relative ease with which genetic disorders (including different epilepsies) can be modelled. Moreover, recent advances in microscopy now allow fast whole-brain functional calcium imaging at near single-cell resolution, including during epileptic seizures. In line with a variety of other model systems, neuronal activity in the zebrafish brain has recently been found to display markers of criticality, such as powerlaw-like distributions of the size and duration of neuronal avalanches.

Here we report volumetric light-sheet, and two-photon recordings of zebrafish expressing the fluorescent calcium indicator GCaMP6s both at rest and during pentylenetetrazole (PTZ)-induced epileptic seizures. We show both changes of single neuron firing properties and changes in the statistics of neuronal avalanches during PTZ exposure. Furthermore, we test whether functional networks during PTZ exposure are enriched for specific topological features – such as strongly connected cycles – that support these longer avalanches and evaluate brain network topology for these features in fish with an epilepsy-associated GABA-receptor mutation. Our findings indicate that the zebrafish brain deviates from criticality during epileptic seizures. Similar observations have previously been made in human recordings, further supporting the validity of zebrafish as a model for epilepsy and epileptic seizures. Because of the spatial resolution this model system affords, we can then link observations of changes in neuronal avalanche statistics to mesoscale topological features recorded at near-single cell resolution. This work illustrates how advanced imaging in zebrafish models of epilepsy may support a more in-depth understanding of multi-scale dynamics of epileptic seizures.

Quantifying seizure diversity

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Seizures exhibit great diversity in their region of onset, their electrographic patterns, and their underlying pathology. It is natural to consider, then, whether certain types of seizures result from distinct neuronal mechanisms. Our current work explores the potential role of interactions between local and more distant networks during seizure generation. We measured network interactions by quantifying changes in cross-frequency coupling (CFC) between low (delta and theta) and high frequencies (ripples and fast ripples) in seizures with five different electrographic onset patterns arising from six different classes of cortical and subcortical regions. We found that while each region could give rise to seizures with multiple onset patterns, certain patterns were more likely to be associated with particular brain regions. Further, we employed unsupervised machine learning algorithms to cluster seizures based on differences between pre- and post-onset power within different spectral bands. Intriguingly, we found that the electrographic patterns observed at onset are not the only way to distinguish between seizures and aspects like region of onset needs to be considered.

Our findings suggest that relying solely on one seizure characteristic (e.g. the electrographic pattern) may yield misleading information about its nature. Indeed, inferences made about a seizure's mechanism are likely to be improved by considering other, quantifiable aspects of the electrographic recording, such as the onset region, or spectral band interactions. These findings should inform the development of more targeted pharmacological, surgical and neuromodulatory interventions that suppress and/or disrupt the specific mechanisms underlying ictogenesis.

Controllability of Brain Networks in Patients Receiving Responsive Neurostimulation

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Over one third of the estimated 3 million people who suffer from epilepsy in the US are medication resistant. Responsive neurostimulation (RNS) from chronically implanted electrodes provides a

promising treatment option and alternative to surgery. However, determining optimal stimulation parameters including when and where to intervene to guarantee a positive patient outcome remains an elusive task. Network neuroscience and control theory offer useful tools that may guide improvements in parameter selection for control of anomalous neural activity, and recent work has demonstrated that the brain's functional network response is greater when stimulated at points of low modal structural controllability [1]. Here we extend this work to assess how proximity of RNS electrodes to points of low modal or average controllability relate to patient outcomes. We build effective connectivity networks based on partial correlations between interictal recordings from stereo electroencephalography (SEEG) electrodes implanted during the diagnostic evaluation of 10 medication-resistant epilepsy patients. We assess average and modal controllability in those networks and assign controllability values to co-registered RNS electrodes to evaluate how spatial placement relates to a positive treatment response, measured as the total reduction in seizures since a pre-stimulation baseline. Our results find a negative correlation with modal controllability and a positive correlation with average controllability and patient outcome, demonstrating that the underlying EC network during the interictal phase may inform the most effective RNS locations for reducing seizure frequency, and motivating the use of linear control theory to provide translational benefits.

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Patterns of white matter degeneration and reorganization following temporal lobe resection: A longitudinal imaging study

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Objective: Seizure freedom after resective surgery in temporal lobe epilepsy (TLE) is complex and dynamic. It still remains unclear the reasons why seizures persist in some patients. In this study, we investigate white matter changes pre- to post-operatively. Our aim is to identify patterns of brain reorganization and/or degeneration, which may explain post-operative seizure relapse. Methods: We use diffusion MRI data to investigate white matter changes over 3 months following surgery in 50 patients. We analysed changes in fractional anisotropy (FA) in 45 white matter bundles from the connectome atlas, excluding the area of resection. The FA changes were compared with diffusion data in 28 controls for the same time period using inference tests with FDR correction. This analysis was conducted separately for left TLE and right TLE patients. We also analysed FA changes across all patients by grouping the bundles as ipsilateral and contralateral.

Results: We found significant FA changes after 3 months post-surgery in patients when compared with controls over the same period. Most significant changes were found ipsilaterally in addition to the contralateral fornix. Decreased FA after the surgery was mainly observed in bundles in the vicinity of the resection area, whilst increased FA was observed in some projection bundles.

Conclusion: We demonstrate that there are significant changes in white matter following resective surgery in TLE. The observed FA changes indicate degeneration in the vicinity of the resection area and in the contralateral fornix as well as possible mechanisms of reorganization. These different patterns of degeneration and possible reorganization may, in future, be useful in prognosis of late recurrence and improved patient stratification.

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Pre-surgical node abnormality informed with surgery plan predicts seizure outcome and relates to long-term relapse

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Objective: We assessed structural brain networks (connectomes) of patients with drug resistant temporal lobe epilepsy (TLE) to investigate post-surgical seizure outcome at 1 year and relapses up to 5 years.

Methods: We retrospectively examined data from 51 consecutive TLE patients who underwent anterior temporal lobe resection (ATLR) and 29 healthy controls. Using pre-operative diffusion and structural MRI, we generated 'pre-surgery networks'. Incorporating information on location of surgery from post-operative MRI, we inferred 'surgically-spared networks', which are a subnetwork expected to be unaffected by surgery and hence present post-operatively. After standardising and thresholding networks with respect to controls, we computed 'node abnormality' which captures the number of abnormal connections to each network node.

Results: Patients with more abnormal nodes had poorer surgical outcome at one-year and, if seizure free at 1 year, were more likely to relapse within five years. In the surgically-spared networks of poor outcome patients, the number of abnormal nodes was greater and their location more widespread than in good outcome patients. Incorporating abnormality measures into a predictive model gave 81.4% cross validated test accuracy (0.77 AUC) of 1-year seizure outcome. Further, the model

output was correlated with the grade of surgical outcome at year-one, being ILAE1 in those who were entirely seizure free, and was associated with relapse up-to five years post-surgery.

Conclusion: Node abnormality offers a personalised non-invasive marker, that can be combined with clinical data, to better estimate the chances of seizure freedom at 1 year, and subsequent relapse up to 5 years after ATLR.

Computer modelling of connectivity change suggests epileptogenesis mechanisms in idiopathic generalised epilepsy

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Patients with idiopathic generalised epilepsy (IGE) typically have normal conventional magnetic resonance imaging (MRI), hence diagnosis based on MRI is challenging. Anatomical abnormalities underlying brain dysfunctions in IGE are unclear and their relation to the pathomechanisms of epileptogenesis is poorly understood.

In this study, we applied connectometry, an advanced quantitative neuroimaging technique for investigating localised changes in white-matter tissues in vivo. Analysing white matter structures of 32 subjects we incorporated our in vivo findings in a computational model of seizure dynamics to suggest a plausible mechanism of epileptogenesis.

Patients with IGE have significant bilateral alterations in major white-matter fascicles. In the cingulum, fornix, and superior longitudinal fasciculus, tract integrity is compromised, whereas in specific parts of tracts between thalamus and the precentral gyrus, tract integrity is enhanced in patients. Combining these alterations in a logistic regression model, we computed the decision boundary that discriminated patients and controls. The computational model, informed with the findings on the tract abnormalities, specifically highlighted the importance of enhanced cortico-reticular connections along with impaired cortico-cortical connections in inducing pathological seizure-like dynamics.

We emphasise taking directionality of brain connectivity into consideration towards understanding the pathological mechanisms; this is possible by combining neuroimaging and computational modelling. Our imaging evidence of structural alterations suggest the loss of cortico-cortical and enhancement of cortico-thalamic fibre integrity in IGE. We further suggest that impaired connectivity from cortical regions to the thalamic reticular nucleus offers a therapeutic target for selectively modifying the brain circuit for reversing the mechanisms leading to epileptogenesis.

Forecasting Pharmacoresistant Epileptic Seizure from human Intracranial Electroencephalography Recordings

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About 60 million people in the world are afflicted with Epilepsy and of which, 30% of the patients have recurrent disruptive seizures that are resistant to anticonvulsant drugs and resective surgery. Intracranial Electroencephalography(iEEG) is used to record neural activity in the brain and classify seizures by correlating them with common epileptiform iEEG patterns. The inter-ictal and pre-ictal states of a seizure are highly patient-specific and follows a dynamic temporal pattern, which makes it challenging to model a system to promptly warn patients about imminent seizures. In this paper, we demonstrate different statistical models and recurrent neural networks to classify the seizure states of a patient.These models were then evaluated on their AUROC scores, which translates to a high recall rate as desired by most patients with implanted device. The results show that the work in this paper is a promising step towards closed-loop seizure therapy when implemented on a neuromorphic chip.

Predicting neurosurgical outcomes in focal epilepsy using intracranial EEG data

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Intracranial recordings are commonly used in the presurgical evaluation of epilepsy to attempt delineation of epileptogentic tissue. Clinical assessment of these recordings typically considers properties of each electrode contact individually. However, recent modelling studies suggest functional networks constructed from pairwise interactions between electrode contacts also hold predictive information. Here, we will highlight some limitations of current techniques, and suggest strategies to mitigate the impact of these limitations. We will show that the application of these strategies substantially improves prediction of post-surgical seizure freedom. We also discuss the limitations in the context of practical application in a clinical setting.

Signatures of thalamic ictal state in drug-resistant epilepsies

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Rationale

Epilepsy surgery or RNS may not be a therapy option when seizures are non-localizable or the onset involves widespread network. Open loop thalamic DBS is indicated in this cohort, but frequent stimulations can potentially disrupt physiological activities like sleep and memory. Feedback stimulation in response to an incipient seizure could be advantageous by minimizing stimulation-related side effects. However, the challenge is in detecting cortical onset seizures in the thalamus. We aimed to identify biosignatures of the thalamic ictal state using spectral and temporal features using local field potentials (LFP) recorded from the anterior thalamic nuclei(ANT) in 14 consenting adults undergoing stereo EEG investigation for localizing seizures.

Methods

Through an IRB approved process, we archived continuous 7-10 days SEEG recordings (including ANT) from 14 subjects (94 seizures). We applied Linelength(LL)[1] on seizure onset zone, and ANT to detect seizure state. RandomForest(RF) model[2] was trained using features: DWT RWE (9), MSE (29 scales), PSD (9), Hjorth (3), Kurtosis, Skewness, Teager Energy, Linelength, difference between Teager Energy and Linelength, and Katz fractal dimension calculated in 4s (3s overlap) using LL detection time +10s seconds with Atlman's modification to select significant features, and testing on all 94 seizures.

Results

Features that detected thalamic ictal state were:DWT RWE, the first 2 scales of MSE, PSD 4-8, 13-500 Hz, Hjorth, Teager Energy, Linelength, Teager-LL difference and KatzFD. RF outperformed LL by having higher detection rate of thalamic ictal state.

Discussion

Using supervised machine learning, we have discovered candidate biomarkers for thalamic ictal state that hold promise to develop closed-loop DBS in non-localized epilepsies.

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Ictal EEG source imaging and connectivity to localize the seizure onset zone in extratemporal lobe epilepsy

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Electrical source imaging (ESI) and functional connectivity (FC) of ictal EEG have been studied as a help to determine the localization of the seizure onset zone (SOZ) in the pre-surgical evaluation of refractory epilepsy. However, results reported concern mainly temporal lobe epilepsy (TLE) and not extratemporal lobe epilepsy (ETLE).

We reviewed the surgical epilepsy database (St. Luc Hospital, Brussels, Belgium) and selected patients with the following inclusion criteria: (1) resective surgery for ETLE and (2) seizure-free at 6 months follow-up (ILAE class 1). The epileptologist marked seizure onsets characterized by one of the following activities: (1) rhythmical discharges with evolving frequencies in the delta, theta or alpha band (2) rhythmical spiking activity, (3) fast paroxysmal low voltage activity. Exclusion criteria were: (1) spasms or decrement pattern on the EEG (2) seizures with no clear rhythmical changes. Semi-automated analysis of ictal EEG was performed. ESI power and ESI+FC were used to localize the SOZ. For ESI power, we considered as estimated SOZ the source with the highest power (S1); for ESI+FC, we used the source with the highest out-degree (VE1) based on FC analysis using Granger causality. Sublobar concordance between S1, VE1 and resection zone, considered as reference standard, was determined for establishing the accuracy of localization.

We report preliminary results from 11 patients (3 cortectomies, 5 disconnections, 3 hemispherotomies), with 49 seizures analyzed. ESI power could localize the estimated SOZ with an accuracy of 42%. When combining ESI power and FC analysis, the accuracy increased up to 56%.

ESI and FC analysis is a valuable tool in the pre-surgical evaluation of ETLE cases and can be performed on classical 19-21 channel scalp EEG. This is the first study using ictal ESI and FC in a cohort of strictly ETLE cases.

Data-driven extraction of epileptic seizure archetypes and principal dimensions

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Epileptic seizures are spatio-temporal processes that have been conceptualised and categorised – so far – based on clinical criteria, which heavily rest on EEG observations. However, apart from

visual inspection, it remains extremely difficult to compare seizures objectively between patients, or even within patients.

Here, we propose a framework of objectively analysing the similarity of pairs of epileptic seizures. This pairwise similarity measure enables us to group seizures into archetypes or distinguish principal dimensions of seizure variance. This powerful generic framework can be applied to univariate and multivariate properties of spatio-temporal seizure processes, and can also be generalised from within-subject comparisons to across-subject analyses.

We will discuss some example application cases and their implications for understanding and treating the seizure process.

Performance comparison and optimization of feature combinations for epileptic seizure prediction based on long-term iEEG measurements

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An automated reliable prediction of epileptic seizures is highly desired in order to improve the quality of life of epilepsy patients and for the development of new therapeutic perspectives. The strong variation of different epilepsies among all patients calls for the development of patient-specific algorithms, which requires the availability of long-term multichannel iEEG recordings. Based on the data provided by the Seizure Prediction Challenge 2014 organized on Kaggle.com, we are going to present here a comprehensive comparison of the prediction performance for a large collection of univariate and multivariate features that have been reported to characterize well iEEG signals in time and frequency domains. In addition to the commonly used ROC based AUC analysis, precision-recall AUC values have been calculated in order to determine the prediction performance, which are more suitable for data with imbalanced class distributions as studied here. To the best of our knowledge, the obtained optimal feature combinations we determined in our investigations and applied to standard classifiers such as support vector machine and multilayer perceptrons, outperform the best results reported so far for the same data set. With the repartition of a validation set which is temporally non-overlapping with train and test sets, we can demonstrate the generalization stability of our method. It is expected that our results can serve as a state-of-the-art reference for further studies on this data set of long-term iEEG measurements.

Analysis of neurostimulation effects in a large-scale model of the limbic system

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Deep brain stimulation (DBS) is increasingly used for the symptomatic treatment of drug-refractory epilepsy, however its parameterization still remains mostly empirical. Stimulation parameters are indeed adapted according to trial and error method to abort or reduce seizures over a period of time, which does not guarantee optimal DBS. There is therefore an urgent need to understand in depth the intricate effects of brain stimulation on neuronal assemblies. More specifically, one unsolved issue is the identification of the combined stimulation parameters (amplitude, frequency, location as other parameters) that are optimal for seizure abortion. Here, we focus on mesial temporal lobe epilepsy (MTLE), where the hippocampus is considered as having a central function in seizure generation. However, this is not the only structure involved in MTLE, and recent studies investigated the role of parahippocampal structures such as the entorhinal cortex (EC). In the recent years, the anterior thalamus nucleus (ATN) also attracted significant attention as a remote structure stimulation site for DBS for epileptic treatment. ATN is indeed part of the Papez circuit, and its modulation could play a role in the suppression of MTLE seizures. This study explores the effects of DBS in a large-scale hippocampus-EC-ATN network model, which was built on neurophysiological and neuroanatomical considerations using the mesoscopic neural mass framework. Electrical stimulation perturbation was integrated in the model as a perturbation of mean membrane voltages in stimulated neuronal populations. It is thus possible to explore a large variety of electrical stimulation protocols, and to quantitatively evaluate, in silico, the impact of stimulation parameters on the hippocampus-EC-ATN complex, prior to experiments. Extensive simulation were performed. Depending on the tested parameter values (amplitude, frequency, targeted structures), some stimulations were shown to have the potential to abort a seizure, initiate a seizure, or might have no effect at all. Results emphasize the importance of optimal selection of stimulation parameters to achieve seizure abortion.

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Design Challenges of Real-time Hardware Implementation of Seizure Prediction Chip

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Epilepsy is a chronic neurological disorder from which around 50 million people at different ages suffer worldwide. While the main approach to treatment is using pharmacological antiepileptic drugs,

20-40% of cases are intractable. This results in a continuous anxiety for patients about when the next seizure happens and the consequences. Moreover, regular medication causes side effects like cognitive impairment and physical characteristics. Real-time seizure prediction analyses bio-signals e.g., intracranial electroencephalography (iEEG) or electroencephalography (EEG), to predict the onset of seizure. It opens a promising window for study, control and treatment of impending seizures and could also warn the patients to avoid performing the risky tasks or to take medicine. To achieve this goal, the advancement of Integrated Circuit (IC) design technology could be leveraged to miniaturize signal acquisition and classification systems. Such systems could be implanted to record neuronal activity in real-time and perform the required computation such as machine learning-based analysis, within the device. This approach opens perspectives in creating intelligent closed-loop systems can then be utilized to apply inhibitory electrical neuromodulation in the focal region as a means of seizure suppression. The main design challenges of such systems are power consumption and prediction accuracy. In this contribution we present a systematic design paradigm, dividing the processing into analog and digital domains where recorded signals are undergoing various processing stages. The analog domain is dealing with the very small amplitude input neural signal which is recorded in the presence of noise and then converts it to digital values, and the digital domain performs the varios signal conditioning and complex machine learning algorithm to predict the seizure. We elaborate on the main challenges and design approaches in real-time hardware implementations of seizure prediction systems both in analog and digital domains.

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Understanding the mechanism and treatment of the focal epilepsy: a computational modelling method

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Focal epilepsy is one of the most common type of epilepsy that arises from localized brain areas. Understanding focal epileptic network mechanisms is of great significance in clinical diagnosis and treatments [1]. We begin to address the local changes in tissue leading to focal seizures. We elucidate how the coupling strength between neural population columns, external stimuli and different time scales can induce seizures. After establishing the focal epileptic network, we explore that global changes can drive the network from an intermittent seizure state to a continuous seizures state (status). Results show that the network has the capability of reproducing different seizures states due to global changes of network, which also lays the foundation for a control strategy. Based on our network modeling framework, we propose various local control strategies based on the hub node to suppress seizures [2]. Nevertheless, local control may be insufficient to suppress morbid seizures activity during the continuous seizures state. By comparing local stimulation in different seizures states, we conclude that the optimal opportunity of exerting stimuli is before the system reaches to the continuous seizure state.

Clinically, anatomical connections between nodes can be detected by magnetic resonance imaging (MRI) method to estimate the hub node. In the case of the whole brain, the hub node may be a brain region, which needs more stimulation sites to suppress seizures. It also highlights that the diagnosis of seizure state determines a successful control. Our modeling provides a theoretical approach to investigate the dynamical possibility of a pathological focal epileptic network. These insights also provide a new way of exploring strategies for seizures suppression. Future work will involve the combination of clinical data and computational model, and develop potentially simple but effective control therapies.

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