IWSP7: Seventh International Workshop on Seizure Prediction

Epilepsy Mechanisms, Models, Prediction and Control

Melbourne Brain Centre, Kenneth Myer Building
The University of Melbourne,
Australia
3-6 August, 2015

IWSP7: Seventh International Workshop on Seizure Prediction
Melbourne Brain Centre, Kenneth Myer Building
The University of Melbourne, Australia

Schedule
(including the overlapping Melbourne Epilepsy ME@MBC'15 meeting)

Monday August 3 2015 – IWSP7 Educational Day

08:00-08:30 - Registration

08:30-10:00 – Session 1a – Introduction to Epilepsy

08:30-10:00 – Session 1b – The Virtual Brain Tutorial Part 1

10:00-10:30 – Morning Tea Provided

10:30-12:00 – Session 2a – EEG analysis, Networks and Machine Learning

10:30-12:00 – Session 2b – The Virtual Brain Tutorial Part 2

12:00-13:00 – Lunch Provided

13:00-15:00 – Session 3a – Oscillations, Seizure Prediction, and Devices for Epilepsy

13:00-15:00 – Session 3b – IEEG Database Tutorial Part 1

15:00-15:30 – Afternoon Tea Provided

15:30-17:30 – Session 4a – Modelling and Engineering for Epilepsy

15:30-17:30 – Session 4b – IEEG Database Tutorial Part 2

17:30-18:30 – Mentoring Session

18:30-19:00 – Opening Networking Reception

19:00-21:00 – IWSP7 Poster Session

Tuesday August 4 2015 – IWSP7 day 1

08:00-09:00 - Registration

09:00-10:00 – Introduction: Goals and hot topics

10:00-10:30 – Morning Tea Provided

10:30-12:30 – Advances in Seizure Prediction and Detection Part 1

12:30-13:30 – Lunch Provided

13:30-15:00 – Computational Modelling of Epilepsy

15:00-15:30 – Afternoon Tea Provided

15:30-17:00 – Epilepsy Mechanisms and Neural Oscillations

17:00-18:00 – Split-groups: problems & solutions

18:30-21:30 – Conference Dinner for all registrants

Wednesday August 5 2015 – IWSP7 day 2

08:30-09:30 – Databases and Contest developments

10:00-12:00 – Imaging, Networks and Epilepsy

12:00-13:00 – Lunch Provided

13:00-14:30 – Advances in Seizure Prediction and Detection Part 2

14:30-15:00 – Afternoon Tea Provided

15:00-16:30 – Model-Based Estimation and Control in Epilepsy

16:30-17:30 – Outcomes and Targets for the Seizure Prediction Community

Thursday August 6 2015 – IWSP7/ME@MBC'15 joint day

08:45-10:30 – Epilepsy: From DNA to multi-faceted disease

10:30-11:00 – Morning Tea Provided

11:00-12:30 – Sudden Unexpected Death in Epilepsy (SUDEP)

12:30-13:30 – Lunch Provided

13:30-15:00 – Brain Stimulation and Monitoring

15:00-15:30 – Afternoon Tea Provided

15:30-17:00 – Imaging

17:00-20:00 – ME@MBC Networking Reception and Poster Session (Open to IWSP7

registrants)

Friday August 7 2015 – ME@MBC'15 day 2 (Open to IWSP7 registrants)

08:45-10:15 – Data Blitz: Students and Post-docs present

10:15-10:45 – Morning Tea Provided

10:45-12:00 – Basic Science

12:00-12:15 – Closing Remarks

Welcome

It is our great honor to host the Seventh International Workshop on Seizure Prediction (IWSP7: Epilepsy Mechanisms, Models, Prediction & Control). The IWSPs are a forum that brings together an international interdisciplinary group of epileptologists, engineers, physicists, mathematicians, neurosurgeons and neuroscientists with the goal of developing engineering-based epilepsy treatments.

This meeting continues the series' goal of reporting progress in seizure prediction and related fields. While this goal has not changed over the previous six workshops, the group has recognized that there needs to be a balance in developing an understanding of the biological mechanisms underlying epilepsy in parallel with treatment oriented approaches in order to improve the performance of seizure prediction, detection and control algorithms, with the ultimate objective of improving quality of life for the epileptic patient. At a fundamental level, the goal of seizure prediction is to identify the underlying mechanisms of seizure generation and to engineer systems that will detect those dynamics and provide for intervention.

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

We would like to express our deep appreciation to our organising partners the Alliance for Epilepsy Research, Pennsylvania State University and Yale University for their contributions to the organisation of this meeting and to the many sponsors and donors that have made this workshop possible. We hope you will enjoy the workshop and take the opportunity to interact with other members of the seizure prediction community during your visit to Melbourne, Australia.

The Organizing Committee

Kuhlmann, Levin, PhD
Grayden, David B., PhD
Cook, Mark J., MD
Burkitt, Anthony N., PhD
Freestone, Dean R., PhD
Kameneva, Tatiana, PhD
Lai, Alan, PhD
O'Sullivan-Greene, Elma, PhD
Peterson, Andre, PhD
Susan Arthurs, Alliance for Epilepsy Research

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This conference is supported in part by a grant from the National Institute Of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R13NS090888. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily represent the official views of the National Institutes of Health.

Partner Events

Melbourne Epilepsy brings together and presents the best of Melbourne's epilepsy research. This meeting is being held in the same venue as IWSP7, and overlaps with IWSP7 on Thursday August 6th 2015 and finishes on Friday August 7th 2015. Attendance is free for IWSP7 registrants. For more information email **organizingcommittee@iwsp7.org**.

BioBreakfast on Innovation in Epilepsy at the Interface of Industry and Research, hosted in partnership with the BioMelbourne Network, will occur in the same venue as IWSP7 on the morning of August 6th 2015. This will involve a panel-based question and answer discussion with researchers working closely with industry to develop innovations in epilepsy treatment. There is a special attendance fee for IWSP7 registrants. For more information email **organizingcommittee@iwsp7.org**.

Swinburne Brain Imaging Symposium 2015: Principles and Applications of Magnetoencephalography is a meeting on MEG and neuroimaging occuring in Melbourne in the week preceding IWSP7 from July 29-30 2015.

AusMedtech 2015 will be held at the Pullman Melbourne on the Park (formerly Hilton on the Park) from 29-30 April 2015. This not-to-be-missed event will feature a comprehensive program, trade exhibition, networking events and AusPartnering, a networking and partnering platform enabling delegates to schedule 30-minute meetings with other attendees. AusMedtech is Australia's premier medical technology conference for medtech executives, providing business partnering opportunities for decision-makers. It brings together key stakeholders of the Australian and international medical devices and diagnostics sector to discuss the major factors in global medtech success.

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

IWSP7 Program

Including the overlapping Melbourne Epilepsy (ME@MBC'15) meeting.

Monday August 3 2015 – IWSP7 Educational Day

08:00-08:30 – Registration – Foyer

08:30-10:00 – Session 1a – Introduction to Epilepsy – Ian Potter Auditorium

Educational Day Welcome 08:30
Levin Kuhlmann, University of Melbourne

Basic Epilepsy 08:35
Andreas Schulze-Bonhage, University of Freiburg

Brain Activity and Seizure Statistics in Epilepsy 09:15
Mark Cook & Philippa Karoly, University of Melbourne

08:30-10:00 – Session 1b – The Virtual Brain Tutorial Part 1 – Education Room
Timothée Proix, Aix Marseille Université; Paula Sanz-Leon, University of Sydney

10:00-10:30 – Morning Tea Provided – Foyer

10:30-12:00 – Session 2a – EEG analysis, Networks and Machine Learning – Ian Potter Auditorium

The Network Theory of Epilepsy: Concepts, Questions and Analysis 10:30
Klaus Lehnertz, University of Bonn; Hitten Zaveri, Yale University

Machine Learning and EEG analysis 11:30
Theoden Netoff, University of Minnesota

10:30-12:00 – Session 2b – The Virtual Brain Tutorial Part 2 – Education Room
Timothée Proix, Aix Marseille Université; Paula Sanz-Leon, University of Sydney

12:00-13:00 – Lunch Provided – Foyer

13:00-15:00 – Session 3a – Oscillations, Seizure Prediction, and Devices for Epilepsy – Ian Potter Auditorium

Normal and Pathological High Frequency Oscillations 13:00
Liset Menendez de la Prida, Instituto Cajal – CSIC

Introduction to Seizure Prediction 13:40
Catalina Alvarado-Rojas, Pontificia Universidad Javeriana

Current & Next Generation Devices for Epilepsy 14:20
Greg Worrell, Mayo Clinic

13:00-15:00 – Session 3b – IEEG Database Tutorial Part 1 – Education Room
Brian Litt, Hoameng Ung, Lohith Kini, Ankit Khambhati, University of Pennsylvania

15:00-15:30 – Afternoon Tea Provided – Foyer

15:30-17:30 – Session 4a – Modelling and Engineering for Epilepsy – Ian Potter Auditorium

Keys and Challenges of modeling epileptiform behaviour 15:30
William Stacey, University of Michigan

A physicist's take on epilepsy – neural field models of seizure transition 16:10
Andre Peterson, University of Melbourne

Why Would a Seizure Prediction Investigator Need To Care About Group Theory? 16:50
Steven Schiff, Pennsylvania State University

15:30-17:30 – Session 4b – IEEG Database Tutorial Part 2 – Education Room
Brian Litt, Hoameng Ung, Lohith Kini, Ankit Khambhati, University of Pennsylvania

17:30-18:30 – Mentoring Session – Ian Potter Auditorium
18:30-19:00 – Opening Networking Reception – Level 5 Common Room
19:00-21:00 – IWSP7 Poster Session – Level 5 Common Room

Tuesday August 4 2015 – IWSP7 day 1

08:00-09:00 – Registration – Foyer

All talks will be in the Ian Potter Auditorium

09:00-10:00 – Introduction: Goals and hot topics
Session Moderator: Mark Cook, University of Melbourne

Introductory Remarks/Welcome 09:00
Iven Mareels, Dean of Engineering, University of Melbourne

Goals and hot topics in epilepsy mechanisms, models, prediction and control
Mark Richardson, Kings College London 09:10

Panel positions:
Bjoern Schelter, University of Aberdeen 09:30
Bruce Gluckman, Pennsylvania State University 09:35
Liset Menendez de la Prida, Instituto Cajal – CSIC 09:40

10:00-10:30 – Morning Tea Provided – Foyer

10:30-12:30 – Advances in Seizure Prediction and Detection Part 1
Session Moderators: David Grayden, University of Melbourne; William Stacey, University of Michigan

Forecasting seizures in dogs with naturally occurring epilepsy 10:30
Gregory Worrell, Mayo Clinic
Introduced by *Chris Meisel, National Institutes of Health*

Cross-frequency coupling and seizure prediction 11:00

Catalina Alvarado-Rojas, Pontificia Universidad Javeriana
Introduced by *Joana Soldado Magraner, University College London*

Seizure prediction and the EPILEPSIAE project 11:30
Antonio Dourado, University of Coimbra
Introduced by *Kais Gadhoumi, McGill University*

Mathematical characterization of epileptiform limbic events 12:00
Wytse Wadman, University of Amsterdam

12:30-13:30 – Lunch Provided – Foyer

13:30-15:00 – Computational Modelling of Epilepsy
Session Moderators: Anthony Burkitt & Andre Peterson, University of Melbourne

The role of macroscopic brain networks in seizure initiation 13:30
John Terry, University of Exeter
Introduced by *Amirhossein Jafarian, University of Melbourne*

Modelling of neuronal and ionic dynamics during ictogenesis 14:00
Piotr Suffczynski, University of Warsaw
Introduced by *Sebastien Naze, Institut de Neuroscience des Systèmes*

Seizure spread in a virtual epileptic patient 14:30
Timothée Proix, Aix Marseille Université; Paula Sanz-Leon, University of Sydney

15:00-15:30 – Afternoon Tea Provided – Foyer

15:30-17:00 – Epilepsy Mechanisms and Neural Oscillations
Session Moderators: Liset Menendez de la Prida, Instituto Cajal – CSIC; Theoden Netoff, University of Minnesota

Neurons, neuronal populations and networks during seizure initiation, propagation and termination 15:30
Sydney Cash, Massachusetts General Hospital, Harvard Medical School
Introduced by *Hoameng Ung, University of Pennsylvania*

Experimental control of ictogenesis to identify proictal biomarkers 16:00
William Stacey, University of Michigan

Post-malarial epilepsy - dynamics in an animal model 16:30
Bruce Gluckman, Pennsylvania State University

17:00-18:00 – Split-groups: problems & solutions
Co-ordinated by Organizing Committee

18:30-21:30 – Conference Dinner for all registrants – Level 10, Woodward Conference Centre, Law Building, 185 Pelham St, Carlton VIC 3053 (See map at back of program)

Wednesday August 5 2015 – IWSP7 day 2

All talks will be in the Ian Potter Auditorium

08:30-09:30 – Databases and Contest developments

Session Moderators: Alan Lai & Tatiana Kameneva, University of Melbourne

Seizure prediction algorithm development and validation via kaggle.com 08:30
Benjamin Brinkmann, Mayo Clinic

Kaggle competition seizure prediction algorithm 08:50
Simone Bosshard, University of Queensland

Data Integration, Neuroengineering and Collaboration on the Cloud 09:10
Brian Litt, University of Pennsylvania

09:30-10:00 – Morning Tea Provided – Foyer

10:00-12:00 – Imaging, Networks and Epilepsy

Session Moderators: Klaus Lehnertz, University of Bonn; Hitten Zaveri, Yale University

Spatio-temporal dynamic EEG source imaging of epileptogenic activity 10:00
Bin He, University of Minnesota
Introduced by *Ankit Khambhati, University of Pennsylvania*

Multimodal imaging and modeling of epileptic seizures and interictal epileptiform activity in humans 10:30
Louis Lemieux, University College London
Introduced by *Stephan Lau, University of Melbourne*

Revealing a brain network endophenotype in families with idiopathic generalized epilepsy 11:00
Wessel Woldman, University of Exeter

Regional and network relationship in the intracranial EEG and its second spectrum 11:30
Rasesh Joshi, Yale University

12:00-13:00 – Lunch Provided – Foyer

13:00-14:30 – Advances in Seizure Prediction and Detection Part 2

Session Moderator: Gregory Worrell, Mayo Clinic; John Terry, University of Exeter

An extracerebral biosignal pattern for epileptic seizure detection 13:00
Diana Cogan, University of Texas at Dallas

Cortical excitability measurement and seizure prediction utilizing electrical probing 13:30
Farhad Goodarzy, University of Melbourne

Adaptation of the phase clustering index to the rat model of epilepsy 14:00
Karin Somerlik-Fuchs, University of Freiburg

14:30-15:00 – Afternoon Tea Provided – Foyer

15:00-16:30 – Model-Based Estimation and Control in Epilepsy

Session Moderators: Steven Schiff, Pennsylvania State University; Dean Freestone, University of Melbourne

Recent advances in data-based modelling and their role in epilepsy research 15:00
Bjoern Schelter, University of Aberdeen
Introduced by *Helmut Schmidt, University of Exeter*

Can the mathematics of networked oscillators explain the challenges in predicting epileptic seizures? 15:30
Elma O'Sullivan-Greene, University of Melbourne

Real-time automated EEG tracking of brain state parameters using neural field theory: Application to brain stability and seizures 16:00
Romesh Abeysuriya, University of Sydney

16:30-17:30 – Outcomes and Targets for the Seizure Prediction Community

Moderators: IWSP7 Organising Committee

Participants:
Theoden Netoff, University of Minnesota
Andreas Schulze-Bonhage, University of Freiburg
William Stacey, University of Michigan

Thursday August 6 2015 – IWSP7/ME@MBC'15 joint day

All talks will be in the Ian Potter Auditorium

07:15-08:40 – BioBreakfast on Innovation in Epilepsy at the Interface of Industry and Research (Not included in IWSP7 registration fee. To register see details on the www.iwsp7.org website)

08:45-10:30 – Epilepsy: From DNA to multi-faceted disease

Session Moderator: Mark Cook, University of Melbourne

Welcome 08:45
Mark Cook, University of Melbourne

Genetics and the individual-specific nature of epilepsy 09:00
Samuel Berkovic, University of Melbourne
Introduced by *Michael Chang, Toronto Western Research Institute*

Unification of spikes, seizures and spreading depression 09:30
Steven Schiff, Penn State University
Introduced by *Ann Vanleer, United States Naval Academy*

Sources of functional heterogeneity in the cellular activity of hippocampal microcircuits in temporal lobe epilepsy 10:00
Liset Menendez de la Prida, Instituto Cajal – CSIC
Introduced by *Jennifer Robertson, Australian National University*

10:30-11:00 – Morning Tea Provided – Foyer

11:00-12:30 – Sudden Unexpected Death in Epilepsy (*SUDEP*)

Session Moderator: Anne McIntosh, Austin Health

Plenary: SUDEP: An Overview 11:00
Philippe Ryvlin, Lyon University
Introduced by *Vanessa Senger, Technical University of Dresden*

Genetics of SUDEP 11:45
Doug Crompton, Northern Health

Sudden unexpected death, epilepsy and familial cardiac pathology 12:00
Alana Eastaugh, Austin Health

Chronic epilepsy causing an acquired cardiac channelopathy – more than just HCN 12:15
Sakshi Singh, Royal Melbourne Hospital

12:30-13:30 – Lunch Provided – Foyer

13:30-15:30 – Brain Stimulation and Monitoring

Session Moderator: Brian Litt, University of Pennsylvania

Responsive direct brain stimulation for the treatment of epilepsy 13:30
Martha Morrell, Stanford University, Neuropace
Introduced by *Roman Sandler, University of Southern California*

Anterior thalamic stimulation 14:00
John Archer, Austin Health

Tracking seizure dynamics using data-driven neural-field modelling 14:15
Dean Freestone, University of Melbourne

Implantable devices 14:30
Mark Cook, University of Melbourne

Fit-bit epileptology 14:45
Patrick Kwan, Royal Melbourne Hospital

Discussion/Extra time 15:00

15:30-16:00 – Afternoon Tea Provided – Foyer

16:00-17:30 – Imaging

Session Moderator: Sarah Wilson, University of Melbourne

Dynamic changes in the peri-ictal period 16:00
Jennifer Walz, Florey Institute of Neuroscience & Mental Health

Functional networks in focal epilepsy 16:15
Mangor Pedersen, Florey Institute of Neuroscience & Mental Health

Autobiographical memory breakdown: using event-related ICA to study higher cognitive functions 16:30
Chris Tailby, Epilepsy Research Centre

Networks in Lennox-Gastaut syndrome 16:45
Aaron Warren, Florey Institute of Neuroscience & Mental Health

White matter tract abnormalities in Periventricular Nodular Heterotopia 17:00
Shawna Farquharson, Florey Institute of Neuroscience & Mental Health

Simultaneous EEG-MEG in refractory focal epilepsy 17:15
Chris Plummer, St. Vincent's Hospital Melbourne

17:30-20:00 – ME@MBC Networking Reception and Poster Session – Foyer (Open to IWSP7 registrants; does not involve IWSP7 posters)

Friday August 7 2015 – ME@MBC'15 day 2 (Open to IWSP7 registrants)

All talks will be in the Ian Potter Auditorium

08:45-10:15 – Data Blitz: Students and Post-docs present
Session Moderator: Graeme Jackson, Florey Institute of Neuroscience & Mental Health

10:15-11:00 – Morning Tea Provided – Foyer

11:00-12:30 – Basic Science
Session Moderator: Levin Kuhlmann, University of Melbourne

Epileptogenesis in the developing brain 11:00
Bridget Semple, Royal Melbourne Hospital
Can a spider toxin fix Dravet syndrome? 11:15
Kay Richards, Florey Institute of Neuroscience & Mental Health
Human iPS cells as a model of genetic epilepsy 11:30
Snezana Maljevic, University of Melbourne
In vivo myelo-architecture using whole-brain diffusion MRI 11:45
Fernando Calamante, Austin Health
Using diamonds to measure neuronal activity 12:00
David Simpson, University of Melbourne

Closing Remarks: *Levin Kuhlmann* 12:15

Organizing Committee

Email: organizingcommittee@iwsp7.org

Kuhlmann, Levin, PhD
Grayden, David B., PhD
Cook, Mark J., MD
Burkitt, Anthony N., PhD
Freestone, Dean R., PhD
Kameneva, Tatiana, PhD
Lai, Alan, PhD
O'Sullivan-Greene, Elma, PhD
Peterson, Andre, PhD
Susan Arthurs, Alliance for Epilepsy Research

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Terry, John, PhD, University of Exeter

Tetzlaff, Ronald, PhD, University of Dresden

Vonck, Kristl, MD, University of Ghent

Wendling, Fabrice, PhD, University of Rennes

Worrell, Gregory A. MD, PhD, Mayo Clinic

Zaveri, Hitten, PhD, Neurology, Yale University

Invited Speakers

Catalina Alvarado-Rojas, Pontificia Universidad Javeriana, Colombia
(Cross-frequency coupling and seizure prediction)
Samuel Berkovic, University of Melbourne, Australia
(Genetics and individual-specific nature of epilepsy)
Sydney Cash, Massachusetts General Hospital, Harvard Medical School, USA
(Neurons, neuronal populations and networks during seizure initiation, propagation and termination)
Antonio Dourado, University of Coimbra, Portugal
(Seizure Prediction and the EPILEPSIAE project)
Bin He, University of Minnesota, USA
(Spatio-temporal dynamic EEG source imaging of epileptogenic activity)
Louis Lemieux, University College London, UK
(Multimodal imaging and modeling of epileptic seizures and interictal epileptiform activity in humans**)**
Liset Menendez de la Prida, Instituto Cajal - CSIC, Spain
(Sources of functional heterogeneity in the cellular activity of hippocampal microcircuits in temporal lobe epilepsy)
Martha Morrell, Stanford University, Neuropace, USA
(Responsive direct brain stimulation for the treatment of epilepsy)
Philippe Ryvlin, Lyon University, France
(Sudden unexplained death in epilepsy)
Bjoern Schelter, University of Aberdeen, UK
(Recent advances in data-based modelling and their role in epilepsy research)
Steven Schiff, Penn State University, USA
(Unification of spikes, seizures and spreading depression)
Piotr Suffczynski, University of Warsaw, Poland
(Modelling of neuronal and ionic dynamics during ictogenesis)
John Terry, University of Exeter, UK
(The role of macroscopic brain networks in seizure initiation)
Gregory Worrell, Mayo Clinic, USA
(Forecasting seizures in dogs with naturally occurring epilepsy)

BASIC EPILEPTOLOGY

Andreas Schulze-Bonhage

Epilepsy Center, University Hospital Freiburg, Germany
andreas.schulze-bonhage@uniklinik-freiburg.de

Epilepsies are diseases of the brain characterized by a disposition to generate transient hypersynchronous neuronal activity in local or extended networks. These states of hypersynchronous activity are called "seizures" if accompanied by subjective symptoms or objective behavioral signs. A wide spectrum of pathophysiological mechanisms can underly epilepsies, ranging from genetic alterations of membrane-intrinsic channels or synaptic receptors to various structural alterations of the brain. Depending on the brain regions involved, seizures are reflected by transient subjective sensations ("auras"), motor signs (clonic or tonic movements, loss of motor control or complex motor behavior), vegetative signs (e.g. heart rate changes, changes in breathing), and in cognitive impairments (e.g. aphasia or loss of consciousness); frequently, localized/short epileptic discharges occur "subclinically", i.e. without overtly noticeable change.

When recording the bioelectric acitivity of the brain in an electroencephalogram (EEG), biomarkers of epilepsy are found not only during seizures (ictally) but also between seizures (interictally). Interictally, steep negative potentials ("spikes", "sharp waves") and high frequency oscillations (HFO) are found focally or widespread, depending on the epilepsy syndrome. During seizures, various patterns ranging from low amplitude fast activities to rhythmic activities at various frequency bands can be found. When surgical removal of epileptogenic brain regions is considered, also invasive EEG recordings are performed using electrodes placed in the subdural space or penetrating the brain. These recordings frequently allow identifying circumscribed brain regions of a few cm^3 volume to trigger ictal patterns, the so-called seizure onset zone. In contrast, interictal spiking may occur quite extended, possibly representing different underlying generator mechanisms.

For clinical purposes, the standard of EEG interpretation is yet based on visual inspection and pattern recognition, but increasingly computerized EEG analyses are used for specific purposes and for the analysis of long-term recordings. Whereas ictal periods are mostly easily recognizable, preictal periods for visual inspection look like any interictal period, and in particular the epilepsy biomarkers spikes and HFO appear not to increase in frequency. Computerized linear and non-linear analyses of preictal periods so far may show statistically significant alterations with, however, relatively low specificity for the periods immediately preceding seizures.

[1] Osorio I, Zaveri HP, Frei MG; Arthurs S. Epilepsy-The intersection of Neurosciences, Biology, mathematics, Engineering, and Physics. CRC Press, Boca Raton, 2011

[2] Schelter B, Timmer J, Schulze-Bonhage. Seizure Prediction in Epilepsy. From Basic Mechanisms to Clinical Applications. Wiley, Berlin 2008

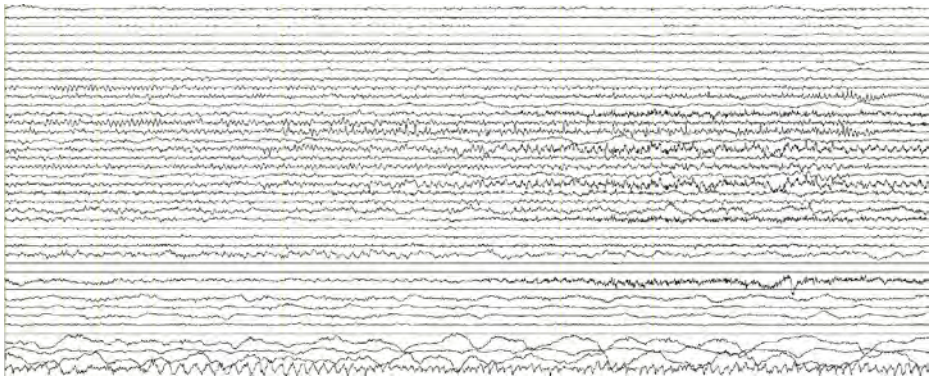

Fig. 1. Subdural rhythmic ictal pattern (bottom) with gradual increase in frequency and spread to other contacts in a seizure arising from the frontal lobe.

BRAIN ACTIVITY AND SEIZURE STATISTICS IN EPILEPSY

Mark J Cook1, Philippa J Karoly1,2#,Dean R Freestone1,2,3, David Himes6, Kent Leyde6, Samuel Berkovic4, Terence O'Brien5, David Grayden1,2 and Ray Boston1
1Departments of Medicine, University of Melbourne and St Vincent's Hospital, Melbourne
2Department of Electrical and Electronic Engineering, University of Melbourne
3Department of Statistics, Columbia University, New York, 10027, USA
4Austin and Repatriation Medical Centre
5Royal Melbourne Hospital
6NeuroVista Corporation, Seattle, WA 98109 USA
#pkaroly@student.unimelb.edu.au\

Valuable insight in seizure dynamics can be obtained from high-level statistics. However, obtaining constructing distributions of seizure characteristics has been limited by a lack of long-term data. This work presents a thorough, quantitative analysis of seizure duration, inter-seizure interval (ISI) and long-term patterns of seizure occurrences. The results provide information about generative and regulatory mechanisms and inherent predictability of epileptic events, and will inform future directions for improved seizure prediction.

Analysis was performed on continuous, ambulatory, intracranial electroencephalographic data for 15 subjects with drug-resistant epilepsy. Subjects were enrolled in a previous clinical trial (6 months to 2 years duration) for an implantable seizure prediction device[1]. The device identified potential seizure activity, which was confirmed manually. At least ten and up to thousands of seizures (including clinical and sub-clinical) per subject were confirmed, which were analyzed using a range of statistical methods.

Our analyses resulted in a number of important findings. First, the seizures of some subjects showed dynamics consistent with a long-memory process, indicating that the timing of past events influences future events[2]. Results also showed well-resolved groups of seizure duration and inter-seizure intervals (ISI), which were either mono- or multi-modal, and highly subject-specific. The presence of clear duration and ISI groups implies that seizures follow distinct, pre-determined time courses of set duration, rather than representing a build-up and dissipation of excess energy in the brain. The occurrence of epileptic events showed consistent, subject-specific circadian regulation and, some subjects also demonstrated longer-term patterns evident over weeks to months.

As well as improving understanding of seizures, the statistics can be used to enhance prediction. The aforementioned results were found to have clear implications on the predictability of subjects' seizures, as the presence of long-memory dynamics or a unimodal population of seizure durations were linked to improved predictive performance. Persistent circadian rhythms and other patterns of seizure occurrence also provide an avenue to enhance prediction by constructing prior probabilities from underlying patterns.

[1] Mark J Cook, Terence J O'Brien, Samuel F Berkovich, Michael Murphy, Andrew Morokoff, Gavin Fabinyi, Wendyl D'Souza, Raju Yerra, John Archer, Lucas Litewka and others (2013) Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study, *The Lancet Neurology*, vol. 12, no. 6, pp. 563-571
[2] Cook, M. J., Varsavsky, A., Himes, D., Leyde, K., Berkovic, S. F., O'Brien, T., & Mareels, I. (2014). The dynamics of the epileptic brain reveal long-memory processes. Frontiers in Neurology, 5, 217. http://doi.org/10.3389/fneur.2014.00217

PRACTICAL BRAIN NETWORK MODELING IN EPILEPSY WITH THE VIRTUAL BRAIN

Timothée Proix[1,#], Paula Sanz-Leon[2,3] and Viktor Jirsa[1]
[1]Aix Marseille Université, Inserm, INS UMR_S 1106, 13005, Marseille, France
[2]School of Physics, The University of Sydney, Sydney, Australia
[3]Centre of Integrative Brain Function, The University of Sydney, Sydney, Australia
#timothee.proix@etu.univ-amu.fr

The Virtual Brain (TVB) [1,2] is a neuroinformatics platform that allows for the modeling of large-scale brain dynamics and simulation of brain signals including M/EEG, stereotactic EEG and fMRI. In this tutorial, we will learn in practice how to use TVB to model seizure propagation in a virtualized brain. We will experiment with a phenomenological neural mass model which is able to reproduce several features of seizure dynamics, the Epileptor model[3]. Using connectomes obtained from diffusion datasets of real patients, we will couple several Epileptors together, in particular with permittivity coupling [4], and reproduce the propagation patterns of partial seizures.

TVB allows for the testing of multiple virtual scenarios interesting for clinical epilepsy, such as simulation of electrical stimulation, or partial resection of a brain. TVB also includes a framework for data management (generation, organization, storage, integration and sharing) and a simulation core written in Python, accessible through both a Graphical User Interface and a Console Interface. TVB can interact with third-party toolboxes written in MATLAB, e.g. the well-known Brain Connectivity Toolbox.

After this tutorial, you should have a basic practical understanding of how to model a virtual epileptic patient in TVB. In the first one hour and a half session, we will give a theoretical introduction to The Virtual Brain (see [2] for details) and learn in a hands-on session how to use both the Graphical User Interface and the Console Interface of TVB, with time left for questions. The second session will be dedicated to the modeling of seizure propagation through the virtualized brain of a patient. Participants are encouraged to install a working version of TVB before attending this tutorial[5,6].

[1] Sanz Leon P, Knock S, Woodman M.M, Domide L, Mersmann J, McIntosh A, Jirsa V.K (2013) The Virtual Brain, a simulator of primate brain network dyanmics, *Frontiers in Neuroinformatics,* vol. 7, no. June, pp. 1-23
[2] Sanz-Leon P, Knock SA, Spiegler A, Jirsa VK (2015) Mathematical framework for large-scale brain network modelling in The Virtual Brain. Neuroimage 1;111:385-430.
[3] Jirsa V.K, Stacey W.C, Quilichini P.P, Ivanov A.I, Bernard C (2014) On the nature of seizure dynamics, *Brain,* vol. 137, no. 8, pp. 2210-2230
[4] Proix T, Bartolomei F, Chauvel P, Bernard C, Jirsa VK (2014) Permittivity Coupling across Brain Regions Determines Seizure Recruitment in Partial Epilepsy, *Journal of Neuroscience,* vol. 34, no. 45, pp. 15009-15021
[5] http://thevirtualbrain.org/tvb/zwei
[6] http://docs.thevirtualbrain.org/

THE NETWORK THEORY OF EPILEPSY: CONCEPTS, QUESTIONS AND ANALYSIS

Klaus Lehnertz[1#] and Hitten Zaveri[2]
[1]Department of Epileptology & Helmholtz Institute for Radiation and Nuclear Physics & Interdisciplinary Center for Complex Systems, University of Bonn; Bonn; Germany
[2]Department of Neurology, Yale University, New Haven, CT 06520, USA
#Klaus.Lehnertz@ukb.uni-bonn.de

The brain is a typical example of a system composed of a large number of highly interconnected dynamical units. In order to capture the properties of such a system, it can be modelled as a graph or network whose nodes represent the dynamical units, and whose links stand for the interactions between them. There are now a large number of concepts and tools available that allow one to characterize structural and dynamical properties of complex networks. This short tutorial provides an overview of how to infer underlying network structure from time-series data. We will discuss the data-driven identification of links, which is usually based on linear or nonlinear bivariate time series analysis techniques, as well as commonly used methods to characterize network properties on various scales. An important new conceptual understanding of epilepsy is offered by the network theory of epilepsy. We discuss questions raised by this theory for epiletogenesis, ictogenesis, the notion of a seizure onset area within a network theory of epilepsy, localization of nodal or network aberrance, prediction of seizures, and the use of targeted therapy (for example, resective brain surgery) for treating a network disorder. Examples drawn from human and animal studies will be used to discuss important assumptions underlying the network approach as well as potential pitfalls and remedies.

MACHINE LEARNING AND EEG ANALYSIS

Tay Netoff
University of Minnesota
Department of Biomedical Engineering

tnetoff@umn.edu

Machine learning can be used to identify differences in data collected under different conditions, such as differences in EEG that occurs prior to a seizure from interictal times, or to identify differences in EEG between epileptic from non-epileptic patients. Machine learning algorithms can also be used to find optimal solutions to problems, such as tuning stimulation parameters to maximize seizure suppression while minimizing stimulation energy. These problems first depend on good representation of the patient's state, as discussed in the previous two speakers. In this session I will first provide a tutorial on supervised machine learning algorithms, such as Linear Discriminate Analysis and Support Vector Machines, and how they can be used to identify and quantify differences between groups of data. Then, I will provide a brief tutorial on unsupervised algorithms, such as Reinforcement Learning, which utilize an action-state-reward approach to optimize parameters. This tutorial will focus on implementation of these algorithms in Matlab.

NORMAL AND PATHOLOGICAL HIGH FREQUENCY OSCILLATIONS

Liset Menendez de la Prida
[1]Instituto Cajal CSIC, Madrid 28002, Spain

#lmprida@cajal.csic.es

Pathological high-frequency oscillations (HFOs) (80-800 Hz) are considered biomarkers of epileptogenic tissue, but the underlying complex neuronal events are not well understood. Here, we will discuss about several conflicting issues in regards to the recording, analysis, and interpretation of HFOs in the epileptic brain to critically highlight what is known and what is not about these enigmatic events. High-frequency oscillations reflect a range of neuronal processes contributing to overlapping frequencies from the lower 80 Hz to the very fast spectral frequency bands. Given their complex neuronal nature, HFOs are extremely sensitive to recording conditions and analytical approaches. We will discuss whether adopting basic standards will facilitate data sharing and interpretation that collectively will aid in understanding the role of HFOs in health and disease for translational purpose.

[1] Menendez de la Prida L, Staba R.J and Dian J.A (2015) Conundrums of high-frequency oscillations (80-800 Hz) in the epileptic brain. *J Clin Neurophysiology*, vol.32, no.3, pp. 207-219

INTRODUCTION TO SEIZURE PREDICTION

Catalina Alvarado-Rojas[1]
[1]Department of Electronics Engineering, Pontificia Universidad Javeriana, Bogotá, Colombia
catalina_alvarado@javeriana.edu.co

The development of a closed-loop system for automatic seizure anticipation will clearly improve the quality of life of epileptic patients. The idea of such a system was first proposed 4 decades ago, and does not have a solution yet, despite a huge amount of studies. In this educational session, we will define what a seizure prediction method is (according to literature), and describe its main stages and basic requirements for a clinical application. The evolution of seizure prediction algorithms will be presented, explaining the main types of measures extracted from signals and highlighting the breakthroughs that stablished the actual state of the art. Some thoughts about how far we are from the development of a clinical system will close the session.

CURRENT & NEXT GENERATION DEVICES FOR EPILEPSY

Greg Worrell, MD, PhD [1#]
[1]Mayo Clinic
Department of Neurology
Rochester, MN USA

#worrell.gregory@mayo.edu

Epilepsy affects an estimated 60M people worldwide making it a major cause of neurological disability. Approximately, 1/3 of patients continue to have seizures despite anti-epileptic drugs. Epilepsy surgery remains the most effective treatment for *drug-resistant focal epilepsy*, but defining a surgically resectable focus yielding long-term seizure freedom remains challenging, and is irreversible with potentially significant neurological deficits. Advances in neural engineering have led to implantable devices capable of sensing, electrical stimulation, and secure telemetry. Available neurostimulation devices include Cyberonic's Vagus Nerve Stimulator (VNS), Medtronic's Activa PC, PC+S, and RC+S family of Deep Brain Stimulator (DBS) devices, Neuropace's Inc. Responsive Neural Stimulator (RNS), and NeuroVista's seizure advisory system (SAS). In this talk the range of device capabilities and published epilepsy studies will be reviewed.

IEEG DATABASE

Brian Litt, Hoameng Ung, Lohith Kini, Ankit Khambhati [1#]
Univ. of Pennsylvania, Philadelphia USA
littb@mail.med.upenn.edu

In this workshop we will present an update on IEEG.org and its capabilities. IEEG.org is a cloud-based, data management solution for storing, sharing and analyzing time series, imaging and metadata. We will also present development in progress and solicit constructive input from the community regarding features needed and vision.

In the second half of the workshop we will run a group experiment to upload, annotate, access, analyze and share data, code and results. Participants should bring their laptop computers for hands-on experience with the platform. This will require MATLAB to be installed on their computers. The workshop is intended to further collaboration, sharing and validation of science among the ISPW community. At the end of the workshop we will discuss future directions and our plan to sustain and expand this valuable resource long-term.

KEYS AND CHALLENGES OF MODELING EPILEPTIFORM BEHAVIOR

William Stacey[1#]
[1]University of Michigan, Ann Arbor, MI USA
#william.stacey@umich.edu

Seizures have intrigued computational modelers for decades. Several different types of models have been developed to describe seizure dynamics on multiple different scales. This has led to four main types of models: neural mass, neural field, detailed physiological, and abstract mathematical/dynamical [1]. While modeling seizures is academically intriguing and is clearly needed given their complexity, special care must be taken to assure that results are valid, useful, and provable—both to assure scientific utility and peer acceptance. Meticulous selection of 'what, 'how', and 'why' to simulate is crucial, as is remembering your audience. Using examples of a canonical dynamical model [2], detailed cortical models [3, 4], and a collection of poignant, candid quotations from prominent modelers, we will discuss the pathways that lead to modelling success… and failure.

[1] Wendling, F., et al., Computational models of epileptiform activity. (2015). *J Neurosci Methods*, epub ahead of print.
[2] Jirsa, V.K., et al. On the nature of seizure dynamics. (2014) *Brain*, vol. 137, pt. 8, p 2210-30.
[3] Traub R.D. and Bibbig, A. A model of high-frequency ripples in the hippocampus based on synaptic coupling plus axon-axon gap junctions between pyramidal neurons. (2000). *J Neurosci*. Vol. 20, no. 6, p. 2086-93.
[4] Fink, C.G., et al., Network mechanisms generating abnormal and normal hippocampal High Frequency Oscillations: A computational analysis. (2015). *eNeuro,* June, epub.

A PHYSICIST'S TAKE ON EPILEPSY – NEURAL FIELD MODELS OF SEIZURE TRANSITION

Andre D.H. Peterson[#]
[1]Department of Medicine, St. Vincent's Hospital, University of Melbourne
#peterson@unimelb.edu.au

This tutorial will develop an understanding of the transition to a seizure state from the point of view of a physical scientist. A brief outline of theoretical methods that describe the brain as an interacting many-bodied, dynamical complex system is presented. The transition to seizure reflects a collective change of physiological state or change of phase, in this case in cortical excitability. This phase transition of the collective dynamics of the system can be described nicely by bifurcation theory, which reproduces the seizure transitions found in the corresponding EEG time series.

A mathematical approach describing seizure dynamics in terms of the average behaviours of populations of neurons is introduced in terms of mesoscopic neural field models. A family of neural mass/field models is briefly introduced, discussed and critiqued, particularly with respect to their main physiological and anatomical assumptions and the current state of the field. The importance of synaptic mechanisms in neural field models is also discussed in relation to seizure transitions and the role of endogenous regulatory mechanisms. Understanding the transition from normal resting state to seizure-like behaviour through neural models provides valuable insights into some of the physiological mechanisms behind epileptic dynamics, which could lead to novel interventional therapies.

WHY WOULD A SEIZURE PREDICTION INVESTIGATOR NEED TO CARE ABOUT GROUP THEORY?

Steven J. Schiff
Center for Neural Engineering, Departments of Neurosurgery, Engineering Science and Mechanics, and Physics

sschiff@psu.edu

Observability and controllability are essential concepts to the design of predictive observer models and feedback controllers of networked systems, whether power grids, the internet, or brains.

Observability indicates how well we can reconstruct the full state of a system from incomplete measurements, and controllability measures how well the state of a system can be directed through control perturbations - that is, how much of the potential state space of the system can be reached through control.

Observability and controllability were largely solved for linear systems by the 1970s. However, of the implications from studies of linear, and more recently nonlinear networks, is that symmetries compromise our ability to observe and control a system. Therefore in our use of model-based representations of a system to track and predict its behavior, symmetries in the brain, or in the models used to observe the brain, limit such observability.

We illustrate the concepts and background of how symmetries affect network observability and controllability. We show recent work [1] exploring the effect of differing topologies and symmetries on nonlinear networks. Using group representational theory, we are able to demonstrate that it is not symmetry per se that prevents observability and controllability of a nonlinear network, but rather the type of group symmetry.

Such findings open up a range of new possibilities, and cautions, in understanding how the symmetries of networks must be taken into account to predictively observe brain activity.

[1] Whalen AJ, Brennan SN, Sauer TD, Schiff SJ (2015) Observability and Controllability of Nonlinear Networks: The Role of Symmetry. *Physical Review X* 5, 011005.

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Forecasting seizures in dogs with naturally occurring epilepsy

Greg Worrell, MD, PhD
Mayo Clinic
Departments of Neurology & Physiology and Biomedical Engineering
#worrell.gregory@mayo.edu

There are many animal models of epilepsy, however, in the majority of models the epilepsy is induced by chemical or physical insults and may differ significantly from human epilepsy. In contrast, epilepsy occurs naturally in dogs with prevalence, age of onset, and clinical presentation similar to human epilepsy. Specifically, canine epilepsy has a prevalence of 0.5 to 5.7% with 65% of seizures characterized as focal onset. The majority of dogs with epilepsy do not have structural brain, serum, or spinal fluid abnormalities, and are neurological normal. The etiology of cryptogenic epilepsy in dogs is believed to be as varied as epilepsy in humans. The EEG and efficacy of AEDs in canine epilepsy and human epilepsy are similar, with approximately 25% of dogs not controlled by medications. In summary, the clinical, electrographical, and pharmacological features of naturally occurring canine epilepsy are similar to human epilepsy. Importantly, the canine brain and body size are large enough to accommodate human-scale implants and for these reasons are an excellent platform for epilepsy device development.

CROSS-FREQUENCY COUPLING AND SEIZURE PREDICTION

Catalina Alvarado-Rojas[1]

[1]Department of Electronics Engineering, Pontificia Universidad Javeriana, Bogotá, Colombia
catalina_alvarado@javeriana.edu.au

Recent evidence suggests that some seizures are preceded by preictal changes that start from minutes to hours before an ictal event. Nevertheless an adequate statistical evaluation in a large database of continuous multiday recordings is still missing. Here, we investigated the existence of preictal changes in long-term intracranial recordings from 53 patients with intractable partial epilepsy (in total 531 days and 558 clinical seizures). We described a measure of brain excitability based on cross-frequency coupling: the slow modulation of high-frequency gamma activities (40–140 Hz) in ensembles of intracranial contacts. In prospective tests, we found that this index identified preictal changes at levels above chance in 13.2% of the patients (7/53), suggesting that results may be significant for the whole group ($p<0.05$). These results provide a demonstration that preictal states can be detected prospectively from EEG data. Furthermore, we explored cross-frequency coupling at more local scales. First, we explored the slow modulation of high frequency activities (30-500Hz) recorded with microelectrodes some seconds before the seizure onset. We present some preliminary results about the changes in modulation observed in 6 patients. Second, we investigated the neuronal correlates of high-frequency oscillations (150-250Hz) coupled to slower components of interictal and preictal spikes in human epileptic tissue in vitro. We show that whether the oscillations coupled to two distinct events are on the same frequency range, the neuronal correlates differ. Studying the dynamics and cellular mechanisms of cross-frequency coupling in epileptic networks could help to advance the understanding of network dynamic leading to seizure and to develop novel seizure prediction algorithms.

[1] Alvarado-Rojas C, Valderrama M, Fouad-Ahmed A, Feldwisch-Drentrup H, Ihle M, Teixeira C.A, Sales F, Schulze-Bonhage A, Adam C, Dourado A, Charpier S, Navarro V, Le Van Quyen M (2014) Slow modulations of high-frequency activity (40-140 Hz) discriminate preictal changes in human focal epilepsy. *Sci. Rep*, vol. 4, no. 4545.

[2] Alvarado-Rojas C, Huberfeld G, Baulac M, Clemenceau S, Charpier S, Miles R, Menendez de la Prida L, and Le Van Quyen M (2015) Different mechanisms associated with ripple-like oscillations (150-250 Hz) in the human epileptic subiculum in vitro. *Ann Neurol*, vol. 77, no. 2, pp. 281–290.

SEIZURE PREDICTION AND THE EPILEPSIAE PROJECT

António Dourado
Center for Informatics and Systems, University of Coimbra, Portugal
dourado@dei.uc.pt

EPILEPSIAE- Evolving Platform for Improving Living Expectations of Patients Suffering from Ictal Events (Grant FP7 211713, www.epilepsiae.eu), aimed at developing a transportable adaptive system, comfortable for patients, to warn coming seizures.

The project delivered three main outputs:

(i) The Brainatic [1] proof of concept, prototype of the transportable system with 6 EEG surface electrodes, communicating wirelessly with a notebook running software for EEG features extraction and seizure prediction. The prediction is made as a classification problem followed by pos-processing. The EEG acquisition hardware was further developed by Micromed as a commercial product actually in the market, http://www.micromed-it.com/prodsel.asp?cat=2&prod=11 .

(ii) The European Epilepsy Database[2], commercialized by Freiburg University, http://epilepsy-database.eu/. It is filed with long-term data from 275 patients (from Freiburg, Paris, and Coimbra), metadata and a total of 45375 hours of EEG recordings, 217 surface, 49 intracranial, 9 both surface and intracranial. The total number of seizures is 2262.

(iii) The Epilab [3], a Matlab platform for feature extraction (single channel and multichannel) and seizure predictors construction and training. The implemented predictors are based on computational intelligence (artificial neural networks, support vector machines) and on threshold algorithms (singe or combined). http://www.epilepsiae.eu/project_outputs/epilab_software .

Serious challenges remain to give Brainatic clinical usability. Although an extensive and intensive study has been made for the 275 patients, in three research centers, the performance of the seizure prediction algorithms proved effective (over the analytic random predictor) only for a limited number of patients.

Pure data-based predictors need to be complemented by knowledge-based algorithms exploring neuroscience and brain physiology. New features must be researched.

[1] Klatt, J.,Ihle, M.,Navarro, V. , Neufang, M. , Teixeira, C. , Adam, C.,Valderrama, M. ,Alvarado-Rojas, C. , Witon, A. , Le Van Quyen, M., Sales, F., Dourado A., Timmer, J., Bonhage, A.S., Schelter, B. (2012), The EPILEPSIAE database-An extensive electroencephalography database of epilepsy patients, *Epilepsia*, 2012

[2] Teixeira, C., Bruno Direito, Costa, R. , LeVanQuyen, M.,Schelter, B., Dourado A. (2011), EPILAB: A software package for studies on the prediction of epileptic seizures, *Journal of Neuroscience Methods*, 2011

[3] Teixeira, C.,Favaro, G., Bruno Direito,Bandarabadi, M, Feldwirsch-Drentrup, H., Ihle, M., Alvarado-Rojas, C., LeVanQuyen, M. Schelter, B. , Bonhage, A.S., Sales, F., Navarro, V., Dourado A. (2014), Brainatic: A System for Real-Time Epileptic Seizure Prediction, in *Brain-Computer Interface Research: A State-of-the-Art Summary -2*, vol. 6, pp. 7-18.

MATHEMATICAL CHARACTERIZATION OF EPILEPTIFORM LIMBIC EVENTS

Wytse J Wadman[1#], Celine Marie Dube[2], and Tallie Baram[2]
[1]Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, The Netherlands
[2]Anatomy/Neurobiology and Pediatrics, University of California-Irvine, Irvine, CA, USA;

#wjwadman@gmail.com

Seizures are the essential manifestation of epilepsy, the third most common brain disorder. Whereas motoric seizures are recognized empirically, the defining features of seizures arising from the limbic circuit, that commonly have few or no motor components, have not been fully characterized. Criteria enabling their distinction from other biological events have been a topic of intense discussion. Here we examined limbic EEGs associated with behaviorally defined short events arising in adult rats that had experienced prolonged experimental febrile convulsions early in life [1, 2].

Hippocampal EEG was differentially recorded from a pair of implanted metal electrodes, bandpass filtered between 0.1 Hz and 50 Hz and then digitized at a resolution of 16 bits with a sampling rate of 100 Hz. The EEG events and accompanying behavioral phenomena were aligned using the onset of the behavioral epileptic event and sampled as data traces of 6 seconds, the typical duration of the events. Next the FFT spectrum was calculated from the event and used for further characterization.

Principal component analysis of their spectral properties enabled mathematical characterization of these events without a priori assumptions regarding their nature. The analysis resulted in the description of the events by a few characteristic spectral components, and these components separated the events from both background and also from theta rhythms. Controlling for amplitude, the EEG spectra of the events were remarkably uniform for individual rats as well as across rats. Notably, principal component analysis demonstrated that the background EEG of rats with epileptic events, a measure of network function, differed substantially from that of naïve rats, indicating a compromised network.

This mathematical approach identified the behavioral / electrographic events that arise in adulthood after early-life, prolonged febrile seizures as epileptic. Importantly, the analysis defines and characterizes epileptic events without a priori parameterization of EEG phenomena, a finding with significant general relevance for both basic research and clinical practice.

[1] Dubé CM, Brewster AL, Richichi C, Zha Q, Baram TZ (2007) Fever, febrile seizures and epilepsy. Trends Neurosci 30: 490-496
[2] Dubé CM, Richichi C, Bender RA, Chung G, Litt B, Baram TZ (2006) Temporal lobe epilepsy after experimental prolonged febrile seizures: prospective analysis. Brain 129: 911-922.

THE ROLE OF MACROSCOPIC BRAIN NETWORKS IN SEIZURE INITIATION

John R. Terry[1,2#], Fahmida Chowdhury[3], Marc Goodfellow[1,2], George Petkov[1,2], Mark P. Richardson[3], Helmut Schmidt[1,2] and Wessel Woldman[1,2]

[1]College of Engineering, Mathematics & Physical Sciences, University of Exeter, Exeter, EX4 4QF, UK
[2]Wellcome Trust Centre for Biomedical Modelling and Analysis, University of Exeter, EX2 4DW, UK
[3]Institute of Psychiatry, Psychology & Neuroscience, King's College London, SE5 8AF, UK
#J.Terry@exeter.ac.uk

We introduce the concept of seizures as an emergent property of complex brain networks. That is they arise as a result of the interplay between the dynamics of brain regions (nodes) and the connectivity structures that link them (edges) [1]. We present evidence that the properties of the brain networks of people with idiopathic generalized epilepsies (IGE) are altered in comparison to those of healthy controls [2] and demonstrate, using computer models of seizure initiation, that these network alterations contribute to an enhanced likelihood of seizures (which we term Brain Network Ictogenicity) [3]. Finally we present recent results that demonstrate potential for a computer model based interrogation of routine clinical EEG recordings to provide a marker of IGE with accuracy greater than 0.85.

[1] Terry J.R., Benjamin O. and Richardson M.P. (2012) Seizure generation: The role of nodes and networks, *Epilepsia*, vol. 53, pp. e163-e166.
[2] Chowdhury F.A. *et al* (2014) Revealing a brain network endophenotype in families with idiopathic generalized epilepsy, *PLoS One*, vol. 9, pp. e110136.
[3] Schmidt J., Petkov G., Richardson M.P. and Terry J.R. (2014) Dynamics on networks: The role of local dynamics and global networks on the emergence of hypersynchronous neural activity, *PLoS Comp Biol*, vol. 10, pp. e1003947.

MODELLING OF NEURONAL AND IONIC DYNAMICS DURING ICTOGENESIS

Piotr Suffczynski[1#], Damiano Gentiletti[1], Vadym Gnatkovski[2], and Marco De Curtis[2]

[1]Department of Experimental Physics, University of Warsaw, 5 Pasteur St., 02-093 Warsaw, Poland
[2]Fondazione Istituto Neurologico Carlo Besta, via Celoria 11, 20133 Milan, Italy
#Piotr.Suffczynski@fuw.edu.pl

Traditionally it is considered that neuronal synchronization in epilepsy is caused by a chain reaction of synaptic excitation. However, using in vitro isolated guinea pig brain model of focal seizures it has been shown that seizures were initiated with increased firing of inhibitory interneurons and neuronal silence of principal cells, which correlated with low-voltage fast local field potential oscillations. Neuronal firing of principal cells was subsequently restored with acceleration-deceleration firing pattern followed by rhythmic burst activity. Increased firing of principal cells correlated with ictal discharges in the local field potential signal. In order to investigate the respective roles of various neural elements during seizures we developed a computational model of hippocampal cells, involving extracellular space, realistic dynamics of Na^+, K^+ and Cl^- ions, the glial uptake system and diffusion mechanism. We show that network behaviour with fixed ionic concentrations may be quite different from the neurons' activities when more detailed modelling of ionic dynamics is included. In particular, we show that in the extended model, strong discharge of inhibitory interneurons may result in long lasting accumulation of extracellular K^+, which sustains depolarization of principal cells and causes their pathological discharges. This effect is not present in a reduced, purely synaptic network. These results point to the importance of non-synaptic mechanisms in initiation and progression of ictal episodes.

SEIZURE SPREAD IN A VIRTUAL EPILEPTIC PATIENT

Timothée Proix[1#], and Viktor Jirsa[1]
[1]Aix Marseille Université, Inserm, INS UMR_S 1106, 13005, Marseille, France
#timothee.proix@etu.univ-amu.fr

In patients with refractory partial epilepsy, seizures are generated by several brain regions, referred to as the epileptogenic zone (EZ), before other areas get recruited over short and long distances. Correctly outlining the EZ is crucial for successful resective surgery. We propose a new model to better understand and predict the spatio-temporal seizure dynamics. We identified the invariant properties of seizure dynamics to establish a mathematical neural mass model based on first principles of non-linear dynamics [1]. This model reproduces autonomously the predominant class of seizures, thanks to a slow permittivity variable capturing effects evolving on slow timescales, such as extracellular ionic concentrations and energy metabolism. We developed a permittivity coupling [2] between these neural masses to reproduce indices such as stereoataxic EEG (SEEG) signals showing long delays of recruitment (up to seconds), effects of stimulation, and Epileptogenicity Index. Further, we constructed a large-scale network based on patient-specific diffusion MRI, and predicted the recruitment network given the seizure origin for a dataset of 15 different patients. We validated our study against clinical expertise and SEEG presurgical evaluation data. We strengthen our results with surrogate connectivity and models. Our results emphasize the role of large-scale network in constraining the recruitment process and might reveal an approach to improve the success rate of epilepsy surgery.

[1] Jirsa V.K, Stacey W, Quilichini P.P, Ivanov A.I, Bernard C (2014) On the nature of seizure dynamics, *Brain*, vol. 137, no. 8, pp. 2210-2230

[2] Proix T, Bartolomei F, Chauvel C, Bernard C, Jirsa V.K (2014) Permittivity coupling across brain regions determines seizure recruitment in partial epilepsy, *Journal of Neuroscience*, vol. 34, no. 45, pp. 15009-15021

NEURONS, NEURONAL POPULATIONS AND NETWORKS DURING SEIZURE INITIATION, PROPAGATION AND TERMINATION

Sydney S. Cash
Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
scash@mgh.harvard.edu

Our understanding of the pathophysiology which underlies epilepsy and ictogenesis is becoming increasingly nuanced. Over the last decade we have come to appreciate that seizure initiation, spread and termination represents an interplay of activities which encompass different spatial and temporal scales and different neuronal types and functions. In this presentation, I will discuss some of those events which lead up to seizure initiation and characterize the spread of a focal seizure as well as its termination. The spotlight will be on the role of single neurons, both excitatory and inhibitory, during this process based on data obtained from a variety of different types of high density microelectrode array recordings performed in patients with intractable focal epilepsy undergoing surgery. In particular, we will discuss the dynamics of excitation and inhibition before overt (EEG) seizure activity, and through the remainder of the seizure dynamic evolution. This information will be placed in the context of ongoing larger scale activity and the multiscale functional networks which underlie such activity. We find a distinction in many of these characteristics between seizures with different large scale signatures – seizures characterized by spike-wave discharges versus low voltage fast activity in particular. We will also explore how the dynamics of activity outside the canonical seizure focus impact seizure spread and the way the dynamics of that spread may inform our ability to control seizure activity. Ultimately we are using these types of data to create a hypothetical model of seizure dynamics which incorporates the physiological characteristics of different neuronal classes at the level of individual neurons and small populations – a model framework whose implications we hope will allow for better seizure prediction and control.

[1] Roman T.N, and Name A.B (1999) Title, *Journal*, vol. 9, no. 9, pp. 1-9

EXPERIMENTAL CONTROL OF ICTOGENESIS TO IDENTIFY PROICTAL BIOMARKERS

William C. Stacey[1,2#], Phillip A. Starski[3], and Hiram Luna-Munguia[1]
[1]Department of Neurology, University of Michigan
[2] Department of Biomedical Engineering, University of Michigan
[3] Department of Neuroscience, Mayo Clinic
#william.stacey@umich.edu

We have very limited understanding of the mechanisms of ictogenesis, and insufficient models in which to explore them. This work presents the first *in vivo* model of ictogenesis, in which the timing of *endogenous* temporal lobe seizures can be experimentally controlled via physiological pathways. This model is based upon our recent theoretical and *in vitro* work demonstrating that seizure threshold can be controlled via upstream random synaptic activity, and that proximity to seizure threshold produces measureable changes [1]. In the current work, we adapt those concepts to an *in vivo* rodent model of temporal lobe epilepsy. Using spontaneously-seizing pilocarpine rats, focal microinjection of KCl or bicuculline into the thalamus [2] triggered typical seizures in 8/10 of animals. The induced seizures were quantitatively and qualitatively indistinguishable from spontaneous seizures, using a combination of clinical and electrophysiological measurements. This procedure therefore modulates the threshold of *spontaneous seizures* without any direct modifications to the seizure focus, having great potential for future research into seizure mechanisms. In particular, this model allows direct investigation of the putative 'proictal' state, providing the opportunity to (1) search for early biomarkers that indicate proximity to the seizure threshold and to (2) develop and compare pre-emptive antiseizure treatments with high throughput. Our preliminary data show proictal changes in the EEG signals, and we are currently searching for biochemical changes as well with serial microdialysis.

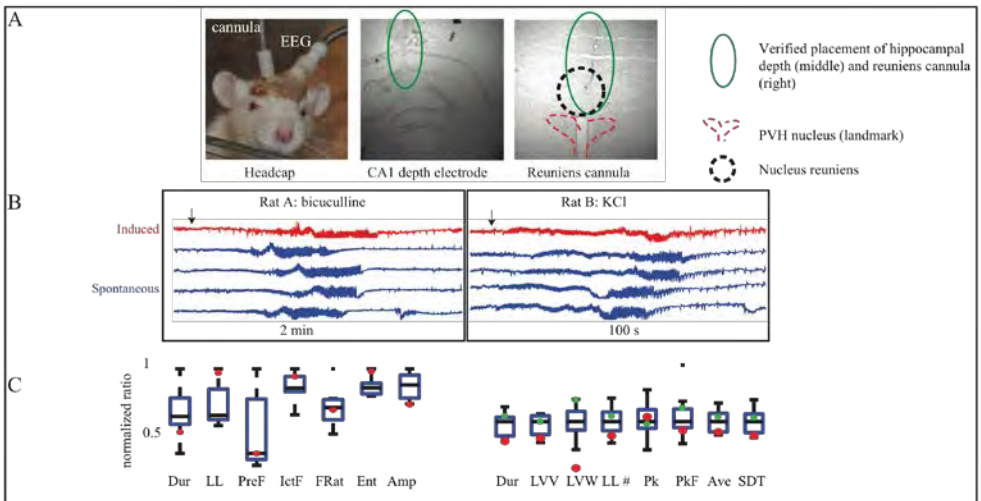

Fig. 1 In vivo ictogenesis. **A:** Pilocarpine rats have hippocampal depth electrodes and a cannula placed into the nucleus reuniens. The reuniens has extensive excitatory connections to bilateral CA1 neurons. B: Spontaneous seizures (blue) were indistinguishable from induced ones (red) in 8/10 animals. The effect was present with bicuculline (left) and/or KCl (right) injection into the reuniens. C: A battery of quantitative measurements showed that the induced seizures (dots) were statistically similar to the distribution of 8 spontaneous seizures (boxplots). Features: Dur: Duration. LL: line length. PreF: preictal peak frequency. IctF: ictal peak frequency. FRat: frequency ratio. Ent: entropy. Amp: amplitude. LVV: log of variance (volts). LVW: log of variance (5 sec window). #Pk: number of peaks. PkF: peak frequency. Ave: average of Teager-Kaiser energy. SDT: Std of Teager Kaiser energy.

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POST-MALARIAL EPILEPSY - DYNAMICS IN AN ANIMAL MODEL

Paddy Ssentongo[1], Anna Rubuccio[1], Fatemeh Bahari[1,2], Ali Nabi[1], Myles Billard[1,2], Emma Price[1], Patrick J. Drew[1,2], Andrew Read[3], Steven J. Schiff[1,2,4], Bruce J. Gluckman [1,2,4 #]

[1] Center For Neural Engineering
[2] Department of Engineering Science and Mechanics
[3] Departments of Entomology and Biology
[4] Department of Neurosurgery
Penn State Univeristy, University Park, PA 16802, USA
BruceGluckman@psu.edu

It is well established – though relatively unknown – that cerebral malaria (CM) leads to epilepsy. For the nearly 500,000 children who survive CM per year in sub-Saharan Africa, the estimated epilepsy rate after two-years is approximately 10% [1], making this arguably the largest source of preventable epilepsy. We have been investigating murine models of CM for evidence of post-malarial epilepsy. During the acute infectious phase, different mixture of mouse strain (C57/BL, CBA, and Swiss-Webster) and parasite (Plasmodium-berghei types NK65 and ANKA) express different histological similarities to human brain during CM including red and white blood cell sequestration in blood vessels, edema and micro-hemorrhage. We developed a chronic recording system for long-term monitoring of brain and heart dynamics with DC sensitivity, and collected long-term recordings in 4 of the 6 possible model combinations. Across over 2100 mouse-days of recording, with typical per-animal recordings lasting from 1-8 months, we find model dependent epilepsy rates of between 25% and 75%, and model-dependent latencies between infection and emergence of clear seizure dynamics of 4 weeks to 3 months. Seizures with behavioral manifestations are observed as electrographically focal, focal generalizing, with origin in hippocampus or in cortex, or fully generalized once measureable. Seizures are observed to emerge from all states of vigilance, including in some animals whose seizures predominantly emerge from REM sleep. Most model combinations have high seizure-related death rates consistent with SUDEP, with many recorded examples of seizure-associated deaths. All combinations studied demonstrate heart arrhythmias whose dynamics appear bidirectionally coupled to seizure dynamics. Critical to the seizure prediction community, much of the evolution of the electrographic signatures of both normal and preseizure EEG evolves significantly throughout the lifetime of these animals.

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Day 2, Wednesday August 5 2015

SEIZURE PREDICTION ALGORITHM DEVELOPMENT AND VALIDATION VIA KAGGLE.COM

Benjamin H. Brinkmann PhD[1#], Joost Waagenar PhD[2], Vladimir Cherkassky PhD[3], Edward Patterson DVM, PhD[4], Zack Ives[2] PhD, Brian Litt MD[2], and Gregory A. Worrell MD PhD[1]

[1]Mayo Clinic Dept. of Neurology, Rochester MN, USA
[2]University of Pennsylvania, Dept. of Bioengineering, Philadelphia PA, USA
[3]University of Minnesota, Dept. of Electrical and Computer Engineering, Minneapolis MN USA
[4]University of Minnesota, Dept. of Veterinary Medicine, Minneapolis MN USA
#Corresponding author: Brinkmann.Benjamin@mayo.edu

Accurate prediction of epileptic seizures has the potential to help patients manage their epilepsy. However, development of reliable algorithms for predicting seizures has proven challenging. Efforts have been hampered by lack of access to long duration recordings with an adequate number of seizures, and the inability of investigators to compare algorithms directly on common data sets. Kaggle.com is a web-based collaborative tool for posing difficult machine learning and computational problems to a broad community of engineers, mathematicians, and data scientists in a competition format on shared data. With support from NIH, AES, and EFA we organized a seizure prediction competition on Kaggle.com using chronic ambulatory intracranial EEG (iEEG) from 5 canines with naturally occurring epilepsy implanted with a wireless ambulatory recording device, and two human patients undergoing prolonged wide-bandwidth iEEG monitoring. Data was provided to participants as 10-minute interictal and preictal clips, with approximately half of the 60Gb data bundle provided labelled (interictal/Preictal) for algorithm training, and half provided unlabelled and in a random order for algorithm evaluation. The contest ran from Aug to Nov 2014, and 654 participants submitted 17,856 classifications of the test data. The top performing entry scored 0.83993 area under the classification curve (AUC). Following the conclusion of the kaggle.com prediction contest we provided additional held-out interictal and preictal data clips to the top finishing participants. The participants ran their algorithms on the held-out data without retraining, and submitted classifications for the new unseen data. The resulting AUC scores showed a mean (min,max) 6.54 (0.29, 20.2) percent decline, suggesting that some overtraining likely occured in the kaggle.com format. This contest supports the value of "crowdsourced" algorithm development for seizure forecasting. In addition the kaggle.com model of data sharing and algorithm development and testing permits immediate and direct comparisons between algorithms, and promotes transparency and reproducible science.

KAGGLE COMPETITION SEIZURE PREDICTION ALGORITHM

Simone C. Bosshard[1#], Drew Abbot[2], Min Chen[1], David C. Reutens[1], Phillip Adkins[2], and Quang M. Tieng[1]
[1]Centre for Advanced Imaging, University of Queensland, Brisbane, Australia
[2] AiLive Inc., Mountain View, California, USA
#simone.bosshard@cai.uq.edu.au

Epilepsy, a disorder characterized by recurrent epileptic seizures, affects about 65 million people worldwide. In many patients, antiepileptic drug treatment achieves prevention of seizures. However, for approximately 30% of epilepsy patients, medications and/or surgery are not effective in controlling seizures and they continue to experience spontaneous seizures.

Seizure forecasting has the ability to create new therapeutic strategies for epilepsy, such as providing patient warnings and delivering preemptive therapy. Methods to forecast seizures have the potential to greatly improve the life quality of drug-resistant patients. The methods presented here were developed as a submission of the Seizure Prediction Contest organized by Kaggle and sponsored by the National Institutes of Health (NINDS), the Epilepsy Foundation, and the American Epilepsy Society [1]. The aim was to develop a computational algorithm which reliably identifies periods of increased seizure probability based on EEG recordings.

The datasets provided were intracranial, long duration EEG recordings from dogs with naturally occurring epilepsy, and from epilepsy patients. One hour sequences in ten minute data segments were provided for interictal (at least 4 hours before or after a seizure) and preictal (covering one hour prior to seizure with a 5 min seizure horizon) data. The challenge was to distinguish between preictal and interictal data.

For seizure prediction, the proposed algorithm has two different stages: learning and prediction. The information used in these stages is extracted from raw EEG recordings.

Statistical features such as Entropy, Spectral energy, Correlation across channels, Hjorth parameters and moments are used in this approach. For the learning stage, these features are divided into two classes labeled as preictal and interictal and the approach will find optimal model parameters to classify these two classes. In the prediction stage, the learned model is applied on unlabeled features to determine which class these features originate from (Fig.1).

The proposed algorithm is a weighted average of three separate models: a Generalized Linear Model regression with Lasso or elastic net regularization (via MATLAB's *lassoglm* function), a Random Forest (via MATLAB's *TreeBagger* implementation), and a bagged set of linear Support Vector Machines (via Python's *scikit-learn* toolkit). The results show that by combining 3 different models the performance was improved as compared to each individual model. For the given test data set, the final area under the curve of ROC (Receiver Operating Characteristic) of the combined three models is 82%, in comparison to 72% with Random Forest, 75% with Bagged SVM and 81% with Lasso GLM.

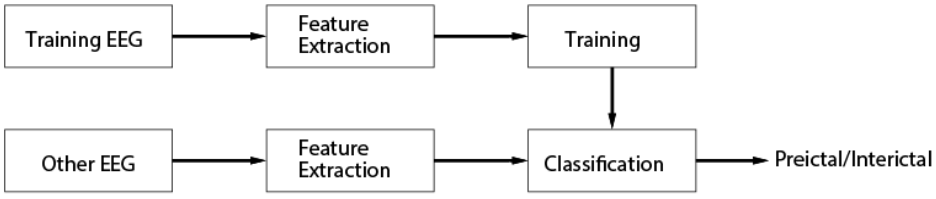

Figure 1 Diagram illustrating the learning and prediction stages of the proposed algorithm.

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DATA INTEGRATION, NEUROENGINEERING AND COLLABORATION ON THE CLOUD

Brian Litt
University of Pennsylvania, Philadelphia, USA
littb@mail.med.upenn.edu

The availability of computing and storage resources on the cloud afford unprecedented opportunities for sharing data, algorithms and scientific validation than ever before, yet progress has been limited. Two major reasons for this are a lack of low-energy infrastructure, and that incentives are poorly aligned. We present proposed solutions to these challenges, using http://ieeg.org and its successor, ***Blackfynn***. We use 3 examples: (1) evaluation of EEG biomarkers of epileptogenesis after head trauma, (2) evaluation of epileptogenesis biomarkers in a murine hypoxia model for assessing therapeutics, and (3) last year's AES/ NIH sponsored algorithm competition for seizure detection and prediction. We demonstrate use of the platform for rapid, reproducible pipeline analysis of data in these 3 settings, present results, and propose an infrastructure, based upon it, for encouraging collaboration and validation of research to accelerate global progress. We propose a "Data Impact Index" for crediting investigators for collecting and sharing high quality data, and a sustainable framework for disseminating this approach among ISPW participants and the scientific community.

SPATIO-TEMPORAL DYNAMIC EEG SOURCE IMAGING OF EPILEPTOGENIC ACTIVITY

Bin He
University of Minnesota, Minneapolis, USA
binhe@umn.edu

Epilepsy is one of the most common neurological disorders, affecting about 50 million people worldwide. In approximately 30% of these patients the seizures are not controlled by medical therapy. Partial epilepsy represents the most common type of drug resistant epilepsy. Epilepsy surgery has the best chance of curing partial epilepsy, but is only an option if the brain region generating seizures can be accurately localized and safely removed. Accurate localization of seizure origin and seizure onset zone is of paramount importance for successful epilepsy surgery.

This presentation will review our efforts to develop and validate an array of spatio-temporal dynamic imaging techniques to localize epileptogenic zone and seizure sources from scalp recorded EEG. We have developed novel algorithms to directly image seizure sources by means of an oscillatory imaging approach. We have demonstrated that the high frequency oscillation can be noninvasively localized from scalp-recorded EEG. We have applied Granger causality and graph theory to analyse connectivity in epileptic networks. These noninvasive imaging results have been validated by intracranial EEG recordings and surgical resection outcomes, demonstrating the excellent performance of EEG source imaging of epileptic activity with high spatio-temporal resolution.

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MULTIMODAL IMAGING AND MODELLING OF EPILEPTIC SEIZURES AND INTERICTAL EPILEPTIFORM ACTIVITY IN HUMANS

Louis Lemieux[1#], Umair J Chaudhary[1], Marco Leite[1], Maria Centeno[1,2], David W Carmichael[2], Anna Vaudano[3], Margarita Papadopoulou[4], Karl J Friston[1], Beate Diehl[1], Matthew C Walker[1], John S Duncan[1], Stefano Meletti[3]

[1]UCL Institute of Neurology, Queen Square, London, U.K.
[2]UCL Institute of Child Health, Guildford Street, London, U.K.
[3]University of Modena and Reggio Emilia, Modena, Italy.
[4]University of Ghent, Ghent, Belgium.
#louis.lemieux@ucl.ac.uk

I will present some of our main findings of our studies of epileptic events in humans suffering from focal and generalized epilepsies. The main data acquisition technique employed for our studies is resting-state EEG-correlated fMRI, combined with video, which has allowed us to capture spontaneous epileptic activity in hundreds of patients over the last 15 years. While emphasis will be put on seizures, interictal events and some of the differences in the findings for the two types of epileptic activity will also be discussed. I will discuss the fMRI patterns correlated with spontaneous and triggered focal seizures, and generalized spike-wave discharges, including absence seizures, in patients with generalized epilepsies [1, 2]. I will also discuss efforts to model connectivity in a causal, biophysically-inspired framework [3]. Our studies often reveal brain activity patterns and causal links involving regions beyond what is considered the epileptogenic zone, particularly during the transition to the ictal state, in line with the notion of an important role for fluctuations in 'normal' brain state in relation to the occurrence of seizures.

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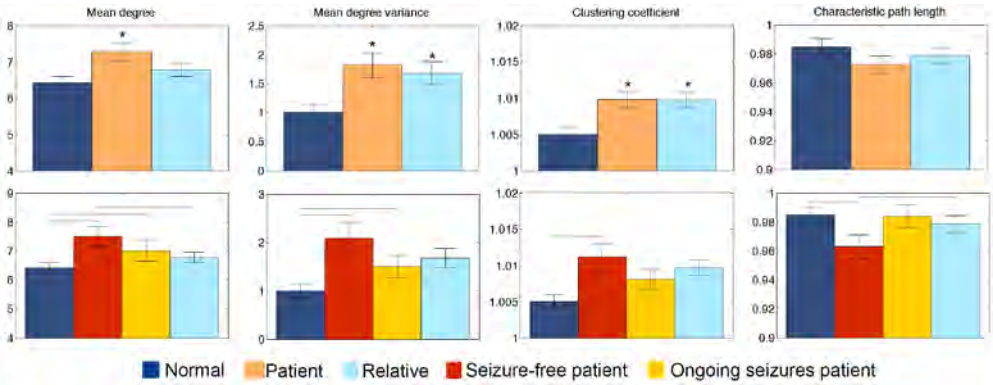
REVEALING A BRAIN NETWORK ENDOPHENOTYPE IN FAMILIES WITH IDIOPATHIC GENERALISED EPILEPSY

Wessel Woldman[1#], Fahmida A. Chowdhury[2,3], Thomas H.B. FitzGerald[2,4], Robert D.C. Elwes[3], Lina Nashef[3], John R. Terry[1], Mark P. Richardson[2,3]

[1] College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter, United Kingdom
[2] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[3] Centre for Epilepsy, King's College Hospital, London, United Kingdom
[4] Wellcome Trust Centre for Neuroimaging, UCL, London, United Kingdom
#www201@exeter.ac.uk

In [1] we studied resting state electroencephalogram (EEG) recordings from people with idiopathic generalised epilepsy (IGE) and their unaffected first-degree relatives, to test the assumption that abnormal brain network properties would manifest as a familial endophenotype. The study included 117 participants: 35 people with IGE, 42 unaffected first-degree relatives, and 40 normal controls, using scalp EEG. Network topology was derived using phase-locking factors, and graph measures were used to describe brain network topology in five frequency bands for each subject. Significant differences were found in the 6-9-Hz band: degree distribution variance was greater in patients and relatives ($p=0.0005$, $p=0.0009$), mean degree was greater in patients and healthy controls ($p=0.0064$), and clustering coefficient was higher in patients and relatives than controls ($p=0.0025$, $p=0.0013$). No differences were found between patients and unaffected relatives.



These findings suggest brain network topology differs between patients with IGE and normal controls, and that some of these network properties present themselves in unaffected relatives who do not themselves have epilepsy. This suggests brain network topology may be an inherited endophenotype of IGE, a necessary, although not a sufficient condition for epilepsy. Strikingly, no additional significant differences were found when the patient-cohort is divided in people with ongoing seizures and people classified as seizure-free. To explore these ideas further, we use a computational network model of the mechanisms underlying seizure initiation to explore the interplay between network topology and the dynamics in localised brain regions on the likelihood of seizures. Our findings support the concept that in order to understand how epileptic brains respond to clinical interventions (such as treatment or surgery), it is essential to combine the study of complex brain networks with mathematical models that describe the dynamics of localised brain tissue. Our work goes some way towards removing the idiopathic category of generalised epilepsy altogether in the overall task of defining and redefining epilepsy [2].

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REGIONAL AND NETWORK RELATIONSHIP IN THE INTRACRANIAL EEG AND ITS SECOND SPECTRUM

Rasesh B. Joshi[1], Dominique Duncan[2], Nicolas Gaspard[1], Irina I. Goncharova[1], Robert B. Duckrow[1], Jason L. Gerrard[3], Dennis D. Spencer[3], Lawrence J. Hirsch[1], Hitten P. Zaveri[1]
[1]Department of Neurology and 3Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut 06520, U.S.A.
[2]Department of Mathematics, University of California – Davis, Davis, California 95616, U.S.A.
hitten.zaveri@yale.edu

Objective: In this study, we tested if a relationship between distant parts of the default mode network (DMN), a resting state network defined by fMRI studies, can be observed with intracranial EEG recorded from patients with localization-related epilepsy. It has recently been suggested that low-frequency changes in blood flow measured in fMRI may be reflected in correlated low-frequency activity in the intracranial EEG (icEEG) band-power time series, the so-called second spectrum, rather than in synchronization of the raw icEEG. We thus, also, examined the icEEG second spectrum, in addition to the icEEG, for evidence of support for spatial relationships between different parts of the brain and the DMN.

Methods: Magnitude squared coherence, mutual information, cross-approximate entropy, and the coherence of the gamma power time-series were estimated, for one hour intracranial EEG recordings of background activity from 9 patients, to evaluate the relationship between two test areas which were within the DMN (anterior cingulate and orbital frontal, denoted as T1 and posterior cingulate and mesial parietal, denoted as T2), and one control area (denoted as C) which was outside the DMN. In addition, we calculated the running power, at a one-second resolution, in different frequency bands (delta, theta, alpha, beta, and gamma). Magnitude-squared coherence (MSC) below 0.15 Hz was estimated for each of these band power time-series for every possible electrode contact pair. We aggregated these estimates for all patients and examined how these second spectrum relationships vary with lobe, distance, and frequency. We tested if the relationship between T1 and T2 was stronger than the relationship between each of these areas and C.

Results: A low level of relationship was observed in the icEEG among the 3 areas tested. We also observed very low values of second spectrum relationship between different parts of the brain, except at very short distances (between 0 and 2 cm). We further found that these relationships were strongest in the delta band and decrease with increasing frequency, with the weakest relationships in the gamma band. We additionally found relatively higher relationships in the frontal lobes in the delta and theta bands, and in the occipital lobes in the alpha and beta bands. Our DMN-specific analysis showed no enhanced connectivity in DMN locations.

Conclusions: This study suggests a lack of intracranial EEG support for the fMRI defined default mode network.

AN EXTRACEREBRAL BIOSIGNAL PATTERN FOR EPILEPTIC SEIZURE DETECTION

D. Cogan[1], M. Nourani[1], J. Harvey, DO[2], V. Nagaraddi, MD[2]
[1]Quality of Life Technology Laboratory, The University of Texas at Dallas, Richardson, TX 75080
[2]Texas Epilepsy Group, Dallas, TX 75230
{diana.cogan, nourani}@utdallas.edu[1] {jhharvey, vnagaraddi} @texasepilepsy.org[2]

Motivation: Recent work using heart rate to detect seizures has achieved fairly accurate results for patients in epilepsy monitoring units (EMUs), but the authors concede that there is much room for improvement to their algorithms [1][2].

Seizure Detection Methodology: We are working with five biosignals which can be monitored at the wrist and are associated with seizures: heart rate (HR), arterial oxygenation (SpO_2), accelerometry, electrodermal activity (EDA) and temperature. At IWSP6 we reported how to distinguish physical, cognitive and emotional stresses using these five signals [3]. Recently, we found a pattern created by HR, SpO_2 and EDA during all seven of the seizures (2 secondarily generalized and 5 complex partials) suffered by three patients monitored in an EMU. This pattern is much less likely to be reproduced by nonseizure events during daily life than are changes in HR alone. We developed a signal processing algorithm which uses this pattern to detect the patients' seizures.

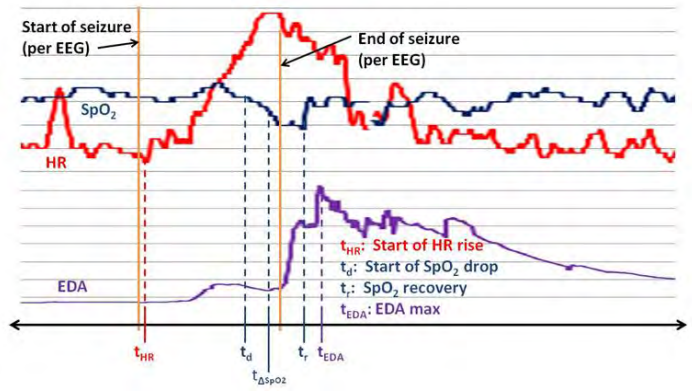

Fig. 1 illustrates the pattern we found using data from one seizure. The HR increase starts at t_{HR}. Next, the SpO_2 drops below baseline at t_d. After the SpO_2 level recovers (t_r), the EDA peaks (t_{EDA}). The four events must occur in this order for a seizure to be recognized.

Fig. 1: HR↑ ⇒SpO_2 ↓⇒ EDA↑ Seizure Pattern

Experimental Results: Our algorithm found only 13 time windows during which all three biosignals were active in the 108 hours of data: all seven seizures, correctly classified, and six additional events, classified as: 4 non-seizures, 1 indeterminate (lack of data) and 1 seizure. The patient was off EEG when this last event occurred, so we don't know what its classification should be. After the algorithm was personalized based on each patient's data, 11 active time windows were found: 7 seizures, 3 non-seizures and 1 indeterminate.

Although our data set is small, we believe our finding is significant because the number of occasions on which all three biosignals are active at the same time is small relative to the hours of data we collected. Even without personalization, we found only one potential false positive in 108 hours of data, or less than 0.01 potential false positives/hour compared to 1.1 reported in [1]. Further, our algorithm's accuracy (100%) was higher than the accuracy reported in [2] (84.72% for complex partials and 88.33% for secondarily generalized seizures). We are continuing to collect data, so we will have opportunity to verify our findings.

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CORTICAL EXCITABLITY MEASUREMENT AND SEIZURE PREDICTION UTILIZING ELECTRICAL PROBING

F. Goodarzy[1#], A. Lai[1], D.R. Freestone[1,2], D.B. Grayden[1], A.N. Burkitt[1], M.J. Cook[1,2]
[1]NeuroEngineering Laboratory, Dept. of Electrical & Electronic Engineering, University of Melbourne, VIC 3010, Australia
[2]Dept. of Medicine, University of Melbourne, St. Vincent's Hospital Melbourne, Fitzroy, VIC 3065, Australia
#goodarzy@unimelb.edu.au

With recent advances in seizure prediction methods, improved algorithms and implanted devices are required to accurately predict the onset of seizures and apply appropriate electrical stimulation to prevent the occurrence of seizures [1]. Probing is a promising technique since it actively monitors the brain 'state' in contrast to most commonly used techniques in seizure prediction, which use passive monitoring techniques. In probing, small electrical pulses are delivered to the brain and the response to these stimulations, referred to as electrically evoked potentials (EEPs), are measured [2]. The stimulation and recording is continuously carried out to monitor the patient's 'brain excitability'. This stimulation and measurement is performed utilizing surface grid electrodes. We have previously shown the use of this technique in studying sleep-wake cycles and seizure prediction capabilities exploiting mean phase variance (MPV) and phase-locking value (PLV) analysis [3].

Here, we have developed new methods with less computational effort that can be deployed in existing implantable devices with stimulation and recording capabilities to enhance the performance of the device. In this study, the EEP recordings from 128 grid electrode arrays are analyzed. These recordings consist of 100 bi-phasic pulses, delivered every 10 min, and the responses are analyzed externally in MATLAB. The values of interest are the first and second peak of the EEP (P1 and P2) and their times of occurrence relative to the stimulation pulses (T1 and T2). The electrodes are categorized into four different combinations of 32 electrodes according to horizontal/vertical position and small/large size electrodes. The recorded responses are averaged in segments of an hour and then averaged across all electrodes in each group. The 100 stimulations are used as measurement repetitions to calculate the correlation coefficients. The results show strong correlation between the recorded EEP and seizure occurrence, which can be used as a seizure onset indicator.

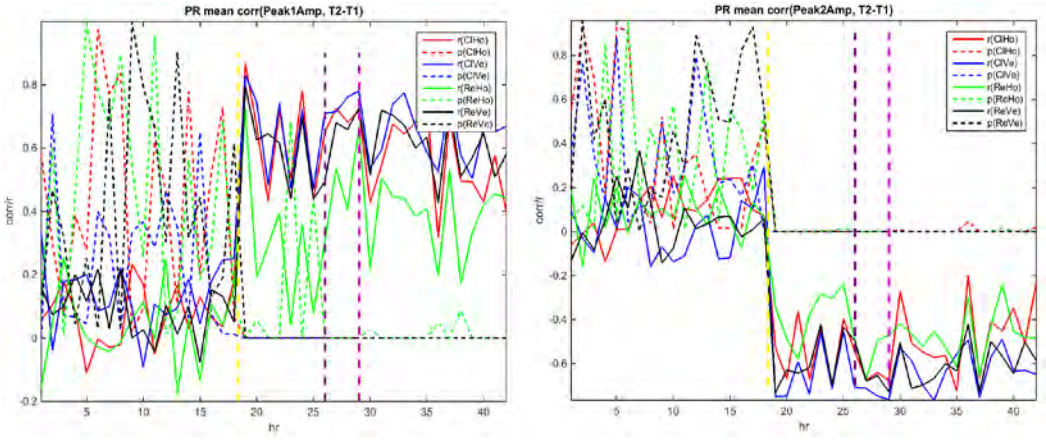

Figure 2. Correlation coefficient measurement of averaged peak1 and peak2 vs. respective occurrence time activity over all the recoding channels and over the duration of hour. These values are also plotted for 4 different combinations of channels on the electrode.

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ADAPTATION OF THE PHASE CLUSTERING INDEX TO THE RAT MODEL OF EPILEPSY

Karin H Somerlik-Fuchs[1,2,3#], Ulrich G Hofmann[2], Thomas Stieglitz[1,3] and Andreas Schulze-Bonhage[2,3]
[1]Albert-Ludwigs-University Freiburg, Germany
[2]University Medical Centre Freiburg, Germany
[3]Bernstein Centre Freiburg, Germany
#karin.somerlik@uniklinik-freiburg.de

The relative phase clustering index (rPCI) was introduced by Kalitzin et al. [1] as a method to localize the seizure onset zone as well as a measure of the probability for an upcoming seizure. The ability to predict epileptic seizures in advance does not only offer the possibility to warn the patient but also to initiate a therapeutic action. That could ideally be able to prevent the seizure to happen which is not possible with today's detection algorithms as the seizure has already progressed too far at the time point of detection. For animal research in favor of investigating new therapies it would even provide the ability to evaluate different treatments much faster than today as a lot of research is done empirically and hence suffer from low seizure counts that demand a high number of animals and long experiments. We therefore studied the usability of this paradigm to the rat model of epilepsy.

The rPCI is an active measurement paradigm in which the reaction of the neural tissue to a small stimulation pulse is analyzed. If the recorded signals are phase locked to the stimulation frequency the brain area is characterized as easily synchronizable, which is the bases of an epileptic seizure. Accordingly, we examined the stimulation parameters in the first step. We could show that the amplitude and the pulse width do influence the rPCI while changing the frequency of the stimulation between 5 and 20 Hz seemed not to influence the determined rPCI value. During the epileptogenesis of the kindling model we could not observe a trend in the rPCI, however there was a reduction in phase clustering following ictal discharges. In the kainate model we could see an increase of the rPCI in the early weeks after the injection of the kainic acid and a high variability of the index for the time after. Currently we investigate the relation of this variability to the appearance of seizures.

The experiments show that the parameters of the probing stimulation need to be carefully adapted to the animals. We did not find a clear increase of rPCI correlating to the progress of epileptogenesis which may refer to fluctuations related to ictal events.

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RECENT ADVANCES IN DATA-BASED MODELLING AND THEIR ROLE IN EPILEPSY RESEARCH

Bjoern Schelter[1,2#] and Marco Thiel[1]

[1]Institute for Complex Systems and Mathematical Biology, University of Aberdeen, Aberdeen, UK

[2]Department of Electrical and Electronic Engineering, Melbourne School of Engineering, University of Melbourne, Australia

#b.schelter@abdn.ac.uk

Recent years have seen a large increase in the availability of data. In fact, increasing amounts of data play a key role in every aspect of our lives, including physics, such as for the Large Hadron Collider (CERN) and the Square Kilometer Array (South Africa), biology, e.g. genomic data, medicine, e.g. functional magnetic resonance imaging or electroencephalography, and data mining in the social sciences or digital economies.

Dealing with these data sets efficiently employing data-based modelling and model-based data analysis determines the success of projects, treatments, assessments, and analyses. The necessity to better understand, model and analyze data has led to an outburst of research into advanced methods of data-based modelling. The inference of networks underlying complex systems such as the human brain is of utmost importance. Especially when dealing with complex data sets the algorithms for network inference have to fulfill certain fundamental requirements: (i) they need to deal with truly multivariate data, i.e. they must distinguish between direct and indirect influences, (ii) they have to account for various concurrent noise sources, (iii) they need to addresses both linear and non-linear systems, (iv) provide results for each sampling point, (v) and estimate the strengths of the directed interactions. Finally, (vi) they need to provide a rigorous statistical framework to allow their evaluation and (vii) be numerically efficient.

A multitude of algorithms has been developed to address these extremely challenging requirements, but until now only very few can address them simultaneously. This is partly due to the fact that a rigorous mathematical framework, i.e. a theory of a suitable highly versatile class of mathematical models to comprise all of these features, is challenging. Having such a framework at one's disposal will have major implications onto various aspects of our lives.

In this talk, the challenges will be introduced and means to address these will be discussed. The impact of novel approaches to data-based modelling on seizure prediction and seizure control in epilepsy will be reviewed. Various methods will be compared and their abilities and limitations will be presented based on simulated data as well as electroencephalography data.

CAN THE MATHEMATICS OF NETWORKED OSCILLATORS EXPLAIN THE CHALLENGES IN PREDICTING EPILEPTIC SEIZURES?

Elma O'Sullivan-Greene[1#], Levin Kuhlmann [1,2], Anthony Burkitt [1], and Iven Mareels[1]
[1] Department of Electrical and Electronic Engineering, The University of Melbourne, VIC 3010, Australia
[2] Brain & Psychological Sciences Research Centre, Swinburne University of Technology, Hawthorn VIC 3122, Australia
#elmaog@unimelb.edu.au

INTRODUCTION: Following decades of research [1], the recently published NeuroVista device trial [2] provides evidence that the elusive goal of seizure prediction has made progress**.** The study shows large variability in success between patients with sensitivity performance from 65% to 100% across 11 patients and a further 3 unsuccessful patients. Can mathematical modelling of an electroencephalogram (EEG) measurement from brain activity explain this variability in performance? Simply put, we hypothesise the complexity of underlying brain dynamics renders classic passively recorded EEG measurements too imprecise to provide a reliable prediction of the next epileptic episode.

METHODS: The prediction problem is abstracted to an observability problem applied to a network of coupled oscillators. Using ideas from network information theory, we show that the system can be split into a network model (brain activity) and a channel model (EEG). The network model is fixed, but we can tune the channel model to optimise information flow from the network. This mirrors, for example, the possibility to record brain activity from the cortical surface using multiple EEG electrodes of various configurations, and in turn provides a way to assess which configuration is optimal.

RESULTS: EEG measurement gathers very limited information from underlying oscillatory brain activity and prediction success becomes highly dependent on the precise location of the EEG electrodes. High variability in patient-specific performance should thus be expected.

CONCLUSIONS & RELEVANCE: Future promise centres on a departure from the current standard of passively acquiring EEG to an active paradigm. Active EEG, by stimulating with specific frequency content to 'shine a selective light' on a known portion of dynamics, could maximise neural information in a more reliable and repeatable manner across patients for therapeutic benefit.

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REAL-TIME AUTOMATED EEG TRACKING OF BRAIN STATE PARAMETERS USING NEURAL FIELD THEORY: APPLICATION TO BRAIN STABILITY AND SEIZURES

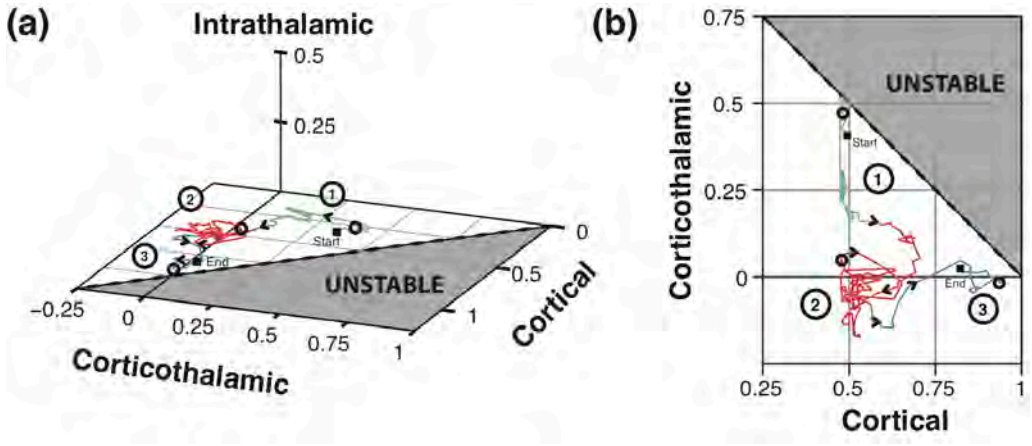
R.G. Abeysuriya[1,2,3,#], P.A. Robinson[1,2,3]
[1]School of Physics, University of Sydney, New South Wales 2006, Australia
[2]Center for Integrative Brain Function, University of Sydney, NSW 2006, Australia
[3]Neurosleep, 431 Glebe Point Rd, Glebe, NSW 2037, Australia
#r.abeysuriya@physics.usyd.edu.au

In a recent physiologically-based model of the corticothalamic system, seizures correspond to nonlinear dynamics occurring in a subset of parameter regimes [1,2]. The transition into a seizure corresponds to the model parameters crossing a stability boundary as they evolve over time. In this study, a real-time Monte-Carlo based fitting system is developed and used to fit the predictions of a physiologically-based neural field model to EEG, yielding a trajectory in a parameter space that measures cortico-cortical, cortico-thalamic and intrathalamic feedback strengths. This framework enables investigation of the dynamics of seizure onset, and whether parts of the parameter space are seizure-precursor zones for an individual.

Because crossing the stability boundaries of the model corresponds to seizure onset, the proximity to a stability boundary at a single point in time can be calculated from the fitted parameters, and is interpreted as a risk factor for a seizure. Further, the parameter trajectory over time provides information about the trajectory of the system toward or away from the stability boundary. In addition, as a consequence of a specific neurological condition, seizures may always begin from the same region of the model's parameter space. Using the real-time tracking system, it may thus be possible to warn susceptible individuals as their fitted parameters approach these 'danger zones'.

Figure 1 shows a fitted parameter trajectory for 4 minutes of experimental data during the wake-sleep transition: (a) isometric view (b) plan view. The fitting routine robustly tracks the physiological arousal parameters as they change over time. The color of the trajectory indicates the corresponding traditional sleep stage: wake (green), S1 (red), S2 (blue). The numbers on the figure show the ordering, and arrows indicate the direction of the trajectory. The fitting routine is entirely automatic, does not require special configuration for different individuals, and can be run in real-time on a PC.

In Figure 1, the initial transition from wake to sleep involves moving away from a stability boundary, and is reversed when waking up. Seizures occurring immediately after waking up may thus be the result of the normal 'wake up' trajectory continuing too far, and crossing the stability boundary. The trajectory is individualized, which enables customized predictions for subjects with different conditions.



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Day 3/ME@MBC Overlap Day, Thursday August 6 2015

Not all talks on this day have abstracts

GENETICS AND THE INDIVIDUAL-SPECIFIC NATURE OF EPILEPSY

Samuel F Berkovic
Epilepsy Research Centre, University of Melbourne, Austin Health, Heidelberg, Victoria
s.berkovic@unimelb.edu.au

Genetic factors play a role in essentially every patient with epilepsy, although these vary from crucial to clinically trivial. Enormous progress has recently occurred in the understanding of epilepsy genetics, both at clinical genetic and basic science levels. The astonishing advances in genomic technology, with the "$1000 genome" now almost a reality, has opened up new research opportunities with rapid translational benefit to patient care.

There have been many surprises as research has unfolded in the last two decades. First, the complexities of phenotype–genotype relationships—one syndrome having multiple genetic causes (genetic heterogeneity) and one gene being associated with different phenotypes (pleiotropy). Second, the discovery of the importance of de novo mutations, that is new mutations not present in parents. Third, the emerging significance of somatic (postzygotic) mutations where the mutation may be largely restricted to the brain. Finally, the large number of genes that appear to raise risk for epilepsy.

Currently, genetic defects underlying epilepsies can be identified in an important minority of cases. Many epilepsy genes discovered to date encode ion channel subunits, leading to the concept that the genetic epilepsies are, at least in part, a family of channelopathies. Non-ion channels genes are also emerging as important, including the gene encoding the glucose transporter GLUT-1, a variety of genes encoding synaptic proteins and *DEPDC5* which is a regulator of the mTOR pathway.

When the field began we had a view, which in retrospect was naïve, that there would be a simple correlation of epilepsy syndrome with gene defects – one syndrome, one gene. Now we realize that even in epilepsies where there is evidence for a single major gene (Mendelian epilepsies) there is a great deal of heterogeneity. Such epilepsies account for a few per cent of all cases whereas, in the majority of cases, the genetics determinants are complex with multiple genes probably contributing to each individual case. Taken to the extreme, one might argue that each person with epilepsy is genetically different. This conclusion makes it difficult to reconcile the clinical observation of groups of easily-recognizable epilepsy syndromes. The resolution of this paradox will be essential to fundamental understanding of the genetic architecture of epilepsies and designing strategies to harness genetic knowledge to develop and implement precision medicine strategies.

UNIFICATION OF SPIKES, SEIZURES AND SPREADING DEPRESSION

Steven J. Schiff
Center for Neural Engineering, Departments of Neurosurgery, Engineering Science and Mechanics, and Physics
sschiff@psu.edu

The pathological phenomena of seizures and spreading depression have long been considered separate physiological events in the brain. By incorporating conservation of particles and charge, and accounting for the energy required to restore ionic gradients, we extend the classic Hodgkin–Huxley formalism to uncover a unification of neuronal membrane dynamics. By examining the dynamics as a function of potassium and oxygen, we now account for a wide range of neuronal activities, from spikes to seizures, spreading depression (whether high potassium or hypoxia induced), mixed seizure and spreading depression states, and the terminal anoxic "wave of death." Such a unified framework demonstrates that all of these dynamics lie along a continuum of the repertoire of the neuron membrane. Our results demonstrate that unified frameworks for neuronal dynamics are feasible, can be achieved using existing biological structures and universal physical conservation principles, and may be of substantial importance in enabling our understanding of brain activity, and in the prediction and control of pathological states such as seizures [1].

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SOURCES OF FUNCTIONAL HETEROGENEITY IN THE CELLULAR ACTIVITY OF HIPPOCAMPAL MICROCIRCUITS IN TEMPORAL LOBE EPILEPSY

Liset Menendez de la Prida
[1]Instituto Cajal CSIC, Madrid 28002, Spain

#lmprida@cajal.csic.es

Recent evidence from fine-scale spatiotemporal recordings using multi-electrode arrays in human focal epilepsies suggests that seizures progresses through heterogeneous single-cell firing (increases/decreases) and circuit dynamics (synchronous/ asynchronous). To date we fail to understand the impact of this heterogeneity on epileptogenesis and ictogenesis. Here, we use transient high-frequency oscillations (HFOs; 150-600Hz) of the local field potentials recorded in the hippocampus as a proxy of microcircuit dynamics and heterogeneous cell responses. We show data on a disparate behavior of pyramidal cell activity during physiological and pathological HFOs in the rat hippocampus in vivo, depending on their deep (closer to stratum oriens) or superficial (closer to stratum radiatum) position within the CA1 pyramidal cell layer. Biased contribution of perisomatic GABAergic inhibitory inputs together with cell-type specific microcircuit control may explain the differential selection of CA1 pyramidal cells during physiological HFOs. We discuss the implication of this discovery in the context of temporal lobe epilepsy and propose that single-cell heterogeneity in epileptogenic territories should be understood in terms of the specific neuronal identity and connectivity profile within the network.

SUDEP: AN OVERVIEW

Philippe Ryvlin
[1]Department of Clinical Neurosciences, CHUV, Lausanne, Switzerland
[2]Institut des Epilepsies IDEE, Lyon, France
philipperyvlin@gmail.com

Sudden unexpected death in epilepsy (SUDEP) is the second leading neurological cause after stroke of years of potential life lost, and one of the main non-suicidal, non-accidental cause of sudden death in young adults. Its incidence is estimated at 0.81 cases per 100,000 population, and 1.16 cases per 1,000 patients with epilepsy. In patients with uncontrolled seizures, incidence might raise up to about 0.4%, resulting in high cumulative risk in childhood onset epilepsy that remains active through life.

The main risk factor for SUDEP is the presence and frequency of generalized tonic-clonic seizure (GTCS), with odd ratio of up to 20 for GTCS frequency $\geq$ 3/years in comparison to no GTCS. This is in line with the observation that most witnessed and video-EEG recorded SUDEP occurred in the immediate aftermath of a GTCS. The mechanisms underlying GTCS-induced SUDEP are not completely understood, but appear to involve a post-ictal shutdown of brainstem cardiorespiratory centers, possibly promoted by a combination of factors such as: prone position, ictal hypoxemia, endophenotypes involving seotoninergic or other neurotransmission systems, post-ictal release of adenosine and/or endogenous opiates.

Beside this pathophysiological framework, evidences point to the possibility of genetic variants which might contribute to SUDEP in various ways: 1) sudden cardiac death in relation to long-QT syndrom due to ion channel mutations also responsible for epilepsy (i.e. KCNH2, SCN5A, CACNA1C), 2) propensity to develop seizure-triggered cardiorespiratory dysfunction, including those described in the above section.

There is currently no evidence-based treatment to prevent SUDEP, except than those aiming at reducing seizure frequency. Indeed, a meta-analysis of all phase III randomized placebo-controlled trials performed in patients with refractory epilepsy demonstrated a seven-fold lower risk of SUDEP in patients receiving an add-on antiepileptic drug as compared to those allocated to placebo. A number of other potential interventions to prevent SUDEP are being considered but require further understanding of the mechanisms of SUDEP before being tested in clinical trials, as well as progress in delineating biomarkers in order to identify patients carrying a sufficiently high risk of SUDEP to be recruited in such studies.

The development of medical devices aiming at detecting seizures and associated changes in cardiorespiratory function offers opportunities to develop both the awaited biomarkers as well as relevant input to closed-loop anti-SUDEP devices.

RESPONSIVE DIRECT BRAIN STIMULATION FOR THE TREATMENT OF EPILEPSY

Martha J. Morrell MD
NeuroPace and Stanford University
mmorrell@neuropace.com

The RNS® System (NeuroPace®, Mountain View CA) is the first closed-loop responsive direct brain stimulation device and is approved by the U.S. FDA as an adjunctive therapy for medically intractable partial onset seizures.

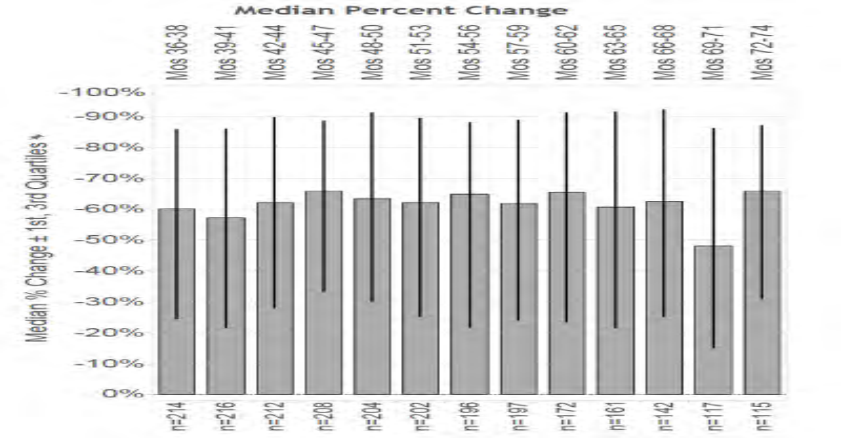
Components of the RNS System include a cranially implanted neurostimulator that continually monitors the electrocorticogram (ECoG) through one or two 4 electrode containing depth and/or subdural cortical strip leads placed at the seizure focus. When physician defined ECoG activity is detected (usually epileptiform activity typical of that which precedes that patient's seizures), the neurostimulator delivers short trains of current-controlled, charge-balanced pulses through the electrodes. A typical patient receives about 1000 100-msec stimulation pulses/day (cumulative stimulation of ≤ 3 minutes). Other components are a programmer to noninvasively program detection and stimulation, a patient remote monitor to transmit data, and an internet-based secure interactive database for patient data storage.

The neurostimulator stores the time and date of detections and stimulations, as well as segments of ECoG immediately before and after prespecified events such as a detection of abnormal electrographic activity or a magnet swipe (used by the patient to indicate a clinical seizure). The 3 detection algorithms (Line Length, Area, and Bandpass) are computationally efficient and highly configurable to optimize detection for each patient.

Safety and effectiveness of the RNS System for the indicated patient population was demonstrated in a multicenter, randomized, sham-stimulation controlled 2-year study (RCT) in 191 patients, an earlier 2 year feasibility study in 65 patients and in an ongoing, prospective study to collect an additional 7 years of safety and effectiveness data. During the 12-week blinded period of the RCT, treated patients had a significantly greater reduction in seizures than did sham stimulated patients (-37.9% v. -17.3, p=0.012)[1]. During open-label periods of the studies, seizure reductions continued to improve. At 2 years in the RCT, there was a median percent seizure reduction of 53%[2]. After 2 years, median percent reduction in seizures were ≥ 60% [Figure 1][3]. The risk for implant site infection was 3.5% and the risk of haemorrhage was 2.1%, with no patient experiencing neurological sequelae. There were no adverse effects on neuropsychological function and mood[2].

The RNS System has demonstrated sustained effectiveness in reducing the frequency of partial seizures in a highly treatment refractory patient population with acceptable safety and without adverse cognitive effects. Additional clinical experience and ongoing research will contribute to the optimization of this therapeutic approach.

Figure 1. Median percent reduction in seizures for subjects treated with the RNS System in an on-going long term treatment study[3].



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TRACKING SEIZURE DYNAMICS USING DATA-DRIVEN NEURAL MODELING

Dean R. Freestone[1,4#], Philippa J. Karoly[1,2], Levin Kuhlmann[2], Dragan Nešić[2], Parham Aram[3], Mark J. Cook[1], Daniel Soudry[4], Liam Paninski[4], and David B. Grayden[2]

[1] Department of Medicine, St. Vincent's Hospital Melbourne, The University of Melbourne, 19 Regent St., Fitzroy, Victoria, 3065, Australia

[2] NeuroEngineering Laboratory, Department of Electrical and Electronic Engineering, The University of Melbourne, Parkville, Victoria, 3010, Australia

[3] Department of Automatic Control and Systems Engineering, University of Sheffield, Sheffield, United Kingdom

[4] Department of Statistics, Columbia University, New York, 10027, USA

#deanfreestone@gmail.com

This research introduces a new method for functional brain imaging via a process of model inversion [1]. By estimating parameters of a computational model, we are able to track effective connectivity and mean membrane potential dynamics that cannot be directly measured using electrophysiological measurements alone.

The method is based on approximating brain networks using an interconnected neural population model. The neural population model is based on a neural mass model that describes the functional activity of the brain, capturing the mesoscopic biophysics and anatomical structure. The model is made subject-specific by estimating the strength of intra-cortical connections within a region and inter-cortical connections between regions using a novel Kalman filtering method. The Kalman filter is novel because we propagate the mean and variance of the states using a semi-analytic method, which improves the filters accuracy and stability. We demonstrate through simulation how the framework can be used the track the mechanisms involved in seizure initiation and termination.

The ability to track the hidden aspects of neurophysiology will have a profound impact on the way we understand and treat epilepsy. For example, under the assumption the model captures the key features of the cortical circuits of interest, the framework will provide insights into seizure initiation and termination on a patient-specific basis. It will enable investigation into the effect a particular drug has on specific neural populations and connectivity structures using minimally invasive measurements.

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LENNOX-GASTAUT SYNDROME SHOWS PERVASIVELY ABNORMAL INTERACTIONS BETWEEN COGNITIVE BRAIN NETWORKS

Aaron E.L Warren[1#], David F. Abbott[1,2], David N. Vaughan[2,3], Graeme D. Jackson[1,2,3], and John S. Archer[1,2,3]
[1]Department of Medicine, The University of Melbourne, Heidelberg, Victoria, Australia
[2]Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia
[3]Department of Neurology, Austin Health, Heidelberg, Victoria, Australia

#aewarren@student.unimelb.edu.au

Background: Lennox-Gastaut Syndrome (LGS) is an epileptic encephalopathy associated with intractable seizures and severe cognitive impairment. Patients show a shared electroclinical profile, suggesting that the epileptic process may be expressed through common brain networks. Using functional MRI and concurrent electroencephalography (EEG-fMRI), we have recently demonstrated[1,2] that transient epileptic discharges in LGS recruit diffuse association cortex, including simultaneous activity changes in key brain networks involved in different cognitive functions. However, the ongoing behaviour of these brain networks, during periods with and without epileptic activity, is unknown.

Aims: i) To compare spontaneous interactions between key cognitive brain networks in LGS patients and a group of healthy controls. ii) To compare network interactions in LGS patients during periods with and without observable epileptic activity.

Methods: EEG-fMRI was performed in 15 LGS patients (8 females; mean age 28.7±10.6 years) and 17 healthy controls (6 females; 27.6±6.6 years). Resting-state fMRI data were acquired for 25 mins using a 3T scanner. Common networks of brain activity (each represented by a spatial map and timecourse) were determined from the fMRI data using group independent components analysis (group ICA). Functional interactions between seven key cognitive networks were explored by calculating the Pearson's correlation between each pair of network timecourses. Network correlation strengths were compared between patients and controls using a multivariate analysis of covariance. In a subset of 6 LGS patients, we further compared network interactions during fMRI periods when epileptic discharges were present (discharge-affected) or absent (discharge-unaffected) on each patient's simultaneous EEG recording.

Results: i) Relative to controls, patients showed a) stronger interactions between networks involved in *distinct* cognitive functions, including networks involved in internally-oriented attention (default-mode network [DMN]) and externally-oriented attention (visuospatial attention and anterior salience networks), and b) weaker interactions between networks involved in *related* cognitive functions, including anterior and posterior aspects of the DMN (Figure 1). ii) Comparison of network interactions during discharge-affected and discharge-unaffected periods revealed no significant differences.

Conclusions: LGS shows a failure to *segregate* functional networks with distinct cognitive roles, and a failure to *integrate* networks with related cognitive roles. Abnormal network interactions are similar during periods with and without observable epileptic activity.

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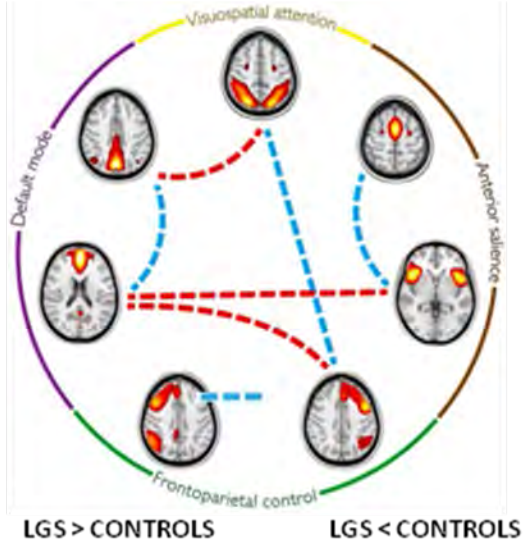

Figure 1: Spatial maps of seven key brain networks, arranged by cognitive function (colour of outer circle rim). Dotted red lines show network interactions stronger in LGS relative to controls; blue lines show interactions weaker in LGS (p<0.05, false-discovery rate correction).

Poster Session Abstracts, Monday August 3 2015

Poster Session Details

The IWSP7 poster session will be held in the 5th floor common room of the Kenneth Myer Building. To get there take the lift in the foyer. The lift location is shown in the back of this program.

Poster numbers occur at the beginning of the titles for each abstract. On the day it should be pretty easy to find the posters you want to see.

Posters will be arranged into 5 categories:

Epilepsy Mechanisms
Prediction, Detection & Control
Seizure Localisation, Imaging, and Networks
Computational Modelling
Model-based Estimation

For poster presenters: the maximum poster dimensions allowed are A0 (portrait or landscape). To determine your poster number check the list of poster titles below.

List of Numbered Poster Titles and First Authors

Epilepsy Mechanisms

1. INTERICTAL SPIKES AND EPILEPTIC SEIZURES

Philippa Karoly

2. EPILEPSY IN A DISH: DELIVERING THE PROMISE OF PRECISION MEDICINE

Dulini Mendis

3. FUNCTIONAL RESOLUTION OF LOCAL FIELD POTENTIALS IN THE RAT EPILEPTIC HIPPOCAMPUS

François Laurent

4. NEUROVASCULAR DECOUPLING DURING EPILEPTOGENESIS IN RATS

Rafael Torres

5. GABAA RECEPTOR ACTIVATION TRIGGER ICTAL EVENTS IN IN VITRO/IN VIVO SEIZURE MODELS

Michael Chang

6. TARGETED DRUG THERAPY IN DRAVET SYNDROME

Carol J. Milligan

7. CARBAMAZEPINE AND PHENYTOIN INHIBIT NATIVE SODIUM CURRENTS IN MURINE OSTEOBLASTS – A PROPOSED MECHANISM FOR REDUCED BONE QUALITY IN EPILEPSY

Sandra J. Petty

8. A POSSIBLE MECHANISM FOR THE INVOLVEMENT OF THE PIRIFORM CORTEX IN SEIZURE GENERALISATION

Robertson JJR

9. FUNCTIONAL CORRELATES OF SEVERITY IN GLUT1 DISORDERS

Sasha M. Zaman

10. ISSUE OF PHARMACORESISTANCE: IS SK-CHANNEL OPENER AN EFFECTIVE DRUG TARGET?

Muhammad Liaquuat Raza

11. EVALUATION OF EPILEPTIFORM DISCHARGES AS ELECTROGRAPHIC BIOMARKERS FOR EPILEPTOGENESIS

Hoameng Ung

Prediction, Detection, and Control

12. PREICTAL TIME, POSTICTAL EFFECTS, AND SEIZURE CLUSTERING IN EEG-BASED SEIZURE PREDICTION IN NATURALLY OCCURRING CANINE EPILEPSY

Yogatheesan Varatharajah

13. EARLY SEIZURE TYPE PREDICTION BASED ON A SINGLE INTRACRANIAL EEG CHANNEL - A PROOF OF CONCEPT

Cristian Donos

14. SCALE-FREE PROPERTIES OF INTRACEREBRAL EEG IMPROVE SEIZURE PREDICTION IN MESIAL TEMPORAL LOBE EPILEPSY

Kais Gadhoumi

15. CONTINUOUS SINGLE PULSE ELECTRICAL STIMULATION AS A SEIZURE PREDICTOR

Antonio Valentin

16. INTRINSIC EXCITABILITY MEASURES TRACK ANTI-EPILEPTIC DRUG ACTION AND UNCOVER INCREASING/DECREASING EXCITABILITY OVER THE WAKE/SLEEP CYCLE

Christian Meisel

17. A SUB-SCALP SEIZURE MONITORING IMPLANT FOR EPILEPSY PATIENT MANAGEMENT

Alan Lai

18. DESIGNING PATIENT-SPECIFIC OPTIMAL NEUROSTIMULATION PATTERNS FOR SEIZURES FROM HUMAN SINGLE UNIT HIPPOCAMPAL DATA

Roman A. Sander

19. EVALUATING SUBSPACE ANGLES OF EEG SIGNALS FOR THE DETECTION OF EPILEPTIC SEIZURES

Wanzhi Qiu

20. PERFORMANCE OF SYNCHRONY AND SPECTRAL-BASED FEATURES IN EARLY SEIZURE DETECTION: EXPLORING FEATURE COMBINATIONS AND EFFECT OF LATENCY

Vincent Adam, Joana Soldado-Magraner

21. DETECTION OF EPILEPTIC SEIZURE USING SUPPORT VECTOR MACHINE AND LINEAR DISCRIMINANT CLASSIFIERS

Muhammad Khizar Abbas

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Epilepsy Mechanisms

1. Interictal Spikes and Epileptic Seizures

Philippa Karoly[1,2#], Dean Freestone[1,2,3], Ray Boston[1], David Grayden[1,2] and Mark Cook[1]
[1]Departments of Medicine, University of Melbourne and St Vincent's Hospital, Melbourne
[2]Department of Electrical and Electronic Engineering, University of Melbourne
[3]Department of Statistics, Columbia University, New York, 10027, USA
#pkaroly@student.unimelb.edu.au

The relationship between interictal spikes and epileptic seizures is controversial. It has variously been suggested that spikes promote seizure onset, provide some protective benefit either through dissipation of excess energy or post-spike depression, or that spikes are merely a secondary consequence of epilepsy and uncorrelated with seizure[1]. To investigate the relationship between spikes and seizure, automated spike detection was performed on continuous, ambulatory intracranial EEG recordings collected from 15 subjects with intractable epilepsy. Subjects were selected for a previous clinical trial of an implantable seizure warning device[2], with recording duration ranging from 6 months to 2 years.

The study showed that spike rate significantly decreased prior to seizure, which is not consistent with spikes promoting seizures. However, the probability distribution of spikes and seizures were notably similar, i.e. at times of high seizure likelihood the probability of epileptic spiking also increased. This result suggests spikes and seizures are not wholly independent processes but may share generative or regulatory mechanisms. Furthermore, both spikes and seizures showed clear evidence of circadian regulation and, for some subjects, there were also longer term patterns visible over weeks to months. Identifying candidate biophysiological mechanisms that cause circadian and longer-term rhythms may shed light on mechanisms of seizure generation. Since interictal spikes demonstrate similar patterns to seizures and can be recorded non-invasively, they can be used as a proxy to study periodicity in seizures.

If spike rate is modulated by common regulatory factors as seizures then spikes may be useful biomarkers of cortical excitability. For instance, features of spikes, such as spatio-temporal distribution or morphology, could be used to measure the resilience of the underlying network to perturbation. Simple point process models of spikes or other interictal events may also provide an estimate of the state of the epileptic network. Another consequence of the likelihood for spikes and seizures showing similar patterns is that prediction algorithms may appear to be incorrectly predicting seizures while in fact correctly identifying smaller epileptic events. In light of this, computational and statistical models that are capable of uniting a range of epileptiform activity are necessary to distinguish between multiple possibilities.

[1] Marco de Curtis and Giuliano Avanzini (2001) Interictal spikes in focal epileptogenesis, *Progress in neurobiology*, vol. 63, no. 5, pp. 541-567
[2] Mark J Cook, Terence J O'Brien, Samuel F Berkovich, Michael Murphy, Andrew Morokoff, Gavin Fabinyi, Wendyl D'Souza, Raju Yerra, John Archer, Lucas Litewka and others (2013) Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study, *The Lancet Neurology*, vol. 12, no. 6, pp. 563-571

2. EPILEPSY IN A DISH: DELIVERING THE PROMISE OF PRECISION MEDICINE

Dulini Mendis[1], Emma Morrisroe[2], Chris Reid[2], Saman Halgamuge[1], and Steve Petrou[1,2]
[1]School of Engineering, University of Melbourne
[2]Florey Institute of Neuroscience & Mental Health, Parkville
dcmendis@student.unimelb.edu.au

Recent advances in neurogenetics, stem-cell biology, genome editing and electrophysiology have converged to enable next generation "brain in a dish" modelling. Neurogenetic disorders such as the epileptic encephalopathies (EE) are ideal candidates for this approach. They are a class of severe childhood epilepsies often associated with frequent seizures as well as intellectual, movement and development disorders. The EE's typically present as *de novo* autosomal dominant single gene disorders. Modelling these disorders for repurposing or new drug screening is often attempted using mouse models that are time consuming, expensive, lack human pharmacology and are not amenable to primary drug discovery. Differences between rodent and human neurobiology also limit the recapitulation of the primary disease phenotype, further limiting their potential for development of precision therapeutics that are based on targeting disease mechanisms. Cultured neuronal network models derived from genome edited human stem cell lines or patient stem cells themselves is one means of incorporating a complex functional scale with advantages of human or even patient specific pharmacology. Micro-electrode arrays (MEAs) are a scalable technology that allows for investigation of disease phenotype of cultured neuronal networks as well as screening the short and long term actions of drugs.

As a prelude to generation of such models the development of an assay workflow is a critical step for efficient implementation of human stem cell based MEA brain in a dish models. Here we describe the first steps towards the implementation of such an assay where we use mouse primary cultured neurons to characterise the mechanism of action (MOA) novel analgesic compound called conolidine. Neurons in culture display a host of behaviours that can be measured either as extracellular action potentials (spikes) or synaptic potentials (local fields) and a range of parameters can be extracted using automated software and characterized using advanced pattern recognition algorithms. We characterise the network profile in the presence of conolidine and compare this to the activity profiles of drugs with known MOA to propose a potential MOA for conolidine itself. Our studies suggest that conolidine has action on the $GABA_B$ and $GABA_A$ pathways. Future effort will focus on developing profiles for network activity in neurons from a model of Dravet Syndrome to develop a diagnostic signature as well as evaluate several promising drug candidates. Finally we will incorporate human stem cell neurons into this model for precision medicine application in genetic epilepsy and other neurological disorders.

3. FUNCTIONAL RESOLUTION OF LOCAL FIELD POTENTIALS IN THE RAT EPILEPTIC HIPPOCAMPUS

François Laurent[1#], Jorge R. Brotons-Mas[1], Diego Lopez-Pigozzi[1], and Liset Menendez de la Prida[1]
[1]Instituto Cajal, CSIC, Madrid 28002, Spain
#f.e.j.laurent@gmail.com

Local field potential signals (LFPs) result from currents that are local in nature but can contribute remotely by their electrical field. There has been controversy about how far from the recording site an electrical event is detectable, or how large in space should be a current distribution to be detectable. Such an extent may depend on the ongoing physiological process, especially if the dynamics of this process is characterized by synchronized oscillatory activity.

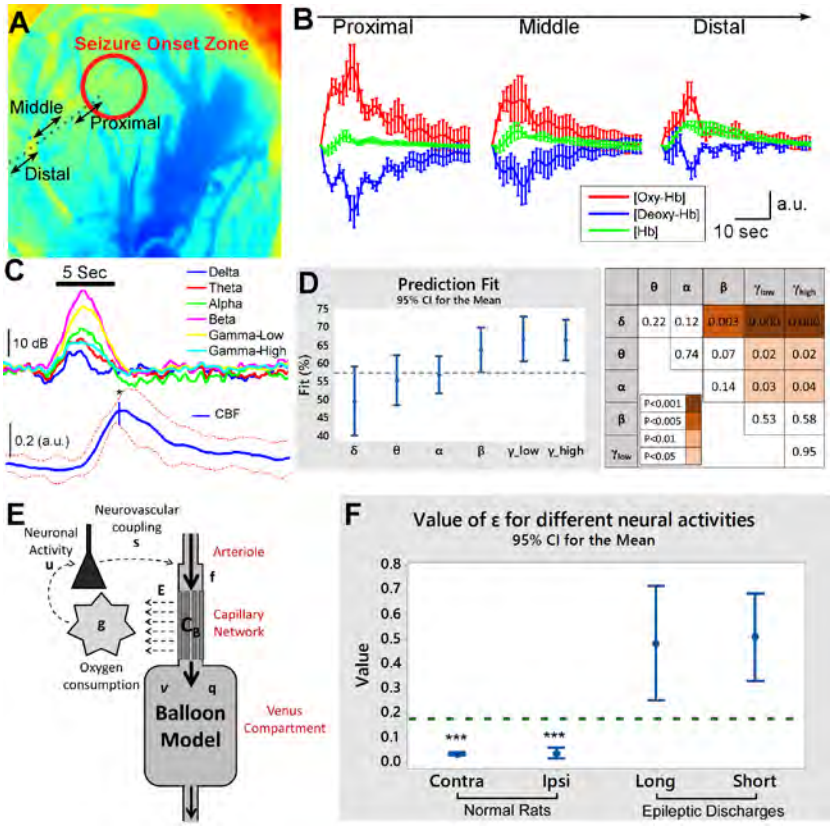
To examine this issue, we recorded in the rat hippocampus with linear multi-channel silicon probe and evaluated how much local current source densities (CSD) "explain" the hippocampal LFP in normal and epileptic rats using a model that integrated these CSD within a radius around the axis of the probe, under a few hypotheses of the spatial distribution of cellular current sources.

We first observed that the local CSD better explained the LFP when we considered a layer-specific radius instead of a single radius for all the layers considered in the model (explained variance increased from 70% to 84%), thus providing a suitable volume conduction model to evaluate local LFPs. Importantly, the optimal radius at CA1 stratum pyramidale was lower than at the granule cell layer of the dentate gyrus (DG), especially for high frequency oscillations (HFOs, >100 Hz). In the transition to seizures the average optimal radius progressively increased from 260 microns to 542 microns at the onset, to then decrease at the post-ictal period. We discuss our data in the context of the functional resolution of ictal dynamics across different frequency bands, from theta (4-12 Hz) and gamma (30-90) to HFOs (>100 Hz).

4. NEUROVASCULAR DECOUPLING DURING EPILEPTOGENESIS IN RATS

Rafael Torres, Yinchen Song, Wei-Chiang Lin, Jorge Riera Diaz
Florida International University
jrieradi@fiu.edu

Refractory epilepsy is a serious neurological disorder not controlled by medication. Neurosurgery is the only therapeutic option. EEG-fMRI is one of the neuroimaging techniques potentially useful to determine the epileptogenic brain regions. Current canonical hemodynamic response functions (HRF) used in most of the available software to perform EEG-fMRI analysis fail to take account of pathophysiological phenomena in the epileptic brain, such as the abnormal metabolic rates and impaired neurovascular coupling. These phenomena will lead to atypical HRFs; hence, they confound localization of the epileptogenic area, precluding EEG-fMRI use. To obtain accurate HRFs for the epileptic cortex, a better understanding of the mechanisms for neurovascular/metabolic coupling (NV/M-C) is needed. In this study, a metabolically-coupled balloon model[1] was employed to evaluate the NV/M-C in a preclinical model of chronic focal epilepsy (13 Wistar rats). This model is an extension of the standard balloon model to include modulatory effects of changes in tissue oxygenation, capillary dynamics, and variable O_2 extraction fraction (Fig. 1E). Brain source imaging of interictal epileptiform discharge (IED) was performed on these rats using 32-channel scalp EEG recordings to localize the irritative zone. Subsequent to the craniotomy on top of the irritative zone (Fig. 1A), recordings of LFP/MUA, CBF, CBV, [Deoxy-Hb] were acquired simultaneously (Fig. 1B-C) to evaluate the different parameters of the NV/M-C in this extended balloon model. Similar intracranial recordings were also obtained from the somatosensory cortex for forelimb in 5 normal rats undergoing forepaw stimulation, and hence, used as control in this study. Different types of IEDs were observed from intracranial recording in all epileptic rats. Four of them underwent seizure episodes multiple times during the intracranial recordings. Significant increases in CBF were associated with epileptogenesis.



Reflections of such abnormal activity within the optical field of view usually resembled an increase of CBV and a decrease of [Deoxy-Hb] with an epicentric origin followed by a peripheral propagation (Fig. 1A-B). Our results indicate dissimilar contributions from LFP frequency bands to the CBF responses for epileptic activities (Fig. 1D). Parameters linking the CBF to neuronal activity in this metabolically-coupled balloon model during epileptic activity and forepaw stimulation were compared and show significant differences (Fig. 1F). Our result will have an impact on the way we use EEG-fMRI analysis in epilepsy and guide us to a better knowledge of this pathology.

[1] Zheng Y, Martindale J, Johnston D, Jones M, Berwick J, Mayhew J, (2002) "A model of the hemodynamic response and oxygen delivery to brain." *Neuroimage*, vol. 16, no. 3, pp. 617-637

5. GABAA RECEPTOR ACTIVATION TRIGGER ICTAL EVENTS IN IN VITRO/IN VIVO SEIZURE MODELS

Michael Chang[1], Joshua A. Dian[1], Suzie Dufour[1], Lihua Wang[1], Taufik A. Valiante[1#]
[1]Division of Fundamental Neurobiology, Toronto Western Research Institute, Toronto, ON
#taufik.valiante@uhn.ca

GABAergic neurotransmission is known to play a critical role in cortical synchrony during physiological brain activity, while excessive interneuronal activity has been correlated to pro-epileptogenic activity[1-3]. To explore the causal role of GABAergic neurotransmission in the initiation of interictal spikes and ictal events, we utilized optogenetic mice expressing channelrhodopsin-2 in GABAergic interneurons. We found that 30 ms pulses of light reliably evoked either isolated interictal spikes or an interictal spike followed by ictal events in both *in vitro* and *in vivo* 4-AP seizure model. These light-triggered events were visually identical to the spontaneous events at the onset and shared the same prototypical characteristics throughout. We were able to replicate light-triggered ictal events in other distinct *in vitro* seizure models (zero Mg^{2+}, and low Mg^{2+}/high K^{+}) and in both the neocortex and hippocampus of mice. Moreover, we showed that this phenomenon is abolished by $GABA_A$ blockade and absent in wild-type mice. Whole cell recordings in putative pyramidal cells under 4-AP conditions consistently revealed hyperpolarizing responses to light were followed by rebound spiking and a long lasting membrane depolarization that were both blocked by tetrodotoxin. Gramicidin-perforated patch recordings confirmed the hyperpolarizing response to light in pyramidal cells just prior to ictal onset. The post-inhibitory rebound spiking was confirmed at a larger spatial and cellular scale using multi-electrode array recordings. This suggests a putative mechanism underlying the light-triggered ictal events involves GABA-mediated rebound excitation of pyramidal cells. To translate these findings to the human brain, we demonstrate that in 4-AP treated human neocortical tissue, brief pulses of GABA reliably triggered ictal events. We conclude that brief activation of $GABA_A$ receptors in unison can paradoxically trigger ictal events, and the potential underlying mechanism may be rebound spiking that follows the synchronous activation. Furthermore, optogenetic activation of GABAergic interneurons provides a useful extension to standard *in vitro*/*in vivo* seizure models that allow for precisely timed generation of ictal events in a manner less invasive, and more specific than electrical stimulation. Lastly, our findings suggest that novel therapies directed at disrupting or preventing interneuronal synchrony may be further explored as alternate therapeutic strategies to control seizures.

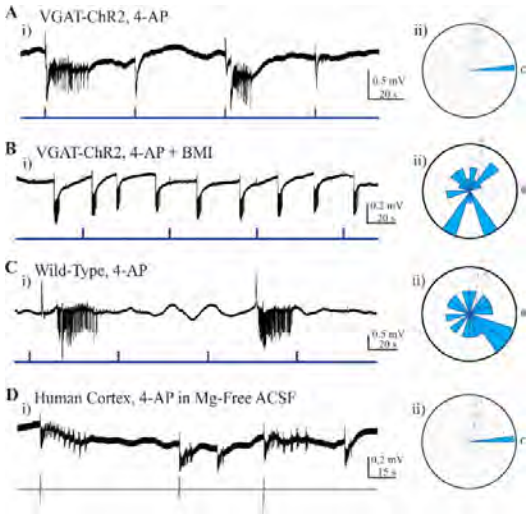


Figure 1 | Ictal events are correlated with light stimuli *in vitro*. Local field potential recording (black) and associated angular histogram of ictal event distribution. Light stimuli (30 ms; blue) and puffs of GABA (100 mM) (175 ms at 20 psi; brown) are depicted in lower traces and correspond to an angle of 0° in the angular histogram. **A**i) Light-triggered ictal events in VGAT-ChR2 mouse. ii) Angular histogram of ictal phases ($p = 1.3e^{-14}$, *circ_vtest*; $n = 20$ events). **B**i) Spontaneous burst-like discharges recorded in VGAT-ChR2 mouse following application of 10 μM BMI. ii) Angular histogram of burst phases ($p = 0.23$, *circ_vtest*; $n = 19$ events). **C**i) Spontaneous ictal events from wild-type mouse. ii) Angular histogram of ictal phases ($p = 0.16$, *circ_vtest*; $n = 20$ events). **D**i) GABA puff-triggered ictal events from human cortical tissue. ii) Angular histogram of ictal phases ($p = 1.9e\text{-}7$, *circ_vtest*; $n = 13$ events).

6. TARGETED DRUG THERAPY IN DRAVET SYNDROME

Carol J. Milligan[1], Kay Richards[1], Elena V. Gazina[1], Rob Richardson[1], Umesh Nair[1], Christopher A. Reid[1], Glenn King[2], David Julius[3], Steven Petrou[1,4-5]

[1]Ion Channels & Disease Group, Epilepsy Division, The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia. [2]Division of Chemistry & Structural Biology, Institute for Molecular Bioscience, The University of Queensland, St. Lucia, Queensland, Australia. [3]Department of Physiology, University of California, San Francisco, USA. [4]Department of Anatomy and Neuroscience, The University of Melbourne, Melbourne, Victoria, Australia. [5]Centre for Neural Engineering, The University of Melbourne, Melbourne, Victoria, Australia.
steven.petrou@florey.edu.au

Dravet syndrome (DS) is a rare early onset epileptic encephalopathy characterized by frequent intractable seizures, intellectual disability, movement disorders, autistic features and premature death. The vast majority of cases have mutations in *SCN1A*, the gene encoding the voltage-sensitive sodium channel NaV1.1, resulting in channel dysfunction. We propose that seizures and comorbidities in DS might be best treated by a drug that specifically elevates NaV1.1 activity in inhibitory interneurons, restoring their ability to regulate brain excitability, and making this disorder an ideal candidate for precision medicine. Heterozygous deletion of NaV1.1 in the mouse model of DS causes a reduction in excitability in fast-spiking, parvalbumin-expressing interneurons and somatostatin-expressing interneurons resulting in disinhibition of cortical networks. Spider venoms are a rich source of stable peptides that modulate the activity of sodium channels. However, selectivity is an issue as most toxins act indiscriminately. Here, using a planar patch-clamp assay, we examine the effects of a synthetic peptide toxin on a range of voltage-gated sodium channel isoforms (*SCN1A*-*SCN10A*) stably expressed in HEK293 cells. The peptide (5 nM) caused a significant enhancement of the sustained current of NaV1.1, but not the other channel isoforms, although a small effect was noted for $Na_V1.3$. The peptide also caused a small, but significant increase in the peak current amplitude of NaV1.2 and NaV1.6. In addition, we examined the effect of peptide (10 nM) on the action potential (AP) firing rate of hippocampal neurons using brain slice preparations from WT mice (P17-P20), with a patch-clamp assay. The peptide causes an increase in AP firing rate of stratum radiatum interneurons, with no impact on CA1 pyramidal neurons. Finally, *in vivo* analysis was used to examine the affect of peptide delivery on interictal epileptiform discharges measured in *Scn1a* heterozygote knock-out mice. ECoG recordings before and after delivery of 5nM peptide via an intracerebroventricular (ICV) cannula showed that *Scn1a* mice (n=10) had a significant reduction in interictal events (p=0.0065). These data demonstrate that enhancement of NaV1.1 current is possible and produces a favourable *in vivo* effect, paving the way for therapeutic application in DS. Exploiting toxin peptides is one avenue for creating targeted therapeutics in genetic disorders, such as DS, that promise to not only control seizures but also reduce associated co-morbidities.

7. CARBAMAZEPINE AND PHENYTOIN INHIBIT NATIVE SODIUM CURRENTS IN MURINE OSTEOBLASTS – A PROPOSED MECHANISM FOR REDUCED BONE QUALITY IN EPILEPSY

Sandra J. Petty[1-5*#], Carol J. Milligan[2*], Marian Todaro[1], Kay L. Richards[2], Pamuditha K. Kularathna[6], Charles N. Pagel[6], Chris French[1,3,5], Elisa L. Hill-Yardin[7], Terence J. O'Brien[1,3,5], John D. Wark[5,8], Eleanor J. Mackie[6], Steven Petrou[2].

1. Melbourne Brain Centre at The Royal Melbourne Hospital, The Department of Medicine, The University of Melbourne, Parkville, VIC, Australia
2. The Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia
3. Department of Neurology, The Royal Melbourne Hospital, Parkville, Vic, Australia
4. Academic Centre, Ormond College, Parkville, VIC, Australia
5. Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne, Parkville, VIC, Australia.
6. Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, Parkville, VIC, Australia
7. Department of Physiology, University of Melbourne, Parkville, VIC, Australia
8. Bone and Mineral Medicine, The Royal Melbourne Hospital, Parkville, VIC, Australia

* Petty and Milligan equal first authorship

#pettys@unimelb.edu.au

Objective: Fracture risk is a serious comorbidity in epilepsy and may relate to the use of anti-epileptic medications (AED). Many AEDs inhibit ion channel function and the expression of these channels in osteoblasts raises the idea that altered bone signaling increases bone fragility. We aimed to: (1) precisely define the subtypes of voltage-activated sodium channels (NaV) expressed in mouse osteoblast, and (2) investigate the action of carbamazepine (CBZ) and phenytoin (PHT) on NaV channels.

Methods: Immunocytochemistry and RNASeq were performed on primary calvarial osteoblasts extracted from neonatal C57BL/6J mice. In addition whole cell patch clamp recordings were made to identify the native currents expressed and also assess the actions of CBZ (50 μM) or PHT (50 μM).

Results: NaV expression was demonstrated with immunocytochemistry, RNASeq and functionally with demonstration of robust TTX sensitive and voltage-activated inward currents. Application of CBZ or PHT resulted in significant inhibition of current amplitude: for CBZ 31.6 ± 5.9 % ($n = 9$; $p<0.001$), and for PHT 35.5 ± 6.9 %, $n = 7$; $p<0.001$).

Interpretation: Mouse osteoblasts express NaV1.2, NaV1.3, NaV2.1 and NaV2.2 and native NaV currents are blocked by CBZ and PHT supporting our hypothesis that AEDs can directly influence osteoblast function and presumably impact bone strength.

8. A POSSIBLE MECHANISM FOR THE INVOLVEMENT OF THE PIRIFORM CORTEX IN SEIZURE GENERALISATION

Robertson JJR[1#] and Bekkers JM[2]

[1,2]Eccles Institute of Neuroscience, John Curtin School of Medical Research, Australian National University

u4517241@anu.edu.au

Recent human imaging studies have demonstrated the early involvement of the piriform cortex (PC) in the generalisation of focal seizures.[1,2] However, little is known about the mechanisms involved. The normal role of the PC is to combine odour information from the olfactory bulb with information from other brain regions to form our sense of smell. Grossly, the PC has a "simple" trilaminar structure, which masks the complexity of its internal connectivity.[3] Our aim was to elucidate the mechanism of the PC's involvement in seizure generalisation by studying neuronal activity in the PC in an *in vitro* epilepsy model.

Experiments used 450 µm-thick slices of the PC from 18-30 day-old C57Bl6 mice. Two-photon imaging of the Ca^{2+} indicator OGB1-AM was used to monitor the simultaneous activity of 20-60 neurons in layer 2 of the PC. Hyperexcitability was generated by perfusing the slices with artificial cerebrospinal fluid containing no added Mg^{2+} and high K^{+} (0Mg/HK), a common *in vitro* epilepsy model. Next, we applied an electrical stimulus via a bipolar stimulating electrode placed in the association layers of the PC. We found that, before electrical stimulation, the neurons exhibited unsynchronised activity (n=49 slices), and after mild stimulation the synchrony increased dramatically ($p<0.001$, n=15 slices). Thus, mild electrical stimulation (perhaps mimicking a seizure) can alter patterns of epileptiform activity in the PC. Application of 50 µM D-APV to block NMDA receptors inhibited the induction of synchronous activity (n=4 slices), suggesting that some form of long-term synaptic plasticity is involved. All activity was also blocked by 10 µM DNQX (n=4 slices) or 1 µM TTX (n=4 slices), confirming the requirement for intact excitatory synaptic transmission. Finally, we repeated these experiments in the hippocampus (n=7 slices) and the neocortex (n=6 slices). Interestingly, in contrast to the PC, the neurons in these tissues were synchronised *before* electrical stimulation was applied, and electrical stimulation had no further effect. This suggests that the synchronisation phenomenon may be unique to the PC. In this study we have found a possible mechanism by which the PC becomes involved in the early stages of epileptic seizure generalisation. Further understanding of the mechanisms may aid the development of treatments to prevent seizure generalisation in epileptic patients.

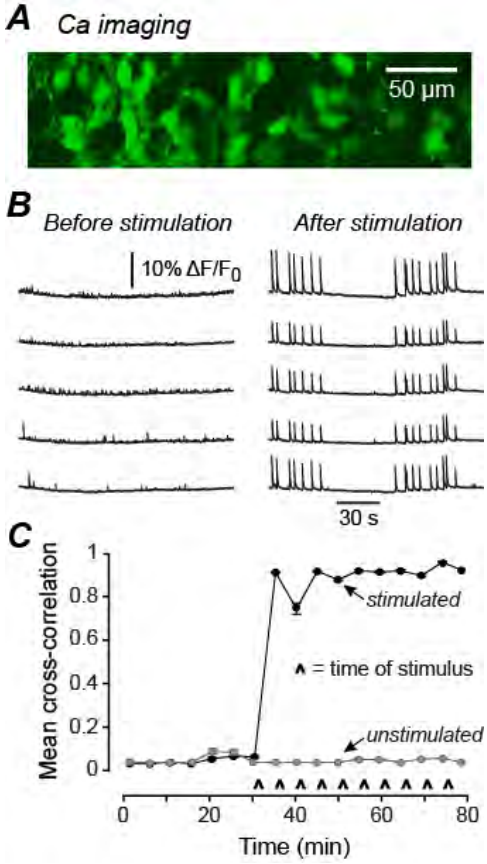


Figure 1: Mild electrical stimulation alters patterns of epileptiform activity in the piriform cortex (PC), A: 2-photon Ca^{2+} imaging of PC neurons, B: Neuronal activity before and after electrical stimulation. C: Stimulation increases synchrony

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9. FUNCTIONAL CORRELATES OF SEVERITY IN GLUT1 DISORDERS

Sasha M. Zaman[1,2#], Elena Gazina[1], Marie Phillips[1], Holger Lerche[4], Yvonne Weber[4], Sam Berkovic[3], Ingrid E Scheffer[3], Christopher A. Reid[1], Saul Mullen[3], Steven Petrou[1,2]

[1]Florey Neuroscience Institute, Parkville, Australia – Times New Roman 10pt

[2]University of Melbourne, Parkville, Australia

[3]Austin Hospital, Heidelberg, Australia

[4]University of Tubingen, Tubingen, Germany

#sasha.zaman@florey.edu.au

Purpose: We investigated the function of *SLC2A1* variants from patients with mild and severe forms of epilepsy to develop an understanding of how combined genetic and functional assessment can be used to reveal pathomechanisms and develop precision diagnostics. *SLC2A1* accounts for approximately 1% of genetic generalised epilepsy patients and encodes the glucose transporter 1 (GLUT1) protein found in glia and the epithelium of the blood brain barrier. Very severe GLUT1 deficiency disorders, such as De Vivo disease, are associated with complete loss of GLUT1 transporter function. However, the association between mutation severity and phenotype is less clear in the more common cases harbouring GLUT1 mutations.

Method: A *Xenopus laevis* oocyte glucose uptake assay was employed to measure the kinetics and affinity of the expressed GLUT1 transporter with a minimum n=5 for each group. This characterisation was undertaken in GLUT1 mutations from control cases and patients with two grades of clinical severity. "Unaffected" is comprised of variants found in the control population, "mild" is treatment responsive epilepsy and "severe" is characterised by refractory epilepsy and/or mild intellectual disability.

Results: A total of 20 variants were analysed with 12 from the mild cohort, 4 from the severe and the remaining 4 from unaffected cases. Although there was a spectrum of functional change within each grouping, with overlap Vmax and Km's of unaffected (Vmax M=21.35, SEM=2.841, Km M=47.38, SEM=3.435) with mild (Vmax M= 14.18, SEM=2.426, Km M=41.26, SEM=7.421) and severe (Vmax M= 4.417, SEM=2.484, Km not ascertainable), population level analysis showed an overall correlation of molecular dysfunction with clinical severity (Unaffected vs Mild r^2=.826, Unaffected vs Severe r^2=.011).

Conclusion: The functional genotype-phenotype correlation found in GLUT1 testing suggests that a risk model for acquiring GLUT1 disorders could be developed by the functional profiling of a patient's variant. A better understanding of the relationship between clinical severity and GLUT1 function will provide a foundation
for building our understanding of the neurobiology of GLUT1 disorders critical for diagnosis and targeted therapy.

10. ISSUE OF PHARMACORESISTANCE: IS SK-CHANNEL OPENER AN EFFECTIVE DRUG TARGET?

Muhammad Liaquuat Raza[#] and Uwe Hinemann
Institute of Neurophysiology, Charite - Universitätmedizin Berlin
#liaquathej@yahoo.com

SK-Channel plays important function for controlling neuronal hyperexcitability [1]. In epilepsy neurons experiences hyperexcitation, available anticonvulsants tends to reduce or overcome the excitation thus suppressing seizures. Unfortunately, despite medication 35 % patients are facing issue of drug resistance. We test SK-channel opener to address this question of pharmacoresistance.

Neocortical tissue after surgical resection from pharmacoresistant patient is transferred immediately into chilled transport solution (bubbled with carbogen) and shifted to laboratory for slicing. Using vibratom 500 micron thicker slice were cut and transferred to an interphase chamber supplied with carbogen and aCSF. After 4 hrs of recovery local field potential recordings were performed using glass microelectrode from layer IV/V. For attaining stable seizure like events (SLEs) 8 mM potassium + Bicuculline (50 µM) was added to aCSF.

NS-309 at 100 µM blocked SLEs in all the studied slices n=8, whereas, at 50 µM it was not as effective in blocking SLEs since out of 6 studied slices it failed to suppress SLEs in five slices. Beside other parameter such as duration and amplitude of SLEs were analyzed at lower dose that failed to block SELs.

Based on these findings we may suggest that SK-channel have positive effect to block SLEs in neocortical tissue from pharmacoresistance patients. Further cellular studies are needed to investigate the precise mechanism.

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11. EVALUATION OF EPILEPTIFORM DISCHARGES AS ELECTROGRAPHIC BIOMARKERS FOR EPILEPTOGENESIS

Hoameng Ung[1#], Jason Moyer[1], Joost Wagenaar[2], Abba Krieger[3], Asla Pitkanen[4], Brian Litt[1,2,5]

[1]Department of Bioengineering, University of Pennsylvania
[2]Department of Neurology, University of Pennsylvania
[3]Department of Statistics, University of Pennsylvania
[4]Department of Neurobiology, University of Eastern Finland
[5]Penn Epilepsy Center, University of Pennsylvania
#hoameng@upenn.edu

Objective: Up to 53% of patients with traumatic brain injury (TBI) develop spontaneous recurrent epileptic seizures. The ability to predict epileptogenesis in these patients may reduce the burden of post-traumatic epilepsy by enabling earlier interventions in the disease process as well as personalized therapy according to the likelihood of developing epilepsy. Here, we use a two-stage machine learning detection algorithm and analyze the utility of postulated epileptiform spikes and bursts as potential electrographic biomarkers of epileptogenesis in a rat model of TBI.

Methods: Hippocampal depth recordings from 23 rats monitored continuously for a one-week period three months following a fluid-percussion-induced traumatic brain injury (17) or sham surgery (6). Eight of the 17 rats with injury developed spontaneous seizures after the initial recording period. Novel hierarchical algorithms were developed to detect and cluster epileptiform spikes and bursts at a time before any clinical seizures were observed. Statistical analyses across three groups (sham, no-seizure, and seizure) were conducted.

Results: Epileptiform spikes and bursts were detected in all groups that received surgery and electrode implantation. Three subtypes of bursts were detected and subsequently classified into rhythmic bursts, epileptiform bursts, and electrode artifact. While no significant difference was found in the number of spikes between the sham, seizure, and non-seizure groups, the rats that developed seizures post-injury displayed significantly more epileptiform bursts per day than the rats that did not develop seizures ($p=0.015$). In addition, the bursts were of longer duration compared to both sham and non-seizure groups ($p=0.017$).

Significance: Our results show that in this sample, epileptiform bursts are more prevalent in rats that undergo epileptogenesis versus rats that do not. This suggests that bursts may be a potential electrographic biomarker of epileptogenesis and warrants further investigation in humans.

Prediction, Detection, and Control

12. Preictal Time, Postictal Effects, and Seizure Clustering in EEG-Based Seizure Prediction in Naturally Occurring Canine Epilepsy

Yogatheesan Varatharajah[1], Benjamin H. Brinkmann PhD[2#], Edward Patterson DVM, PhD[3] , Vladimir Cherkassky PhD[4], and Gregory A. Worrell MD PhD[2]

[1]University of Illinois at Urbana-Champaign, Electrical and Computer Engineering, Urbana, IL, USA
[2]Mayo Clinic Dept. of Neurology, Rochester MN, USA
[3]University of Minnesota, Dept. of Veterinary Medicine, Minneapolis MN USA
[4]University of Minnesota, Dept. of Electrical and Computer Engineering, Minneapolis MN USA
#Corresponding author: Brinkmann.Benjamin@mayo.edu

Management of drug resistant partial epilepsy would be greatly assisted by a reliable warning system capable of alerting patients prior to seizures to allow the patient to adjust activities or medication. Such a system requires successful identification of a preictal, or seizure-prone state. Identification of preictal states in continuous long-duration intracranial electroencephalographic (iEEG) recordings of dogs (1 deceased, 4 living) with naturally occurring epilepsy was investigated using a support vector machine (SVM) algorithm on interelectrode correlation features. The dogs studied were implanted with a 16-channel mobile iEEG recording device with average channel reference for a mean (st. dev.) of 380.4 (87.5) days producing 220.2 (104.1) days of intracranial EEG recorded at 400 Hz for analysis. The iEEG records had mean (st. dev.) 51.6 (52.8) seizures identified, of which 35.8 (30.4) seizures were preceded by more than 4 hours of seizure-free data. Recorded iEEG data were stratified into 11 contiguous, non-overlapping frequency bands and binned into one-minute synchrony features for analysis.

Prior studies have not given clear rationale for the duration and timing of the preictal signature, nor the duration of postictal effects in the EEG. As a result, a rather arbitrary restriction of 4 or 8 hours [1-3] between seizures has been enforced in prior seizure prediction studies to ensure prediction of lead (non-clustered) seizures. In addition it remains unclear whether the temporal course of seizure clustering and related EEG signatures can offer clues to the nature of the preictal state and hence aid prediction. In order to address these questions, preictal classification sensitivity with SVM was assessed varying the length and timing of the preictal period used in the classifier. EEG characteristics of the postictal period are also analyzed statistically and SVM is used to estimate the duration of these effects, and classification performance is analyzed at different lead seizure intervals.

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13. EARLY SEIZURE TYPE PREDICTION BASED ON A SINGLE INTRACRANIAL EEG CHANNEL - A PROOF OF CONCEPT

Cristian Donos[1,2#], Mihai Dragos Maliia[3], Matthias Dümpelmann[1], Andreas Schulze-Bonhage[1]
[1]Epilepsy Center, University Hospital of Freiburg, Freiburg, Germany
[2]Physics Department, Bucharest University, Bucharest, Romania
[3]Neurology Department, University Emergency Hospital, Bucharest, Romania
#cristian.donos@uniklinik-freiburg.de

Introduction: We propose an early seizure type prediction algorithm, than can be used to trigger an alarm for severe type of seizures or, in the case of closed loop stimulation devices, to save power by not stimulating on subclinical seizures and to evaluate a triggered stimulation's success on disrupting a clinical seizure.

Methods: The patient set consists of 20 epileptic patients investigated with grid and depth electrodes from the European Epilepsy Database[1]. For the seizure onset zone (SOZ) contacts, we compute a set of 25 time and frequency domains features from the first 3, 5 and 10 seconds of ictal activity (IA) and feed them to a random forest classifier[2]. Three classifiers are used to discern between clinical (CS) and subclinical seizures (SS), secondary generalized (SG) and partial seizures (PS), respectively simple (SP) and complex (CP) partial seizures. We group SP and CP as PS and PS and SG as CS, to obtain two classes for each classifier. The patient selection criteria require at least 2 seizures recorded from each class. For the CS-SS classifier, the SS has at least 10 seconds duration and, where available, equal number of CS and SS are used. From the total number of SOZ contacts of each patient, we select the contact with the best prediction rate (PR) and we compute the confusion matrix. We sum the confusion matrices of each patient and we calculate the PR at the population level. Spearman's rank correlation is used to check for correlations between the PRs and the number of seizure patterns or the number of SOZ contacts. The differences in PRs between grid vs. depth contacts is assessed by Mann-Whitney's U-test and the generalized linear regression using a probit model.

Results: The mean PR for the CS-SS, SG-PS and SP-CP classifiers was 70.2%, 80%, respectively 59.8%, with a standard deviation (SD) of ±1% in all three cases, showing no significant improvement when using longer IA periods. Spearman's rank correlation coefficient showed significant correlation between the PRs and the number of SOZ contacts (ρ=0.474, p=0.035) for the CS-SS classifier, when using 10 seconds of IA. Although no statistically significant difference was found between grid vs. depth contacts, grid contacts had the mean PRs systematically higher and the SD systematically lower.

Conclusion: This study is a proof of concept, demonstrating the existence of information about the seizure's future evolution in the first seconds of IA.

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14. SCALE-FREE PROPERTIES OF INTRACEREBRAL EEG IMPROVE SEIZURE PREDICTION IN MESIAL TEMPORAL LOBE EPILEPSY

Kais Gadhoumi [12#], Jean Gotman [12], and Jean-Marc Lina [2345]

[1] Montreal Neurological Institute, McGill University, Montréal, Québec, Canada; [2] McGill University, Biomedical Engineering, Montréal, Québec, Canada; [3] École De Technologie Supérieure, Département de Génie Électrique, Montréal, Québec, Canada; [4] Centre de recherches mathématiques, Montréal, Québec, Canada; [5] U678, INSERM, Paris, France

kais.gadhoumi@mail.mcgill.ca

Rationale: Although treatment for epilepsy is effective for nearly 70 percent of patients, many remain in need of new therapeutic approaches. Predicting seizures in these patients could enhance their quality of life if the prediction performance is clinically practical. In this study, we investigate the improvement in the performance of a recent seizure prediction algorithm [1] using a novel measure of scale-free dynamics of the intracerebral EEG. The performance of the algorithm is evaluated on continuous multi-day depth-electrode EEG of 17 patients with intractable mesial temporal lobe epilepsy who underwent presurgical evaluation.

Methods: Scale-free dynamics are characterized by the invariance of statistical properties along different time scales. We investigate such dynamics in the intracerebral EEG by means of a robust multifractal analysis based on wavelet leaders and bootstraps [2]. Scale-free properties are quantified through estimates of the scaling exponents — the first and second cumulants — that characterize power laws describing the inter-scale relations. The cumulants are first investigated for their ability to discriminate preictal and interictal epochs. The patient-specific classifier-based seizure prediction algorithm is then trained using combinations of cumulants and features originally proposed with the algorithm and referred to as state-similarity measures. Its performance was out-of-sample tested using 1446 h of continuous data containing 128 seizures. The sensitivity, the false prediction rate and the proportion of time under warning were evaluated for seizure prediction horizons ranging between 5 and 60 min. The sensitivity of the algorithm was statistically compared with that of an analytical Poisson predictor to evaluate its superiority to chance. Correction for multiple comparisons was performed using the Benjamini-Hochberg procedure.

Results: Using a combination of the first cumulant and the state-similarity measures, seizures were predictable above chance level (corrected p-value < 0.05) in 13 of 17 patients (76 %; an increase from 7/17 patients compared to our original results). The average sensitivity reached 80.5 % across these patients and the proportion of time under warning was 25.1 % for the critical false prediction rate of 0.15/h (fig. 1). Preictal changes were detected between 27.2 and 90 min. Surgery outcome and seizure above-chance predictability showed no significant association.

Conclusions: A substantial improvement in seizure prediction performance was possible by using descriptors of scale-free properties of intracerebral EEG in patients with mesial temporal lobe epilepsy. The results suggest that scale-free dynamics may have different properties in the preictal state compared to the interictal state. Robust quantifiers of these dynamics carry a predictive power useful in seizure prediction and possibly in characterizing the preictal state.

Supported by CIHR MOP-10189, RSC-NSERC CHRPJ 323490-06.

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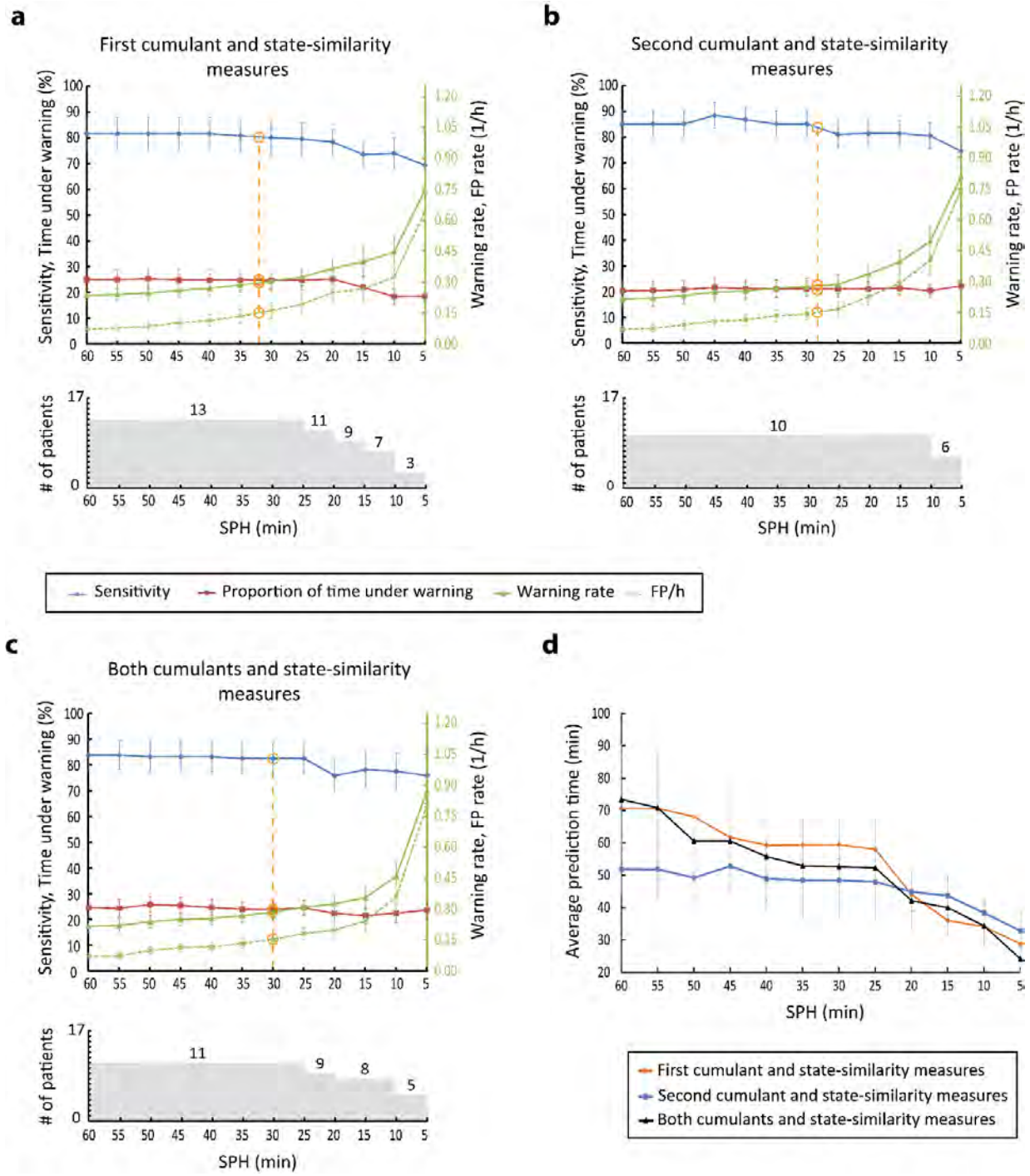

Fig. 1. Performance of the seizure prediction algorithm using combination of cumulants and state-similarity measures. a-c top: Performance metrics for the range of seizure prediction horizons (SPH) analysed when state-similarity measures are combined with the first cumulant, with the second cumulant, and with both cumulants. Orange circles indicate interpolated values of sensitivity, proportion of time under warning and warning rate corresponding to the critical false prediction rate of 0.15 /h. a-c bottom: Number of patients in whom seizures are predicted above chance level as a function of the seizure prediction horizon. d. Average prediction time per patient as a function of the seizure prediction horizon.

15. CONTINUOUS SINGLE PULSE ELECTRICAL STIMULATION AS A SEIZURE PREDICTOR

Antonio Valentin[1], Amir Eftekhar[3#], Gonzalo Alarcón[1], Sharon Jewell[1], Richard Selway[2], Christofer Toumazou[3], Mark P. Richardson[1]
[1] Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[2]Department of Neurosurgery, King's College Hospital, London, United Kingdom
[3]Center for Bio-Inspired Technology, Department of Electrical and Electronic Engineering, Imperial College London, London, United Kingdom.
#a.eftekhar@imperial.ac.uk

*Introduction***:** Single Pulse Electrical Stimulation (SPES) is used during intracranial EEG, as part of presurgical evaluation [1]. SPES involves a single pulse of constant monophasic current between adjacent electrodes. This elicits responses that correlate with the seizure focus [1].

Methods: This proof-of-principle study was designed to determine whether changes in SPES responses over several hours may precede seizure onset. 22 patients were implanted with intracranial strips, grids, and/or depth electrodes. Areas hypothesized to be seizure foci were stimulated with a pair of SPES (ISI 5 seconds), 1ms duration and 2-5mA amplitude, repeated every 5 minutes and monitored over 12-72 hours.

Analysis: Data was pre-processed using ANT Neuro ASA, using stimulation artifacts on adjacent channels to trigger the extraction of a 4 second window (2 seconds before and 2 after each stimulus). Pairs of stimulation responses were averaged. Further analysisfiltered (50Hz) and removed stimulation artefacts (using a polynomial fitting, Matlab v8.4). Channels with a clear visual response to SPES were selected for analysis The amplitudes of early (onset <100ms post stimuli) and delayed responses (>1000ms) were extracted and subsequently used as features for seizure prediction

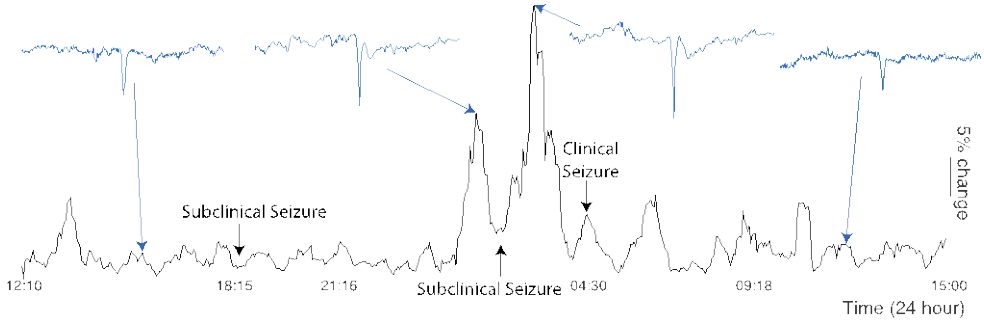

Figure ***3***.

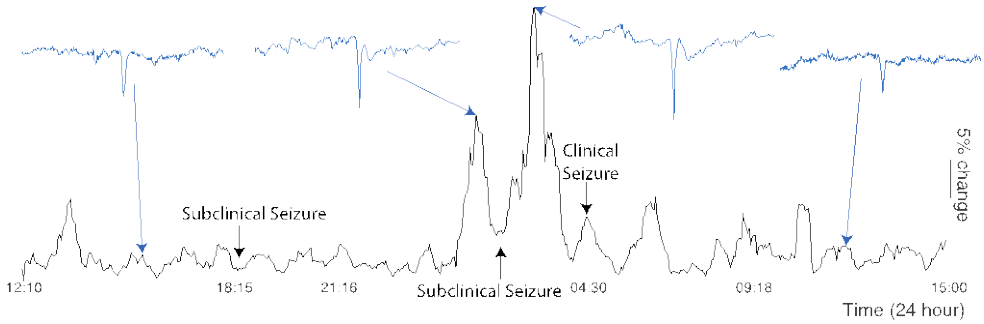

Figure 3 – Amplitude of normal (early) response to SPES on single channel over a period of approximately 27 hours. Subclinical and clinical seizures are indicated, and examples of SPES responses over this period.

Results: 14 patients had seizures, 8 had none. Due to the limited data for each patient, 20% of patient data with seizures (3 patients) was used for training of the seizure occurrence period and prediction horizon [2]. Using these features from each patient, and the statistical framework outlined in [2], all possible combinations (364) were tested and compared to a chance predictor using sensitivity and false prediction rate (FPR, per hour). Clinical seizures showed a 43.2% sensitivity and FPR 0.05, while subclinical seizures showed a sensitivity of 26.6% with a FPR 0.035. All clinical seizures exceeded the upper critical sensitivity of a random predictor, while only 50% of subclinical cases exceeded this critical value. Interestingly, for

all 364 combinations, nonseizure patients showed a FPR of 0 in 90% of cases, with those exceeding 0.05 being the result of poor artifact removal.

Conclusion: We show in these initial trials that continuous SPES identifies response changes in cortical tissue that shows significant seizure prediction of seizure onset against that of a random predictor.

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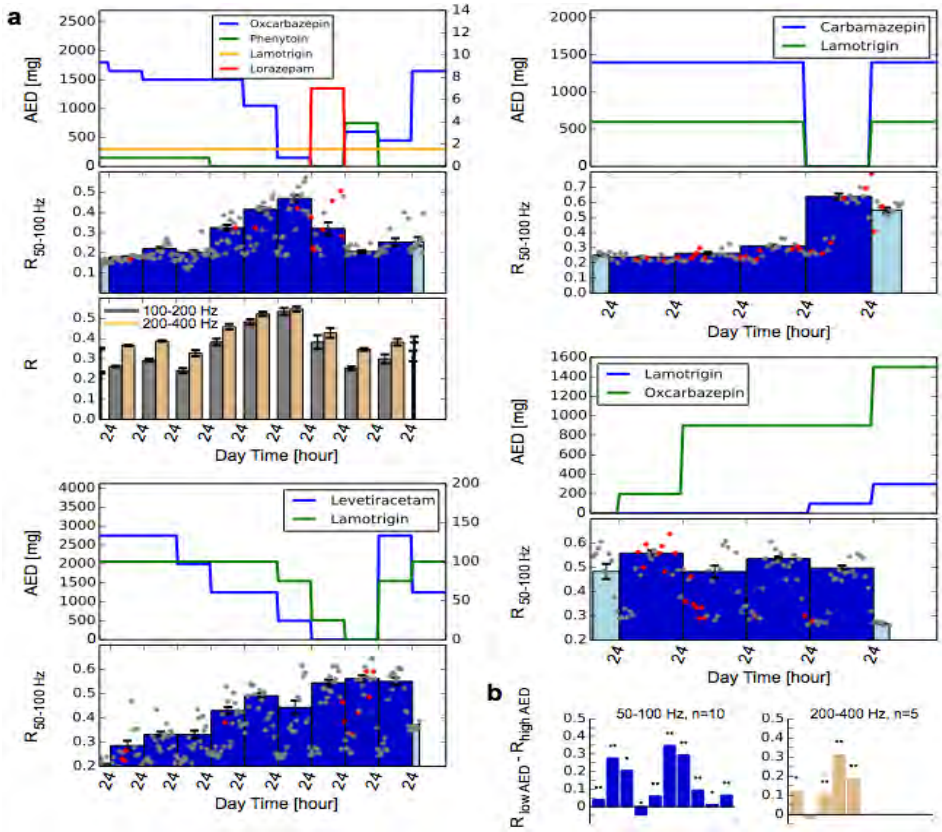
16. INTRINSIC EXCITABILITY MEASURES TRACK ANTI-EPILEPTIC DRUG ACTION AND UNCOVER INCREASING/DECREASING EXCITABILITY OVER THE WAKE/SLEEP CYCLE

Christian Meisel[1#], Andreas Schulze-Bonhage[2], Dean Freestone[3], Mark Cook[3], and Dietmar Plenz[1]
[1]National Institutes of Health, Bethesda, Maryland, USA
[2]Department of Neurology, University of Freiburg, Freiburg, Germany
[3]University of Melbourne, Melbourne, Australia
#christian@meisel.de

Dynamic changes of excitability are relevant in both healthy and pathological cortical network dynamics. This is particularly highlighted by the pathological changes in excitability of cortical tissue commonly underlying the initiation and spread of seizure activity in patients suffering from epilepsy. Accordingly, controlling excitability using anti-epileptic drugs (AED) and monitoring their effect on network excitability is of prime importance for adequate clinical care and treatment. To date, adequate measures of excitability and action of AED have been difficult to identify. Recent insights into normal ongoing activity in humans, non-human primates and cortical in vitro preparations have identified the entropy and global level of phase synchronization which characterize normal levels of excitability and quantify any deviation therefrom. Here, we explore the usefulness of these measures to quantify cortical excitability in humans using ongoing multi-day intracranial EEG recordings. We first report a high correlation of these intrinsic excitability measures (IEM) to direct cortical excitability measurements using electrical stimulation. Second, we observe a significant covariation of IEM with the level of AED and a characteristic 24-h time course which increases during the day and returns to baseline at night. Our results indicate that excitability in epileptic networks is effectively reduced by AED and suggest the proposed markers as useful candidates to quantify excitability in routine clinical conditions without the need of electrical or magnetic stimulation. The intradian time course of these metrics provides unprecedented evidence in humans for a homeostatic role of sleep: to rebalance cortical excitability.



17. A SUB-SCALP SEIZURE MONITORING IMPLANT FOR EPILEPSY PATIENT MANAGEMENT

Alan Lai[1,2#], Chris Williams[3], Owen Burns[3], Yuri Benovitski[3], Rodney Millard[3], Matthias Le Chevoir[4], David B. Grayden[1,2], Wendyl D'Souza[1,2], Michael Murphy[1,2], Mark J Cook[1,2].

[1]Department of Electrical and Electronic Engineering, The University of Melbourne
[2]Department of Neurosciences, St. Vincent's Hospital Melbourne
[3]Bionics Institute, East Melbourne
[4]Faculty of Veterinary Science, The University of Melbourne
#alan.lai@unimelb.edu.au

Current clinical practice in anti-epileptic therapy optimization is based on seizure diaries kept by patients. However, it has been shown that patient seizure reporting is not reliable (Cook et al., 2013, Hoppe et al., 2007). Thus, there is a need for a clinical tool to count seizures accurately in order to provide a robust, quantitative method to assess and optimize anti-epileptic therapy for epilepsy patients (Fisher et al., 2012).

We are developing a sub-scalp EEG recording implant to accurately and continuously count seizure over a long term (months and more). This device will be invaluable for trials of new epilepsy treatments, which are also typically based on patient-reported events as the primary efficacy endpoint. Furthermore, this device has the potential to revolutionise epilepsy patient management in terms of diagnosis and prognosis, when seizures can be continuously monitored. An animal study is currently being conducted to assess different electrode designs in terms of EEG signal quality versus ease of implantation. A sample of the EEG recordings from the different types of electrodes is shown in Figure 1.

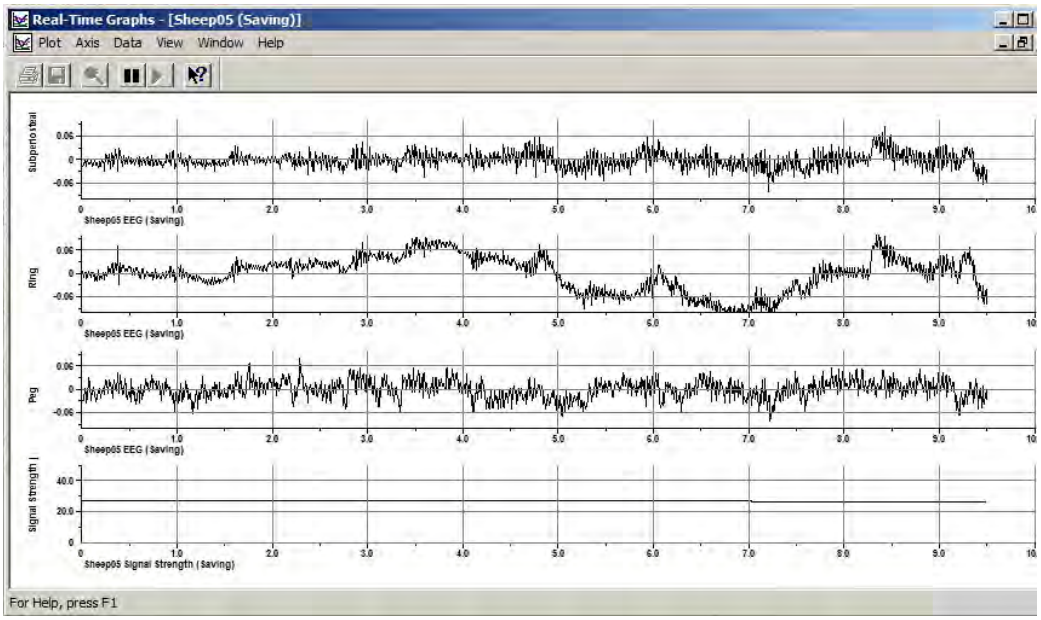


Figure 1: A sample of the EEG recordings from three different electrode designs.

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18. DESIGNING PATIENT-SPECIFIC OPTIMAL NEUROSTIMULATION PATTERNS FOR SEIZURES FROM HUMAN SINGLE UNIT HIPPOCAMPAL DATA

Roman A. Sander[1#], Dong Song[1], Theodore Berger[1], Sam A. Deadwyler[2],
Robert E. Hampson[2], and Vasilis Marmarelis[1]
[1]Dept. of Biomedical Engineering, University of Southern California, Los Angeles, CA, USA
[2]Dept. of Physiology & Pharmacology, Wake Forest University, Winston-Salem, NC, USA
#rsandler00@gmail.com

Responsive Deep Brain Stimulation (DBS) is a promising alternative to traditional treatments for epilepsy such as respective surgery and antiepileptic medication. However, an open issue with DBS is identifying the optimal temporal patterns of stimulation to abate seizures. Identification of these patterns is made difficult by the lack of a controllable experimental framework by which to test them. Namely, the experimenter is unable to obtain consistent seizures 'on demand', he can only apply a single pattern of stimulation to each seizure, and he is unable to know how the seizure would have evolved had no stimulation been applied. Furthermore, these issues become significantly magnified when dealing with humans.

To overcome these issues, we have developed a data-derived in-silico hippocampal network to function as a testbed for designing optimal DBS spatiotemporal patterns. Each network (Fig.1a) is obtained by estimating the causal and dynamic (effective) connectivity between neurons recorded from the CA3 region of human hippocampus. Causal connectivity was estimated using granger-causality like stepwise input selection and interneuronal dynamics were modeled by a nonlinear Volterra model estimated using the generalized linear modeling (GLM) framework [1].

Once the dynamical network was estimated, spontaneous seizure activity was induced in the network by raising the baseline potential, as is done in-vitro using low-Mg^{2+}/high-K^{+} perfusion. It was found that the network was capable of entering into two distinct seizure states. By beginning each simulation in the seizure state, we were able to obtain a controllable experimental setup by which to test applied stimulation patterns. Finally, using simulated annealing, an efficient global estimation algorithm, we were able to identify which neurons to stimulate how to stimulate them. Our optimized spatiotemporal DBS pattern was able to significantly reduce the length and intensity of seizures. Notably, this result was not achieved by simple periodic stimulation of the entire network, no matter the frequency of stimulation. In future work, we hope to verify our obtained DBS pattern by testing it on the rodent from which the network was estimated from, an impossibility with many other computational studies of DBS.

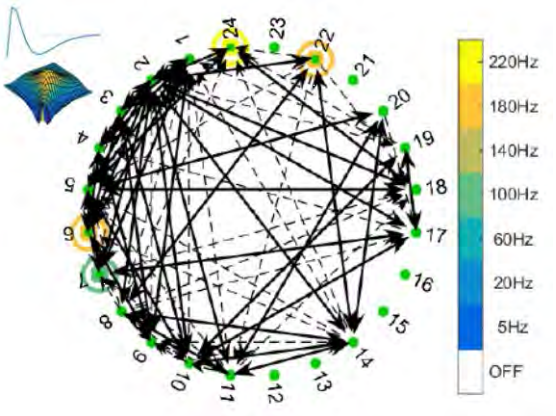

Figure 1: Estimated hippocampal network from 24 recorded human neurons. All arrows indicate causal nonlinear dynamic relationships between neurons, as encapsulated by sample Volterra model shown on top left. Circled electrodes indicate which neurons the algorithm has identified need to be stimulated, and their colour indicates the frequency of stimulation, as described by colorbar on right.

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19. Evaluating Subspace Angles of EEG Signals for the Detection of Epileptic Seizures

Wanzhi Qiu[1#], Callum Hollis[2], Terence O'Brien[2], Christos Pantelis[3], Patrick Kwan[2], and Efstratios Skafidas [1]

[1]Centre for Neural Engineering and Department of Electrical and Electronics Engineering, The University of Melbourne, 203 Bouverie Street, Carlton, Victoria 3053, Australia

[2]Royal Melbourne Hospital, 300 Grattan Street, Parkville VIC 3050

[3]Department of Psychiatry, The University of Melbourne, 161 Barry Street, Victoria 3053, Australia

#qiuw@unimelb.edu.au

Automated epilepsy detection devices based on EEG have the potential to enable novel therapeutic and alerting systems that reduce the harm of epileptic seizures. Due to lack of accuracy and reliability, automated seizure detection, in the form of either onset or event detection, has not been widely accepted in clinical practices. Seizure onset detection is a more challenging task in that it identifies the beginning of abnormal brain electrical activities before they become sustainably pronounced.

Seizure detection techniques based on morphological waveform analysis do not take full account of the spatial nature of multichannel EEG data and suffer from low signal-to-noise ratios. Algorithms utilizing time-frequency features rely on sustained rhythmic activities of the signals that only develop at later episodes of seizures. Artificial neural network approaches require extensive training using patient data and, therefore, their successful implementation is limited by the variability of EEG signals between and within subjects.

Although eigenvalues have been employed in EEG signal analysis, subspaces spanned by EEG signals remain largely unexplored. Since eigenvectors and eigenvalues measure the directions and magnitudes, respectively, of data correlations, variations in the data inevitably lead to changes in the subspace spanned by eigenvectors as well as eigenvalues. In this work we first investigate statistical properties of those subspaces associated with various states of brain electrical activities including dimensionality, robustness to noise and relative positions. We show, as demonstrated in Fig. 1, that subspace differences between normal, pre-ictal and ictal signals are significantly different. Those differences are measured by principal angles [1] that describe canonical correlations of subspaces. We then propose an automated epilepsy onset detection scheme that is based on monitoring both the subspaces and eigenvalues of data covariance matrices of EEG signals. The proposed scheme is training-free, processes the multichannel time series simultaneously, and establishes decision rules solely according to the characteristics of measured signals.

In addition, since epilepsy patients often experience seizures on only one side of the brain, our proposed scheme is augmented with a procedure that detects imbalance between the left- and right-side signals. Real patient data are used to demonstrate the performance of the proposed method, and computational cost utilizing subspace tracking techniques for real-time implementation is addressed in our study.

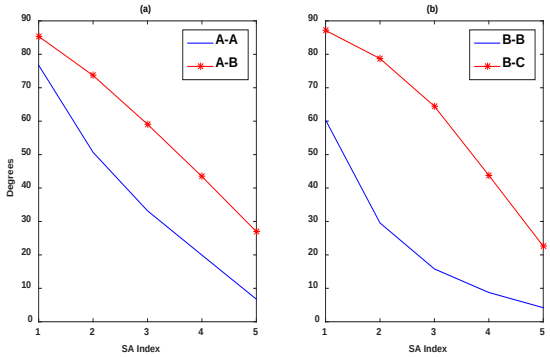

Fig. 1 Averaged subspace angles (SA) of real patient EEG data. a) SA between normal states (A-A), and normal and pre-ictal states (A-B). b) SA between pre-ictal states (B-B), and pre-ictal and ictal states (B-C).

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20. PERFORMANCE OF SYNCHRONY AND SPECTRAL-BASED FEATURES IN EARLY SEIZURE DETECTION: EXPLORING FEATURE COMBINATIONS AND EFFECT OF LATENCY

Vincent Adam[1#], Joana Soldado-Magraner[1], Wittawat Jitkrittum[1], Heiko Strathmann[1] , Balaji Lakshminarayanan[1], Alessandro Davide Ialongo[1], Gergő Bohner[1], Ben Dongsung Huh[1], Lea Goetz[2], Shaun Dowling[3], Iulian Vlad Serban[3], Matthieu Louis[3]

[1]The Gatsby Computational Neuroscience Unit, UCL, London, UK

[2]Wolfson Institute for Biomedical Research, UCL, London, UK

[3]The Centre for Computational Statistics and Machine Learning (CSML) , UCL, London, UK

#vincenta@gatsby.ucl.ac.uk

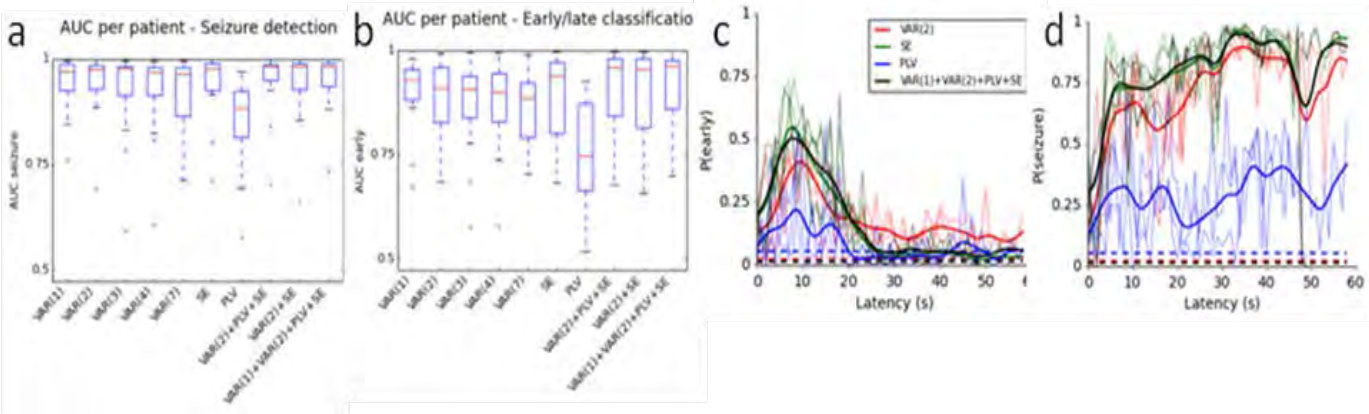
Motivation: Accurate early seizure detection is key to building effective devices to treat epilepsy. Availability of large scale iEEG datasets and recent advances in machine learning techniques make it possible to design efficient algorithms for this purpose. The success of detecting seizures from recorded iEEG signals relies heavily on extracting discriminative features in the data which characterize different brain states. In this study, we combine a small set of features based on neural synchrony, including fitted parameters of multivariate autoregressive (VAR) models and pairwise phase-locking-values (PLV), and single channel features based on spectral energy (SE). We pair these features with the state-of-the-art random forest classifier to yield an algorithm which is able to accurately identify ictal iEEG data segments and detect early periods of the seizures (latency from seizure onset<15s). Our algorithm relies on neither patient-specific features nor information about the localization of the electrodes.

Task: Multi-channel iEEG data from human patients and dogs with epilepsy was provided by the UPenn-Mayo Clinic Seizure Detection Challenge, hosted on kaggle.com, which was sponsored by the American Epilepsy Society. We evaluate our classifiers using the Area Under the

ROC Curve (AUC) as the metric. Here we provide a summary of our method and share our code [1], developed for this competition. In addition, we analyse the importance of the different features for classification performance. Finally, we compare the estimated probabilities of seizure and early seizure against latency to characterize how accuracy changes as the seizure progresses.

Results: We observe that features extracted with VAR models beyond 2nd order do not improve classification performance (*fig1.a,b*). A combination of SE+VAR+PLV achieves the best results in both tasks. Using this method, we ranked among the top 10 in the kaggle seizure detection competition [2].

iEEG data segments are more confidently classified as ictal as seizure progresses (*fig c*. human patient example - shallow lines: seizure prediction for individual ictal epochs, thick lines: mean seizure prediction. Dashed lines: mean seizure prediction for interictal segments). PLV features perform poorly regardless of latency. Low confidence predictions in the first 10 seconds reveal the increasing difficulty of the detection task for segments closest to seizure onset. As expected (*fig d.*), classifier has lower confidence in telling apart early vs late for earliest segments and close to early/late boundary at 15s.



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Kaggle Seizure detection challenge, https://www.kaggle.com/c/seizure-detection

21. Detection of Epileptic Seizure Using Support Vector Machine and Linear Discriminant Classifiers

Muhammad Khizar Abbas[1#], Syed Sajjad Haider Zaidi[1], Muhammad Liaquat Raza[2], Uwe Heinemann[2]
[1]PN Engineering College (Karachi) - National University of Sciences and Technology (NUST) - Islamabad, Pakistan
[2]Inst. of Neurophysiology Charite - Universitätmedizin Berlin, Germany
[#]khizar@pnec.nust.edu.pk

Epilepsy is a neurological disorder affecting 50 million people worldwide (WHO fact sheet165). In Pakistan, over 1.38 million people suffer from epilepsy (Khatria et.al.2003). As epileptic seizures occur unwarned, automatic seizure prediction and detection is becoming an increasing area of research and investigation.

In the presented study, we focused on sK-channel agonists to test them in acute rat slices after inducing 4-aminopyridine (4-AP) generated SLEs and analyse the obtained data in offline mode to develop an algorithm for seizure prediction and detection. Slices were prepared from young adult rats of 400 μM thickness and transferred into inter phase chamber. Further 4-AP, 100 μM is used to induce epileptic form activities in slices. Local field potentials were recorded using microelectrode from medial entorhinal cortex.

Segmentation of epileptic events was performed on the data after subtraction of noise from original trace. Distinct patterns were observed before seizure onset and after drug induction. Before the seizure onset multiple ripples were produced which led towards a dc shift. On the basis of feature vector, seizure classifiers were designed and algorithms were developed. Classification efficiency of two different pattern recognition classifiers, namely support vector machine (SVM) classifier and linear discriminant (LDC) classifier, was compared. In case of SVM, input feature vector was mapped in high dimensional space for realization of linear classification system. The output of SVM consisted of two discrete options: epileptic seizure and normal brain activity. The same feature vector was also used for classification by LDC. However, as the sample size was not adequate performance of SVM was much better.

Results suggest that pattern recognition techniques can be employed to predict seizure beforehand. It was observed that Electrophysiological data is a good litmus to develop representative vectors which provides easier and refined method to detect epileptic seizure. The designed algorithm can be ported on a suitable embedded device to develop standalone system for prediction. For this purpose Field Programmable Gate Array (FPGA), Programmable System on Chip (PSoC) or suitable Digital Signal Processing (DSP) can be being considered.

22. SEIZURE PREDICTION IN EPILEPSY: LEVEL CROSSING ANALYSIS

V. Senger, R. Tetzlaff – Chair for fundamentals of Electrical Engineering, Faculty of Electrical Engineering and Computer Science, Technische Universität Dresden, Dresden, Germany.
Email: vanessa.senger@tu-dresden.de

Introduction

A huge variety of multivariate seizure prediction features has been proposed in the past. Even though recently a first clinical study of a seizure warning device showed high acceptance in patients, the lack of computation efficient seizure prediction algorithms showing a sensitivity and specificity suitable to clinical applications has, up to now, hindered the realization of a seizure warning device. In this contribution, the analysis of two new methods based on a signal prediction approach will be presented.

Methods

Firstly, a Principal Component Analysis (PCA) is applied in the first algorithm to multichannel recordings of several patients. Components are chosen based on two strategies: components for which a low prediction error during seizure free intervals is observed are considered. Additionally, components associated with small eigenvalues are analyzed as possible seizure prediction features. Afterwards, a Cellular Nonlinear Network (CNN) – based nonlinear signal prediction algorithm is performed for different polynomial orders of the coupling weights and the prediction error is evaluated as a seizure prediction feature.
The second algorithm is based on a multivariate signal prediction as well. Following a prediction by taking into account three electrodes of a certain brain region, a level-crossing behavior analysis of the prediction error is carried out by adjusting the error level assumed in an automated iterative procedure. In the next step, the average level-crossing interval will be analyzed in order to uncover possible changes before the onset of an epileptic seizure

Results

We observe a similar performance for both algorithms; however, patients for which a significant seizure prediction was obtained are different for both methods. In this contribution, the seizure prediction performance of both methods will be discussed in detail for 20 patients suffering from focal epilepsy.

Conclusion

We propose two seizure prediction algorithms based on nonlinear signal prediction: A PCA-based signal pre-processing, and a post-processing method based on a level-crossing behaviour analysis. Siginficantly improved results as compared to those of previous investigations are obtained for different patients. Therefore, the joint application of the proposed two methods could be beneficial in a seizure warning approach. Future work will focus on the implementation of these algorithms on dedicated FPGA hardware, as well as on further improving sensitivity and specificity of the suggested algorithms.

23. A WIRELESS SYSTEM FOR MONITORING EPILEPSY IN HYDROCEHALUS PATIENTS

Anand Narayanaswamy[1], Diana Cogan[1], Mehrdad Nourani[1], Lakshman Tamil[1] and Sabatino Bianco[2]

[1] Quality of Life Technology Laboratory, The University of Texas at Dallas, Richardson, TX 75080
[2] Arlington Memorial Hospital, Arlington, TX 76012
[1]{asn107020, diana.cogan, nourani, tamil}@utdallas.edu, [2]sbianco@biancosurgery.com

Motivation: Hydrocephalus is a neurological disorder caused by excessive accumulation of cerebrospinal fluid (CSF), resulting in increased pressure in the brain. Hydrocephalus is usually treated by surgically inserting a shunt system [1] which diverts excess CSF from the brain to another area of the body such as the abdominal cavity. Several authors have reported a higher incidence of epileptic seizures following shunt placement, although the cause of the increased risk is uncertain [2]. Many factors, such as shunt malfunction, infection, the presence of the shunt (a foreign body), and the burr hole location - not hydrocephalus itself - are thought to cause seizures. A higher occurrence of epilepsy was seen in children who had a shunt malfunction, infection or increased intracranial pressure (ICP).

Monitoring System & Prototype: A prototype system we built to detect shunt malfunction using four flow-through pressure sensors (S1, S2, S3, and S4) is shown in Fig. 1. It can be employed to effectively monitor some of the potential causes of seizures. The prototype is a platform for interfacing with multiple sensors placed inside the shunt catheter. The sensor data is wirelessly transmitted to a reader outside the body. Based on experimental results from the prototype system, we can detect the location of clogs in the catheter, thereby reducing complications in shunt revision surgery and the corresponding risk of seizure. The system can determine the location of a clog to be in the i) proximal catheter, ii) distal catheter or iii) valve with 100% accuracy when the patient is in standing posture. The flow rate measured by the system is 90% accurate compared to the ground truth flow measured by a Thomas Scientific 3500 Traceable ultra-low flow meter. Sensor S1 in Fig. 1 measures ICP; monitoring ICP continuously will provide insight into the role of ICP in seizures. It will also assist in optimizing the drain rate of CSF which will help maintain ICP at a normal level and potentially reduce the risk of seizure. A glucose sensor can be easily interfaced to our existing prototype to provide information on the presence of shunt infection. Shunt infection causes increased glucose and white blood cell levels in the CSF [3], and is suspected of causing seizures. This sensor will prevent the necessity of performing a lumbar puncture to obtain a CSF profile - the normal procedure for determining the presence of infection in patients with recurring seizures [3].

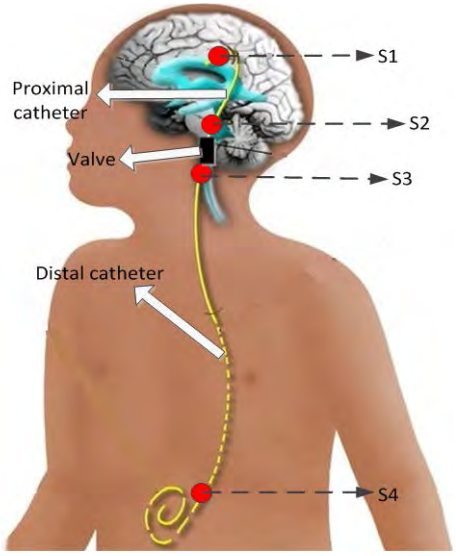

Figure 4. Proposed monitoring system for shunts

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24. PATIENT-AWARE EPILEPTIC SEIZURE PREDICTION IN THE CONTEXT OF M-HEALTH SYSTEMS

Zaher Dawy[1], Ahmad El-Hajj[1], Mohammad Hussein Nasralla[1], Nabil Abbas[2], Jamil El-Imad[2]
American University of Beirut (AUB), Beirut, Lebanon
NeuroPro AG, Zurich, Switzerland
Corresponding author: zd03@aub.edu.lb

The development of devices with multi-sensing capabilities and high computational power is advancing mobile health (m-health) systems [1]. M-health is defined as the use of information and communications technologies, including wearable and diagnostic devices, for medical health applications including monitoring neurological disorders. Epileptic seizure prediction has recently constituted an active area of research, driven by the availability of public EEG databases and advances in big data analytics. Common seizure prediction techniques rely on feature extraction of key EEG characteristics combined with machine learning models that provide prediction decisions with certain accuracy. It has been recently recommended to develop new techniques that can more explicitly utilize available knowledge about brain dynamics to further enhance accuracy [2].

In this work, we present a comprehensive seizure prediction framework for epilepsy prediction in the context of m-health systems, that captures the real-time and reduced complexity requirements of m-health systems and the accuracy requirements of seizure prediction algorithms. The proposed framework processes collected EEG signals in quasi-real time utilizing a sliding window approach; its differentiating characteristics include patient and vigilance awareness combined with multi-dimensional spatio-temporal feature extraction. Patient-awareness is achieved by utilizing patient-specific clinical data to tune the prediction algorithm, such as seizure type and foci, patient history, available recorded EEG data in normal and seizure states, etc. Vigilance-awareness is achieved by utilizing the person's physiological state (awake, moving, sleeping stage, etc.) during data recording in order to model possible artefacts that impact accuracy. Our algorithm employs time-based (N-grams [3]) and frequency-based (wavelet statistics) feature extraction, combined with spatio-temporal correlation among the measured channels across space (different locations on the scalp) and time (different intervals). The extracted features and available patient information are then combined in a machine learning-based prediction model to identify as many seizure markers as possible. For a given patient, vigilance state, and EEG segment, the derived model is used to predict seizures and warn users in real time. Preliminary results with support vector machine learning led to sensitivity of 82% and specificity of 71% using patient data from the Freiburg database. In terms of processing, it is divided between the user's smartphone/tablet (interface to the EEG headset) and remote cloud server architecture. In terms of performance analysis, we are also focusing on practical aspects that are of central importance to m-health systems, such as the number/location of electrodes in the EEG headset and time window size for prediction before seizure onset.

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25. EARLY DETECTION OF EPILEPTIC SEIZURES

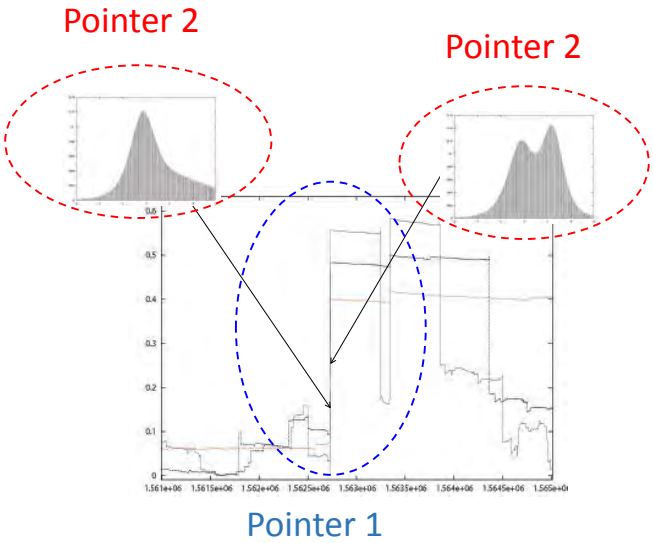
, Hilda A. Cerdeira[1,2#], Paula Gómez[2]
[1] Instituto de Física Teórica, UNESP, São Paulo, Brazil
[2] Epistemic, www.epistemic.com.br, São Paulo, Brazil
hilda.cerdeira@epistemic.com.br

Early detection allows people with epilepsy to lead a more normal life. Here we present a device with a non-invasive method for early detection of epileptic seizures. The method and the corresponding algorithm were tested on information collected from electroencephalograms from epileptic patients, some with seizures and some without. It had more than 85% of predictability assertiveness. Results showed detection up to 50 minutes before the occurrence of the seizure. This method, used in a portable device, can improve the quality of life of people with epilepsy, opening doors for a more autonomous life without serious consequences and also counting with the security of a faster help BEFORE a seizure happens. In addition to alerting the user, the planned device sends an SOS message to an application that can be installed in the smartphone of the user's caregiver. In the case of a child, this person could be a parent.

The device is composed of a pair of electrodes connected to a processor and a wearable. The electrodes, small and subtle, will detect and send an electroencephalogram signal to the processor, which contains the software that runs constantly. In case of a detected anomaly, it sends a warning to the patient's wearable (it could be a bracelet) and to the phone, which in turn sends a warning to someone else´s cell phone.

The project consists in an algorithm able to detect anomalies in an electroencephalogram; this can be used to show the appearance of a signal, which suggests to be a precursor of a seizure. Studying many encephalograms of patients with epilepsy prior to a seizure with our method, we found consistent and sturdy signs which we can use to alert the patient that a seizure may happen in a short time.

In the figure, we see how two variables or pointers of our algorithm vary in time some minutes before a seizure occurred. Pointer 1 presents a strong jump, while pointer 2 has a strong variation in shape (one to two maximums). We noticed that there are significant changes in both figures which can be used to generate an alert.



These pointers, after complete analysis, can be used to send an alert to the patient. Analyzing many seizures and their corresponding precursors, we obtain a distribution of the latter as a function of time with a strong peak at 23-25 minutes before the seizure. That is, most seizure alerts happen between 23 and 25 minutes in advance.

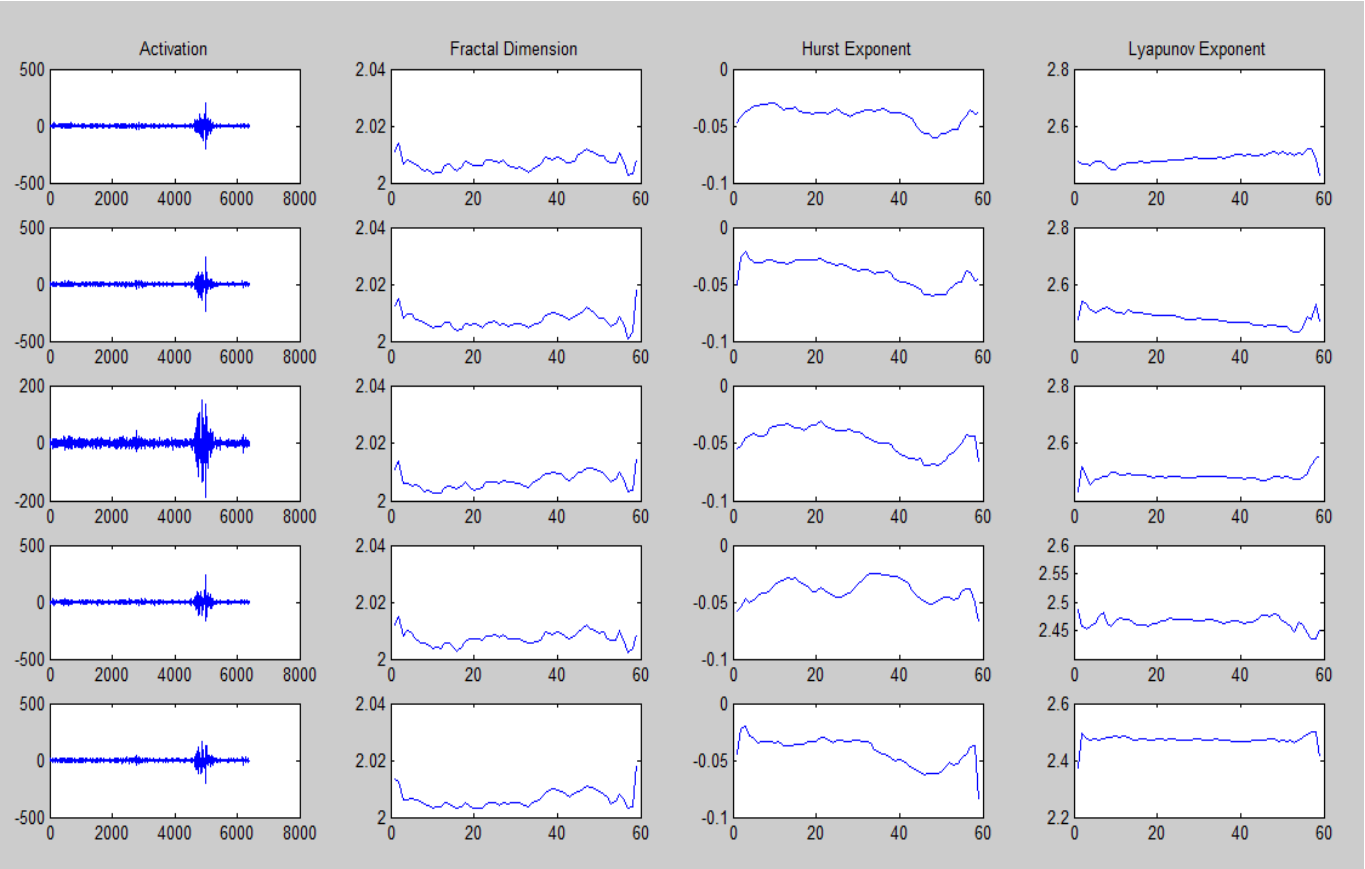
26. EPILEPTIC SEIZURE PREDICTION: NONLINEAR DYNAMIC FEATURES AND MACHINE LEARNING TECHNIQUES

Arya Rajendran[1#], Nair G.J[2#]
[1,2]Amrita Vishwa Vidyapeetham (University), Kollam, India 690525
[1#]aryarajendran1990@gmail.com, [2#]gjnair@am.amrita.edu

Recent research suggests that electrophysiological changes develop minutes to hours before the actual epileptic seizure onset. In this study, we use machine learning techniques and new approaches for features extraction of pre-ictal and inter-ictal regions of EEG to predict onset of seizures with a lead time of ten to sixty seconds. EEG signals used for analysis are taken from open source database http://www.physionet.org/pn6/chbmit/ of Children's Hospital Boston. Along with the EEG recordings, the database provides information about records with seizures, number of seizures per subject, seizure start time and end time. The key step involved is modeling the EEG time series as a nonlinear dynamic problem and to develop an algorithm for identifying the deterministic features, forward modeling of the extracted features, identifying statistical features and then classify the extracted feature using machine learning methods. Supervised learning is used to train known cases and is then used to predict new cases. Independent component analysis (ICA) followed by reduction of dimension is used to generate source time series from which statistical feature sets such as Fractional fractal dimension, Hurst exponent and Lyapunov exponents are estimated. Time series obtained from each of the three statistical measures are divided into five non-overlapping windows and mean, standard deviation and total energy on each of the windows are calculated. A total of 45 features are found and the processed data are classified into preictal and interictal regions using Support Vector Machine (SVM) with radial basis function kernels.

We have tested the set of nonlinear dynamic measures on different segments and analyzed its performance. A total of 50 preictals and 50 interictals from EEG data of ten patients are taken for analysis. From each segment five significant source time series obtained are used to find the statistical measures. A plot of ICA activation and time series of the statistical measures are given in Figure1. It is found that the statistical features of preictal regions show significant changes in their values before the actual occurrence of seizure, where as interictal regions does not show any such indication. The statistical measures in preictal region indicates sudden elevation of their values prior to seizure onset. A comparative study is done for evaluating specificity and sensitivity. Seventy five percentage of the data was taken for training and remaining data was used for testing. The analysis and results indicate 69% of Specificity and 60% of sensitivity ratios.

Figure1: The energy of ICA activation time plots of patient Chb23_06, along with its time series of fractional Fractal dimension, Hurst exponent and Lyapunov exponents are given below. Activation obtained for 5 components of preictal region of the patient shows a higher energy variation around 50 seconds. In component 5, the fractional fractal dimension is increasing, whereas Hurst and Lyapunov exponents are decreasing. Frames ranging from 10 to 40 seconds can be used for the prediction purpose.



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27. SEIZURE PREDICTION USING POLYNOMIAL SUPPORT VECTOR MACHINE CLASSIFICATION

Zisheng Zhang and Keshab K. Parhi
University of Minnesota, Minnesota, MN 55455
{zhan1116, parhi}@umn.edu

Objectives

Seizure prediction based on continuous electroencephalogram (EEG) recordings is important for improving the lives of epileptic patients. A device that can predict seizures can be used in a closed-loop therapy system to deliver an anti-epileptic drug or stimulate the brain as needed. We proposed an implantable seizure prediction system that reliably predicts seizures with low hardware complexity and low power consumption.

Methods

Intracranial EEG (iEEG) dataset from the recent American Epilepsy Society Seizure Prediction Challenge are analyzed. Fragmented long-term intracranial EEG recordings sampled from 16 electrodes at 400 Hz were recorded from five dogs with naturally occurring epilepsy. In addition, iEEG recordings from patients undergoing presurgical evaluation sampled at 5000 Hz from varying numbers of electrodes are also analyzed. First, spectral features including *relative* spectral powers in specific bands and all possible *ratios* of the spectral powers between them are extracted from each electrode. Then the feature set is subjected to an electrode and feature selection step by *classification and regression tree* (CART). The selected features are then subjected to training and classification using *polynomial* support vector machine (SVM) with degree of 2 and 4. A sigmoid function is used to convert the decision variables from the output of the classifier to pre-seizure probability. Ten percent of the training data are selected randomly for feature selection and training the classifier. The remaining data are used for testing.

Results

Three sets of results are compared. The baseline results are obtained using all features from selected electrodes and uses RBF-SVM as the classifier. The proposed method further selects a small number of the features from selected electrodes according to their importance and uses polynomial SVM (p-SVM) with degree $p = 2$ or $p = 4$ as the classifier. Linear classifiers are not used as these features are not linearly separable. The baseline achieves a sensitivity of 100% and an average AUC of 0.9985. The proposed algorithm achieves a sensitivity of 100% and an average AUC of 0.9795 with degree of 2 and 0.9840 with degree of 4.

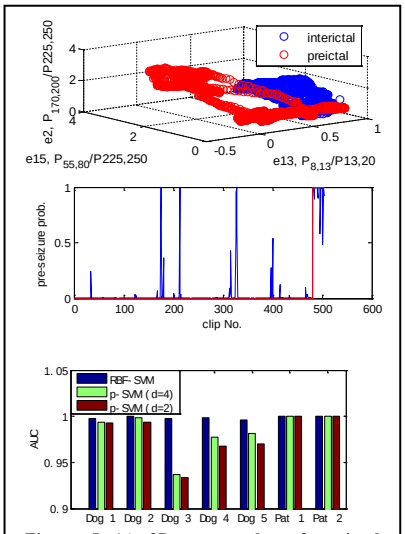

Figure 5 (a) 3D-scatter plot of preictal feature vectors and interictal feature vectors for Patient No. 1 (b) pre-seizure probability of Dog 1 (c) AUC for each subject using different classifiers.

Conclusion

In this paper, a patient-specific algorithm for seizure prediction using few features from 3-5 channels has been proposed. The baseline experiment achieves a 100% sensitivity and an average AUC of 0.9985. The proposed algorithm achieves a 100% sensitivity and an average AUC of 0.9795 with degree of 2 and 0.9840 with degree of 4. Therefore, combining the PSD features such as relative spectral powers and spectral power ratios and then carefully selecting a small number of these features from a few electrodes can achieve a good prediction performance. The proposed method also has the advantage of low hardware complexity and low power consumption.

28. AUTOMATED DETECTION OF EPILEPTIFORM SIGNATURES IN ELECTROENCEPHALOGRAPHY

Piyush Swami[1,2#], Sneh Anand[1,2], Bijaya K. Panigrahi[3]
[1]Centre for Biomedical Engineering, Indian Institute of Technology Delhi, INDIA
[2]Biomedical Engineering Unit, All India Institute of Medical Sciences, New Delhi, INDIA
[3]Department of Electrical Engineering, Indian Institute of Technology Delhi, INDIA
#piyushswami@cbme.iitd.ac.in

Identifying seizures patterns in electroencephalogram signals by visual inspection is often very perplexing and tedious even for any experienced neurophysiologist. This problem has motivated development of many expert systems which could automate the seizure detection process. However, most of the currently available expert models suffer from computational complexity and high false alarm rates which vastly limit their applications in actual clinical scenario. Extending our previous research, this study presents a de novo expert model using empirical mode decomposition. The resultant intrinsic mode functions were used to evaluate standard deviation features. This was followed by Bayesian optimization based probabilistic neural network classifier. Here, we tested the expert model designed using rotation estimation technique with ten folds. Finally, accuracy and statistical performance of the expert model were evaluated. Also, computation timings for executing each fold set were noted. The model presented in this work achieved > 98 % accuracy with coherent statistical performances in < 0.03 seconds of time elapses. These results were validated with online data as well as, data collected from the hospital. The expert model designed from this study minimizes human errors and thus, assist neuro-clinicians or neurophysiologists to efficiently diagnose epilepsy. The proposed scheme will be of at-most help in developing and under-developed countries where there is an acute shortage of trained neurophysiologists.

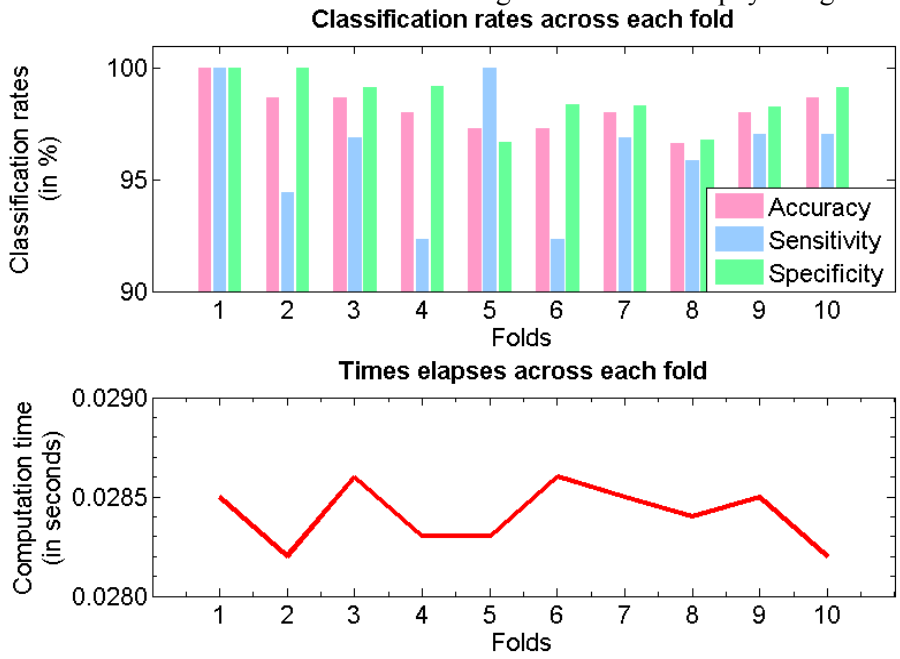

Figure 1. Classfication performance of the developed expert model.

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29. A STUDY OF EEG–EMG FEATURE CORRELATION FOR STARTLE TYPE EPILEPTIC SEIZURES

B.Pushpa [1], D.Najumnissa Jamal [2], C.Tharini [3]
[1]Assistant Professor, Electronics and Instrumentation Engineering Department, B.S.Abdur Rahman University, India
[2]Professor, Electronics and Instrumentation Engineering Department, B.S.Abdur Rahman University, India
[3]Professor, Electronics and Communication Engineering Department, B.S.Abdur Rahman University, India
pushpa_akm@bsauniv.ac.in, najumnissa.d@bsauniv.ac.in

Surveys report that about 1% of the people in the world suffer from epilepsy and about 30% of epileptics are not helped by medication. Electro-encephalography (EEG) is an inexpensive and an important clinical tool for the evaluation and treatment of neurophysiologic disorders. The study of relationship between EEG and EMG provides us with physiological information about how activities of the cerebral cortex, mainly those of the sensory-motor cortex, are related to the movement of interest, whether it is voluntary or involuntary. In case of voluntary movement, we study the EEG-EMG correlation mainly to investigate mechanisms underlying the central motor control and its disorders. Since the movement-related cortical electric activities are usually small as compared to the background EEG activity, they cannot be identified by visual inspection of the raw record, even if they might occur in close time relation to the movement.

In this work the startle type epileptic seizure signals and EMG signal is analyzed. 4 Male and 6 Female are enrolled in this study. In all cases a patient hearing a sound or sudden touch on a particular body area, will induce a jerk on the right leg which leads to subsequent tonic contraction with intact consciousness. A 24hr-Viedo-EEG and EMG is taken into account to analyze the signal. Correlation analysis is a convenient technique to find the similarity of two different signals. Four second EEG and EMG signal is analyzed. The features like Intra Quartile Range, Mean Absolute deviation, Maximum of the signal, minimum of the signal, Mean, Variance, standard deviation, entropy, skewness and kurtosis are extracted. These features are subjected to Correlation and Canonical correlation for all 24-channels of the Multi channel EEG with EMG. During the seizures the electrodes Fz, Cz, and Pz show the correlation with the EMG signal and other electrodes does not show the similarity. It was observed that the central line EEG electrodes show good response in association between EMG signals. In the central line EEG, Fz shows more variations than the Cz and Pz electrodes.

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30. EPILEPTIC SEIZURE DETECTION OF MULTICHANNEL EEG USING RELATIVE POWER FEATURES AND PARTICLE SWARM OPTIMISATION METHOD

D.Najumnissa Jamal[1], T.R.Rangaswamy[1], B.Pushpa[2], C.Tharini[3]
[1,3]Professor, [2]Assistant Professor
[1,2] Department of Electronics and Instrumentation Engineering
[3]Department of Electronics and Communication Engineering
B.S.Abdur Rahman University, Chennai, India
najumnissa.d@bsauniv.ac.in

Background: The problem of analyzing and detecting channels of high discrimination between epileptic seizure and controls in a 16 channel EEG signal is modeled as a feature selection technique that can improve classification accuracy between groups. This study is investigated which results in reduction of analysis time by expert Neurologist.

Methodology: We find relative power along with statistical features of 16 channel EEG. A variability measure is applied to choose the channel which has the maximum class of separability. MLP - BP neural network and Particle swarm optimization classifiers neural network are used to discriminate the features of epileptic seizure and control. Appropriate filters are used to remove eye blink and artifacts.

Results: MLP-BP and PSO-NN classifier exhibit excellent classification accuracy of 95%. The relative power for controls the delta and beta band give the impression to have larger values of PSD than the theta and alpha band. The PSD values of delta band appear to be lesser for delta band for epileptic seizure patients. Consistently it is observed that the maximum and minimum PSD power exists on the electrodes placed on the left hemisphere for epileptic seizure patients whereas they are spread over both hemispheres for control subjects.

Conclusion: Improvement is found in accuracy based on the proposed features. Relative power is found to be an effective feature to detect the epileptic seizure The results confirm that there is an extensive difference between the normal and seizure data. Further, it appears that the proposed method can be used for clinical diagnosis.

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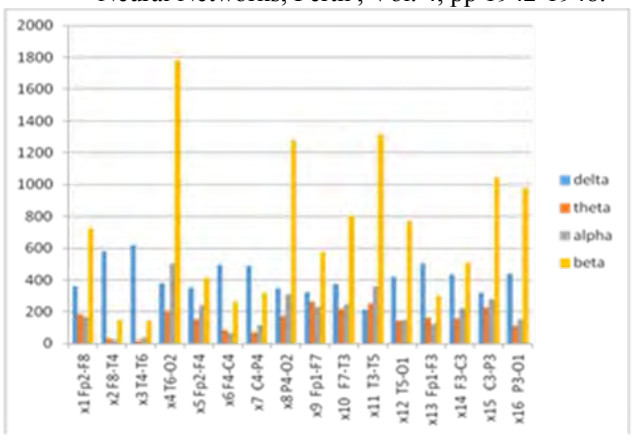
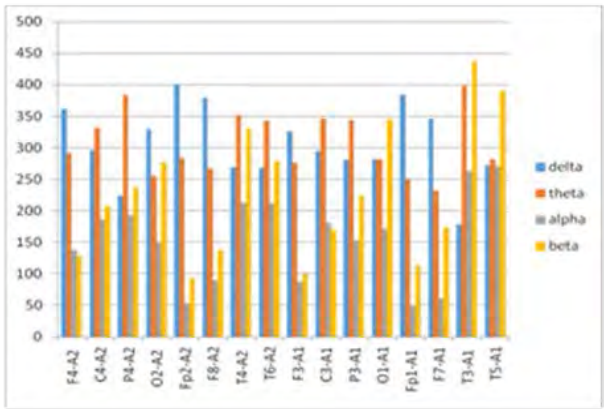


Relative Power for Control Group



Relative Power for Epileptic Seizure Group

31. EEG SIGNAL COMPRESSION USING COMPRESSIVE SENSING METHOD AND DETECTION OF ALZHEIMER'S DISEASE (AD) BASED ON RELATIVE POWER

Parnasree Chakraborty[1], Dr.Najumunissa Jamal[2], Dr.C.Tharini[3]
[1]Assistant Professor, BSA University, India
[2]Professor, BSA University, India
[3] Professor, BSA University, India

Electroencephalography (EEG) is a very useful tool for investigation of neurological disorders. Alzheimer's disease (AD) is one of the fastest growing neurological diseases in the world. Compared to normal subjects, EEG of Alzheimer's disease (AD) patients are known to have slowing effect. In slowing effect there is an increase in the relative power of the delta (0.5–4 Hz) and theta (4–8 Hz) bands of frequency, along with decrease in the power of alpha (8–13 Hz) and Beta (12-40Hz) frequency bands. In principle, EEG is a powerful and relatively cheap way for screening of AD in their early stages although not reaching the specificity prescribed for clinical use.

This paper proposes a novel technique to combine the 16 channel EEG signal and identify Alzheimer's disease using the relative power of the signal. Relative power of the signal is used as an important parameter to classify normal and abnormal patient. Result indicates that this method is a promising method to identify Alzeimer's disease at an early stage. The compressive sensing algorithm or compressed sensing algorithm is an effective compression algorithm used in many field of engineering for data compression but not widely used for bio-medical signal compression. This project proposes an extended application of compressive sensing algorithm with different basis function for real time EEG signal compression. The EEG signals are collected using EEG sensors placed at different parts of human head. Since the recorded EEG data is of high volume sometimes it is essential to compress the data for transmission of data to a remote place for clinical investigation by medical supervisor. In this project a hospital scenario is considered, where the patient's EEG data is to be periodically monitored by medical supervisor who is at a far distance from the patient. Therefore it is essential to compress the recorded EEG data by an efficient compression algorithm and to be transmitted via wireless sensor node. The compressive sensing algorithm is considered to be efficient compression algorithm and hence it is used for compression of recorded EEG signal. Compressive sensing algorithm is implemented and deployed in sensor node for compression of EEG data and the compressed data is transmitted from source node to gateway node. Reconstruction is done in Gateway and the RMSE value is calculated. Results indicate that this method provides the better RMSE value than any other existing methods. The purpose of this project is to exploit compressive sensing (CS) method in dealing with electroencephalography (EEG) signals at a high compression ratio. In order to generate sparse data which is an essential step for compressive sensing algorithm, different basis functions are used at the transmitter side and the performance of the algorithm is analyzed for different basis functions. At the receiver side, Orthogonal Matching Pursuit (OMP) algorithm is used for reconstruction of the original signals. The hardware implementation of EEG data acquisition and compressive sensing algorithm is performed and simulation of reconstruction algorithm is also performed in order to verify the effectiveness of the proposed algorithm for bio-medical application. Results indicate that the proposed algorithm is very much effective for bio-medical signal compression.

32. NON-CONTACT ELDERLY INFRARED BODY TEMPERATURE TELEMONITORING SYSTEM WITH XBEE WIRELESS PROTOCOL

Tonny Heng Yew Ling[1], Lim Jin Wong[2]
[1]Electrical and Electronic Department
University College of Technology Sarawak
[2]Electrical and Electronic Department
Laila Taib College
tonnyling@ucts.edu.my
wlimjin@yahoo.com

Real time non-contact elderly infrared body temperature telemonitoring system with XBee wireless protocol is an emerging technology in both electronics and computer world. It plays the important role in elderly health care services. Non-contact elderly infrared body temperature telemonitoring system with XBee wireless protocol help in monitoring body temperature of the elderly and base on the elderly healthcare's history provide the necessary treatment. Doctor or nurse can check the complete details of the elderly's profile from remote location and can recommend a suitable medication.

The main purpose of this technology is to provide efficient healthcare facility remotely and to monitor the elderly in their natural environment which the non-contact infrared thermometer devices are attached at their home. Real time non-contact elderly infrared body temperature telemonitoring system with XBee wireless protocol can also greatly assist in disease management to maximize health, prevent complications, and conserve healthcare resources.

Body temperature is a vital sign and it is important to measure it accurately. A healthy body maintains its temperature within a narrow range using homeostatic thermoregulation mechanisms. The normal range for core body temperature in the literature varies, although 36°C-37.5°C is acceptable in clinical practice [1]. Measuring body temperature is important in the study of human body temperature regulation in daily life [2].

Elderly may have difficulty telling when elderly are becoming overheated. Fever is an important sign of illness in elderly persons. Fever is often the only symptom for several days of an illness. Any fever that is not explained by a known illness should be checked by a health care provider. Body temperature is a vital sign and it is important to measure it accurately [1].

XBee needs to be configured by using the X-CTU program before it can be used. X-CTU is used to update or change the firmware on the radios. X-CTU can switch XBee radio from router to coordinator or switch between API and AT modes. Two XBees are needed as the wireless protocol sends the blood pressure reading obtained by Arduino Uno to the computer. In order to use those two XBees, it is required to program one of the XBees into a coordinator device and another as the end device. The first XBee is configured as a coordinator and the second XBee is configured as an end device. Those two XBees need to have same PAN ID in order to send and receive data in the same ID. The Adruino Uno able to display the serial data through com port.

Real time non-contact elderly infrared body temperature telemonitoring system with XBee wireless protocol is useful and able to give the earlier symptom. It also can help care givers rest at ease that their loved ones are safe. Its will bring advantages to hospitals and physicians, where hospitals and physicians need reliable wireless monitoring system to observe real time physiological data from elderly's patients outside the hospital with high and reliable accuracy.

The system incorporating with the advanced wireless transceiver and non-intrusive body biomedical sensor able to record and documented the elderly body temperature reading, hence healthcare can maintain at it optimum.

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Seizure Localisation, Imaging, and Networks

33. Effect of General Anaesthesia on Epileptiform Discharges and BOLD Signal during EEG-FMRI in Children with Lennox Gastaut Syndrome

Catherine Bailey[1#], Simon Vogrin[4], Andrew Davidson[2,4], Aaron Warren[4,5], Michael Kean[3,4], A. Simon Harvey[1,4,5], John Archer[4,5]

[1] Department of Neurology, Royal Children's Hospital, Melbourne
[2] Department of Anaesthesia and Pain Management, Royal Children's Hospital, Melbourne
[3] Department of Medical Imaging, Royal Children's Hospital, Melbourne
[4] Murdoch Children's Research Institute, Melbourne
[5] Florey Institute for Neuroscience and Mental Health, Melbourne
[6] Department of Medicine, Austin Health, University of Melbourne
catherine.bailey@rch.org.au

Background

EEG-fMRI is being increasingly used to localize epileptic foci and networks in patients with uncontrolled epilepsy. EEG-fMRI in children is limited by cooperation and need for general anaesthesia (GA), the latter potentially suppressing epileptiform discharges on EEG and BOLD signal on fMRI. We examined the effect of GA on epileptiform discharges and BOLD signal during EEG-fMRI in children with Lennox Gastaut syndrome (LGS).

Method

Fourteen children with LGS age 2-15 (median 11) years underwent EEG-fMRI under GA. GA induction was with sevoflurane in 12 and propofol in 3. GA maintenance was with low-dose isoflurane and remifentanil. Time from induction to EEG-fMRI recording was 45-100 (median 65) minutes. Imaging was performed on a Siemens 3T Trio using a 32-channel headcoil and a 64-channel EEG cap Maglink system (Compumedics Neuroscan). EEG was sampled at 5kHz and post-processed to remove artefacts. EEG recorded during fMRI under GA was reviewed for bursts of generalized spike-wave (GSW) and paroxysmal fast activity (GPFA). EEG during fMRI under GA was compared with sleep EEG from the most recent routine EEG (median interval 5 months). Statistical maps of each patient's BOLD signal changes associated with GPFA were generated from event-related GLM design matrix within FEAT 6.00 (FSL v5.0.8, FMRIB, Oxford), incorporating additional motion regressors. The fMRI findings were compared with those reported with GPFA in older LGS patients undergoing fMRI without GA [1].

Results

Routine EEG monitoring revealed frequent GSW in 14 patients and GPFA in 11. High quality EEG during fMRI under GA was obtained in all patients, with minimal ballistocardiac and gradient artefacts. EEG under GA was similar to sleep, with prominence of alpha and beta frequencies. GSW of similar morphology and frequency to that recorded on routine EEG was seen in 13 patients. GPFA that was clearly distinguishable from GSW and sleep spindles was seen in 8 patients. The results of fMRI analysis of GPFA will be presented.

Conclusion

Our GA EEG-fMRI protocol yielded high-quality EEG recordings with GSW and GPFA typical of those recorded during natural sleep. We anticipate that BOLD signal activation with GPFA will be similar to that reported in non-anaesthetised LGS patients. The findings suggest that our GA EEG-fMRI protocol might provide clinically-useful localizing information in children with refractory epilepsy.

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34. SEIZURE DYNAMICS, NETWORK TOPOLOGY AND THE INFORMATION SPREAD BETWEEN DIFFERENT BRAIN REGIONS

George Petkov[1], Marc Goodfellow[1], Mark P. Richardson[2], John R. Terry[1]
[1]College of Engineering, Mathematics & Physical Sciences, University of Exeter, Exeter, EX4 4QF, UK.
[2]Institute of Psychiatry, King's College London, De Crespigny Park, London, SE5 8AF, UK.
J.Terry@exeter.ac.uk

Brain networks are important for the generation and spread of seizures in people with epilepsy, but the relationship between the network topology and the presence of epilepsy remains unclear. Here we study small networks of coupled bistable units [1, 2], which provides a model of seizure generation whilst also allowing to study network measures that provide important quantification of networks in the clinical setting. We find that closeness centrality can distinguish these networks, thus uncovering a novel aspect of their topology that could be implemented as a biomarker for epilepsy. We test this prediction by studying the functional networks [3] derived from background EEG of patients and controls and find that increases in the closeness centrality of networks is significantly associated with the presence of seizures. This suggests that networks in which information flow is "quicker", may support the presence of seizures.

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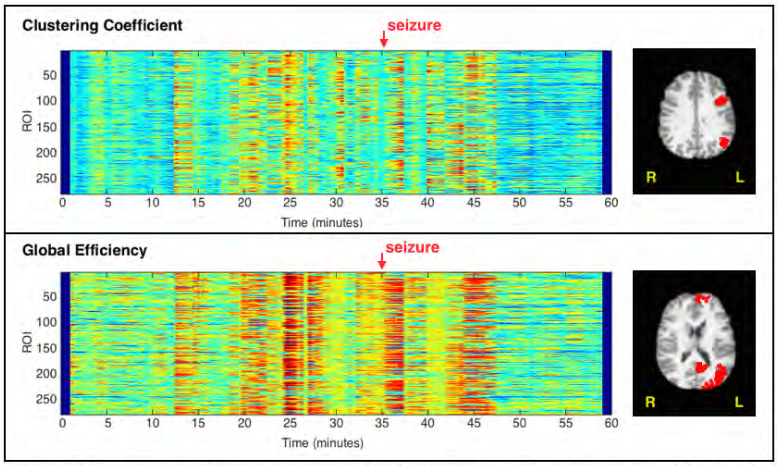
35. PERI-ICTAL CHANGES IN GRAPH THEORY MEASURES OF FUNCTIONAL MRI CONNECTIVITY IN FOCAL EPILEPSY

Jennifer M. Walz[1#], Mangor Pedersen[1,2], Amir H. Omidvarnia[1], David F. Abbott[1], David N. Vaughan[1,2,3], and Graeme D. Jackson[1,2,3]
[1]The Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia
[2]The University of Melbourne, Florey Department of Neuroscience and Mental Health, Melbourne, VIC, Australia
[3]Department of Neurology, Austin Health, Melbourne, VIC, Australia
#jennifer.walz@florey.edu.au

Resting state functional brain connectivity is known to be disordered in focal epilepsy [1], but much is still unknown about how connectivity within and between large scale networks varies across time. In particular, changes in various measures of brain connectivity are thought to be related to seizure initiation, propagation, and termination [2]. Here we use a sliding window approach with measures of fMRI connectivity based in mathematical graph theory [3] to observe peri-ictal changes in brain network behaviour. We focus this study on a simultaneous EEG-fMRI dataset during which a focal seizure occurred midway through the scan.

We acquired one hour of task-free EEG-fMRI data from an 11-year-old female patient who was diagnosed with left frontal lobe epilepsy. We performed slice-timing correction, motion correction, GLM-based denoising (with 24 motion parameters and mean signals from CSF and white matter), scrubbing of volumes exceeding 0.5 mm framewise displacement, and bandpass filtering from 0.001–0.1 Hz. Next we extracted the mean time series from each of 278 ROIs. We generated connectivity graphs by pairwise correlation of each ROI time series and thresholding at Pearson R>0.25. From these weighted graphs we computed both global and node-based measures of clustering coefficient (indexing segregation) and global efficiency (indexing integration). The graphs and subsequent measures were computed independently on 2-min-wide windows of data while sliding the window in single volume intervals (TR=3s). This provided time series of each measure across the entire scan.

We found an increase in the magnitude and variability of all measures during the middle portion of the scan, lasting from 12-47 min, and no significant correlation with the seizure, which occurred at 35 min and lasted 1 min. For clustering coefficient, the changes were most strongly driven by left-lateralised nodes in the middle frontal gyrus and parietal cortex. Global efficiency changes were most strongly driven by left-lateralised frontal pole, posterior cingulate, and intra-parietal sulcus.



Peri-ictal changes in node-based graph metrics. Left: Changes in clustering coefficient (top) and global efficiency (bottom) across the entire scan. Right: ROIs driving these changes (determined by Pearson R>0.75 correlation with the global measure after motion was linearly regressed out), shown overlaid on the subject's anatomical image in MNI space.

Our results show an abnormal large-scale network reorganisation ipsilateral to the seizure focus during peri-ictal periods, particularly within the fronto-parietal brain network. Existence of such an altered state would explain the peri-ictal cognitive deficits some patients experience. This network reorganisation may play a role in seizure suppression (albeit sometimes unsuccessfully) and subsequent termination. Abnormal changes directly related to focal seizure occurrence may be limited to small local networks.

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36. Virtual Cortical Resection of the Epileptic Network Reveals Controllers of Seizure Dynamics

Aankit N. Khambhati[1,2], Brian Litt[1,2,3], and Danielle S. Bassett[1,2,4]
[1]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104
[2]Center for Neuroengineering and Therapeutics, University of Pennsylvania, Philadelphia, PA 19104
[3]Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104
[4]ADepartment of Electrical and Systems Engineering, University of Pennsylvania, Philadelphia, PA 19104
ankk@seas.upenn.edu

Introduction: Functional architecture of the epileptic neocortex has been studied extensively to better identify the optimal target for surgical resection and, more recently, implantable devices. However, the optimal network target for a chronic device is elusive and requires further dissection of how seizures evolve within the epileptic network. Biomarkers of epileptiform activity, such as epileptic spikes and high-frequency oscillations, believed to circumscribe optimal resection regions, often only partially overlap with the seizure-generating network and poorly relate to patient outcome. Seizure dynamics are often characterized by stages with varying degrees of synchronization. Could the efficacy of resective surgery be improved by controlling network synchronization? Specifically, we ask, "How would network synchronizability respond to virtual resection of specific brain regions (or network nodes)?" Furthermore, can we use this method to pinpoint control regions that regulate network synchronizability?

Materials and Methods: We constructed time-evolving functional networks from electrocorticography recorded from 6 patients diagnosed with drug-resistant neocortical epilepsy undergoing routine pre-surgical evaluation through the International Epilepsy Electrophysiology Portal (IEEG Portal, http://www.ieeg.org). We analyzed *seizure* and *pre-seizure* epochs. In each epoch we divided EcoG signal into 1s non-overlapping time-windows and estimated functional connectivity in gamma (30–40 Hz) and high-gamma (95–105 Hz) frequency bands using multitaper coherence estimation. We assessed the impact of virtually resecting each node from the network over all time-windows by computing a novel control centrality metric. The control centrality of a node is the fraction change in synchronizability as a result of removing the node from the network. Positive (negative) values of control centrality indicate the node has a desynchronizing (synchronizing) influence on pre-resection synchronizability.

Results and Discussion: We computed the control centrality over 16 secondarily generalized complex partial seizures. In gamma and high-gamma functional networks, we observed a few nodes that either substantially increased (desync nodes) or decreased (sync nodes) synchronizability. Moreover, these influential controllers were not necessarily seizure-generating nodes. Furthermore, we found that strong controllers outside the seizure-generating network exhibited unique changes in desynchronizing and synchronizing roles preceding and during seizures.

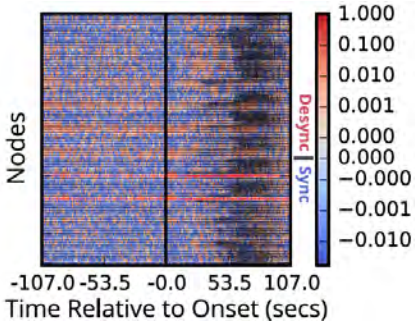


Figure 1. Temporal dynamics of control centrality in an example pre-seizure/seizure event. Desynchronizing control centrality is more red, and synchronizing control centrality is more blue. Electrocorticography signal is overlayed in black (red signal indicates seizure-generating nodes).

Conclusions: Virtual resection of the epileptic network is a novel and powerful method to probe network response to targeted surgical resection. Using virtual resection, we identified influential nodal controllers of network synchronizability that occupy network regions away from the seizure-generating network. Future work will validate the mechanistic role of controllers in regulating spatial extent of seizure evolution.

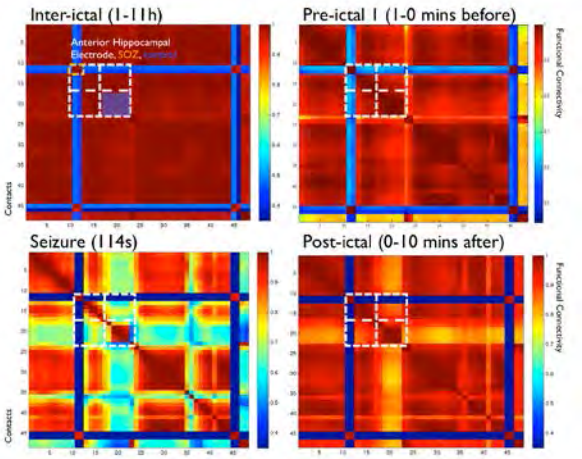
37. NETWORK SEGREGATION PATTERNS HALLMARK SEIZURE-NEIGHBORING STATES IN PATIENTS STUDIED WITH SEEG

Alessandro Principe[1#], Adrià Tauste[2], Rodrigo Rocamora[1] and Gustavo Deco[2]
[1]Epilepsy Monitoring Unit, Neurology dept., Hospital del Mar, Barcelona, Spain
[2]Computational Neuroscience Group, UPF, Barcelona, Spain
#Aprincipe@parcdesalutmar..cat

Defining the boundaries of an epileptogenic zone is crucial for the surgical treatment of epilepsy. In 10-15% of all epileptic patients, this identification is necessary and made prior to surgery through intracranial electrodes and, in our centre, with stereotactic EEG (SEEG) recordings.

Epilepsy research has gradually adopted a network perspective (1) to investigate how network organisation gives rise to epileptic seizures. Many studies focus on the emergence of graph-theoretical properties during different epileptic periods while only a few describe how epileptic networks dynamically evolve across them (2). One of the main result of these works is that epileptic networks are functionally fragmented at seizure onset and are reconstructed near termination. In the present work, we further complement this description by resorting to the concept of network segregation which evaluates the information disruption of the whole network into smaller sub-networks leading to different connectivity patterns (states). In particular, we propose a method to measure network segregation at different connectivity scales based on marginal and partial temporal correlations respectively, which detects state transitions across interictal, pre-ictal and ictal periods and the involvement of single channels within the segregated sub-networks of each state.

We evaluated network segregation on simultaneous long (>18h) SEEG recordings of successive seizures in four patients with drug resistant temporal lobe epilepsy and one where the seizure onset zone was not mapped. First, seizures were manifested by sharp segregation increases at large scale, which were gradually balanced during post-ictal periods. Moreover, these events were typically preceded by a pre-ictal connectivity pattern consisting in the isolation of cortical areas from the mesial structures, which could be detectable from hours to minutes before the seizure onset depending on the patient (see figure for a seizure analysis example using Pearson correlation-based connectivities). These findings were consistent in all patients including the one who resulted to have occipital epilepsy and whose seizure onset zone was not mapped.



Although previous works have focused on defining connectivity patterns during interictal and seizure periods (3), to the best of our knowledge this is one among very few studies that also investigates connectivity across pre-ictal periods (2) through invasive recordings and probably the first one using SEEG. Defining and measuring brain states will not only help understand and potentially control the epileptic activity at a network level but also open new ways to consider the physiological activity of living neural networks.

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38. SEIZURE PROPAGATION IN TUBEROUS SCLEROSIS - INTRACRANIAL EEG ANALYSIS

Lakshminarayanan Kannan[1], Catherine Bailey[1], Simon Vogrin[2], Wirginia Maixner[3], A. Simon Harvey[1,2,4]

1. Department of Neurology, The Royal Children's Hospital, Melbourne
2. Murdoch Childrens Research Institute, Melbourne
3. Department of Neurosurgery, The Royal Children's Hospital, Melbourne
4. Florey Neurosciences Institute, Melbourne
Correspondence: Simon.Harvey@rch.org.au

Background: In tuberous sclerosis complex (TSC), seizures may arise from multiple sites and propagate widely. The seizure generators (tuber vs perituberal cortex) and spread pathways are not well understood in TSC. The implications for epilepsy surgery are obvious, with potential for incorrect seizure localisation and resection.

Objective: To describe spatio-temporal seizure evolution and propagation in children with TSC using intracranial EEG (iEEG) analysis.

Methods: Ictal rhythms on iEEG were analysed retrospectively in patients with TSC undergoing epilepsy surgery. Patients who underwent extra-operative iEEG monitoring or intra-operative electrocorticography (ECoG) with simultaneous recording from two or more non-contiguous tubers and surrounding cortex were included. The location of electrode contacts in relation to different tubers, and in relation to the tuber centre, tuber rim and perituberal cortex were defined using the post implantation MRI and operative photographs. Ictal rhythms were analysed visually to characterise onset patterns, tuber(s) involved at the onset, and the sequence and latencies of involvement of ictal rhythms. Quantitative methods including time-frequency and coherence analyses were used to examine correlations between the ictal rhythms in the tuber centre, rim and perituberal cortex and between different tubers, independent of spatial assumptions.

Results: Sixty three patients with TSC underwent 102 epilepsy operations between 1997 and 2014. Seizures were recorded in 46 operations with either chronic extra-operative iEEG monitoring or intra-operative ECoG sampling multiple tuberal and cortical regions. In 9 operations/patients, multiple tubers were recorded with depth electrodes in their centre (4 electrodes in one patient, 3 in two, 2 in six), in addition to strip and grid electrodes covering the tuber rim and surrounding cortex. All 9 recordings showed a localised, well-sustained ictal rhythm in the centre or rim of one tuber at onset. The ictal rhythm then propagated to the other tuber(s) in all patients, with or without involving the intervening cortex. The propagated ictal rhythm in the other tuber could have been mistaken for the "onset" rhythm. In some cases, local propagation was seen from tuber centre to tuber rim to perituberal cortex. Patient-specific quantitative analyses will be presented.

Conclusion: Preliminary findings from visual analysis of iEEG indicate seizure propagation from tuber centre to surrounding cortex and from tuber-to-tuber. Understanding seizure propagation in TSC is critical to avoid false localisation, adding another dimension to the complex presurgical localisation in TSC.

39. TOWARDS TRANSLATING HFOS AS A BIOMARKER OF THE SEIZURE ONSET ZONE

S. Gliske[1#], Z. Irwin[2], C. Chestek[2], and W.C. Stacey[1,2]

[1]Neurology, University of Michigan
[2]Biomedical Engineering, University of Michigan
#sgliske@umich.edu

Background. Many previous studies have demonstrated high frequency oscillations (HFOs) are a biomarker of the seizure onset zone (SOZ). However, several considerations are hampering full clinical translation (1). We provide novel solutions to three critical needs: a) treatment of false-positive HFO detections due to frequent artefacts in long time, clinical recordings, b) a determination of what sampling rate and anti-aliasing filter threshold is needed for effective HFO detection and c) prospective algorithms to identify SOZ while avoiding identification of regions which do not need resection.

Methods. New algorithms which directly detect artefacts and redact coincident Staba HFO detections (2) were applied to a sample of 29 patients, 11 known to have good surgery outcomes. The detectors were validated by human review of a random subset of detected events, and the resultant HFO-rates were compared with resected volumes in patients with good surgery outcomes. The methods were then reapplied to data down-sampled to lower values to assess the effect of sampling rate on HFO detection, and various filters were added to assess the required minimum anti-aliasing filter setting. Additionally, a novel prospective algorithm to identify SOZ using HFO-rates (denoted the Michigan method) was developed which includes temporal windowing, non-parametric density estimation, and the possibility to avoid identifying any tissue as SOZ. The full data set was required to tune parameters in Michigan method.

Results. The automated HFO and artefact detection method identified approximately 3 million quality HFOs, had high concordance with human markings, and increased the correlation of HFO-rate with resected volume in all patients with good surgery outcomes. The HFO detection sensitivity was found to be relatively stable for sampling rates from about 1 kHz to 5 kHz, with filter threshold analysis ongoing. Additionally, the Michigan method out-performed other methods by predicting no channels outside of resected volume in all 11 patients with good surgery outcomes. Despite the in-sample tuning, the results are suggestive of the generalizability of the method, though a larger patient cohort is needed.

Conclusions. The combination of these novel methods provide a fully automated means to detect HFOs in clinical settings, reject artefacts, and prospectively use HFO rates to identify seizure onset zone with high pecificity. The results also establish that sampling rates down to about 1 kHz are sufficient for detection of HFOs. Future work will utilise these methods for multi-centre trials to further optimise parameter settings and progress towards clinical translation.

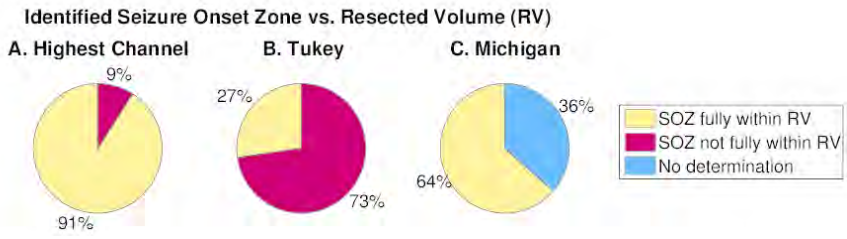

Figure 6: Comparison of automatically identified SOZ with resected volumes in patients with good surgery outcomes. Three methods for identifying SOZ are compared: A) the highest rate channel, B) Tukey's upper fence (see Ref. (3)), and C) our Michigan method.

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40. APPLICATIONS OF PRE-ICTAL AND ICTAL FMRI IN CHILDHOOD EPILEPSY

Sarah Barton[1], A. Simon Harvey[123], Simon Vogrin[1]

1. Murdoch Childrens Research Institute, Melbourne
2. Department of Neurology, The Royal Children's Hospital, Melbourne
3. Florey Neurosciences Institute, Melbourne
Correspondence: Sarah.Barton@mcri.edu.au

Background: Functional MRI (fMRI) studies have shown that changes occur in the brain before the onset of a seizure and can be localised to the site of a presumed seizure focus [1]. Studying blood-oxygen-level dependent (BOLD) changes across the pre-ictal and ictal phases may be a useful imaging technique for localising epileptogenic foci. However, past studies have generally only examined the pre-ictal phase as the patient's seizure disrupts the fMRI acquisition.
Objective: To examine the pre-ictal and ictal phases in two children with refractory focal epilepsy using fMRI. We present two novel situations where multiple events were captured with continuous scanning.
Methods: Patient 1 was a 14 year old girl with poorly lateralised, MRI-negative epilepsy. Her seizures were characterised by sensations in her back and right arm and asymmetrical stiffening in her trunk and limbs. Patient 2 was a 10 year old girl with focal motor seizures in her left foot and leg. Unusual sulcation was noted on MRI but no definite abnormality.
Imaging was performed on a 3T Siemens Trio MRI scanner at the Royal Children's Hospital. A gradient-echo echo-planar imaging (EPI) sequence was acquired (TR 3200ms; TE 40ms; 44 slices of 3.4×3.4×3.0 mm voxels). Each subject had multiple typical seizures in the scanner while continuous data was acquired.
Results: Patient 1 experienced 27 events within a 17 minute EPI sequence, which she indicated the onset and offset of with button-pad responses. Comparison of blocks of ictal and interictal data showed BOLD activation in the right premotor and sensorimotor cortex. A contrast between the 2 volumes immediately preceding the events (pre-ictal) and the interictal baseline showed activation in the left premotor area, sensorimotor cortex and inferior frontal gyrus.
Patient 2 experienced three left foot and leg seizures during a 30 minute EPI acquisition, the timing of which was recorded by an observer. Comparison between the ictal and interictal phases showed focal BOLD activation in the right pre and post central gyri. Significant activation did not emerge in a contrast examining the pre-ictal phase.
Conclusion: The pre-ictal findings for Patient 1 were validated by intracranial EEG monitoring showing seizure onset on the left. For Patient 2, intracranial monitoring validated the ictal findings. The differences between the pre-ictal and ictal analyses highlight the importance of taking timing into account across the fMRI. Differences may relate to uncertainty regarding when the seizure begins, differences in the haemodynamic response function or seizure propagation.

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41. EXPERT-KNOWLEDGE GUIDED DETECTION OF EPILEPTOGENIC CORTICAL MALFORMATIONS IN MULTI-MODAL IMAGING

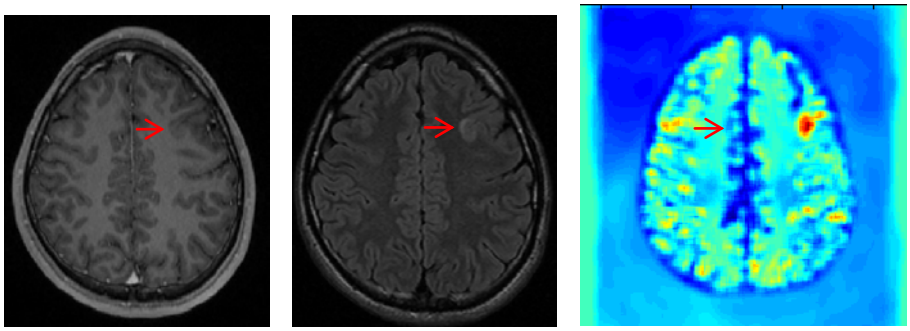
Lohith G Kini[1#], Kathryn A Davis[2], and Brian Litt[1,2]
[1]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA
[2]Department of Neurology, University of Pennsylvania, Philadelphia, PA
#lkini@seas.upenn.edu

Rationale: Pharmacoresistant neocortical epilepsy is highly associated with cortical malformations of neuronal growth and morphology. Identification of these malformations on neuroimaging is crucial for patients in order to undergo presurgical planning and resective surgery. Only ~60% of patients who have brain lesions invisible on brain MRI remain seizure-free post resection surgery [1,2]. This is thought to be in part because epilepsy, being a disorder of large neuronal networks, cannot be cured by resection of a limited region of neocortical tissue [3].

Methods: We apply a combination of voxel-based morphometry, surface-based morphometry and deformation-based morphometry on multimodal imaging (T1-weighted MPRAGE sequence, T2-weighted MRI) from ECoG-implanted patients to automatically identify regions with gray-white junction blur, cortical pseudo-thickening as well as brain atrophy. Seven patients images (T1 and T2) were mapped into a common template domain and then histogram matched to equalize intensities. Grey matter and white matter segmentation maps were also mapped into the same image domain. These multimodal intensities were then converted into z scores through voxel-by-voxel comparison with 95 normal healthy controls with the same MR contrast. The z-score maps were then smoothed to reveal areas of high and low differences. In addition, diffeomorphic deformation vectors from the registration to the common image domain were used to identify areas of atrophy.

Results: Brain morphometry was applied to neuroimaging data from 5 patients. One patient was revealed to have a small left Frontal Type II cortical dysplasia that was consistent with the localization of surgical resection (see figure). In another patient, the tool was able to identify a lesion in the left parietal occipital region that was consistent with either a closed lip schizencephaly or cortical dysplasia. The tool was also successful in identifying small scattered lesions that were visible on FLAIR images but not on T1 weighted images.

Conclusions: We introduce a tool that utilizes a combination of methods of brain morphometry to identify important radiology findings commonly seen in malformations of cortical development. Preliminary results show promise in assisting conventional neuroradiology analysis to improve diagnostic yield of MRI studies in patients with neocortical epilepsy.



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42. EEG SOURCE IMAGING OF INTERICTAL SPIKES USING MULTIPLE SPARSE VOLUMETRIC PRIORS FOR PRESURGICAL FOCUS LOCALIZATION

G. Strobbe[1#], E. Carrette[2], J.D. López[3], D. Van Roost[4], A. Meurs[2], K. Vonck[2], P. Boon[2], S. Vandenberghe[1] and P. van Mierlo[1]

[1]Ghent University - Iminds, Department of Electronics and Information Systems, MEDISIP, Belgium
[2]Laboratory for Clinical and Experimental Neurophysiology, Ghent University Hospital, Ghent, Belgium
[3]SISTEMIC, Department of Electronic Engineering, Universidad de Antioquia, Colombia
[4]Department of Neurosurgery, Ghent University Hospital, Ghent, Belgium
Gregor.Strobbe@Ugent.be

Localizing the generating sources of interictal epileptiform spikes observed in EEG recordings of patients with refractory epilepsy provides useful information for epilepsy surgery evaluation. The selection of the time points of the spikes in order to localize the origin of the activity remains however a typical problem. In this study, we present a Bayesian EEG source imaging technique to obtain a high spatiotemporal resolution of the sources corresponding with different time periods of interictal spikes. The technique is based on a parametric empirical Bayesian framework in which we introduced multiple sets of priors, i.e. the multiple volumetric sparse priors (MSVP) approach [1], and is illustrated using averaged interictal epileptic spikes in six patients who were successfully treated with surgery. Three different time periods were chosen for inversion: (i) a period starting before the spike till 50% of the spike peak during the rising phase of the spike, (ii) a period starting before the spike till the spike peak and (iii) a period starting before the spike till 230 ms after the spike peak. To identify the origin of the spike activity, the source with the maximum energy during the rising phase of the spike was chosen. We compared the MSVP approach with inversions of the spike peaks and at 50% of the peaks using the LORETA approach implemented in the CARTOOL software and an equivalent current dipole (ECD) approach. The resected zone in each of the patients, extracted from post-operative MR images, was used as verification basis. We found equally good or smaller distances to the resection border for the MSVP approach using the largest time period of the spike activity compared to the LORETA and ECD techniques. This means that distances were found smaller than 15 mm, with robust results for all the patients (see Fig. 1). The results we obtained are promising because the approach allows to identify the spatial spread of the sources, allows to study the underlying network of the sources and allows incorporating prior knowledge from other clinical investigations such as PET and fMRI.

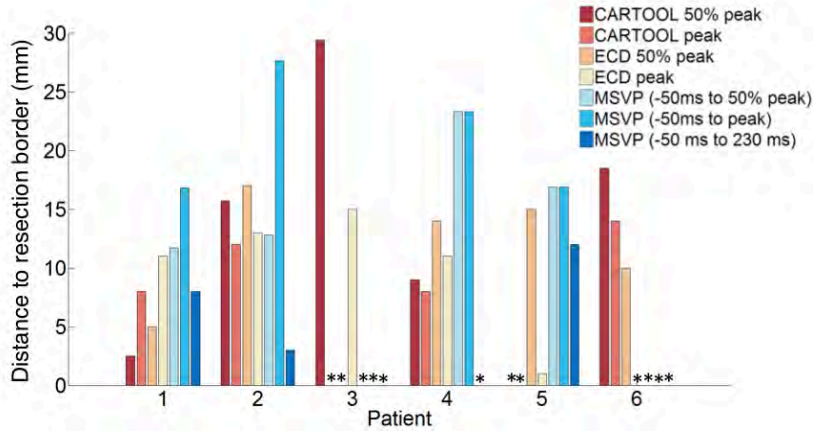

Fig. 1: The distances to the resection border for each of the patients and for the different methods. The stars denote the situations in which the activity was estimated inside the resected area.

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43. Intrinsic Connectivity Network–Based Quantification of the BOLD Changes Associated with Epileptiform Activity

Louis André van Graan[1], Lajos Rudolf Kozák[2], Umair Chaudhary[1], Ádám Szabó[2], Louis Lemieux[1]

[1]UCL Institute of Neurology, London, United Kingdom, [2]MR Research Center, Semmelweis University, Budapest, Hungary

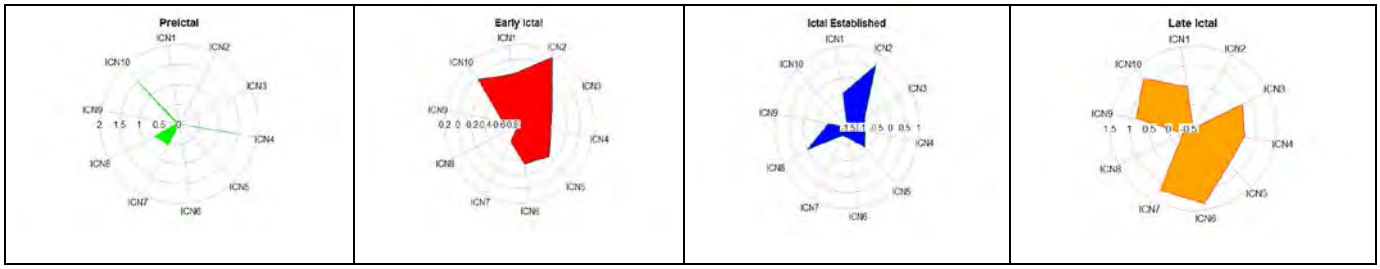
Louis.Graan.12@ucl.ac.uk

Introduction: Combined EEG-fMRI studies in patients with epilepsy can reveal networks associated with epileptic events such as interictal epileptiform discharges (IED) and seizures. The blood oxygen level-dependent (BOLD) maps thus obtained show a spectrum of activity which seems best understood as reflecting networks as opposed to region delineation. Several studies have reported BOLD changes prior to the onset of epileptic events, with a pattern that reflects these early changes to be more widespread for seizures relative to those associated with IED. The network hypothesis in epilepsy is supported by the observation of BOLD changes away from areas conventionally defined as epileptic, together with its relatively wide temporal spectrum relative to seizure onset identified on EEG [1]. Here we propose a quantitative methodology to enhance the interpretation of such BOLD maps based on an atlas framework [2] to characterise epileptic activity-related BOLD patterns in terms of the degree of involvement of Intrinsic Connectivity Networks (ICNs).

Data and Methods: We used our new tool ICNAtlas, an extension to the SPM toolbox (http://www.fil.ion.ucl.ac.uk/spm/), to quantify the level of involvement of ten intrinsic connectivity networks (ICN) during epileptic activity (these ICN are: the 3 visual (medial; occipital and lateral), Default Mode Network, cerebellum, sensorimotor, auditory, executive control, frontoparietal (perception-somesthesis-pain and cognition-language). To illustrate the new approach we applied the ICNAtlas to EEG-fMRI BOLD maps of the pre-ictal phase in a group of patients with frontal lobe (N=6), temporal lobe (N=2), parietal lobe (N=2) and reflex (N=4) epilepsy who had seizures during scans of 20-minute duration. The seizures were partitioned into electro-clinical phases; onset, ictal established and late ictal – and an additional pre-ictal phase comprising the 30 seconds that immediately precede onset. A range of measures of involvement – encompassed, respectively, by voxel counts and ICN activation-weighted involvement (statistical score-weighted) for each ICN were devised and applied in relation to each BOLD map.

Results: Epileptic seizure phase-specific patterns of levels of ICN involvement were revealed. For example, we demonstrate one measure, mean ICN activation (MA), for each phase in one case of temporal lobe epilepsy (TLE) in figure 1; in particular we found that the degree of ICN involvement in the ictal established phase can be understood in relation to specific semiological features. Therefore we envisage that this approach can facilitate the interpretation of seizure evolution, thereby providing a new avenue for the study of ictiogenesis, the interictal-ictal transition and seizure propagation.

Figure 1



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44. Is the Seizure Onset Zone the Most Important Region in Epileptic Brain Networks During Seizures?

Christian Geier[1,2,#], Stephan Bialonski[3], Christian E. Elger[1] and Klaus Lehnertz[1,2,3,#]

[1]Department of Epileptology, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany
[2] Institute for Radiation and Nuclear Physics, University of Bonn, Nussallee 14–16, 53115 Bonn, Germany
[3]Max Planck Institute for the Physics of Complex Systems, Noethnizer Str. 38, 01187 Dresden, Germany
[4] Interdisciplinary Center for Complex Systems, University of Bonn, Bruehler Str. 7, 53175 Bonn, Germany

geier@uni-bonn.de

We investigate whether the brain region responsible for the generation of epileptic seizures -- the seizure onset zone (SOZ) -- represents the most important node in evolving epileptic brain networks [1]. We apply a data-driven method [2] to derive functional brain networks from peri-ictal, intracranial, multi-channel electroencephalographic data recorded from 52 patients with focal epilepsies. We characterize the importance of all sampled brain regions in a time-resolved manner with different centrality metrics [3] and assess significance with surrogate networks. In only 35% of the cases, we observe nodes from within the SOZ to be most important for seizure dynamics. This underlines the high relevance of brain outside of the SOZ but within the large-scale epileptic network for seizure dynamics. Knowledge about the exact functional role of network constituents may elucidate targets for individualized therapeutic interventions that aim at preventing seizure generation and spread.

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45. A BAYESIAN MODEL TO ESTIMATE INDIVIDUAL SKULL CONDUCTIVITY FOR EEG SOURCE IMAGING

T. Verhoeven[1,2#], G. Strobbe[2], P. van Mierlo[2], P. Buteneers[1], S. Vandenberghe[2] and J. Dambre[1]
[1]Reservoir Lab, Department of Electronics and Information Systems, Ghent University, Belgium
[2]Medical Image and Signal Processing Group, Department of Electronics and Information Systems, Ghent University – iMinds, Belgium
#thibault.verhoeven@ugent.be

EEG source imaging (ESI) techniques estimate 3D brain activity based on electrical activity measured on the scalp. In a clinical context, these techniques are typically used for the analysis of epileptiform activity. They play a central role in the pre-surgical planning prior to removal of the epileptic seizure focus, needed in about 30% of people with epilepsy [1]. ESI techniques make use of a parametric model of the geometry and electromagnetic properties of the subject's head. While the geometry can be modelled precisely using an anatomical MR image of the head, there remains high uncertainty in the electrical conductivity of several types of tissue in the head (skull, white and gray matter, scalp etc.). Commonly, these conductivity values are set to a conventional value, based on previous studies. Because individual conductivity values can deviate radically from the conventional values (exceeding an order of magnitude) this can lead to errors that need to be avoided for accurate estimation of the epileptic focus location [2].

In this work, a first Bayesian model is proposed that is able to simultaneously estimate the source location and the subject specific skull conductivity from the measured EEG signals. The expectation-maximization algorithm was used to iteratively update the parameter estimation. As a first proof of concept, we used a three-layered spherical head model and a single dipole source to simulate electrical activity on the scalp, measured at 36 electrode positions, for a range of human skull conductivity values found in literature. We compared the source localization performance with our adaptive conductivity estimation to the performance with several conventional conductivity values used in previous studies. We found that, due to the high variation in individual skull conductivity values, the true source can be located more than 15mm away from the estimated source location using the conventional conductivity. Adaptive estimation of the conductivity with the Bayesian model lowers the maximum location error to only 3mm (see Figure 1).

The first proof of concept looks promising and will be further deployed, including better probabilistic models for the variation in measured EEG, variation in dipole location and prior distribution of conductivity values. The final goal of this work is to estimate all tissue conductivity parameters, making the head model truly adaptive to the individual subject.

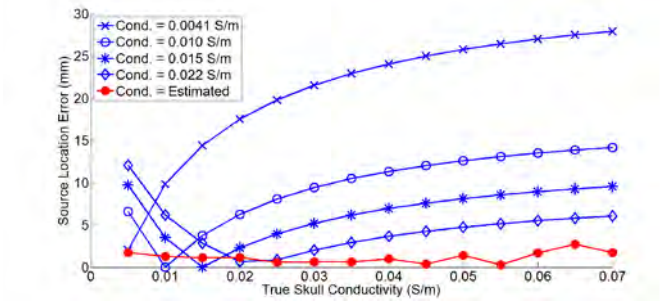

Figure 8 Error on estimated source location as a function of true skull conductivity making use of several conventional skull conductivities and the conductivity estimated with the Bayesian model.

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46. IDENTIFYING DELAYED DIRECTED INTERACTIONS IN EPILEPTIC BRAIN NETWORKS

Henning Dickten[1,2,3#], Christian E. Elger[1] and Klaus Lehnertz[1,2,3,#]
[1]Department of Epileptology, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany
[2] Institute for Radiation and Nuclear Physics, University of Bonn, Nussallee 14–16, 53115 Bonn, Germany
[3]Interdisciplinary Center for Complex Systems, University of Bonn, Bruehler Str. 7, 53175 Bonn, Germany
#hdickten@uni-bonn.de

We present a simple and robust time series analysis technique that is based on symbolic transfer entropy [1] and allows for an identification of delayed directed interactions between coupled dynamical systems and an estimation of the delay [2]. Using our method, we analyze long-term, multi-channel intracranial EEG data from epilepsy patients and investigate the impact of various physiological and pathophysiological factors, that might influence delay and direction of interactions in epileptic brain networks. We show that not taking into account delayed interactions can lead to false characterizations of driver-responder relationships. Our approach can thus help to avoid misinterpretations and to further improve the construction of functional epileptic brain network from data [3].

This work was supported by the Deutsche Forschungsgemeinschaft (Grant No: LE 660/5-2).

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47. DMN DYNAMIC MECHANISM OF TLE: A EEG STUDY

Yan Cui, Tiebin Wang, Daqing Guo, Yang Xia[#], Dezhong Yao

Key Laboratory for NeuroInformation of Ministry of Education, Center for Information in BioMedicine, University of Electronic Science and Technology of China, 610054, Chengdu

[#]corresponding.xiayang@uestc.edu.cn

As a chronic brain disorder in clinical, the temporal lobe epilepsy (TLE) can be characterized by recurrent and unprovoked seizures[1].Default mode network (DMN), which plays a fundamental role in brain organization and supports a variety of self-referential function, has been believed to be associated with many neuropsychological disorders[2]. However, so far how the DMN changes during TLE seizures still remains poorly understood. In the present study, we addressed this issue using the electrophysiological approach. To this end, we recorded the local field potentials (LFPs) from the Pilocarpine-induced TEL rats and analyzed the change of DMN in the process of epileptic discharges. With the methods of coherence and graph theory[3], we discovered several interesting results which are summarized as follows. Firstly, we observed that both the normalized clustering coefficient and the normalized shortest path length significantly reduce during the process of epileptic discharges, implicating that the DMN moves to a more random network. Secondly, different frequency bands play different roles in different stages of epileptic discharges. For instance, our results showed that a significant increase of the low frequency band power (<8Hz) indicates the coming of epileptic discharges, whereas the stage of epileptic discharges is dominated by the alpha and beta band (>13Hz) power. Finally, we found that the DMN can be divided into two modules: the prefrontal cortex module and the parietal cortex module. More interestingly, the epileptic discharges initially originate in the parietal cortex module and then spread to the prefrontal cortex module. Overall, our above results demonstrated that the DNM are dynamically changed during TLE seizures, implying that the DMN might participate into the control and modulation of TLE.

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48. CONNECTIVITY IN THE COURSE OF DYSCOGNITIVE SEIZURES: A CASE SERIES

Kevin Butz[1,2], Yvonne Höller[1], Julia Höfler[1], Giorgi Kuchukhidze[1], Alexandra Taylor[1,2] & Eugen Trinka[1]
[1]Department of Neurology, Christian-Doppler-Medical Center, Salzburg, Austria
[2]Department of Psychology, University of Salzburg, Austria
@ k.butz@salk.at

Background

Recently clinically indicated electrical stimulations between insula and claustrum of an epilepsy-patient caused temporary unresponsivity, the lack of memories and the lack of purposeful behavior, symptoms which often occur during dyscognitive seizures[1]. Since higher cognitive functions are associated which neural network activity, the occurrence of these symptoms might be based on a temporary stimulation-induced impairment of network properties. Based on this, here it is aimed to explore the network activity in the course of dyscognitive epileptic seizures and compare it to network activity during the resting state.

Methods

The data of five epilepsy-patients, which were implanted with intracranial stereotactic electrodes, were included. Even if the locations of these electrodes are inter-individually different there are sites of the brain which were recorded in each patient (like the insula). In order to identify the network activity, we computed the connectivity marker Granger Causality (GC), Direct Transfer Function (DTF) and Partial Coherence (PC). These marker have been computed for each pair of electrodes for each patient during rest, pre-ictal, ictal and post-ictal state. Interactions between brain electrodes are represented graphically, showing the difference between resting and a certain ictal state, respectively (i.e. see fig. 1).

Results

We calculated and evaluated just the DTF-values for two patients, yet.
At the conference, the results and conclusions for the 5 patients will be presented.
The results of the two patients, we calculated yet, partly reveal notable common patterns. Especially electrodes in the region of the amygdala of both patients show strong alterations in information outflow activity to almost all other recorded brain sites.

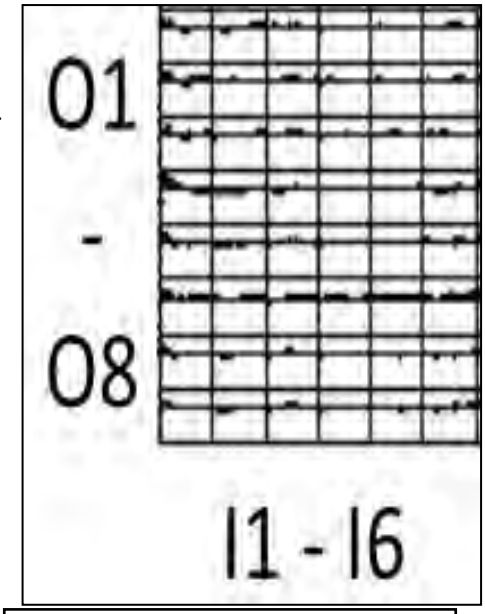

fig. 1 - Showing an example of DTF-values computed between 8 contacts of the electrode O and 6 contacts of the electrode I. Amplitudes above the midline indicate a higher interaction between two sites during the resting state, amplitudes below indicate a higher interaction during the ictal state. Columns indicate information outflow, rows indicate information inflow.

Conclusion

The concordance of strong alterations in information outflow of the amygdale between the two patients might be seen as little evidence for the role of the amygdala as a hub during dyscognitive seizures.
The observed alterations in the amygdala are in line with recent research[2], who showed an abnormal density of receptors and synaptic functions in the lateral amygdala in epilepsy patients. These results need to be confirmed by the analysis of further patients.

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49. ASSOCIATION BETWEEN ACUTE POST TRAUMATIC EPILEPSY AND TYPE OF CEREBRAL ISCHAEMIA – DESCRIPTIVE STUDY

D P C K A Lal
National Hospital of Sri Lanka
Correspondence: chula.kanishka@gmail.com

Introduction: Acute post traumatic epilepsy is a common occurrence following traumatic brain injury. Cerebral ischaemia secondary to primary brain injury is considered a pathogenic mechanism. Whether it has any relationship with the type and severity of brain ischaemia is yet to be determined.

Objective: To describe the relationship between post traumatic epilepsy and type of cerebral ischaemia.

Methodology: 76 adult patients with acute post traumatic convulsions were included in the study. Non contrast computerized tomographies of those patients were analyzed to find out the type of cerebral ischaemia.

Results:

Pathology	Number of patients	Percentage
No evidence of ischaemia	18	23.7
Focal cerebral ischaemia - Unifocal	19	25
Focal cerebral ischaemia – multifocal	21	27.6
Anterior circulation ischaemia	11	14.5
Global cerebral ischaenia	07	9.2

Conclusion: Acute post traumatic epilepsy is commonly associated with focal cerebral ischaemia. Convulsions in non-ischaemic brains are mostly due to cerebral oedema.

Recommendation: Patients with Computerized tomographic evidence of focal cerebral ischaemia following traumatic brain injury need more vigorous observation for convulsions.

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Computational Modelling

50. THE EFFECTS OF CONDUCTANCE-BASED SYNAPSES ON A NEURAL FIELD MODEL OF EPILEPSY

Andre D. H. Peterson[1,2#], Iven M.Y. Mareels[2], Hamish Meffin[3], Mark J. Cook[1], David B. Grayden[2,1] and Anthony N. Burkitt[2]

[1] Dept. of Medicine, The University of Melbourne, St. Vincent's Hospital Melbourne, Fitzroy, Victoria 3065, Australia
[2] NeuroEngineering Laboratory, Dept. of Electrical & Electronic Engineering, The University of Melbourne, Victoria 3010, Australia
[3] National Vision Research Institute, Melbourne, Australia
#peterson@unimelb.edu.au

The overwhelming majority of neural field models use current-based synapses, rather than Hodgkin-Huxley-type spiking neuron models [1]. Although neural field models exist that employ conductance-based synapses, the functional effects on the neuronal dynamics have not been systematically analysed and compared to that of models with current-based synapses. This shortcoming is particularly apparent with respect to epileptic dynamics, where neural field models of epilepsy typically describe the transition to seizure-like activity as a bifurcation [1].

This paper examines and compares the differences between conductance-based synapses and current-based synapses on the transition from normal to seizure-like activity in a neural field model. An established current-based neural field model [2] is used as a canonical neural field model; it did not include time delays or extra neuronal populations such as the thalamus or excitatory interneurons. The model is modified to include more biophysically realistic conductance-based synapses, which are of greater mathematical complexity as they include a multiplicative feedback term from the membrane potential. This makes the input equation nonlinear and more difficult to analyse within an analytic framework compared to current-based synapses that are linear. Comparative bifurcation analyses are performed on the neural field model with both synaptic mechanisms and relevant bifurcation structures that describe a transition to seizure-like behaviour are also analysed.

We demonstrate and explain why conductance-based synapses have a significant effect on the epileptic dynamics of the model, in particular the conditions under which there is a transition to seizure-like behaviour. First, we show that for the same parameter space there is no transition to seizure because the nonlinear multiplicative feedback from the more physiologically realistic conductance-based model acts as an endogenous synaptic regulatory mechanism. Second, we show that the conductance-based model does exhibit transitions to seizure-like behaviour when the reversal potentials take on pathological values. This demonstrates that the micro-ionic environment, including ionic regulatory mechanisms, plays an important role in determining epileptic dynamics, as has been shown experimentally [3]. Third, we construct a homotopic mapping between the two models that confirms that the nonlinear feedback term in conductance-based synapses is responsible for the significantly different dynamics, particularly the transition to seizure-like behaviour.

These results demonstrate a proof of concept, which we anticipate extends to higher dimensional models that incorporate time-delays and extra populations to reproduce more realistic morphologies of EEG waveforms with respect to clinical correlates. These results call into question previous results of neural field models that use current-based synapses, including those used to model epileptic seizures, since using a more biophysically realistic synaptic mechanism in a canonical model yields significantly different results for network behaviour.
This could potentially lead to novel interventional therapies particularly when examining seizure initiation and termination.

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51. PREDICTABILITY OF EXTREME EVENTS IN COMPLEX NEURON NETWORKS

Gerrit Ansmann[123#], Jonathan Brose[12], Ulrike Feudel[45], Klaus Lehnertz[123]
[1] Department of Epileptology, University of Bonn, Sigmund-Freud-Straße 25, 53105 Bonn, Germany
[2] Helmholtz Institute for Radiation and Nuclear Physics, University of Bonn, Nussallee 14–16, 53115 Bonn, Germany
[3] Interdisciplinary Center for Complex Systems, University of Bonn, Brühler Straße 7, 53175 Bonn, Germany
[4] Theoretical Physics/Complex Systems, ICBM, Carl von Ossietzky University of Oldenburg, Carl-von-Ossietzky-Straße 9–11, 26111 Oldenburg, Germany
[5] Research Center Neurosensory Science, Carl von Ossietzky University of Oldenburg, Carl-von-Ossietzky-Straße 9–11, 26111 Oldenburg, Germany
#gansmann@uni-bonn.de

We investigate the predictability of extreme events that are self-generated and -terminated in deterministic complex networks of FitzHugh–Nagumo neurons [1] and integrate-and-fire neurons [2]. These events capture certain dynamical and statistical properties seen for epileptic seizures. We determine whether temporally localised perturbations prevent a given succeeding extreme event in dependence of the perturbation strength and time. This way, we obtain informations as to whether and when generating mechanisms of the extreme events come into action. We show that the onset of a generating mechanism, as found with our perturbation approach, coincides with the occurrence of statistically verified precursors. We conclude that our approach can aid finding precursors of extreme events in the dynamic of model systems and can inform seizure-prediction techniques based on active probing [3].

This work was supported by the Volkswagen Foundation (Grant No. 85392).

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52. THE ROLE OF NETWORK MOTIFS ON SEIZURE GENERATION

Lauric Ferrat[1#], Marc Goodfellow[1], and John Terry[1]
[1] College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter, UK
#corresponding author: lf309@exeter.ac.uk

The concept of networks is established as crucial for the spread of epileptic seizures. However, the reasons why specific network topologies support the spread of seizure dynamics, and how this spread evolves in particular patterns, remains unknown. To investigate this we studied the emergent dynamics on small networks for which we could consider all possible topologies (i.e. 4 or 5 nodes), the dynamics of each node were simulated using an established model of seizure initiation [1], whereby seizures can emerge from steady state due to a saddle-node on invariant circle bifurcation. We assume synaptic-like coupling between nodes and as such, raising the strength of coupling within a network can lead to seizures in the network model.

We find that the coupling strength required for seizure generation is strongly dependent on network topology, even with minor topological modifications. We find that, for this synaptic-like coupling, global efficiency is highly correlated with the number of nodes in seizure. Surprisingly, we find that networks with the largest number of edges are not necessarily the most readily seizure-generating, in the sense that they require the lowest coupling strength for seizure dynamics to emerge. We instead find that networks with an intermediate number of edges that can produce seizures with low coupling strength.

These results suggest that specific topological arrangements are crucial for emergent seizure dynamics even in relatively simple networks. Our findings have implications for the development of treatments that involve perturbations of networks in order to control or abolish seizure generation.

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53. A BIOLOGICALLY CONSTRAINED, MATHEMATICAL MODEL OF CORTICAL WAVE PROPAGATION PRECEDING SEIZURE TERMINATION

Laura R. González-Ramírez[1#], Omar J. Ahmed[2,3], Sydney S. Cash [2,3], C. Eugene Wayne[4], Mark A. Kramer[4]
[1]Instituto de Física y Matemáticas, Universidad Michoacana de San Nicolás de Hidalgo, Cátedras CONACyT
[2]Department of Neurology, Massachusetts General Hospital
[3]Harvard Medical School
[4]Department of Mathematics and Statistics, Boston University
#rgonzalez@ifm.umich.mx

Epilepsy – the condition of recurrent, unprovoked seizures – manifests in brain voltage activity with characteristic spatiotemporal patterns. These patterns include stereotyped semi-rhytmic activity produced by aggregate neuronal populations, and organized spatiotemporal phenomena, including waves. To assess these spatiotemporal patterns, we develop a mathematical model consistent with the observed neuronal population activity and determine analytically the parameter configurations that support traveling wave solutions. We then utilize high-density local field potential data recorded *in vivo* from human cortex preceding seizure termination from three patients to constrain the model parameters, and propose basic mechanisms that contribute to the observed traveling waves. We conclude that a relatively simple and abstract mathematical model consisting of localized interactions between excitatory cells with slow adaptation captures the quantitative features of wave propagation observed in the human local field potential preceding seizure termination [1].

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54. STRUCTURE AND SEIZURE DYNAMICS IN EPILEPTOGENIC NETWORKS

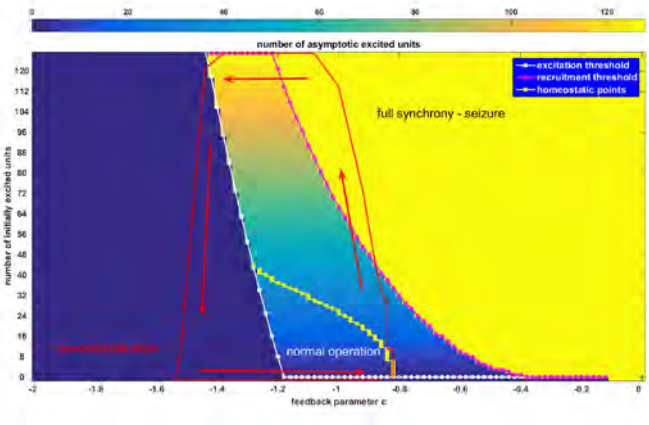
Marc Goodfellow[1#], Mark Richardson[2], and John Terry[1]
[1]College of Engineering, Mathematics and Physical Sciences, University of Exeter, Exeter, UK
[2]Institute of Psychiatry, King's College London, London, UK
#m.goodfellow@exeter.ac.uk

55. AUTONOMOUS DYNAMICS RELATING EPILEPTIC SEIZURE GENERATION, TERMINATION AND POST-ICTAL SUPRESSION. MODEL PREDICTIONS AND CLINICAL VALIDATION.

Stiliyan Kalitzin[1,2#], Prisca Bauer[1], Roland Thijs[1] , Demetrios Velis[1] and Fernando Lopes da Silva[3]
[1]Foundation Epilepsy Institute in The Netherlands (SEIN)
[2]Image Sciences Institute, University of Utrecht
[3] Center of Neurosciences, Swammerdam Institute of Life Sciences, University of Amsterdam, The Netherlands
[#]skalitzin@sein.nl

The autonomous mechanisms underlying epileptic seizure onset, seizure termination and postictal generalized EEG suppression (PGES) in convulsive seizures (CS) are not fully understood. We propose a multi-unit neural mass computational model [1,2] with plasticity modulated connectivity that can generate spontaneously occurring seizure-like activity, deterministic seizure termination and transient postictal periods of suppressed activity[3]. The figure presents a sample trajectory in the collective phase-space of the model to illustrate the transition dynamics. Our model predicts that while interictal intervals have a distribution typical for random, fluctuation-driven transitions, the distributions of ictal and PGES period durations show the characteristics of transient, deterministically terminated processes. The model shows that during seizures, plasticity modulates the ictal state and eventually leads to seizure termination. In addition, we found that the value of the plasticity parameter at the end of the seizure is predictive for the duration of the PGES state before the system fully recovers. Finally, the model shows short but clear periods of pre-ictal synchronization buildup featuring gradual increase of the collective activity towards the impending seizure.

Our model predictions are validated with EEG recordings of 48 human CS, in 37 of which PGES were observed. We confirm a previous finding that both simulated and real ictal periods show a probability distribution suggestive of an underlying deterministic process and here we show that this is also the case for PGES periods. Plasticity towards the end of a CS appears to be reflected in the exponential increase of interclonic intervals (ICIs). We found that in human data, the ICI at the end of a seizure is associated with the occurrence and duration of PGES. These findings point towards an autonomous neuronal process common to both seizure termination and PGES, which may be relevant for understanding and anticipation of epileptic transitions and sudden unexpected death in epilepsy (SUDEP).



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56. FORECASTING EPILEPTIC SEIZURES IN NEURONAL NETWORKS

Marinho A. Lopes[1,2,3#], KyoungEun Lee[3], Alexander V. Goltsev[3,4], and John R. Terry[1,2]
[1]College of Engineering, Mathematics and Physical Sciences, University of Exeter, UK
[2] Wellcome Trust Centre for Biomedical Modelling and Analysis, University of Exeter, UK
[3]Departamento de Física & I3N, Universidade de Aveiro, 3810-193 Aveiro, Portugal
[4]Ioffe Physico-Technical Institute, 194021, St. Petersburg, Russia
#m.lopes@exeter.ac.uk

Epilepsy is a chronic neurological disorder that affects nearly 1% of the population worldwide. The main determinant of epilepsy is the tendency to have recurrent seizures, which are characterised in the electroencephalogram (EEG) by high amplitude paroxysmal activity, across a number of channels. The identification of early changes in neural dynamics prior to seizures may provide a valuable insight into underlying mechanisms. The ability to predict seizures would have important implications for a better understanding, diagnosis and a potential treatment of epilepsy. Namely, it would allow therapeutic measures to be taken before the occurrence of seizures. It would improve the efficacy and efficiency of responsive neurostimulation, a treatment where an electrical stimulation is delivered when the seizure onset is identified to prevent the occurrence of the seizure.

Using a cortical model of neuronal networks comprising of probabilistic excitatory and inhibitory neurons in the presence of noise, we show that paroxysmal-like spikes emerge as nonlinear excitations near a saddle-node bifurcation. We propose that this bifurcation takes place when the brain network dynamics transits from the interictal to the ictal state. In the considered model, the saddle-node bifurcation is the mechanism of a second-order phase transition. It is well known in condensed matter physics that second-order phase transitions are accompanied by critical phenomena that signal the transition, such as a divergence of the susceptibility (linear response function). We identify the variance of the frequency of paroxysmal spikes in the interictal state as the susceptibility-like variable in the neuronal network dynamics. We demonstrate that it diverges at the bifurcation point signaling the transition from the interictal to the ictal state. We propose a method based on the measurement of this susceptibility to forecast the onset of epileptic seizures.

57. NEW INSIGHTS FOR THE BASAL GANGLIA IN CONTROLLING ABSENCE SEIZURES

Mingming Chen[1], Min Li[1], Tao Ma[1], Daqing Guo[1,2#], Yang Xia[1,2], Dezhong Yao[1,2#]

[1] Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China

[2] Center for Information in BioMedicine, University of Electronic Science and Technology of China, China

#dqguo@uestc.edu.cn (DG) and dyao@uestc.edu.cn (DY)

Absence epilepsy, a chronic neurological seizure disease that starts and terminates abruptly, can be characterized by bilaterally synchronous 2-4 Hz spike and wave discharges (SWDs) on the electroencephalogram (EEG) of patients. Recently, an increasing number of studies have reveled that the genesis of the typical 2-4 Hz SWDs during absence seizures is due to the pathological interactions between the cerebral cortex and thalamus. As deep nuclei of brain, the basal ganglia (BG) are regarded as an important intermediate bridge working together with the corticothalamic system. It has been therefore proposed that the BG might have crucial roles in modulating absence seizures. Although several rodent animal data supporting this hypothesis, the biophysical mechanisms of how the BG dynamically control absence seizures are still poorly understood. To address this issue, we have established a biologically based mean-field model for the basal ganglia-corticothalamic (BGCT) system[1]. Both the connectivity and parameters of the BGCT model are compatible with physiological experiments and their values are adapted from previous studies[1,2] (Fig. 1). Using various dynamical analysis techniques, we found that the BG can control absence seizures through two direct GABAergic efferent projections of the substantia nigra pars reticulata (SNr), which targets either on the thalamic reticular nucleus (TRN) or on the specific relay nuclei (SRN) of thalamus. Due to competitions between these two inhibitory pathways, both increasing and decreasing the activation of SNr neurons from the normal level could considerably suppress 2-4 Hz SWDs[1]. To our knowledge, this investigation provides the first evidence on the bidirectional control of absence seizures by the BG. On the other hand, output from the BG to the cerebral cortex is thought to be relayed through the thalamus. Recent experimental data, however, indicated the existence of direct inhibitory pallido-cortical pathway projecting from the globus pallidus externa (GPe) to the cerebral cortex[3]. Inspired from this experimental evidence, we assumed that the novel identified GABAergic projection from the BG to cortex might also play a key role in the control of absence seizures. By computational modeling, we demonstrated that either increasing the activation of GPe neurons from the normal level or enhancing the coupling strength of the inhibitory pallido-cortical pathway could significantly suppress the typical absence seizure activities. Overall, our above model-based findings, on the one hand, highlight the functional roles of the basal ganglia in controlling absence seizures, and on the other hand, might provide some testable hypotheses for future experimental studies.

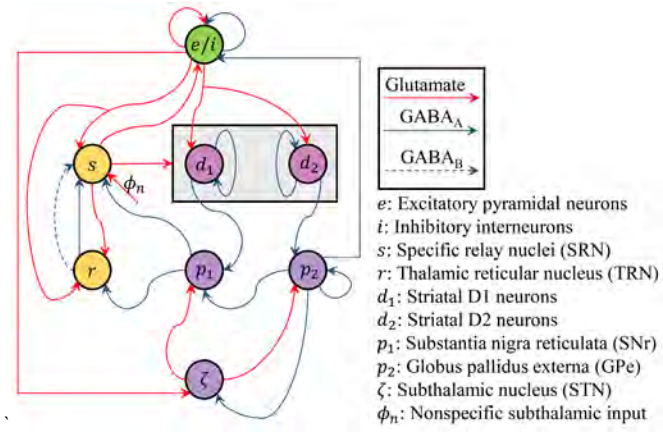

Fig. 1. Framework of the basal ganglia-corticothalamic network.

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58. SEIZURE SUPPRESSION IN A COMPUTATIONAL MODEL USING A REINFORCEMENT LEARNING DEEP BRAIN STIMULATION STRATEGY

Vivek Nagaraj[1] and Theoden Ivan Netoff[1,2]
[1]Graduate Program in Neuroscience, University of Minnesota, Twin-Cities
[2]Department of Biomedical Engineering, University of Minnesota, Twin-Cities
tnetoff@umn.edu

Recent clinical trials have shown some efficacy in seizure control using deep brain stimulation (DBS) for patients with intractable epilepsies [1]. The large stimulus parameter space afforded by modern DBS therapy devices makes it difficult to determine the optimal therapy for patients with various forms of intractable epilepsy. DBS treatments can be improved by implementing adaptive closed-loop algorithms that systematically optimize stimulation parameters to maximize patient outcome and potentially minimizing side effects. In this research we utilize a temporal difference reinforcement learning algorithm, called SARSA(λ) [2] to optimize stimulation to suppress seizures in a computational model. The computational model (Epileptor) reproduces the local field potential (LFP) of a neural population as it transitions between inter-ictal and seizures states [3]. System states (i.e. inter-ictal vs ictal) are determined by extracting an approximate state representation using a filter bank applied to the LFP (Figure 1, A). The goal of the SARSA(λ) algorithm is to learn the optimal state-action pairing in order to maximize reward while minimizing seizure frequency and the total amount of stimulation delivered. The reward in the simulation is inversely proportional to high frequency activity which increases during seizure periods. The algorithm learns the optimal action for each state by iteratively testing each action for every state (Figure 1, B). Our results indicate that the SARSA(λ) algorithm converges on an optimal stimulation regime that completely suppresses seizures within 300 seconds of onset of the learning. The SARSA(λ) algorithm efficiently and systematically identifies optimal stimulation parameters on a patient by patient basis and is computationally efficient enough to implement on a low-power implantable device.

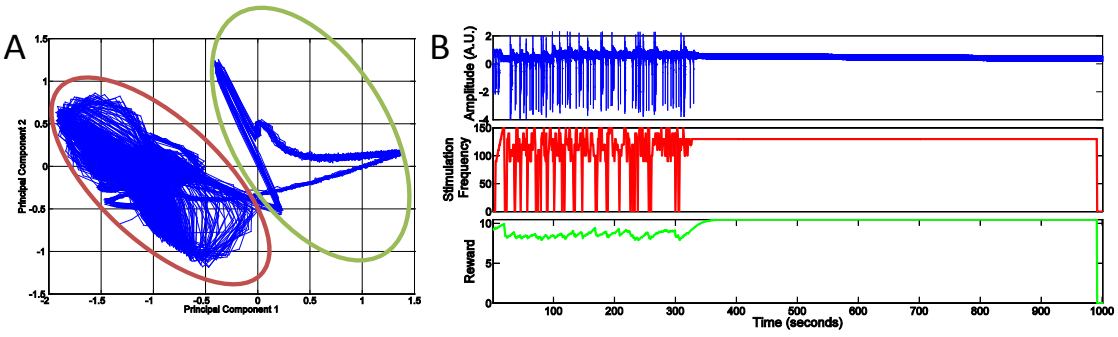

Figure 9 - Reinforcement learning SARSA(λ) algorithm effectively suppresses seizures in a computational model. A, First two principal components are computed from delayed embedding of sample data from the Epileptor model. Seizure and inter-ictal states are represented by the red and green circle respectively. B, The SARSA(λ) algorithm iteratively tests state-action pairs (LFP, top and Stimulation Frequencies, middle) to determine the optimal solution to maximize reward (bottom) while minimizing cost (seizures and stimulation energy). After 300 seconds, the SARSA(λ) algorithm converges on the optimal stimulation frequency, in this case 130Hz, which

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59. MODELLING THE PROPAGATION OF EPILEPTOGENIC DISCHARGES

Sébastien Naze [1#]
[1] Institut de Neuroscience des Systèmes, UMR 1106, 27 Bd Jean Moulin, 13005 Marseille, France
sebastien.naze@univ-amu.fr

As the experimental evaluation of the mechanisms underlying the **initiation, propagation and termination of epileptic seizures** is a difficult problem, theoretical models and numerical simulations provide good tools to investigate seizure mechanisms at multiple scales.

In a previous work [1], we developed of a generic **network model of spiking neurons** and the systematic exploration of conditions under which the network displays the **emergent dynamic** behaviors known from the Epileptor [2], a well-investigated abstract model of epileptic neural activity. This approach allowed us to study the biophysical parameters and variables leading to epileptiform discharges, such as **interictal spikes** and **tonic discharges** at cellular and network levels. Our network model is composed of two neuronal populations, characterized by fast excitatory bursting neurons and regular spiking inhibitory neurons, embedded in a common extracellular environment represented by a slow variable. By analyzing systematically the effects of parameters on neural dynamics, we reproduce typical sequences of activity observed during **status epilepticus**.

As we find that exogenous fluctuations from extracellular environment and electro-tonic couplings between neurons play an essential role in seizure genesis using this approach, we now investigate the influence of chemical synaptic and slow exogenous coupling in the generation of **interictal spikes** and the propagation of spontaneous seizure-like events between two distant brain regions. Each region is modeled by a network of coupled excitatory and inhibitory neurons as above, and specific inter-region coupling is inspired from inter-cortical connectivity principles. We find that cross-neuronal population synaptic gain and background noise level play a major role in the appearance of synchronized spikes preceding seizures. Our simulations extend previous results from coupled abstract Epileptors asserting recruitment of distant brain regions in epilpetiform activity via the coupling between the fast variable of an upstream region to the slow variable of a downstream region [3].

We draw the conclusion that slow variations of global excitability, due to exogenous fluctuations from extracellular environment, and gap junction communication push the system into paroxysmal regimes locally, and that excitatory synaptic and extracellular couplings participate in **seizure spread** globally across brain regions.

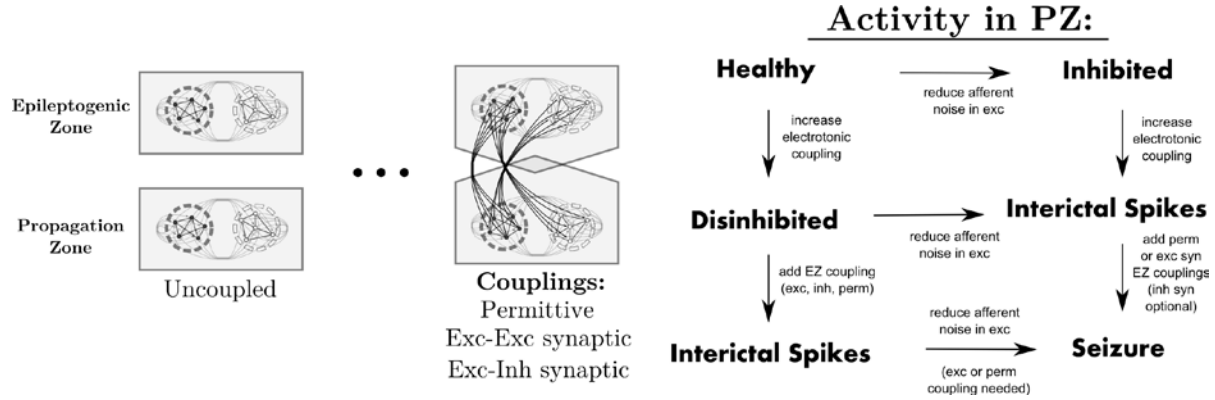

Figure 10: Architecture and behavior of epileptiform activity propagation across two neural populations. Left: An epileptogenic zone is modeled by the system described in [1], in a regime generating spontaneous seizure-like events. A propagation zone is modeled by the same system in a parameter regime that displays normal background activity and interictal spikes. Right: Map of regimes observed in the propagation zone (PZ) when coupled to the epileptogenic zone with different modalities.

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60. A PYTHON IMPLEMENTATION OF A NEURAL FIELD MODEL ON THE CORTICAL SURFACE

Paula Sanz-Leon[1,2#] and Stuart A. Knock[3]
[1]School of Physics, The University of Sydney, Sydney, Australia
[2]Center Of Integrative Brain Function, The University of Sydney, Sydney, Australia
[3]Systems Neuroscience Group, QIMR Berghofer, Brisbane, Australia

[#] P.Sanz-Leon@physics.usyd.edu.au, S.Knock@physics.usyd.edu.au

A Python implementation of the discrete approximation of the Laplace-Beltrami operator (LBO) [1] is presented here. This piece of work allows for a direct numerical integration of a neural field model [2] on a curved surface (i.e., the folded cortex) and it also represents an open-source working code of a neural field model that can be seamlessly integrated in the multiscale hierarchy of The Virtual Brain (TVB) simulator [3]. At the same time, this code contributes to the integration of multiple approaches to large-scale brain modelling that may lead to biophysically realistic explanations of how our brains work and interact with the world. Indeed, having different computational models under the same numerical framework is, to say the least, convinient and desirable if one seeks to compare results and quantify errors. Put simply, we also present here a way to validate computational models methodically. Furthermore, a concurrent pythonic implementation of the neural field model presented in [1] is introduced here, which we call Abstract Field Representation (AFR). This generalized implementation of the dynamical model can be also simplified to the spatially homogeneous case presented in previous studies of various brain states such as rest, sleep and epilepsy. The aforementioned variants of the model can be expressed with the AFR thanks to vector operations and spatialization of parameters. We currently have 56 datasets (*) from the Human Connectome Project (HCP) to verify the methods developed here against recent experimental, analytic and modelling results.

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Code repository: https://github.com/stuart-knock/scientific_library/tree/fields

(*) Thanks to Timothée Proix for preprocessing the structural data.

61. OPTOGENETIC STIMULATION AND EPILEPTIFORM ACTIVITY IN A MEAN FIELD MODEL OF THE HUMAN CORTEX

Prashanth Selvaraj[1,#], Andrew J. Szeri[1,2], Heidi E. Kirsch[3] and Jamie W. Sleigh[4]
[1]Department of Mechanical Engineering, University of California, Berkeley
[2]Center for Neural Engineering and Prostheses, University of California, Berkeley
[3]Departments of Neurology and Radiology, University of California, San Francisco
[4]Waikato Clinical School, University of Auckland
#pselvaraj@berkeley.edu

Epilepsy is a network disorder that manifests when certain elements (neuron types, sub-networks) malfunction or fail [1]. Optogenetics is a promising technique that offers spatially, temporally and cell type specific stimulation of these elements to enable study their role in epilepsy, and eventually to remedy this disorder. It involves the genetic modification of a host cell (e.g. neurons) to express ion channels that are sensitive to a specific frequency of visible light. When illuminated with light of certain intensity, the channels pump ions into the host cell facilitating control over the firing rate of these cells. While optogenetics is not yet safe for use in humans, its use as a stimulation technique can still be explored through physiologically relevant mathematical models of the human brain.

In this talk, we present a method of seizure inhibition in a human cortex via closed loop optogenetic stimulation of specific cell types in a physiologically relevant mean field model of cortical activity. The mean field model simulates cortical activity at the level of neuron populations, and its output can be directly linked to the local field potential of a neuron type, which is the basis of electroencephalography (EEG) and clinical electrocorticography (ECoG) [2]. The wide use of these measurement techniques in the study and treatment of epilepsy forms the basis of our closed loop stimulation strategy where we use the measured signal to calculate the intensity of light required to illuminate the optogenetic channels. We explore the efficacy of this stimulation technique in different parameter spaces of the cortical model that have been found to be the most plausible routes to seizures when statistically compared to patient data [3], and successfully inhibit all types of seizures using illumination intensities well within the range of physiologically safe values.

Finally, we propose the use of optogenetic stimulation as a means to induce seizures in the human cortex to identify epileptogenic zones, and to learn about the role of different network elements in epileptogenesis. We are able to hyperexcite a patch of otherwise normally functioning cortex using optogenetic stimulation, and study the efficacy of this method of stimulation using bifurcation analysis. The wide variety of illumination options, light activated ion channels, and their temporal and spatial specificity make a strong case for consideration of optogenetics as a cortical stimulation modality in seizure research.

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62. DIFFUSION MRI BASED PATIENT-SPECIFIC MODELLING AND CONTROL OF SEIZURES

Peter Neal Taylor[1#], Marcus Kaiser[1,2], Justin Ruths[3]
[1] Interdisciplinary Complex Systems Group, School of Computing Science, Newcastle University, UK
[2] Institute of Neuroscience, Newcastle University, UK
[3] Engineering Systems & Design, Singapore University of Technology and Design, Singapore
peter.taylor@newcastle.ac.uk

Diffusion weighted magnetic resonance imaging (DW-MRI) allows the inference of structural connectivity - the connectome - in human subjects *in vivo*. In many studies, connectivity has been used to investigate group differences between patients and controls. However, few studies have used these networks to investigate emergent pathological dynamics such as the spreading of seizures and optimal seizure control in individual patients [1].

In this study, we use a computational model of epileptic spike-wave discharges (SWDs) [2] and incorporate connectivity from an individual patient with clinically diagnosed generalised epilepsy. We then use this model to test a wide range of stimulation protocols using techniques derived from optimal control theory [3].

We first find that the model is able to reproduce many aspects of the patient's electroencephalographic (EEG) recordings including high amplitude spiking, single and poly-SWDs, and slow waves. Second, due to the heterogeneity of the connectivity underpinning the dynamics, the optimal control requires different energy at different brain regions. Finally, optimal control is successful in suppressing seizure-like activity in our model.

In summary, we suggest that if optimal control of SWD seizures is sought, then the underlying heterogeneity of the brain network should be considered and therefore target-specific solution may be preferred. Our results open up the possibility of clinical studies that trial connectome-based feedback control techniques for seizure prevention.

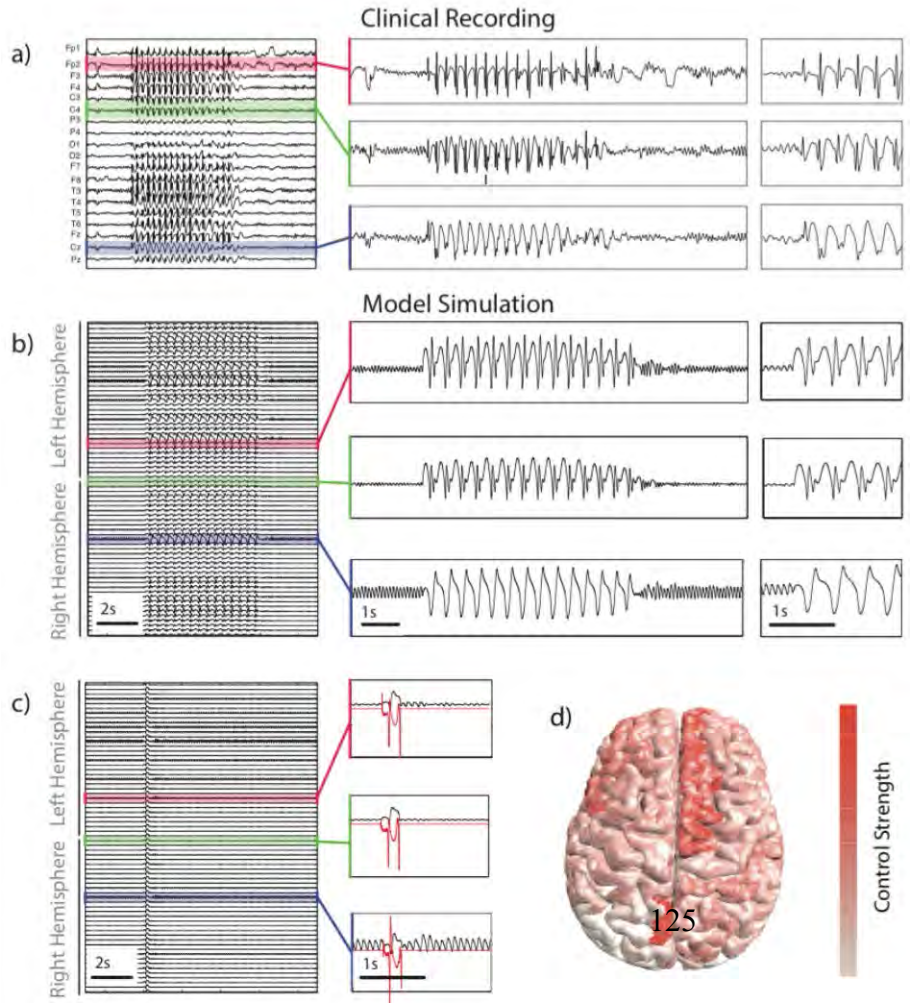

Figure 1. a) Clinical EEG recording of a seizure. **b)** Model simulation of a seizure using DTI based connectivity from a patient with epilepsy. **c)** as in b) but with the optimal control stimulus applied. **d)** different brain areas require different "strengths" of stimulus.

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63. POTASSIUM CURRENTS AND GAMMA OSCILLATIONS IN A REALISTIC COMPUTER MODEL OF THE CA3 HIPPOCAMPAL REGION

Ilya Varfolomeev[1], CR French [1,2#]
[1]University of Melbourne
[2]Royal Melbourne Hospital
#corresponding author frenchc@unimelb.edu.au

INTRODUCTION: Neuronal oscillatory activity in the gamma range (30-80 Hz) has has been suggested to have a significant role in cognitive function. There is also evidence that these oscillations are disturbed in neuropsychiatric disorders including psychotic disorders. Schizophrenia and psychosis can be effectively treated with antipsychotic drugs (APD's), which interestingly have strong suppressive effects on potassium conductances in vitro. Additionally, APD's can reduce gamma power in vivo, and similar effects are seen with APD's and specific potassium channel inhibitors in vitro. We therefore sought to test whether modulation of potassium conductances would alter network gamma frequency resonance in a conductance based computer model with pyramidal and inhibitory neuronal subtypes with realistic topology.

METHODS: A conductance-based 1200 neuron computer model of the CA3 region of the hippocampus was constructed to study the effects of potassium conductances on gamma oscillations on local field potentials. The following potassium channel subtype amplitudes were varied to observe the impact on gamma oscillation power: delayed rectifier (KDR) and A-type current (KA) in basket cells and the H current (IH) in pyramidal cells.

RESULTS: An increase of both KDR and KA conductance in basket cells resulted in a decrease in both the integrated and peak power of gamma oscillations. An increase in pyramidal cell IH resulted an increase in both integrated and peak power of gamma oscillations.

CONCLUSION: Modulation of potassium currents in simulated hippocampal networks strongly impacts gamma oscillatory activity. In general CA3 basket cell KDR and KA conductance are negatively associated with gamma power, while pyramidal IH is positively correlated to gamma power. These results suggest that pharmacological modulation of Kv channels by therapeutic agents may be a component of efficacy.

64. GAMMA OSCILLATION FREQUENCY MODULATES THE EFFICIENCY OF MEMORY ENCODING AND RETRIEVAL IN A COMPUTER MODEL OF THE HIPPOCAMPUS

Ilya Varfolomeev[1], CR French [1,2#]
[1]University of Melbourne
[2]Royal Melbourne Hospital
#corresponding author frenchc@unimelb.edu.au

INTRODUCTION: Neuronal oscillatory activity in the gamma range (30-80 Hz) has been suggested to have a significant role in cognitive function, including the domains of attention and working memory. There is also evidence that these oscillations are disturbed in several neuropsychiatric disorders, including schizophrenia. In particular, it has been shown that working memory tasks cause an increase in gamma power in controls, is impaired in patients with schizophrenia. We therefore sought to test whether the frequency of gamma oscillations in a computer model would impact the ability of the model to encode and retrieve memories.

METHODS: A computer model of the hippocampus that implemented associative memory based on spike timing dependent plasticity (STDP) was used 1. An entorhinal gamma input drove 100 pyramidal cells, 2 basket cells, 1 bistratified cell and 1 axo-axonic cells with voltage-gated conductances with an anatomically and functionally realistic microcircuit topology. The frequency of the gamma input was varied and the effect on recall performance was calculated using a normalised dot product between the recalled and required output pattern.

RESULTS: Varying the input frequency into the simulated CA1 region impacted pattern recall performance. Increase in recall performance was observed between 1 Hz and 75 Hz, with attenuation of recall performance at around 100 Hz. Recall performance was 0.92 at 40 Hz and 0.89 at 1 Hz, falling to 0.89 at 100 Hz.

CONCLUSION: The frequency of the simulated hippocampal CA1 gamma oscillatory activity affected the performance of an associative memory model based on realistic neural conductances and topology. This study provides at least a conceptual link between gamma oscillation parameters and memory encoding in a realistic neural network model. It could also provide a plausible framework for the clinical manifestations of neurocognitive disorders and potential therapeutic strategies.

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65. MECHANISMS UNDERLYING DIFFERENT FOCAL SEIZURE ONSET PATTERNS

Yujiang Wang[1#], Gerold Baier[2], and Marcus Kaiser[1,3]
[1]ICOS, School of Computing Science, Newcastle University, Newcastle upon Tyne, UK
[2]Cell & Developmental Biology, University College London, London, UK
[3]Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK
#yujiang.wang@ncl.ac.uk

With the rise of new recording techniques in the last decade, clinical, experimental, and theoretical works have started to uncover a new understanding of neocortical focal seizure onset [1]. However, a long-standing observation has not been discussed in the context of the new discoveries yet: neocortical focal seizures typically begin with one of two typical waveform patterns -- low amplitude fast oscillations (LAF), or high amplitude spikes/sharp waves (HAS) [2]. Interestingly, only the former of the patterns is associated with a good surgical outcome [3].

Based on previous work [1] we replicate these different onset patterns of intracranial recordings in a spatio-temporal computational model of a neocortical patch of tissue, and show that they are associated with different spatio-temporal patterns at the finer mesoscopic scale (Fig. 1). The LAF is generated by initially independent patches of localized activity, which slowly evolve to a network of epileptic activity over time. In contrast, the HAS occurs as a transition to a globally bistable seizure state triggered by a local event. This indicates a difference in the spatial extent of the underlying pathology, which could explain the different surgical outcome associated with these two seizure onset patterns. Based on the results, we propose alternative treatment strategies for patients with the HAS onset pattern. Finally, we also discuss the implications of the different mechanisms on seizure prediction.

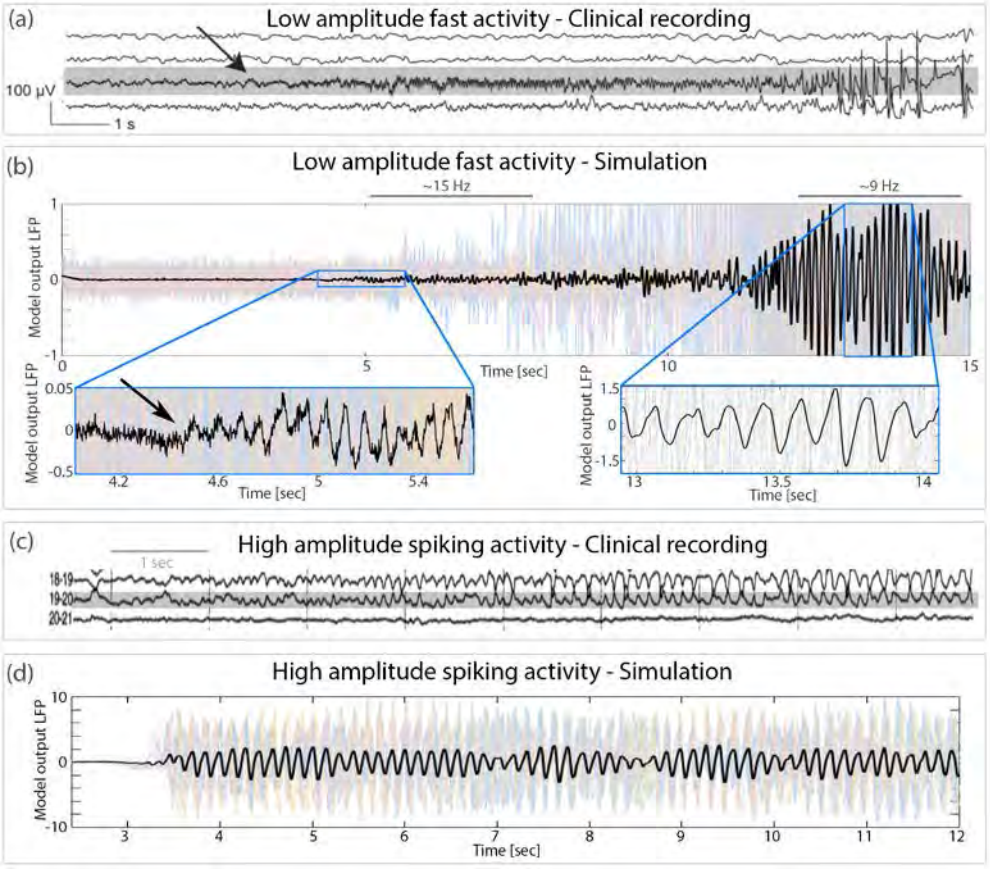

Fig. 1: Spatio-temporal model of two types of different focal seizure onset patterns.

(a) An example clinical recording of the LAF type of focal seizure onset (adapted from [2]). **(b)** Simulation of the low amplitude fast onset pattern (thick black line) calculated as the mean LFP activity from the underlying cortical columns (example traces shown in pastel colours). **(c)** An example clinical recording of the HAS pattern of focal seizure onset (adapted from [3]). **(d)** Simulation of high amplitude sharp waves pattern (thick black line) calculated as the mean LFP activity from the underlying cortical columns (example traces shown in pastel colours).

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66. EFFECTS OF THE EXTRACELLULAR POTASSIUM CONCENTRATION AND T-TYPE CALCIUM CHANNEL BLOCKERS ON NEURAL DYNAMICS

Tianlin Ying[1], Tatiana Kameneva[1,2#]
[1]The University of Melbourne
[2]NeuroEngineering Lab, The University of Melbourne
#tkam@unimelb.edu.au

Anti-epileptic drugs (AED) are the most common treatment method for epilepsy patients to prevent or reduce the number of seizure occurrences. AED are taken chronically and their effectiveness is often decreased with time. To compensate for this consequence, the dosage of AED is often increased often leading to undesirable side effects. The mechanisms of seizure generation have been only partially explained and the ionic mechanisms through which the AED can modulate seizure activity are not completely understood.

Voltage-dependent sodium and calcium channel blockers are the most commonly used groups of AED. Recently, it has been demonstrated that T-type calcium channel antagonists work as anti-seizure and anti-epileptogenesis agents and that increase in the extracellular potassium concentration can lead to a larger number of seizure occurrences.

We present a computational model that combines single cell dynamics from the Hodgkin-Huxley type formalism and the neural population dynamics from the neural mass model (NMM). The firing rate – input current curve, F(I)-curve, links two scales of modeling, similar to [1]. We investigate the effects of the extracellular potassium concentration, $[K^+]_o$, and T-type calcium current, I_T, blockers on neural population dynamics.

First, F(I)-curve for different values of $[K^+]_o$ is taken from [1]. To find F(I)-curve for different values of T-type calcium conductance, a single-compartment Hodgkin-Huxley-type model of a prefrontal neuron is simulated in NEURON. All values are set as in [2] with an addition of T-type calcium current.

Second, a single column NMM is simulated in Matlab. All parameters are set to produce normal background activity with the original values of the static sigmoid as in [3]. Then, different F(I)-curves are used to replace the static sigmoid that links the average postsynaptic potential to the average firing rate in the NMM. Four neural populations are used in modeling: pyramidal cells, excitatory cells, and slow- and fast-inhibitory cells.

To characterize the neural activity type obtained with different sigmoids the power spectrum density analysis is implemented in Matlab.

Results show that increase in the extracellular potassium concentration causes the system to transit from normal background activity to seizure-like activity. Results show that T-type calcium current blockers cause the system to transit from seizure-like to normal background activity. Our modeling framework may help to advance understanding of the effects of AED, improved efficacy of current therapies and may help to develop patient-specific treatments.

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Model-based Estimation

67. IDENTIFICATION OF MULTI-SCALE NEURAL MASS MODELS OF FOCAL SEIZURES

Amirhossein Jafarian[1,2,*], Dean R. Freestone[1,2,3,4], Dragan Nesic[1], David B. Grayden[1,2,3,4]

[1]NeuroEngineering Laboratory, Department of Electrical & Electronic Engineering, The University of Melbourne

[2]Centre for Neural Engineering, The University of Melbourne

[3]The Bionics Institute, East Melbourne

[4]Department of Clinical Neurosciences and Research, St. Vincent's Hospital, Melbourne

*a.jafarian@student.unimelb.edu.au

Average electrical activity of neurons in a small area of the cortex, known as a cortical column, can be measured using EEG. Many neurological conditions, in particular epilepsy, can be diagnosed using EEG. On the other hand, EEG can be related to its underlying biological mechanism generators using a neural mass model (NMM). However, NMMs under stationary conditions (with a set of constant parameters, initial conditions and stationary input) cannot undergo transitions to and from seizures. Therefore, they are limited in their usefulness in modelling underlying mechanisms leading to initiation of seizures from background activity and vice-versa.

In this study, the Jansen and Rit neural mass model [1] is extended such that the model undergoes transitions to and from seizure-like activity. Model extension is performed by augmenting the formulation of the NMM with slow dynamical models for the parameters. In particular, a model of firing thresholds (slow states) that depends upon neural activity (fast states) is used based on Freestone et al. [2].

We propose an approach to fit the slow-fast NMM to EEG data that includes transitions to and from seizures. To evaluate the approach, an artificially generated dataset is used. A genetic algorithm (GA) is employed to estimate the parameters of the slow-state equation. Similarity measures between the envelopes of the output of the model and the observation data are used as the cost function. The unscented Kalman filter (UKF) is employed to further adjust the values of the estimated parameters such that the estimated model replicates the observation data [3].

The genetic algorithm is able to find parameters (with error less than 10% of their values) of the augmented NMM that creates an EEG signal with similar appearance to the observation data. The model obtained from the estimation results from GA is furthered tailored by the UKF to closely emulate the initiation and termination of the seizures. This two-stage identification is a possible framework to be employed to fit a multi-scale NMM to real data.

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68. A MULTIPLE-MODEL BASED ESTIMATION ALGORITHM FOR NEURAL MASS MODELS OF EPILEPSY

Michelle S. Chong[1], Dragan Nesic[1], Romain Postoyan[2] and Levin Kuhlmann[1,3]
[1]Department of Electrical and Electronic Engineering, the University of Melbourne, Australia
[2] Université de Lorraine, CRAN, UMR 7039 and CNRS, CRAN, UMR 7039, France
[3]Brain Dynamics Lab, Brain and Psychological Sciences Research Centre, Swinburne University of Technology, Australia
mstchong@gmail.com

Neural mass models form an important mathematical and computational tool in capturing neural oscillations seen in the electroencephalogram (EEG), which are known to be related to epileptic seizures [1,2,3]. A common thread in neural mass models is that the types of oscillations are captured by the evolution of model parameters such as the synaptic gains of the excitatory and inhibitory neuronal populations. Therefore, detecting the occurrence of an epileptic seizure may be achieved by tracking the model parameters.

We present a model-based estimation algorithm to track the evolution of the parameters (the synaptic gain of each neuronal population) and state variables (the mean firing rate of each neuronal population) for a general class of neural mass models described by (nonlinear) ordinary differential equations. Improving on the deterministic estimation method presented in [4], we drew inspiration from the multiple model architecture prevalent in the stochastic estimation literature and propose an estimation algorithm with rigorously proven convergence guarantees [5]. Contrary to stochastic estimators usually used in the neuroscience literature, such as the nonlinear Kalman filter (see Chapter 2 of [6]), we prove that the estimates converge to a neighbourhood of the true values under certain conditions. Our multiple-model method involves sampling the parameter space sufficiently densely and implementing a state-only estimator for each parameter sample. From this bank of state estimators, we choose one to provide the parameter and state estimates based on a criterion.

We present results showing the efficacy of our algorithm for the Jansen and Rit model [2], where we track the evolution of the synaptic gains (parameters) and the mean membrane potential (states) of the excitatory and inhibitory neuronal populations, respectively, from a simulated EEG time series. This work might pave the way for computational model-based seizure prediction and detection based on parameter estimation, and for feedback and control strategies to abate epileptic seizures.

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69. THE ROLE OF NETWORKS IN IDIOPATHIC GENERALISED EPILEPSY

Helmut Schmidt[1#], George Petkov[1], Mark Richardson[2], and John Terry[1]
[1]University of Exeter, UK [2]King's College London, UK
#h.schmidt@exeter.ac.uk

Epilepsy is a complex dynamic disease, which affects approximately one per cent of the world's population. It is characterised by recurrent seizures, with seizure rates varying between a few seizures per year to multiple seizures per day, depending on the syndrome. Recent studies using different imaging techniques have demonstrated that both functional and structural networks are implicated in persons with idiopathic generalised epilepsy. However, without a modelling approach it is not clear how networks can facilitate seizure activity, and whether they play a critical role in the emergence of seizures.

Seizures may be understood as the synchronisation of large areas of cortex beyond levels required for information processing, thus giving rise to large amplitude oscillations as seen, for example, in EEG. We use a model of phase-coupled oscillators on modular networks to describe large-scale brain activity. Each module represents a particular cortical region, and connections between modules represent long-range connections between different cortical areas. The weight, direction, and time-delay associated with each connection can be inferred from data, such as resting state EEG. We demonstrate that brain networks of persons with epilepsy have a greater tendency to synchronise than do brain networks of healthy controls. This finding indicates a critical role for network structure in the tendency to have seizures. Furthermore, this approach allows us to distinguish resting state EEG between the two groups with up to 80% accuracy, thus presenting a novel method in diagnosing epilepsy.

70. FITTING EPILEPTIFORM SPIKE PROPAGATION PATTERNS TO A MODIFICATION OF THE WILSON-COWAN COMPUTATIONAL MODEL OF NEURAL ACTIVITY

Ann C Vanleer[1#], Jonathan Viventi[2]
[1]Department of Electrical and Computer Engineering, United States Naval Academy, Annapolis, Maryland
[2]Department of Biomedical Engineering, Duke University, Durham, North Carolina
#vanleer@usna.edu

Recent research demonstrates that sub-millimeter, cortical-column-scale domains have a role in seizure generation that may be clinically significant. Additionally, developments in electrode array technologies have begun to yield large area high-density cortical arrays that provide a window into spatio-temporal activity that was previously unobservable. However, a gap remains between recording spatial-temporal wave propagation patterns at a finer spatial scale over larger areas of cortex and the ability to generalize about the dynamics of neural activity giving rise to these patterns. We have previously used high-resolution, active, flexible surface electrode arrays with 500 μm inter-electrode spacing to record epileptiform local field potential spike propagation patterns in two dimensions from subdural micro-electrocorticographic signals *in vivo* in an acute feline model of epilepsy. We subsequently extracted features from these spikes to characterize their spatio-temporal patterns [1]. Here, we present findings following our attempt to fit more than 26,000 detected spikes to the Pinto-Ermentrout modification of the Wilson-Cowan neuroscience model of cortical dynamics [2]. We then discuss the applicability of our findings to inform adjustments to model parameters which could be achieved through the adoption of a Kalman filter control system [3]. Upon the detection of a seizure, our ultimate goal is to positively affect the generation of patterns which might curtail aberrant neuronal activity and lead to the return of a non-epileptic state.

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71. MOLECULE TO MECHANISM – MODELLING NMDA-R AUTOANTIBODY ASSOCIATED ABNORMALITIES IN NEURAL DYNAMICS

Rosch RE[1,2], Friston KJ[1], Goyal S[3], Lim M[3], Cooray G[1,4]

[1]Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK
[2]Centre for Developmental Cognitive Neuroscience, Institute of Child Health, University College London, UK
[3]Children's Neurosciences, Evelina London Children's Hospital, Guy's and St. Thomas' NHS Foundation Trust, London, UK
[4]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

#r.rosch@ucl.ac.uk

Epileptic seizures are stereotyped paroxysmal neuronal events that can occur clinically in response to a wide variety of pathophysiological mechanisms. They are a common feature in the encephalitides, acute inflammatory conditions commonly caused by infectious, or autoimmune causes. In recent years, several discrete autoimmune encephalitis syndromes have been delineated, some of which are characterized by autoantibodies to cell-surface molecular targets with direct relevance for synaptic and neuronal function [1]. Yet there is only limited direct evidence linking the molecular pathophysiology with observable paroxysmal abnormalities in neural dynamics in patients.

In this study, we investigate electroencephalographic (EEG) paroxysms in 8 paediatric patients with serologically proven N-methyl-D-aspartate receptor (NMDA-R) associated encephalitis. Using dynamic causal modelling, we estimate parameters of a biologically plausible neural network model, empirically based on the EEG observations [2]. From the model, we then estimate the changes in intrinsic connectivity among its constituent inhibitory and excitatory neuronal subpopulations, during seizure onset [3].

These results can be used to non-invasively test hypotheses regarding the dynamic abnormalities of neuronal subgroups in NMDA-R associated encephalitis using clinical human EEG recordings. This study is a first step in (i) validating empirically informed models of EEG paroxysms; (ii) identifying the contributions of molecular pathophysiology to observable pathological neuronal responses noninvasively and (iii), extending previous studies in adult patients from single sources to epileptogenic networks. With an increasing number of candidate molecular causes for epileptic paroxysms (including genetic mutations, autoantibodies, and non-specific inflammatory mechanisms), the approach presented here may prove valuable in testing potentially treatment-relevant hypotheses about the network mechanisms through which molecular abnormalities are manifest as a clinical phenotype.

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72. A TAXONOMY OF SEIZURE DYNAMICS

Jared Scott[1], Yuvraj Bhagat[1], Viktor Jirsa[2], Christophe Bernard[2], William C. Stacey[1]
[1]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI 48109
[2]Aix Marseille Université, Institut de Neurosciences des Systèmes, Marseille, France
#wstacey@med.umich.edu

Recent work has shown that focal seizures exhibit a set of general conserved dynamics. We recently developed a canonical model of seizure dynamics based upon the features of seizure onset and termination[1]. This model contained 5 state variables, and was based upon identifying the system bifurcations into and out of seizures. In that initial work, a combination of theoretical and experimental data found that seizures were typically characterized by a saddle node bifurcation at initiation and a homoclinic bifurcation at offset. These bifurcations impose certain constraints on the seizure dynamics, such as predicting a DC shift at seizure onset and logarithmic scaling of interspike intervals nearing the seizure's end. These findings were validated experimentally across brain regions, syndromes, and even across species (humans, mice, rats, zebrafish, etc), suggesting that seizures with vastly different pathophysiologies share fundamental and conserved dynamics. The study also found, however, that in different human patients a small number of recorded seizures (< 20%) did not have log scaling, and thus did not fit with a homoclinic bifurcation. Thus, it is possible that other types of bifurcations may be needed to describe certain seizures. In this study, we analyzed more than 150 seizures across more than 75 patients to identify the types and prevalence of other types of seizure dynamics at seizure offset. We employ curve-fitting techniques to these data and demonstrate several additional dynamical seizure offset behaviors--power-law scaling, linear scaling, and disorganized firing rates--all of which occur less frequently than the logarithmic scaling seen in homoclinic bifurcations. Preliminary modeling shows Saddle-Node-Invariant-Circle (SNIC) and Hopf bifurcation to be promising candidates of offset bifurcations for power-law and linear scaling, respectively. These data will be instrumental in developing an expanded taxonomy of seizure dynamics, aiding in the further characterization and prediction of behaviors of seizure types.

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Attendee List for IWSP7: Epilepsy Mechanisms, Models, Prediction & Control

August 03, 2015 Parkville , Victoria
Participants: 137

David Abbott
Senior Research Fellow
Florey Institute of Neuroscience and Mental Health
Melbourne Brain Centre - Austin Campus
245 Burgundy Street
Melbourne, Victoria 3145
Australia
Phone: 61 3 9035 7025
d.abbott@brain.org.au

Romesh Abeysuriya
University of Sydney
Main Office, Building A28
School of Physics
University of Sydney, NSW 2006
Australia
Phone: 02 8627 4044
r.abeysuriya@physics.usyd.edu.au

Vincent ADAM
Gatsby Unit, UCL
United Kingdom
Phone: 00447442322926
vincenta@gatsby.ucl.ac.uk

Catalina Alvarado-Rojas
Assistant Professor
Pontificia Universidad Javeriana
Bogotá
Colombia
catalina_alvarado@javeriana.edu.co

John ARCHER
Senior Lecturer Medicine
University of Melbourne
Melbourne Brain Centre (Austin)
245 Burgundy St
Heidelberg, Victoria 3084
Australia
Phone: 9035-7071
jarcher@unimelb.edu.au

Catherine Bailey
Chief EMU Scietist
Royal Children's Hospital
Neurology Department
50 Flemington Road
PArkville, 3052
Australia
Phone: 039456909
Fax: 93454478
catherine.bailey@rch.org.au

Sarah Barton
Research Officer
Murdoch Childrens Research Institute
7 Golf Links Cres
Dingley Village, VIC 3172
Australia
Phone: (03)99366728
sarah.barton@mcri.edu.au

Sam Berkovic
Director, Epilepsy Research Centre
University of Melbourne
245 Burgundy St
Heidelberg, Victoria 3161
Australia
Phone: 03 90357093
Fax: 03 9496 2291
s.berkovic@unimelb.edu.au

Simone Bosshard
Postdoctoral Research Fellow
University of Queensland
Centre for Advanced Imaging
Bldg 57 L2
St Lucia, QLD 4072
Australia
Phone: 0733460363
Fax: 0733460330
s.bosshard@uq.edu.au

Benjamin Brinkmann
Assistant Professor of Neurology
Mayo Clinic
Alfred 9-441C
200 First Street SW
Rochester, MN 55905
United States
Phone: 5075385719
brinkmann.benjamin@mayo.edu

Lisseth Burbano
PhD Candidate
The Florey Institute of Neuroscience and Mental Health
Level One, Kenneth Myer Building. 30 Royal Parade.
Parkville
Melbourne, 3064
Australia
Phone: 0469722295
lburbano@student.unimelb.edu.au

Tony Burkitt
Professor
University of Melbourne
Dept Elec Eng
Melbourne, VIC 3010
Australia
Phone: 90353552
aburkitt@unimelb.edu.au

Patrick Carney
The Florey
Melbourne Brain Centre
245 Burgundy Street
Heidelberg, Victoria 3084
Australia
Phone: 0421316303
p.carney@brain.org.au

Sydney Cash
Massachusetts General Hospital
Department of Neurology - Wang730
55 Fruit Street
Boston, MA 02138
United States
Phone: 617-726-3311
Fax: 617-726-9250
scash@partners.org

Hilda Cerdeira
Professor
Epistemic
Rua Jesuino Arruda 294, apt. 21
Sao Paulo, Sao Paulo 04532-080
Brazil
Phone: +5511982880568
hilda.cerdeira@epistemic.com.br

Michael Chang
Toronto Western Research Institute
Canada
Phone: 6479639331
michael.chang@live.ca

Mingming Chen
University of Electronic Science and Technology of China
China
Phone: 13096308335
751230155@qq.com

Warwick Cheung
The University of Melbourne
Australia
Phone: 0432569707
ccheung@student.unimelb.edu.au

Michelle Chong
Department of Electrical and Electronics Engineering, The University of Melbourne
Australia
mstchong@gmail.com

Diana Cogan
PhD student
University of Texas at Dallas
800 West Campbell Road
Richardson, TX 75080
United States
Phone: 972-294-8637
diana.cogan@utdallas.edu

Ian Common
UCB Australia Pty Ltd
1155 Malvern Road
Malvern, 3144
Australia
Phone: +61419340579
ian.common@ucb.com

Mark Cook
Head of Medicine, St. Vincent's
The University of Melbourne
Australia
markcook@unimelb.edu.au

Mark Coulson
UCB
Australia
mark.coulson@ucb.com

Donald Craig
Neurology AT
St George Hospital
Unit 14
33-37 Gray Street
Kogarah, NSW 2217
Australia
Phone: 0449788773
donaldpcraig@gmail.com

Dakota Crisp
University of Michigan
Ann Arbor, MI 48109
United States
Phone: 7349367310
dncrisp@umich.edu

Yan Cui
University of Electronic Science and Technology of China
China
Phone: 13096308335
cuiyanlance@163.com

Evan Curwood
Florey Institute of Neuroscience and Mental Health
245 Burgundy St
Heidelberg, Victoria 3084
Australia
Phone: +61390357334
evan.curwood@florey.edu.au

Lachlan Davies
Clinical Research Manager
Medtronic
67 Windsor St
Paddington
Sydney, NSW 2021
Australia
Phone: 0410312820
Lachlan.Davies@Medtronic.com

Farah Deeba
PhD Student
University of Sydney
Room 436, Madsen Building F09
University of Sydney, NSW 2006
Australia
Phone: 86270504
farah.ju35@gmail.com

SANGWA Deus
Pastor-Counselor and Psychotherapist
MIESF-TRASRM
Kigali
Rwanda
miesftrasrm@yahoo.co.uk

Cristian Donos
PhD
Epilepsy Center, Uniklinik Freiburg
Germany
Phone: 40726338677
cristian.donos@uniklinik-freiburg.de

Antonio Dourado
Professor
University of Coimbra
Dep Informatics Engineering
Polo II Rua Sílvio Lima
Coimbra, 3040-243
Portugal
Phone: +351239790000
Fax: +351239701266
dourado@dei.uc.pt

Wendyl D'Souza
A/Prof
Department of Medicine, St Vincents Hospital, University of Melbourne
PO Box 2900, Fitzroy
Melbourne, Victoria 3070
Australia
Phone: +61407948167
wendyl@unimelb.edu.au

Matthias Dümpelmann
Chief Engineer
Epilpesy Center, Univesity Medical Center Freiburg
Breisacher Str. 64
Freiburg, 79106
Germany
Phone: +49 761 270-52410
Fax: +49 761 270-50030
matthias.duempelmann@
uniklinik-freiburg.de

Dean Freestone
The University of Melbourne
Australia
deanfreestone@gmail.com

Chris French
University of Melbourne
Australia
Phone: 0393492770
frenchc@unimelb.edu.au

Karen Fuller
Neurologist
Wollongong Hospital
Dept Neurology, Level 4, Block C,
Wollongong Hospi
Crown St
Wollongong, NSW 2500
Australia
Phone: 61 2 4253 4430
Fax: 61 2 4253 4436
karen.fuller@sesiahs.health.nsw.gov.au

Kais Gadhoumi
Montreal Neurological Institute
Montreal, QC
Canada
Phone: +15146256660
kais.gadhoumi@mail.mcgill.ca

Stephen Gliske
Research Fellow
University of Michigan
MI 48105
United States
Phone: +1-734-565-9919
sgliske@umich.edu

Bruce Gluckman
Penn State University
W312 Millennium Sciences Complex
University Park, PA 16802
United States
Phone: 011 814 865 0178
bjg18@psu.edu

Laura Gonzalez-Ramirez
Researcher
CONACYT
Michoacan 58070
Mexico
Phone: 857 928 6395
rgonzalez@ifm.umich.mx

Marc Goodfellow
University of Exeter
United Kingdom
Phone: 07891368371
m.goodfellow@exeter.ac.uk

David Grayden
Director, Biomedical Engineering
The University of Melbourne
Dept. of Electrical & Electronic
Engineering
Victoria 3010
Australia
Phone: 61390353796
grayden@unimelb.edu.au

Daqing Guo
Associate Professor
School of Life Science and Technology,
University of Electronic Science and
Technology of China
China
Phone: 8613076073976
dqguo@uestc.edu.cn

Amanda Hargreaves
Eisai
Level 2, 437 St Kilda Road
Melbourne, Victoria 3004
Australia
Phone: 0428647272
amanda_hargreaves@eisai.net

Alan Haszard
Eisai
Level 2, 437 St Kilda Road
Melbourne, Victoria 3190
Australia
Phone: 0428647272
alan_haszard@eisai.net

Bin He
Professor & Director
University of Minnesota
312 Church Street, SE
Minneapolis, MN 55455
United States
binhe@umn.edu

Stephanie Iwanowicz
University of Melbourne
PO box 4459
University of Melbourne
Parkville, Victoria 3052
Australia
Phone: 0400000000
steph3135@yahoo.com.au

Graeme Jackson
Deputy Director
The Florey
Melbourne Brain Centre
245 Burgundy St.,
Heidelberg, Vic 3084
Australia
Phone: 90357068
Fax: 94942291
gjackson@brain.org.au

Amirhossein Jafarian
PhD Student
The University of Melbourne
Dept. of Electrical & Electronic Engineering
Victoria 3010
Australia
Phone: 61390353796
a.jafarian@student.unimelb.edu.au

Najumnissa Jamal
Professor
B.S.Abdur Rahman University
GST Road
Vandalur
Chennai, Tamil Nadu 600048
India
Phone: +9144-22751347
Fax: +914422752520
najumnissajamal@rediffmail.com

Rasesh Joshi
MD/PhD Student
Wake Forest School of Medicine
1845 Legacy Park Ln
Apt. 203
Winston-Salem, NC 27103
United States
Phone: 7047780815
rasesh.joshi@yale.edu

Stiliyan Kalitzin
Clinical Physicist
SEIN
Achterweg 5
2103 SW
Heemstede, 2103SW
Netherlands
Phone: +31235588248
skalitzin@xs4all.nl

Tatiana Kameneva
Research Fellow
The University of Melbourne
The University of Melbourne
Dept Electrical and Electronic Eng, bldg 193
Parkville, Vic 3010
Australia
Phone: 61 3 9035 3592
tkam@unimelb.edu.au

Lakshminarayanan Kannan
Neuroscience Research Fellow
The Royal Children's Hospital
50, Flemington Road
Parkville
VIC 3052
Australia
Phone: 0478701262
Lakshiminarayanan.Kannan@rch.org.au

Philippa Karoly
University of Melbourne
Australia
Phone: 0431905611
pkaroly@student.unimelb.edu.au

Omid Kavehei
Lecturer
Royal Melbourne Institute of Technology (RMIT)
GPO Box 2476
Melbourne, Victoria 3001
Australia
Phone: 0399252450
omid.kavehei@rmit.edu.au

Ankit Khambhati
PhD Candidate
University of Pennsylvania
301 Hayden Hall
3320 Smith Walk
Philadelphia, PA 19104
United States
Phone: 609-2401889
ankk@seas.upenn.edu

Lohith Kini
University of Pennsylvania
United States
Phone: 5712712443
lkini@mail.med.upenn.edu

Jeremy Kirkwood
Student
RMIT
56 Hayward Ln
Melbourne, 3000
Australia
Phone: 0402043365
kirkwood.jeremy@gmail.com

Levin Kuhlmann
The University of Melbourne
Department of Electrical and Electron. Engineering
University of Melbourne
Parkville, VIC 3010
Australia
Phone: +61412552283
levink@unimelb.edu.au

Alan Lai
The University of Melbourne
Australia
alan.lai@unimelb.edu.au

Stephan Lau
University of Melbourne
Australia
Phone: 0420500678
stephanl@unimelb.edu.au

Francois Laurent
CSIC
Spain
Phone: 625296642
f.e.j.laurent@gmail.com

Klaus Lehnertz
University of Bonn
Germany
klaus.lehnertz@ukb.uni-bonn.de

Louis Lemieux
Professor of Physics Applied to Medicine
University College London
UCL Institute of Neurology
Queen Square
London, WC1N 3BG
United Kingdom
Phone: +441494601361
l.lemieux@ucl.ac.uk

Shichuo Li
Lifetime Honorary President & Advisor
China Association Against Epilepsy
China
shichuoli@yahoo.com

Brian Litt
Professor neurology and Bioengineering
University of Pennsylvania
3 west gates, Neurology, UPenn
3400 Spruce st
Philadelphia, 19104
United States
Phone: 2157464850
Fax: 2155738393
littb@upenn.edu

Marinho Lopes
University of Exeter
United Kingdom
Phone: 0351938047996
m.lopes@exeter.ac.uk

KUBWIMANA Marc
Counselor
MIESF-TRASRM
Kigali
Rwanda
miesf2002@yahoo.co.uk

Christian Meisel
NIMH
United States
Phone: 0012025095248
crishen@yahoo.com

Dulini Mendis
University of Melbourne
Australia
Phone: 61416484635
dcmendis@student.unimelb.edu.au

Liset Menendez de la Prida
Instituto Cajal CSIC
Spain
lmprida@cajal.csic.es

Carol Milligan
Senior Research Officer
FINMH
Kenneth Myer Building
Royal Parade
Parkville, Victoria 3010
Australia
Phone: 90359918
carol.milligan@florey.edu.au

Martha Morrell
Clinical Professor/Chief Medical Officer
Stanford University/NeuroPace
455 Bernardo
Mountain View, CA 94043
United States
Phone: 6507143974
Fax: 650-237-2701
mmorrell@neuropace.com

Emma Morrisroe
Florey Institute of Neuroscience & Mental Health
Australia
Phone: 0432741168
emorrisroe@student.unimelb.edu.au

Vivek Nagaraj
Graduate Student
University of Minnesota
312 Church Street SE
6-202 Nils Hasselmo Hall
Minneapolis, MN 55455
United States
Phone: 6126253166
nagar030@umn.edu

Mohamad Hussein Nassralla
PHD Student
AUB
Australia
mfn12@mail.aub.edu

Sebastien NAZE
INS
France
Phone: 003379175019
sebastien.naze@gmail.com

Theoden Netoff
Associate Professor
University of Minnesota
312 Church Street SE
7-105 Nils Hasselmo Hall
Minneapolis, MN 55455
United States
Phone: 6126253618
tnetoff@umn.edu

Ewan Nurse
The University of Melbourne
Australia
Phone: +61425362993
enurse@student.unimelb.edu.au

Terry O'Brien
Neurologist
UoM/RMH
Department of Medicine,
The Royal Melbourne Hospital
Parkville, Victoria 3050
Australia
Phone: +61383445490
obrientj@unimelb.edu.au

Amir Omidvarnia
Postdoctoral research fellow
The Florey Institute of Neuroscience and Mental Health
245 Burgundy Street
Heidelberg
Melbourne, VIC 3084
Australia
Phone: +61 3 3905 7182
a.omidvarnia@brain.org.au

Elma O'Sullivan-Greene
Research Fellow
University of Melbourne
Department of Electrical & Electronic Engineering
The University of Melboiurne
Parkville, Victoria 3010
Australia
Phone: 0406478403
elmaog@unimelb.edu.au

Jayoung Pak
Rutgers Univ. New jersey Medical School
185 South Orange Ave, MSB H 506
Newark, NJ 07103
United States
Phone: 973 972 2922
Fax: 973 972 3185
pakja@njms.rutgers.edu

Bronwen Peace
UCB
Australia
bronwen.peace@ucb.com

Andre Peterson
University of Melbourne
Australia
peterson@unimelb.edu.au

Gueorgui Petkov
Research Fellow
University of Exeter
4 Inglewood House
Sidwell Street
Exeter, Ex4 6AN
United Kingdom
Phone: +447922651571
ghpetkov@gmail.com

Chris Plummer
SVHM
Australia
Phone: 0410625672
chris.plummer@svhm.org.au

Alessandro Principe
M.D. Ph.D.
FUNDACIÓ IMIM
Barcelona, 08003
Spain
Phone: 0034 933160691
omicojoric@gmail.com

Timothée Proix
Institut de Neuroscience des Systèmes
Institut de Neurosciences des Systèmes, UMR1106
Faculté de Médecine, 27 boulevard Jean Moulin
Marseille, 13005
France
Phone: +33(0) 4 91 29 98 14
timothee.proix@etu.univ-amu.fr

Wanzhi Qiu
The University of Melbourne
Australia
Phone: 90354240
qiuw@unimelb.edu.au

Mark Richardson
Head, Division of Neuroscience
King's College London
Institute of Psychiatry, Psychology & Neuroscience
De Crespigny Park
London, SE5 8AF
United Kingdom
mark.richardson@kcl.ac.uk

Jennifer Robertson
PhD Student
Eccles Institute of Neuroscience, JCSMR, ANU
The John Curtin School of Medical Research
ANU Campus
Acton, ACT 2601
Australia
Phone: +61414184979
u4517241@anu.edu.au

Peter Robinson
University of Sydney
Australia
Phone: 0293513779
robinson@physics.usyd.edu.au

Richard Rosch
Clinical Research Fellow
University College London
Wellcome Trust Centre for Neuroimaging
12 Queen Square
London, London WC1N 3BG
United Kingdom
Phone: 07446159330
r.rosch@ucl.ac.uk

Roman Sandler
USC
United States
Phone: 8189239914
rsandler00@gmail.com

Paula Sanz-Leon
University of Sydney
Australia
Phone: 61 02 8627 0504
p.sanz-leon@physics.usyd.edu.au

Jacqui Saw
Advanced Trainee Neurology
Fiona Stanley Hospital
34/150 Stirling Street
Perth, Western Australia 6000
Australia
Phone: 0402782287
jacqui.saw@gmail.com

Graham Schapel
Neurology
North Coast Neurology Centre
PO Box 337
Cotton Tree, QLD 4558
Australia
Phone: +61 7 5443 1143
Fax: +61 7 5443 6083
graham@northcoastneurology.com.au

Bjoern Schelter
University of Aberdeen
Physics, Meston Building
AB24 3UE
Aberdeen
United Kingdom
Phone: 00441224272520
b.schelter@abdn.ac.uk

Steven Schiff
Penn State University
United States
sschiff@psu.edu

Helmut Schmidt
Associate Research Fellow
University of Exeter
United Kingdom
Phone: +49 35951 30108
h.schmidt@exeter.ac.uk

Andreas Schulze-Bonhage
University Hospital Freiburg
Germany
andreas.schulze-bonhage@
uniklinik-freiburg.de

Jared Scott
University of Michigan
United States
Phone: 7344188209
jaredmsc@umich.edu

Prashanth Selvaraj
University of California, Berkeley
880 Spruce Street
Berkeley, CA 94707
United States
Phone: 5105420686
prashanthselvaraj@gmail.com

Vanessa Senger
Technische Universität Dresden
Helmholtzstraße 10
Dresden, Saxony 01159
Germany
Phone: +49 351 463 35069
vanessa.senger@tu-dresden.de

Moksh Sethi
Florey Institute of Neurosciences and
Mental Health
245 Burgundy Street
Heidelberg, VIC 3084
Australia
Phone: 83446008
m.sethi@brain.org.au

Emily Sewell
Medtronic
Level 1/35 Cotham Road
Kew, VIC 3101
Australia
Phone: 0404883770
emily.j.sewell@medtronic.com

Joana Soldado Magraner
The Gatsby Computational
Neuroscience Unit, UCL
United Kingdom
Phone: 004407707384977
jmagraner@gatsby.ucl.ac.uk

Karin Somerlik
University Medical Center Freiburg
Germany
Phone: 0049-761-270-50074
karin.somerlik@uniklinik-freiburg.de

William Stacey
University of Michigan
1500 E. Medical Center Dr.
SPC 5036
Ann Arbor, MI 48109
United States
Phone: 7349367310
Fax: 7349365520
william.stacey@umich.edu

Piotr Suffczynski
Associate Professor
University of Warsaw
Pasteur St. 5
Warsaw, 02-093
Poland
Phone: + 48 22 5532869
Fax: +48 22 5532999
suffa@fuw.edu.pl

PIYUSH SWAMI
PhD Student
Indian Institute of Technology Delhi
Block - III, Room - 399, CBME
Hauz Khas
New Delhi, Delhi 110016
India
Phone: +91-9717085879
Fax: +91-11-26582037
piyushswami@cbme.iitd.ac.in

Peter Taylor
Postdoc
Newcastle University
Newcastle upon Tyne
United Kingdom
Phone: 07790855323
peter.taylor@newcastle.ac.uk

John Terry
Professor of Biomedical Modelling
University of Exeter
Centre for Biomedical Modelling and Analysis
University of Exeter
Exeter, EX4 4QF
United States
J.Terry@exeter.ac.uk

Quang Tieng
Centre for Advanced Imaging, UQ
Australia
Phone: 0733651785
tieng@uq.edu.au

Rafael Torres
Florida International University
7806 NW 193 Terrace
Miami, FL 33015
United States
Phone: 7866837874
rtorr023@fiu.edu

Hoameng Ung
University of Pennsylvania
United States
Phone: 5628818945
hoameng@mail.med.upenn.edu

Louis Andre Van Graan
UCL ION
United Kingdom
Phone: 07966146957
Louis.Graan.12@ucl.ac.uk

Ann Vanleer
Asst. Prof. Electrical and Computer Engineering
United States Naval Academy
United States
Phone: 410-212-3838
vanleer@usna.edu

Thibault Verhoeven
PhD Student
Ghent University
Belgium
Phone: +32494141789
thibault.verhoeven@gmail.com

Simon Vogrin
Neuroimaging Scientist
Department of Medicine, the university of melbourne
1 Regent Street
Fitzroy, Victoria 3065
Australia
Phone: 9288-3653
vogrin@unimelb.edu.au

Wytse Wadman
University of Amsterdam
science park 904
amsterdam, netherlands 1098SM
Netherlands
Phone: +(31)-20-5257641
wjwadman@gmail.com

Jennifer Walz
Postdoctoral Research Fellow
Florey Institute of Neuroscience and Mental Health
2412/27 Little Collins St.
Melbourne, VIC 3000
Australia
Phone: 0428478966
jennifer.walz@florey.edu.au

Yujiang Wang
Research Associate
Newcastle University
United Kingdom
Phone: 07713116724
yujiang.wang@ncl.ac.uk

Aaron Warren
PhD Student
University of Melbourne
245 Burgundy Street
Heidelberg, Victoria 3084
Australia
Phone: 0390357110
a.warren@brain.org.au

Jeremy Welton
Medical Manager
UCB Australia
Australia
Phone: 0408587001
jeremy.welton@ucb.com

Wessel Woldman
University of Exeter
United Kingdom
Phone: 07856951932
www201@exeter.ac.uk

Will Woods
Senior Lecturer
Swinburne University of Technology
Australia
Phone: 0405640422
wwoods@swin.edu.au

Greg worrell
Mayo Clinic
627 14th Ave SW
Rochester, MN 55902
United States
Phone: 5072841599
worrell.gregory@mayo.edu

Dongping Yang
Research Fellow
University of Sydney
School of Physics, A28 University of Sydney
Room 417, Madsen Building University of Sydney
sydney, NSW 2006
Australia
Phone: 0286270894
yangdempe@gmail.com

Louise Young
Medical Manager
Eisai Australia Pty Ltd
Australia
Phone: 0437782905
louise_young@eisai.net

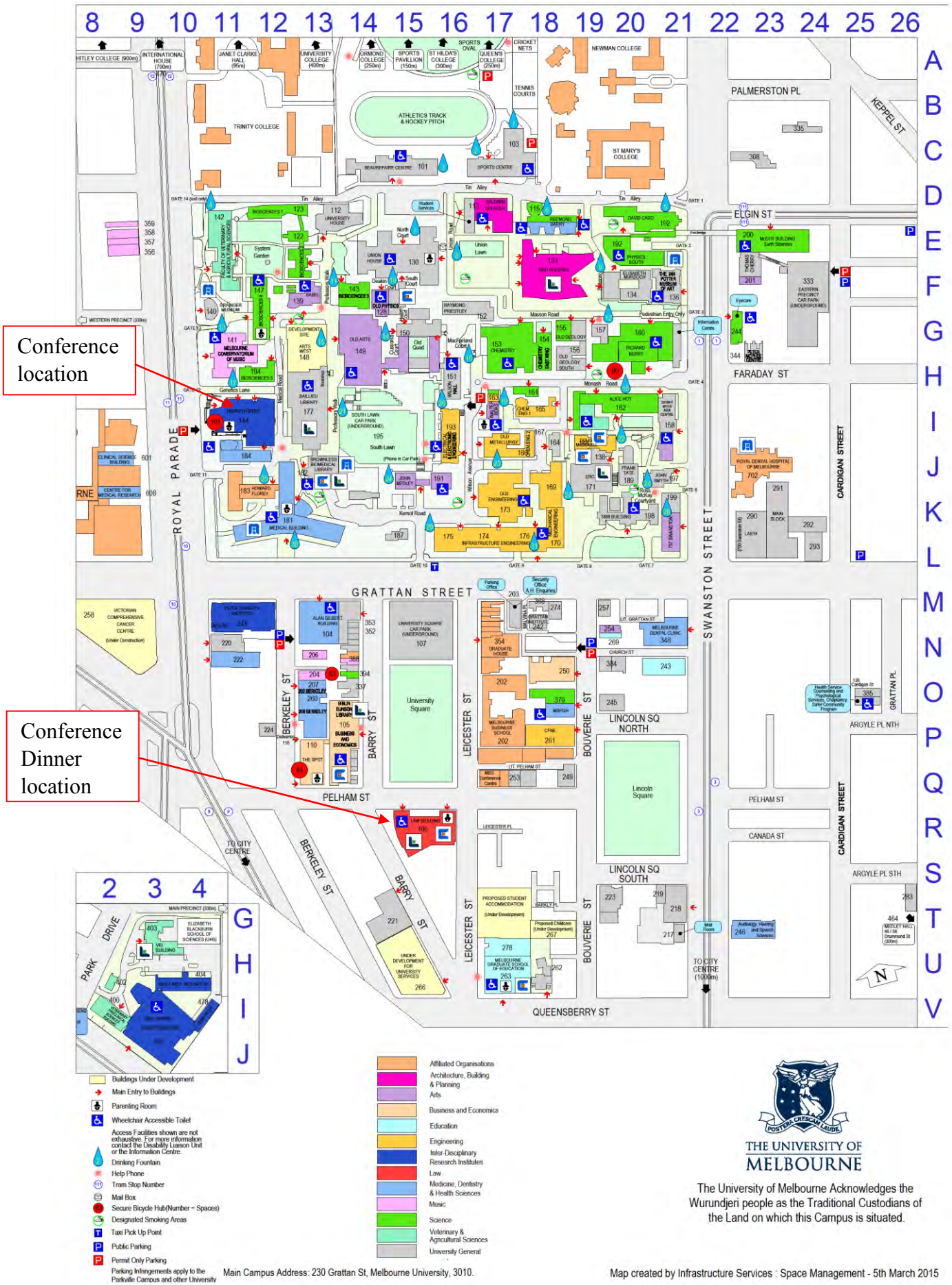
Louise Young
Medical Manager
Eisai Australia Pty Ltd
Australia
Phone: 0437782905
louise_young@eisai.net

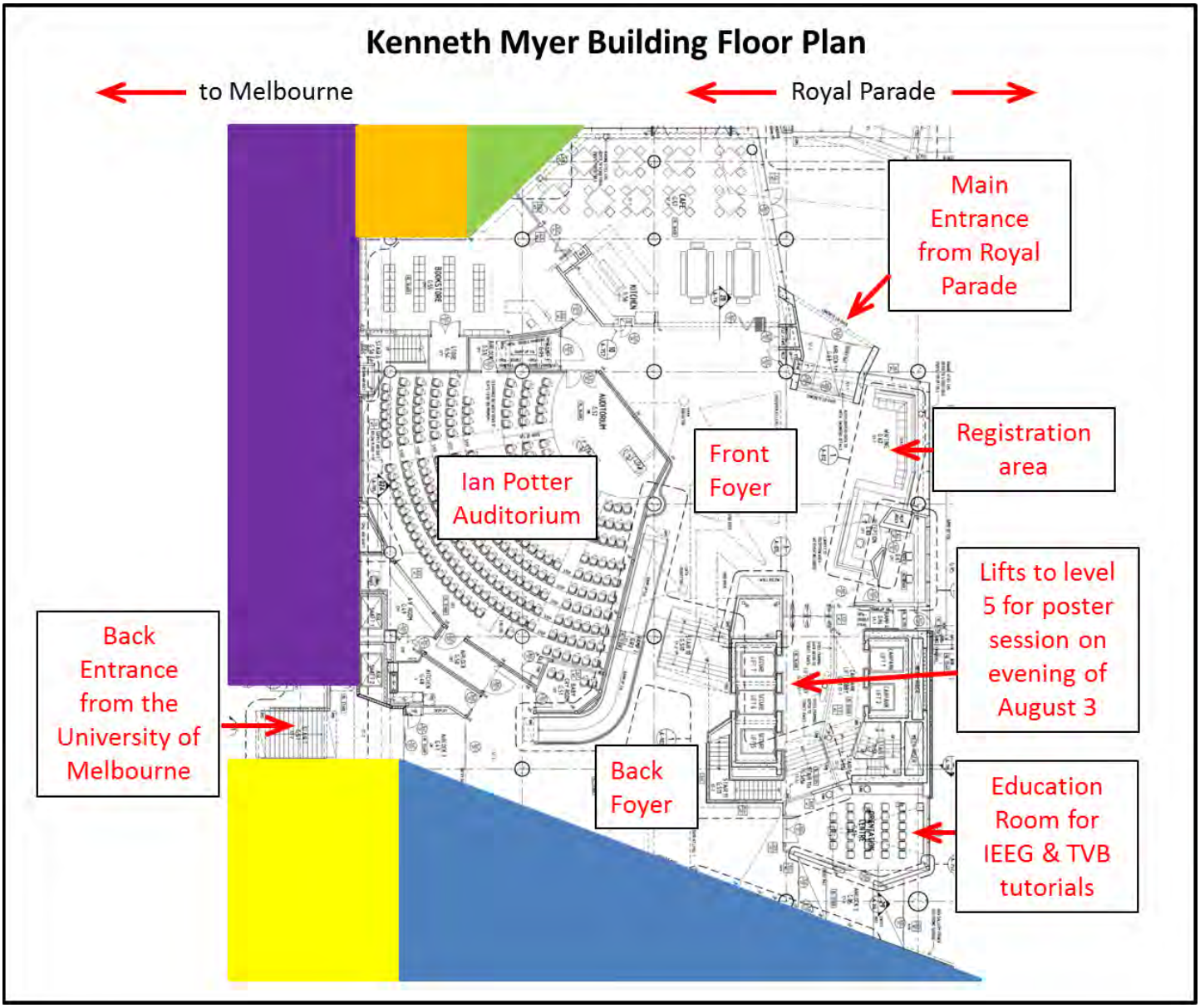
Sasha Zaman
PhD Candidate
Florey Neuroscience and Mental Health Institute
Melbourne, Victoria 3065
Australia
Phone: 90356060
sasha.zaman@gmail.com

Hitten Zaveri
Associate Research Scientist
Yale University
Department of Neurology
333 Cedar Street
New Haven, CT 06511
United States
Phone: 12037375407
Fax: 12037856551
hitten.zaveri@yale.edu

Zisheng Zhang
University of Minnesota
1631 Carl St
APT 4B
Saint paul, MN 55108
United States
Phone: 6124126600
zhan1116@umn.edu

The University of Melbourne Parkville Campus Map





Kenneth Myer Building entrance from Royal Parade