iCSD2018 | Florida

International Conference on Spreading Depolarizations

September 22-24, 2018 | Boca Raton, FL

official satellite meeting of

NEUROCRITICAL CARE SOCIETY

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20th meeting presented by:

Co-Operative Studies on Brain Injury Depolarizations

iCSD2018 | Florida

Welcomes attendees from:

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Brandon Foreman, MD	University of Cincinnati
Bill Shuttleworth, PhD	University of New Mexico
Jens P. Dreier, MD, PhD	Charité University Medicine Berlin
Raimund Helbok, MD	Medical University of Innsbruck
Cenk Ayata, MD, PhD	Massachusetts General Hospital

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Jed A. Hartings, PhD	University of Cincinnati
Cathy Chien	UC Health / UC Gardner Neuroscience Institute
Tonya Hines	GliaMedia / Mayfield Clinic
Christa McAlpin	GliaMedia / Mayfield Clinic
Florine Postell	University of Cincinnati
Adam Soliman	University of Cincinnati

A special thanks to both committees for all their efforts!

Welcome to iCSD 2018 | Florida!

Welcome to one of the most unique meetings in all of neuroscience, where clinicians and scientists gather to discuss the largest pathophysiologic disturbance known to occur in living nervous tissue – spreading depolarizations. From ion channels to clinical outcomes, the translational reach of depolarization research is unparalleled, and the potential for insight into neurologic disease is unlimited.

While COSBID meetings have grown each year since 2003, recent years have been particularly noteworthy for initiatives to reach wider audiences. In 2016 (Albuquerque, New Mexico), there was a surge of participation from American neuroscientists not seen before, infusing new energy and new perspective. In 2017 (Berlin, Germany), we partnered with the International Society for Cerebral Blood Flow and Metabolism and for the first time were recognized as an official satellite of a larger conference, Brain&BrainPET 2017. That 19th meeting was also the first held under the new banner of the **International Conference on Spreading Depolarizations**.

This year's 20th meeting continues this trend of breaking new ground, as iCSD2018 partners with the Neurocritical Care Society as an official satellite of its annual meeting. Both program committees recognized this as an excellent opportunity to enhance translational research and education. We are grateful to NCS for sharing our vision and incorporating iCSD in a week of dynamic programming. The neurocritical care community has been vital in promoting spreading depolarization research, and this role will only increase as the field advances on the path from *observation*, to *insight*, and to *application*.

This year's program builds on strengths from past years. Nearly all submitted abstracts will be Oral Presentations, with poster displays providing opportunity for further discussion. Poster and Networking sessions allow time to make new connections and follow up with past ones. The Moderated Open Discussions will bring some structure –but not too much– to lively group debates on controversial subjects. Finally, the Keynote Speakers will continue the tradition of bringing valuable perspective from experts in closely related fields.

Driven by the *inspiration* of discovery, COSBID has always embraced new collaborations and outreach to basic and clinical scientific communities. So for those new to iCSD – welcome! We hope that you find the program invigorating and engaging, and we thank all the presenters and attendees for making the meeting as unique as it is. And as always, we are especially grateful to our industry partners whose contributions are vital not only for holding this meeting, but also for advancing technology and discovery.

So, enjoy the science, discussions, fellowship, and beautiful Boca. Have a great iCSD2018, and stay thirsty!

Jed A. Hartings, PhD
on behalf of the Program Committee

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The Neurocritical Care Society – Washington University in St. Louis
The Neurocritical Care Society (NCS) is a multidisciplinary, international organization whose mission is to improve health care and outcomes for patients with life-threatening neurological illnesses. With a worldwide membership of health care providers, the NCS is dedicated to promoting quality patient care, professional collaboration, research, training and advocacy.

Exhibitors

EXHIBITORS

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CRANI is a forum for researchers at the University of Cincinnati and affiliates to collaborate in translational research on acute neurologic injury. CRANI is recognized for bringing together experts across a spectrum of related diseases, across department and institutional boundaries, and across clinical and basic sciences.

University of Cincinnati Gardner Neuroscience Institute
UCGNI is a collaboration of the UC College of Medicine and UC Health comprising more than 125 faculty members from 15 clinical specialties who are leaders in treatment, research and teaching for complex neurological and psychiatric conditions.

Hotel At-A-Glance

Boca Raton Resort & Club, A Waldorf Astoria Resort
501 E. Camino Real, Boca Raton, FL 33432
General Inquires: (561) 447-3000
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Poster Location & Time
Poster and Network sessions will be held from 10:00-10:50 on both Sunday, September 23 and Monday, September 24 in the Galeria Room at the Boca Raton Resort & Club.

Poster Set-up
Poster locations are not assigned, but rather chosen by presenter preference and availability.

Posters may be set-up Saturday, September 22 from 12:00 – 14:00 in the Galeria Room. Set-up should be completed by 10:00 on Sunday, September 23, when the Poster and Network session begins. Tear-down of posters should take place before 18:00 on Monday, September 24.

You will be provided one 8 ft. (width) x 4 ft. (height), maximum size, poster board. Pins will be available to affix your poster. The boards are double-sided so there will be another poster displayed on the back of your board.

WIFI network: BOCA-MEETING
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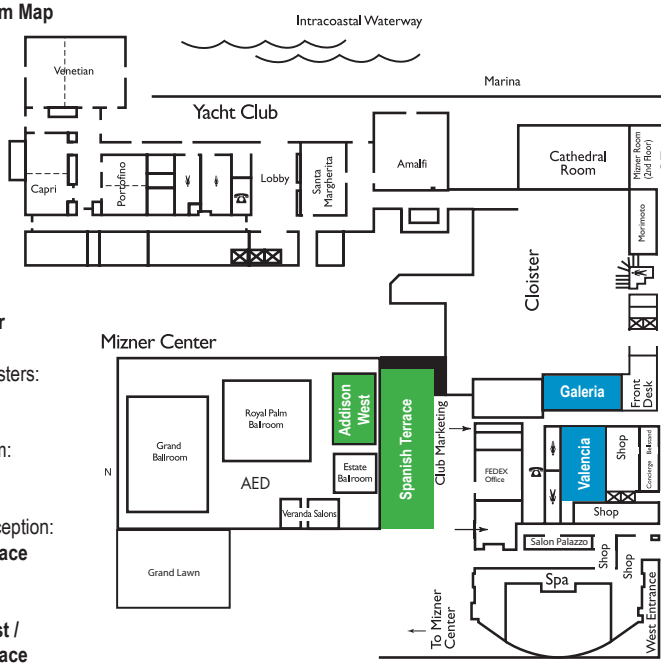
Meeting Room Map



Registration:
Galeria Foyer

Exhibits & Posters:
Galeria

Meeting Room:
Valencia

Welcome Reception:
Spanish Terrace

Lunch:
Addison West / Spanish Terrace

Schedule At-A-Glance

Date	Start	End	Event	Location
22-Sep	12:00	14:00	Registration	Galeria Foyer
	14:00	14:10	Opening and Welcome	Valencia
	14:10	16:00	**Session 1:** SD in TBI	Valencia
	16:00	16:20	Break	Galeria
	16:20	17:20	**Keynote I: David Okonkwo, MD, PhD** CSDs: Next Frontier in Coma Care	Valencia
	17:30	19:30	Welcome Reception	Spanish Terrace
23-Sep	7:00	8:00	Breakfast	Valencia
	8:00	10:00	**Session 2:** SD in Cerebral Ischemia	Valencia
	10:00	10:50	**Posters and Networking 1**	Galeria
	10:50	12:30	**Session 3:** ECoG and EEG	Valencia
	12:30	13:10	Lunch	Addison West
	13:10	15:10	**Session 4:** SD in Injured & Normal Brain	Valencia
	15:10	15:30	Break	Galeria
	15:30	16:30	**Keynote 2: Marc Simard, MD, PhD,** The Endfoot in Charge: SUR1-TRPM4 in Cerebral Ischemia	Valencia
	16:30	17:30	**Open Discussion:** Which SDs are harmful?	Valencia
	19:00	22:00	iCSD Dinner at Matteo's of Boca Raton	Matteo's
24-Sep	7:00	8:00	Breakfast	Valencia
	8:00	9:20	**Session 5:** Mechanisms of SDs	Valencia
	9:20	10:00	**Special Session on Historical Figures in SD Research: George Somjen**	Valencia
	10:00	10:50	**Posters and Networking 2**	Galeria
	10:50	12:30	**Session 6:** Treatments for SDs	Valencia
	12:30	13:30	Lunch	Addison West
	13:30	15:10	**Session 7:** Clinical Neuromonitoring	Valencia
	15:10	15:30	Break	Galeria
	15:30	16:30	**Keynote 3: Ari Ercole, MD, PhD.** Neuromonitoring: From Signals to Service, via Systems & Statistics	Valencia
	16:30	17:30	**Open Discussion:** What should a clinician do when SDs are observed?	Valencia
	17:30		Final Announcements and Adjournment	Valencia

Detailed Schedule: Sept 22

Saturday, September 22, 2018

12:00 - 14:00 Registration

14:00 - 14:10 Opening and Welcome

Session 1: Spreading Depolarizations in Traumatic Brain Injury
Chairs: Raimund Helbok, Justin Cetas

14:10 - 14:40 **Jed A. Hartings** – *University of Cincinnati, OH, USA*
ECoG in surgically managed brain trauma patients. Part I: spreading depolarizations and their relationship to clinical variables

14:40 - 15:00 **Brandon Foreman** – University of Cincinnati, OH, USA
ECoG in surgically managed brain trauma patients. Part II: baseline patterns, seizures, and spreading depolarizations

15:00 - 15:20 **Nils Henninger** – University of Massachusetts Medical School, MA, USA
Cortical spreading depolarizations relate to injury severity in a mouse concussion model

15:20 - 15:40 **Laila M. Mohammad** – University of New Mexico, NM, USA
CSD2 (Cortical Spreading Depolarizations (CSD) in Chronic Subdural Hematoma (cSDH) Patients after evacuation) Trial

15:40 - 16:00 **Brandon Foreman** – University of Cincinnati, OH, USA
Ketamine suppresses spreading depolarizations in a case of severe brain trauma

16:00 - 16:20 Break

Keynote Lecture 1

16:20 - 17:20 **David O. Okonkwo** – University of Pittsburgh, PA, USA
Cortical Spreading Depolarizations: The Next Frontier in Coma Care

17:30 - 19:30 Welcome Reception

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Detailed Schedule: Sept 23

Sunday, September 23, 2018
7:00 - 8:00 Breakfast

Session 2: Spreading Depolarizations in Cerebral Ischemia
Chairs: Jed Hartings, Eszter Farkas

8:00 - 8:20 **Janos Lückl** – University of Pécs, Hungary
Monitoring of spreading depolarizations (SD) in closed skull models of rat brain ischemia

8:20- 8:40 **Kazutaka Sugimoto** – Massachusetts General Hospital, MA, USA & Yamaguchi University, Japan
Optogenetic spreading depolarizations in focal cerebral ischemia

8:40 - 9:00 **K. M. Reinhart** – University of New Mexico, NM, USA
Metabolic heterogeneity in compromised tissues influences excitotoxic consequences of spreading depolarization

9:00 - 9:20 **Candi L. LaSarge** – Cincinnati Children's Hospital Medical Center, OH, USA
The relationship of calcium channel activation and optical intrinsic signals during in vivo cortical spreading depolarizations

9:20 - 9:40 **Yama Akbari** – University of California, Irvine, CA, USA
Spreading depolarization during cardiac arrest in a rodent model as an ultra-early biomarker of neurological outcome after resuscitation

9:40 - 10:00 **R. Meldrum Robertson** – Queens University, Canada
Functional recovery after anoxic depolarization in insect model systems

10:00 - 10:50 **Posters and Networking 1**

Session 3: ECoG and EEG
Chairs: Martin Fabricius, Brandon Foreman

10:50 - 11:10 **Tomas Watanabe** – Vagalume, LLC
Quantitative characterization of spreading depolarizations as an evolving, individualized disease process

11:10 - 11:30 **Alois J. Schiefecker** – Medical University of Innsbruck, Austria
High frequency oscillations on electrocorticography of patients with brain injury – an extension to spreading depolarizations?

11:30 - 11:50 **Sharon L. Jewell** – King's College London & Imperial College London, UK
Fin waves of the cerebral cortex and outcome following acute brain injury

11:50 - 12:10 **Pulkit Grover** – Carnegie Mellon University, PA, USA
Non-invasive and automated algorithms for detection of CSDs with complex patterns

12:10 - 12:30 **Eric S. Rosenthal** – Massachusetts General Hospital, MA, USA
Dynamic Response of Intracranial EEG to Blood Pressure following Subarachnoid Hemorrhage

12:30 - 13:10 Lunch

Detailed Schedule: Sept 23

Session 4: Spreading Depolarizations in Injured and Normal Brain
Chairs: KC Brennan, Sergei Kirov

13:10 - 13:30 **Paul Fischer** – Massachusetts General Hospital/Harvard Medical School, MA, USA & Charité Universitätsmedizin Berlin, Germany
Cortical spreading depolarizations in a mouse model of intracortical hemorrhage: causes and consequences

13:30 - 13:50 **Justin S. Cetas** – Oregon Health & Science University, OR, USA
Mechanical disruption of glymphatic pathways and experimental subarachnoid hemorrhage are associated with similar perivascular inflammation

13:50 - 14:10 **Tsubasa Takizawa** – Massachusetts General Hospital, MA, USA
Cortical and systemic inflammatory markers after spreading depression in mice

14:10 - 14:30 **Marcia Consentino Kronka Sosthenes** – Federal Unviersity of Para, Brazil
Stereological analysis of spreading depression-induced Egr-1 immunolabeled cells in the rat somatosensory cortex

14:30 - 14:50 **KC Brennan** – University of Utah, UT, USA
Effects of edema on neuronal excitability and spreading depolarizations after traumatic brain injury

14:50 - 15:10 **Russell A. Morton** – University of New Mexico, NM, USA
"Concussion"-like impacts induce spreading depolarizations

15:10 - 15:30 Break

Keynote Lecture 2

15:30 - 16:30 **Marc Simard** – University of Maryland, Baltimore, MD, USA
The endfoot in charge: SUR1-TRPM4 in cerebral ischemia

Open Discussion

16:30 - 17:30 **Moderator: Bill Shuttleworth** – University of New Mexico, NM, USA
Which spreading depolarizations are harmful?

19:00 - 22:00 iCSD Dinner, Matteo's of Boca Raton

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Detailed Schedule: Sept 24

Monday, September 24, 2018
7:00 - 8:00 Breakfast

Session 5: Mechanisms of Spreading Depolarizations
Chairs: Bill Shuttleworth, David Andrew

8:00 - 8:20 **Ákos Menyhárt** – University of Szeged, Hungary
Large-conductance Ca2+-activated potassium channels are potently involved in the inverse neurovascular response to spreading depolarization

8:20 - 8:40 **Jiaming Cao** – Carnegie Mellon University, PA, USA
A Model of Neurovascular Coupling with application to Cortical Spreading Depolarization

8:40 - 9:00 **Ghanim Ullah** – University of South Florida, FL, USA
The Role of Glutamate Uptake in Neuronal Ion Homeostasis: A Case Study of Spreading Depolarization

9:00 - 9:20 **Dániel Péter Varga** – University of Szeged, Hungary
The fundamental role of microglia in the induction and propagation of spreading depolarization in the intact mouse brain

Special Session on Historical Figures in SD Research: George Somjen

9:20 - 9:40 **Eszter Farkas and Ákos Menyhárt** – University of Szeged, Hungary
George Somjen and the search for the ion channels mediating sustained, mass depolarization

9:40 - 10:00 **R. David Andrew** – Queen's University, Canada
A putative channel that drives spreading depolarization

10:00 - 10:50 **Posters and Networking 2**

Session 6: Treatments for Spreading Depolarizations
Chairs: Jens Dreier, Isamu Aiba

10:50 - 11:10 **Isamu Aiba** – Baylor College of Medicine, TX, USA
Potassium channel opener retigabine inhibits spreading depolarization by potentiating voltage dependent NMDAR channel block

11:10 - 11:30 **Eszter Farkas** – University of Szeged, Hungary
Administration of nimodipine by pH-regulated nanoparticles restrains metabolic burden imposed by SD in global forebrain ischemia

11:30 - 11:50 **Andreia Lopes de Morais** – Massachusetts General Hospital, MA, USA
Vagus Nerve Stimulation and Cortical Spreading Depression

11:50 - 12:10 **Pulkit Grover** – Carnegie Mellon University, PA, USA
Non-invasive suppression of cortical spreading depolarization using current stimulation

12:10 - 12:30 **Andrew J. Whalen** – Penn State University, PA, USA
Control of Spreading Depression with Electrical Fields

12:30 - 13:30 Lunch

Detailed Schedule: Sept 24

Session 7: Clinical Neuromonitoring
Chairs: Johannes Woitzik, Andrew Carlson

13:30 - 13:50 **Johannes Woitzik** – Charité - Universitätsmedizin Berlin, Germany
History, evidence and current state of the art of multimodal monitoring in neurocritical care

13:50 - 14:10 **Fumiaki Oka** – Yamaguchi University School of Medicine, Japan
Regional temperature, cerebral blood flow and metabolism responses to cortical spreading depolarization in human

14:10 - 14:30 **Alois J. Schiefecker** – Medical University of Innsbruck, Austria
Brain temperature regulation in poor grade patients with subarachnoid hemorrhage – a multimodal neuromonitoring study

14:30 - 14:50 **Martyn G. Boutelle** – Imperial College London, UK
Resolving the metabolic signature of SD using dexamethasone enhanced continuous-online microdialysis (coMD)

14:50 - 15:10 **Chanju Fritch** – University of New Mexico, NM, USA
Spreading Depolarization Probability with Decreasing Mean Arterial Pressure May Be Explained by Disturbed Autoregulation

15:10 - 15:30 Break

Keynote Lecture 3

15:30 - 16:30 **Ari Ercole** – University of Cambridge, UK
Neuromonitoring: from signals to service, via systems and statistics

Open Discussion

16:30 - 17:30 **Moderator: Raimund Helbok** – Medical University of Innsbruck, Austria
What should a clinician do when spreading depolarizations are observed?

17:30 Final Announcements and Adjournment

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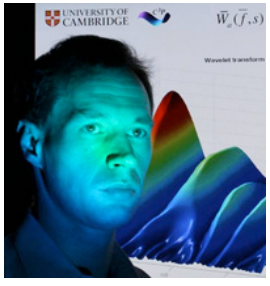
Keynote Speakers

David Okonkwo, MD, PhD, Clinical Director of the Brain Trauma Research Center, University of Pittsburgh. Dr. Okonkwo has advanced novel neuroimaging modalities for personalized management of TBI and is principal investigator of a nationally funded clinical core to study TBI pathophysiology. He has contributed as a thought-leader to many clinical research initiatives and has been one of the most proliferative contributors to COSBID research efforts.

Marc Simard, MD, PhD, Professor of Neurosurgery, Pathology and Physiology, University of Maryland. Dr. Simard is known for ground-breaking research into the molecular pathophysiology of cerebral edema following stroke and cardiac arrest, including discovery of the Sur1-Trmp4 channel. His basic science insights are now being translated in active clinical trials of glibenclamide.



Ari Ercole, MD, PhD, Lecturer and Consultant Anaesthetist, University of Cambridge. With a doctorate in physics, Dr. Ercole adds a unique dimension to the Brain Physics Lab that studies the relationship between volume, pressure, and blood flow in the brain and has developed the pressure-reactivity index and the concept of individual optimal cerebral perfusion pressure. Dr. Ercole also leads efforts in analysis of high-resolution ICU data and is a CENTER-TBI investigator.

ABSTRACTS

Electrocorticography in surgically managed brain trauma patients. Part I: spreading depolarizations and their relationship to clinical variables

Jed A. Hartings[1], Anthony J. Strong[2], Norberto Andaluz[1], M. Ross Bullock[3], Jason M. Hinzman[1], J. Adam Wilson[1], Bruce Mathern[4], Clemens Pahl[5], Lori A. Shutter[6,7], Achala Vagal[8], Hester Lingsma[9], Jens P. Dreier[10], Brandon Foreman[11], Tomas Watanabe[12], Ava M. Puccio[7], and David O. Okonkwo[7]

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[2]Department of Clinical Neuroscience, King's College London, London, UK
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[8]Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[9]Department of Public Health, Centre for Medical Decision Making, Erasmus MC, Rotterdam, The Netherlands
[10]Departments of Neurology and Experimental Neurology, Center for Stroke Research Berlin, Charité University Medicine, Berlin
[12]Lannister-Finn Corporation, Ambler, PA, USA

Introduction: Spreading depolarizations (SDs) are a heterogeneous mechanism of secondary damage after severe traumatic brain injury (TBI). To investigate SD risk factors and the diagnostic/prognostic value of SD monitoring, we conducted a prospective, observational study in adult patients who required neurosurgery for acute TBI treatment. **Methods**: The study was conducted at five centers from 2009 to 2013. Electrode strips were placed intra-operatively for subsequent electrocorticography (ECoG) during intensive care. Clinical variables were collected prospectively and monitored for accuracy. **Results**: 138 of 165 patients were included in the analysis after exclusions for poor or short-duration ECoG recordings. Most patients [75% male; age 45 (29,64)] had cerebral contusions (58%) and/or subdural hematoma (55%), and signs of mass effect (84%). In a median ECoG time of 76 (43,117) hr, SDs (n=2,837) occurred in 83 (60%) patients. 36 (26%) patients had only isolated SDs that induced cortical spreading depression (CSD) in all affected channels. The others (n=46, 33%) had at least one SD cluster (>3 SDs/2 hr). Those with clusters included 22 (16%) of the 23 patients with SDs in isoelectric cortex (ISDs), where spreading depression cannot occur. The isoelectric state of ISDs was clearly induced by prior CSDs in 18 of 23 patients. Patients with no SDs or only isolated SDs significantly improved in neurologic exam through the course of ECoG monitoring (p's<0.05, Fisher's Exact), while those with clusters or ISDs did not (p's>0.75). Patients had normal arterial blood and intracranial pressures for 97% of all SDs observed. There were no associations between SDs and prognostic variables of age, GCS motor score, or pupil reactivity. However, patients with SDs had lower pre-hospital (first measured) systolic blood pressure than those without SDs [132.7 (±31.3) vs. 146.3 (± 33.3) mmHg, t-test, p=0.03], and more severe grade of subarachnoid hemorrhage was associated with greater SD risk (χ^2, p<0.05). 72% of patients had poor 6-month outcomes defined as severe disability or worse. In multivariate regression, classification of SD activity carried odds ratios for worse outcomes equal to or greater than conventional prognostic factors. **Conclusions**: These results suggest the importance of early ischemia and subarachnoid blood as risk factors for SDs and demonstrate the independence of SD information relative to other clinical variables. They further suggest a hierarchical classification of SD activity as (1) none, (2) isolated CSDs only, (3) SD clusters, and (4) ISDs, which may be useful to stratify for prognostic risk, select patients for treatment, or measure the effects of interventions.

Electrocorticography in surgically managed brain trauma patients. Part II: baseline patterns, seizures, and spreading depolarizations

Brandon Foreman[1], Hyunjo Lee[1], David O. Okonkwo[2], Anthony J. Strong[3], Norberto Andaluz[4], M. Ross Bullock[5], Jason M. Hinzman[4], J. Adam Wilson[4], Bruce Mathern[6], Clemens Pahl[7], Lori A. Shutter[2,8], Jens P. Dreier[9], Ava M. Puccio[2], and Jed A. Hartings[4]

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Introduction: Brain activity patterns after injury occur on a continuum from normal to interictal to ictal seizures (Sz), but the diagnostic and prognostic value of these patterns remains uncertain. Here we examined the relationship between electrocorticographic (ECoG) brain activity, ictal-interictal continuum patterns, spreading depolarizations (SD), and outcome after severe brain trauma.
Methods: We analyzed 138 patients with SD scoring as reported in the accompanying abstract (Part I). Based on selection of a single ECoG channel, we characterized background continuity, presence of sleep transients, periodic discharges (PD), and Sz every 4 hours using standardized terminology.
Results: The initial ECoG pattern was continuous in most patients [62/87 (71.3%)] with no SDs or only isolated SDs and was burst-suppressed (BS) or suppressed in 8/87 (9.2%). In contrast, the initial ECoG was continuous in only 19/46 (41.3%) patients who had clustered or isoelectric SDs and was BS/suppressed in 18/46 (39.1%; χ^2, p<0.001). Similarly, 31/91 (34.1%) patients with no SDs or isolated SDs showed sleep transients or maintained continuous background activity throughout the recording period; only 3/47 (6.4%) patients with clustered or isoelectric SDs had the same features (χ^2, p=0.001). PD were observed in 122/138 (88%) patients, and 2841 seizures (Sz; median per patient [IQR]: 19 [5-50]) occurred in 41/138 patients (29.7%). The daily PD burden was greater in those with isolated or clustered SDs (t test, p<0.01). Sz were more common in those with clustered or isoelectric SDs (42.6% (20/47) vs. 23.1% (21/91) than those with no SDs or isolated SDs [χ^2, p=0.018]) with higher daily Sz number and burden (t tests, p<0.01). The degree of *initial* ECoG suppression was significantly associated with greater subsequent daily burden of PD/Sz (ANOVA, p<0.01) and SD (ANOVA, p=0.02). Poor 6-month outcomes (Glasgow Outcome Scale-Extended) occurred in 32/41 (78.0%) patients with Sz vs. 67/97 (69.1%) without Sz (χ^2, p=0.28). In unadjusted ordinal regression, the daily burden of PD/Sz was not associated with outcome. However, the development of sustained ECoG background suppression had an odds ratio of 4.2 (95% CI 1.5-11.8) for poor outcome, which was independent of SD classification.
Conclusions: PD/Sz are common after sTBI and the burden of PD/Sz patterns was related to the initial ECoG background and SD classification. These ECoG patterns are distinct yet relate to each other and provide complementary information. Future efforts should focus on developing patient classification schemes based on these patterns to improve prognostication and patient selection for therapeutic intervention.

Cortical spreading depolarizations relate to injury severity in a mouse concussion model

James Bouley[1], David Y. Chung[2,3], Cenk Ayata[2,3], Robert H. Brown, Jr[1], and Nils Henninger[1,4]

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Introduction: Cortical spreading depolarization (CSD) has been described after moderate-to-severe traumatic brain injury (TBI). However, it is uncertain whether CSD occurs after mild, concussive TBI and whether it relates to brain pathology and functional outcome.
Methods: Male C57BL6/J mice (n=62) were subjected to closed head TBI with a 25g weight (n=11), 50g weight (n=45), or sham injury (n=6). Laser Doppler flowmetry and optical intrinsic signal imaging were used to determine cerebral blood flow dynamics after concussive CSD. Functional deficits were assessed at baseline, 2 h, 24 h, and 48 h. TUNEL and Prussian blue staining were used to determine cell death and presence of cerebral microbleeds at 48 h.
Results: No mouse subjected to a 25g weight drop and 58.9% of mice subjected to 50g weight drop developed a CSD. Mice with concussive CSD displayed significantly greater numbers of apoptotic cell profiles in the ipsilesional hemisphere as compared to mice without a CSD that were subjected to the same 50 g weight drop paradigm (p<0.05, each). All investigated animals had at least one cerebral microbleed (range 1 to 24). Compared to mice without a CSD, mice with a CSD had significantly more microbleeds in the traumatized hemisphere (p<0.05, each) and showed impaired recovery (p<0.05).
Discussion: Incidence of CSD after mild TBI depended on impact severity and was associated with histological and behavioral outcomes. These observations indicate that concussive CSD may serve as viable marker for concussion severity and provide novel avenues for outcome prediction and therapeutic decision making.

CSD² (Cortical Spreading Depolarizations (CSD) in Chronic Subdural Hematoma (cSDH) Patients after evacuation) Trial

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Introduction: Chronic subdural hematoma (cSDH) is one of the most common pathologies treated by neurosurgeons. Most patients recover after evacuation with a straightforward course. There is a subset of patients who do not improve or even worsen after evacuation. While some of these patients may have focal seizures, we hypothesize that worsening in some cases may be related to temporary brain dysfunction caused by cortical spreading depolarizations (CSD).
Methods: Prospective observational study of 30 patients who underwent cSDH evacuation. At the time of surgery, a 1x6 subdural electrode strip was placed on the cortex parallel to the drain and removed at the time of drain removal. CSD was scored using standard criteria of propagating DC shift, with associated depression of high frequency electrocorticography (ECog) activity. Clinical outcomes were assessed utilizing the Markwalder Grading Scale (MGS).
Results: All subjects were found to have a readable ECog for a total recording time of 1,071 hours, 55 minutes. Definite CSD occurred in 4/20 subjects (13%). In these subjects, the number of events varied from 4 to 7, with CSD events generally occurring in clusters. All subjects had adequate evacuation of the cSDH, with improvement in mass effect. A clinical EEG was ordered in 3/30 subjects (10%), with no findings of seizure or epileptiform activity. Of the 4 subjects with CSD, one was noted to have clinical deterioration, which required an EEG for new neurologic deficit. The new deficit was observed 40 hours following the appearance of the first CSD, after the electrode strip was removed.
Discussion: This is the first observation of CSD occurring after cSDH evacuation, at a rate of 13% in our series. Since CSD is known to cause transient neurological dysfunction in eloquent cortex, this phenomenon may be responsible for some cases of protracted recovery. One of our CSD subjects demonstrated delayed clinical deterioration. This may represent a new therapeutic target in these patients.

Ketamine suppresses spreading depolarizations in a case of severe brain trauma

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Introduction: A prospective, randomized, multiple-crossover clinical trial showed that spreading depolarizations (SDs) after brain injury are suppressed by sedative doses of racemic ketamine. However, no effect was observed within patients. Here we present a case report in which a bolus dose of racemic ketamine abruptly interrupts a long-running cluster of SDs, without adverse effect on intracranial pressure (ICP).
Case: A 49-year-old man suffered severe brain trauma from a 30-ft fall. After emergency evacuation of a large left subdural hematoma and hemicraniectomy, a subdural electrode strip was placed on the inferior frontal gyrus to monitor SD; ICP, PbtO2, and EEG were also monitored. From the start of neurointensive care, SDs (n=55) recurred continuously at regular intervals of 20 (±6) min for 18 hr. In this time, ICP steadily increased to >60 mmHg and was refractory to standard treatment. A 1.5 mg/kg intravenous bolus of racemic ketamine was given to maximize sedation while preserving arterial pressure. SDs stopped after the bolus, remained suppressed for 2 hr, but then resumed at regular intervals of 23 (±6) min, totaling 50 events in 19 hr. During the 2 hr of SD suppression, EEG activity recovered in selected channels that had exhibited depressed and fluctuating activity as manifestations of repetitive SDs. Throughout the course, cerebral autoregulation was severely impaired, as indicated by pressure-reactivity index (PRx; moving-average correlation coefficient of ICP and blood pressure) values of 0.75 ± 0.21. Patient manipulations, including the ketamine administration, thus transiently increased blood pressure and ICP by 19 and 6 mmHg, respectively, but values returned to baseline within 15 min. On average, ICP was decreased in the 2 hr period following ketamine administration compared to the 2 hr before and after (65.2+/-2.4 mmHg vs. 67.2+/-2.9 mmHg; $p<0.001$). Ketamine was not continued due to a family decision to withdraw care.
Discussion: This case provides striking evidence for the potency of racemic ketamine to suppress SDs, even in the setting of severe injury with refractory elevated ICP and impaired autoregulation. Historical notions that ketamine may cause ICP elevation have been refuted in randomized studies, and no adverse effects were observed in this case. The continuous recurrence of SDs in this case, particularly in the setting of otherwise medically refractory pathology, raises the question of whether SDs should have been treated throughout the patient course.

Monitoring of spreading depolarizations (SD) in closed skull models of rat brain ischemia

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Introduction: The ultimate goal in monitoring of SDs is the advancement of non-invasive technologies. Scalp EEG combined with optical imaging may hold promise for monitoring SDs in patients. We tested the hypothesis in two separate experimental settings that the changes in EEG parameters **(A)** or the morphology of the hemoglobin (oxy/deoxy) and flow transients **(B)** have a predictive value for the outcome in animal models of focal cerebral ischemia. **Methods (A):** Filament occlusion (90 min) of the middle cerebral artery was performed on Sprague-Dawley rats (n=12) under isoflurane anesthesia. The scalp was chemically depilated and two silver/silver chloride (Ag/AgCl) electrodes were stitched to the skin. Laser Doppler (LD) Flowmetry was achieved by an LD probe affixed over a circularly thinned bone (4-5mm lateral to midline, 1-2mm posterior to Bregma). After 72 hours of survival, the brain was removed, sections stained with haematoxylin, and the infarct size was determined. In a control group (n=8), a bipolar stimulation electrode was placed on the pial surface (2mm frontal to the LD probe) and cathodal pulses (5mA, 100ms) were applied to elicit three SDs. **Results (A):** In the scalp EEG recordings, non-spreading depression occurred 18 (14, 38) s after the drop in CBF. Linear regression showed that the mean scalp AC-EEG power correlated with the infarct volume. The best cut-off value separating the filament occluded animals from the control animals was a reduction of the mean scalp AC-EEG power to 65% from baseline (100%) over at least 15 min. In the scalp EEG recordings DC shifts failed to reach statistical significance. **Methods (B):** The middle cerebral artery was occluded by photothrombosis (4mW) and the ipsilateral common carotid artery was ligated permanently in Sprague-Dawley rats (n=10) under isoflurane anesthesia. A 6x6 mm area centered 3 mm posterior and 4 mm lateral to Bregma was thinned for laser speckle and optical spectroscopic imaging. Nine circular regions-of-interests (ROI) (0.3 mm in diameter) were evenly spaced on the images for the analysis of blood flow and oxy- and deoxyhemoglobin transients. Five different types of morphology of the transients were determined as described previously (Luckl et al. 2009). The infarct size was determined by triphenyltetrazolium chloride staining after 24 hours of survival. **Results (B):** The infarct volume (126±38 mm3) indicated successful occlusions in all animals. By pasting the histological sections together with the ROI map we could distinguish the non-ischemic area (the medial row of ROIs close to the midline) from the penumbral/core area (the middle and lateral rows of ROIs). A contingency analysis showed a strong correlation between the type of transients and regions (non-ischemic versus penumbra) or even individual ROIs. **Conclusion:** The results suggest that the combination of scalp EEG with optical imaging technologies holds promise for the detection of SDs in clinical settings.

Reference: Luckl J, Zhou C, Durduran T, Yodh AG, Greenberg JH (2009). Characterization of periinfarct flow transients with laser speckle and Doppler after middle cerebral artery occlusion in the rat. J Neurosci Res. 2009 Apr; 87(5):1219-29.

Optogenetic spreading depolarizations in focal cerebral ischemia

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Introduction: Peri-infarct depolarizations (PIDs) are believed to contribute to injury progression and worsen the outcome. Previous studies showed that exogenously induced SDs by depolarizing interventions (e.g. topical KCl) results in larger infarct volumes. However, such interventions are inherently highly invasive and often cause primary tissue injury. Here we employed a novel, non-invasive and non-injurious SD induction method using optogenetics in transgenic mice expressing channelrhodopsin-2 in neurons (Thy1-ChR2-YFP).
Method: We transiently (1h) occluded the middle cerebral artery distally using a microvascular clip (dMCAO) or proximally using an intraluminal filament (fMCAO) in Thy1-ChR2-YFP mice (age ~10 weeks, male), and triggered an SD every 5 minutes using optogenetic stimulation (470 nm, 1-2 mw, 10 seconds) of non-ischemic ipsilateral cortex. SDs were detected by optical intrinsic signal (OIS) imaging. Tissue and neurological outcomes were studied 24 hours after fMCAO and 48 hours after dMCAO by TTC staining. We also examined the effect of light on wild-type (C57BL6/J) animal.
Result: Optogenetic stimulation group had 7.8 ± 1.6 PIDs/h (n=5) compared with 0.4 ± 0.9 spontaneous PIDs/h (n=5) in the non-stimulated group during dMCAO. Surprisingly, this 20-fold increase in PID numbers in the optogenetic stimulation group did not alter the infarct volume compared with the non-stimulated group (12.0 ± 2.6 vs. 12.8 ± 2.9 mm^3, respectively; p=0.8427). Moreover, cortical infarct volumes after fMCAO were significantly smaller in the stimulated group than non-stimulated group (18.5 ± 9.0 vs. 50.0 ± 6.0 mm^3, n=6 and 4, p=0.0321), despite 5-fold higher PID numbers (9.0 ± 1.7 and 1.8 ± 1.2 PIDs/h, respectively). Neurological deficit scores did not differ (6.8 ± 1.3 vs. 8.3 ± 0.5, n=6 and 4, in stimulated vs. non-stimulated groups, respectively; p=0.4292). In wild-type mice (i.e. $ChR2^{-/-}$), optogenetic light application did not significantly affect the PID frequencies, infarct volumes or neurological deficits after dMCAO and fMCAO.
Conclusions: Our results suggest that SDs induced non-invasively and non-injuriously away from the primary injury site do not worsen tissue outcome.

Metabolic heterogeneity in compromised tissues influences excitotoxic consequences of spreading depolarization

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Introduction: Slowly-propagating waves of neuronal and glial depolarization (spreading depolarization; SD) can contribute to the progression of stroke and traumatic brain injuries. We are interested in cellular determinants that confer SD vulnerability in order to develop interventions that can limit glutamate-mediated excitotoxicity during SD. We used complementary in vitro and in vivo mouse models of metabolic compromise to assess differences in glutamate and Ca2+ signaling.
Methods: Two photon imaging was used in vivo to examine neuronal intracellular Ca2+ (GCaMP) and extracellular glutamate with viral transfection of iGluSnFr. SDs were initiated with focal KCl microinjection and, in some animals, focal ischemia generated with distal middle cerebral artery occlusion or photothrombosis.
Results: After stroke, SD-associated glutamate and Ca2+ signals were prolonged in penumbral versus remote regions with better perfusion. In non-injured animals, we observed microheterogeneity in neuronal recovery after SD, related to vascular proximity. Thus, decay of Ca2+ signals was significantly delayed in regions more distant from penetrating arterioles. Complementary studies were conducted in brain slices, to model penumbral conditions. Moderate restriction of metabolic substrates did not alone cause damage, but rendered slices vulnerable to SD. The adenosine A1 receptor antagonist DPCPX increased EPSP amplitude and normalized paired pulse ratio, consistent with metabolic compromise and accumulation of extracellular adenosine. KCl-evoked SDs still propagated but resulted in prolonged inhibition of functional recovery. EPSP suppression after SD was partially due to A1R activation, but DPCPX did not fully restore EPSP amplitude, implying persistent dysfunction or injury. Glutamate and neuronal Ca2+ transients were significantly longer, consistent with a role of these mediators in extended dysfunction after SD in vulnerable tissues. These results demonstrate that gradients of tissue metabolic capacity influence glutamate and neuronal Ca2+ loading after SD, and also raise the possibility that neurons distant from arterioles are most vulnerable to deleterious consequences of SD. While improved vascular supply is expected to be helpful for SD recovery, results with the slice model indicate that targeting glutamate-mediated excitotoxicity can significantly improve recovery.

The relationship of calcium channel activation and optical intrinsic signals during in vivo cortical spreading depolarizations

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Introduction: Optical intrinsic signal imaging (OISI) is an established tool for assessing cortical spreading depolarizations (CSD) and offers potential for clinical application. OISI analysis can include information about local blood oxygenation (BOLD) as well as neuronal activation. To better understand the relationship between neuronal polarization states and the OIS in the intact in vivo cortex, we examined simultaneous OISI data and calcium channel activation in transgenic GCaMP6 mice during CSDs from cortical stimulation as well as terminal spreading depolarizations (TSD).
Methods: Thy1-GCaMP6f (n=8) heterozygous C57Bl6 mice underwent surgery with isoflurane anesthesia to install a cranial window while fixed in a stereotaxic frame. Imaging took place on a Nikon Ti-E SpectraX system with ~10 µs fast gating acquisition of 470 nm fluorescence and reflected light from 555 and 640 nm channels. A capillary tube pulled to a sharp tip was inserted into the cortex to induce a CSD. Isoflurane was increased to 5% to investigate TSDs.
Results: A cortical pinprick and isoflurane overdose consistently initiated SDs. However, GCaMP activation traveled faster following the pinprick (4.25 mm/min) compared to ischemic events (2.63 mm/min). After a pinprick, compared to the calcium changes, the OIS peak increase was delayed by 18 s. However, the OIS peak preceded the calcium channel changes in TSD events by 20 s.
Discussion: Fast gated multi-channel imaging allowed the characterization of neuronal activation and provided additional information about local tissue oxygenation levels from the simultaneous OISI. Cortical stimulation initiated CSDs and a subsequent increase of oxygenated blood in the region; isoflurane was associated with an anticipated ischemic decrease in oxygenation before CSD, followed by an increase just prior to neuronal activation. The calcium channel signal propagation through the cortex and OIS data match previously reported velocity and alterations in blood oxygenation. The OIS changes in in vivo cortex appear to couple to calcium changes differently in pinprick induced CSDs vs. ischemic TSDs. These changes may not be entirely explained by BOLD differences.

Spreading depolarization during cardiac arrest in a rodent model as an ultra-early biomarker of neurological outcome after resuscitation

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Introduction: Spreading depolarization (SD) is associated with a variety of neurological disorders. Typically, SDs are detected by ECoG and are associated with worse neuronal injury. Recent studies in animals and humans show terminal depolarizations occurring during death. Our lab focuses on global cerebral ischemia/reperfusion using a preclinical model of cardiac arrest (CA) and cardiopulmonary resuscitation (CPR). We studied the role that SDs may have in our model.
Methods: Rats (n=27) underwent asphyxial CA+CPR. Continuous multimodal monitoring included: ECoG, cerebral blood flow (CBF), brain tissue oxygenation, tissue scattering, cerebral metabolic rate of oxygen (CMRO2), electrocardiogram (ECG), and invasive blood pressure. Neurological deficit scores (NDS) were assessed post-CPR to evaluate outcome. We applied low-pass filters to ECoG data and also measured DC potentials to detect SDs.
Results: Within 3 minutes after onset of asphyxia, we detected SDs in all rats using ECoG. Simultaneously, we observed traveling waves of CBF and tissue scattering changes as well as vasoconstriction of cerebral vessels. Intriguingly, the earlier SDs occurred, the better the neurological outcome as assessed by NDS testing ($r=-0.74$; $p<0.00001$). Within 2 minutes after successful CPR and reperfusion, we detected another wave resembling a spreading repolarization (SR). The SR was corroborated by all multimodal measurements. Rats with earlier SR waves also showed better neurological outcome on NDS testing ($r=-0.69$, $p<0.001$).
Discussion: In our CA+CPR model of global ischemia, multimodal monitoring of the brain demonstrated SDs during ischemia and SRs during reperfusion. Earlier SD and SR is associated with better neurological outcome, suggesting the possibility that they may be ultra-early biomarkers of post-CA outcome in survivors. Our lab is exploring cellular and molecular mechanisms that may be underlying these observations and which may have therapeutic implications.

Functional recovery after anoxic depolarization in insect model systems

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Introduction: In the mammalian brain, the restoration of neural circuit function after spreading depolarization (SD) takes substantially longer than neuronal repolarization and the recovery of ion gradients. This is due, in part, to the accumulation of the low energy metabolite, adenosine, and the activation of A1 receptors. However, in a fly model, activation of AMPK, another indicator of metabolic stress, accelerates functional recovery from an anoxic coma, induced by anoxic depolarization, and this appears to be mediated by glia. The metabolic influences on recovery after SD remain unclear. We characterized determinants of neural recovery after anoxia in locust and Drosophila SD models.
Methods: We used two insect models: respiratory pattern generation in the locust and walking locomotion of adult flies. We compared the timing of coma entry and functional recovery after anoxia induced by N2 gas, CO_2 gas or immersion in water. We also used pharmacological approaches to manipulate adenosine receptors.
Results: In locusts and flies, entry to coma was considerably more rapid with CO_2 than with N2, whereas neural circuit recovery was more rapid after N2 than after CO_2. Locusts immersed under water took longer to succumb than with gas but this is likely a trivial result of the reservoir of air in the trachea. However, in spite of equal coma durations (30 mins), the recovery from water immersion was substantially longer than after a gas anoxia. Treatment with adenosine increased recovery time in a dose-dependent manner. Low doses of caffeine, an A1R antagonist, decreased recovery time but this effect reversed as dosage increased, perhaps due to non-specific actions.
Discussion: It is clear that the method of anoxic coma induction has a considerable effect on the timing of functional neural recovery, independently of the coma duration. We attribute this to different metabolic consequences of the treatments that include a build-up of adenosine in the CNS, as for mammalian systems. In future experiments we will use the power of molecular genetic approaches in Drosophila to tease apart the metabolic pathways and cellular contributors to recovery of neural circuit function after an anoxic coma.

Quantitative characterization of spreading depolarizations as an evolving, individualized disease process

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Background: Spreading depolarizations (SD) are identified by expert visual review of ECoG recordings, and events are scored according to type (depression or isoelectric), pattern (isolated or clustered), and depression duration. Here we undertook a comprehensive quantitative characterization of ECoG recordings with an aim toward (1) developing objective criteria for SD identification, (2) discovering features of SD-related changes beyond those recognized in present scoring practices, and (3) identifying long-term 'contextual' trends that transcend individual SD events.
Methods: We examined 4020 hours (6 channels x 670 hr) of subdural ECoG strip recordings from 10 patients, which included 462 individual SDs. Negative DC shifts were quantified for amplitude, duration, and magnitude after detrending with a 20-min moving average. ECoG power in the 0.5-45 Hz band was estimated with a multi-scale average technique (effective resolution = 1 sec) and, for each SD, was used to measure baseline power, time to max suppression, suppression recovery time, total depression duration, peak depression, and depression magnitude. In addition, we calculated 17 time-dependent quantitative descriptors (resolution = 5 sec) of signal statistics for both global and SD-specific ECoG characterization, including mean, standard deviation, kurtosis, skewness, peak-to-peak amplitude, peak-to-rms, spectrograms, bandwidth estimates, and spectral entropy.
Results: As expected, measures of DC shifts (amplitude, duration) and power depressions of SDs differed across subjects (ANOVA, p's<0.05). Accordingly, separating data by subject and recording channel reduced the variance of all measures, demonstrating a strong degree of intra-subject and intra-channel correlation. Visualization of DC and depression descriptors as a function of event sequence and time revealed the presence of trends correlated with subject, channel, and time. In 9 of 10 cases, at least one indicator showed a continuous trending chance for at least 24 hr. Such trends occurred independent of the rate of SD occurrence, and thus were not limited to clusters. Visualization of global background activity also revealed trends through recording time, suggesting that there is active and continuing evolution of the disease process or tissue state beyond any arbitrary interval set around an SD event.
Conclusions: The presence of strong intra-subject, intra-channel, and temporal correlation limits the validity of statistical analyses that assumes independence between SD events. These results suggest new methods to characterize and track disease progression at the individual level, and also for scoring and classification of SD events and patterns.

High frequency oscillations on electrocorticography of patients with brain injury – an extension to spreading depolarizations?

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Introduction: Neuronal high frequency oscillations have been linked to neuronal plasticity and to the evolvement of cortical spreading depolarizations (SDs). Especially pyramidal cells and interneurons may generate high frequency oscillations, which have been described as "ripples" in the pathophysiologic context of epileptogenesis in patients with temporal lobe seizures using electrocorticography. In this study, high frequency oscillations have been investigated in the context of SDs.
Methods: Patients fulfilling the inclusion criteria were prospectively enrolled in the observational COSBID study (Co-operative Study on Brain Injury Depolarisations) including multimodal neuromonitoring from August 2013 – January 2018. 40 patients were monitored using subdural strip electrodes following craniotomy, one patient had to be excluded because of incomplete data. Electrocortical activity was recorded using Labchart 7.3 or Moberg Device at a sampling rate of up to 600 Hz. An 80Hz high-pass filter was applied for detection of ripples (high frequency oscillations). Statistical analysis was performed using Fisher's Exact Test. Data are presented as median and interquartile range.
Results: 30 patients with ICH, 6 with SAH, 2 with TBI and 1 patient with malignant ischemic stroke were monitored. Median age was 63 years (55-70), 38% of patients (n=15) were female. High frequency oscillations were detected in 74% (n=29) of patients, CSDs in 64% (n=25) of patients. High frequency oscillations occurred significantly more often in patients with CSDs (p=0.001). Quantitative EEG analysis and correlation with clinical parameters and outcome will be presented at the meeting.
Discussion: High frequency oscillations including ripples can be detected using subdural EEG monitoring and may be associated with the occurrence of spreading depolarizations.

Fin waves of the cerebral cortex and outcome following acute brain injury

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Background: A key contributor to outcome following acute cerebral insult, is the development of secondary injury. Any circumstance that imposes new metabolic stress on already damaged tissue can contribute to further injury and may be defined as a secondary insult. Among the most significant, is Spreading Depolarisations (SD). The Electrocorticographic (ECoG) characteristics of SD are apparent and provide a useful means of studying SD. In the course of investigation, we have discovered a distinct feature of the ECoG, previously undescribed. Marked a sharp onset and a slow subsidence, this feature has the appearance of shark fins prowling the baseline activity. We have therefore, designated them "Fin waves" (FW).
Objective: To describe the characteristics of FWs and their behaviour in relation to outcome and well-defined secondary insults.
Methods: In 11 brain injured patients, an ECoG electrode (6 platinum contacts, exposed Ø2.3mm, 10mm centre-to-centre, Adtech, USA), a temperature sensor (Licox, UK) and a pressure transducer (Codman, USA) were placed in tissue at risk. ECoG signals were acquired in a common reference configuration, high-pass filtered at 0.02Hz, digitized at 1kHz and recorded using Labchart (ADInstruments, Australia). Cerebral Perfusion Pressure (CPP) was monitored using ixTrend (ixcellence, Germany). Recording times ranged from 17-120hrs. Analysis was undertaken using Labchart and GraphPad Prism. Frequency was measured as count/30min. Outcome was assessed at 6 months according to the extended Glasgow Outcome Scale.
Results: At a time-base of ≥1mm/min, FWs were typically of negative polarity, developed rapidly, decayed slowly and often displayed a positive overshoot before returning to baseline. Their median (1st, 3rd quartile) amplitude and duration were 164 μV (111, 234) and 23s (20, 26), respectively. Brain temperature was available in 3/11 patients. In 1/3, fever developed. In this patient, frequency correlated with temperature (r= 0.4, P= 0.0042). In 4/11 patients, CPP data was available. In 1/4, episodic falls in CPP were observed. In this patient, frequency correlated inversely with CPP (r = -0.61, P<0.0001). Importantly, frequency was significantly higher in the 6/11 patients that died (Mann-Whitney U-test, p = 0.0152).
Discussion: FWs' associations with fever and low CPP - two well-defined secondary insults – suggests they increase under conditions of metabolic stress. Importantly, FWs' correlation with mortality suggests they may either be directly deleterious or signify on-going destructive processes.
Conclusion: FWs are a novel electrographic finding which convey potentially important clinical significance.

Non-invasive and automated algorithms for detection of CSDs with complex patterns

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Introduction: In this work, we advance on our automated algorithms for non-invasive detection of cortical spreading depolarizations (CSDs). CSDs are waves of neural silence that spread slowly across the brain surface and cause secondary brain injury after brain trauma (TBI) and stroke [*Dreier JP et al., Ann Neurol., 2018*]. In severe cases, CSDs are known to cause neuronal death [*Pietrobon et al., Nat. Rev. Neurosci., 2014*].
Motivation: TBI is a leading cause of death and disability in the United States. CSDs may contribute to poor outcomes. Today, CSD detection is done by visual inspection of invasively recorded signals that require surgical intervention. Only a handful of scientists have the training for visual inspection-based detection of CSDs. Automated non-invasive detection of CSDs is critical to bring CSD detection to the bedside and make it feasible for routine clinical use.
Methods: We model and simulate complex patterns of CSD propagation on real brain and head models, including semi-ring shape SDs in highly uniform media [*Tuckwell, AIP, 2008*], semi-planar SD "wavefronts" splitting from a single CSD wave, and single-gyrus CSD propagation [*Santos et al., ISCBFM, 2017*]. Key challenges in detecting these complex CSD patterns from non-invasive EEG recording include: (i) decay of high spatial frequencies as they travel from the cortical surface to the scalp surface; (ii) presence of sulci and gyri, which makes it difficult to track the CSD wave as it travels across the cortex; (iii) limited time of travel. To address these challenges, our algorithm detects and tracks wavefronts of CSD waves and stitches together data across space and time to decide on the presence of a CSD.
Results: To test our algorithm, we simulated CSD wave patterns on the cortical surface, and the resulting EEG signals, using head models of 4 subjects from the OASIS dataset. We also tested our algorithm for varying widths of "spreading suppressions" (width along the direction of propagation). We observed the accuracy of recovering the cortical signal from scalp measurements will improve with increasing number of electrodes, as has been reported previously [*Grover, et al., Proc. IEEE, 2017*]. The average width of suppressions that a low-density EEG grid of 40 electrodes can detect is 1.1 cm, whereas a high-density EEG grid with 340 electrodes can detect complex patterns of spreading suppressions as thin as 0.5 cm, with wavefront area of greater than 0.2 cm2, and with minimum duration of propagation of 5 minutes (most of the reported CSDs in literature meet these requirements [*Woitzik et al., Neurology, 2017*]). These results also make the case for higher-density EEG monitoring of brain injury sufferers.

Dynamic response of intracranial EEG to blood pressure following subarachnoid hemorrhage

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Introduction: After subarachnoid hemorrhage, changes in alpha and delta activity predict delayed cerebral ischemia (DCI) with high accuracy. Because induced hypertension is a treatment administered after DCI occurs we hypothesized that mean arterial pressure (MAP) may impact intracranial electroencephalography (iEEG) activity in these frequency bands.
Methods: We evaluated consecutive nontraumatic SAH patients who underwent clinical iEEG monitoring with depth electrodes or consented to subdural strip placement. Data was synchronized with physiologic parameters to create time-independent MAP-power frequency spectrograms. Two novel parameters (iEEG-Dx and iEEG-Ax) were defined as the correlation between MAP and power in delta and alpha frequency bands, respectively, and measured: 1) over the entire monitoring period, 2) pre- and post-DCI, 3) stratified by propofol infusion dosage, and 4) over 2-hour windows surrounding vasopressor interventions.
Results: Sixteen high-grade SAH patients (Fisher grade median 3) met criteria for analysis (11 depth, 5 strip electrodes). Averaging over the entire monitoring period, the iEEG-Dx correlation was positive in 6 patients, negative in 6 patients and neutral in 4 patients. The iEEG-Ax correlation was positive in 6 patients, negative in 8 patients, and neutral in 2 patients. The iEEGDx and iEEG-Ax correlations were concordant in 4 patients (2 both positive and 2 both negative) and inverse In 2 patients. There was no apparent relationship between the iEEG-Dx or iEEG-Ax correlation and anesthetic dosing (propofol in all sedated patients). Of 12 patients developing DCI, 8 had sufficient data to evaluate iEEG spectrogram responses to MAP before and after DCI. While differences were heteroegeneous, in 3 of 8, iEEG-Dx and iEEG-Ax both changed from both negative to both positive after DCI, some with a clear MAP threshold. 30 vasopressor challenges (7 patients) met criteria for evaluation. Over the 2-hour window, 19/30 vasopressor interventions (63%) resulted in a positive iEEG-Dx correlation and 19 (63%) demonstrated a positive correlation in iEEG-Ax during the vasopressor window with 14 interventions yielding a concordant iEEG-Dx and iEEG-Ax response. 11 of 30 interventions (37%) yielded a negative iEEG-Ax correlation.
Discussion: A subset of severe SAH patients undergoing intracranial EEG monitoring with depth and subdural electrodes demonstrate an association between mean arterial pressure and EEG alpha or delta power. This relationship is heterogeneous but persists when evaluating the period confined to vasopressor challenges and does is not clearly associated with anesthetic dosing.

Cortical spreading depolarizations in a mouse model of intracortical hemorrhage: causes and consequences

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Introduction: Cortical spreading depolarizations (CSDs) occur in all types of brain injury. Our understanding of CSDs in the setting of intracerebral hemorrhage (ICH) remains limited. We investigated the occurrence of CSDs and how they impact hematoma growth in hyperacute and acute stages of ICH in a mouse model. **Methods**: ICH was induced in CD1 mice (n=50) using intracortical injection of bacterial collagenase VIIs. Femoral artery was cannulated to monitor systemic physiology. Intrinsic optical signals (IOS), laser speckle flowmetry and electrocorticography were recorded for 4 hours starting immediately, 8, 24 or 48 hours after collagenase injection. Brains were harvested at the end of the recording. **Results**: Out of a total of 31 animals studied between 0-4h, only 10 mice developed a total of 20 spontaneous CSDs (median 2 CSDs/animal), occurring between 34 and 217 min after hemorrhage induction. These animals had significantly larger hemorrhages (13.4 ± 6.3 mm^3) than those that did not develop any CSDs (3.7 ± 3.4 mm^3). Spontaneous CSDs always originated from the hematoma. In contrast, not a single CSD was detected at later time points of 8-12h, 24-28h, and 48-52h after hemorrhage induction (n=3 each), despite large hematomas present in these animals (8.8 ± 5.3 mm^3). Importantly, spontaneous CSDs always occurred during periods of rapid hematoma growth (monitored by area of blood overlying the cortical surface using IOS), and often occurred in couplets. Conversely, hematoma expansion appeared to slow down immediately after the occurrence of CSDs, suggesting either that the slowing hematoma growth did not trigger any further CSDs or that CSDs slowed the hematoma growth. To determine the direction of causality, in a separate cohort we exogenously induced CSDs (8/4h) at a remote site by topical KCl. Induced CSDs reduced the hematoma volume compared with controls (9.4 ± 4.1 vs. 15.5 ± 5.3 mm^3). **Discussion**: These data suggest that spontaneous CSDs in ICH are triggered by either the pressure effect or ischemia caused by arterial disruption, while blood constituents or blood breakdown products do not directly contribute. Moreover, we show that CSDs limit hematoma expansion, presumably by their lasting vasoconstrictive effect (post-CSD oligemia). Therefore, CSD inhibition during hyperacute ICH may have deleterious consequences.

Mechanical disruption of glymphatic pathways and experimental subarachnoid hemorrhage are associated with similar perivascular inflammation

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Introduction: The glymphatic system is a recently recognized waste clearance system that is thought to be fundamental to normal cognitive function. Glymphatic disruption likely is a major contributor to morbidity after subarachnoid hemorrhage (SAH). Recent studies have shown that reduced clot burden and improved CSF clearance improves cerebral blood flow. The question remain open: is the "spasmogens" in the clot in the SA space responsible for vascular changes after SAH or is it the mechanical blockage of the glymphatic system with altered waste clearance?
Methods: We used a model of cisternally injected inert microbeads to reproduce the glymphatic blockage following SAH. We assayed expression of AQP-4, GFAP, and Iba1 at 1 hour, 24 hour, and 96 hour post injection, as well as ventricular volume.
Methods: In three treatment groups – either aCSF, autologous blood, or microbeads – was stereotactically injected into the prechiasmatic cistern of adult male rats. Glymphatic flow was assessed by injecting 20 µl of Evans Blue dye into the cisterna magna and then recording surface fluorescence intensity. Sagittal brain slices were immunohistochemically labeled for expression of AQP-4, GFAP, and Iba1 . Secondary antibody fluorescence signal was quantified regionally. ICP was assessed with a pressure transducer.
Results: Microbead and SAH groups showed comparable acute glymphatic dysfunction beginning at 1 hour. In both of these groups, AQP-4 and GFAP fluorescence intensity peaked at 24 hours and then decreased, whereas Iba1 peaked at 96 hours. ICP was increased at 24 hrs (aCSF 8, vs Beads 16, vs SAH 19 mmHg).
Conclusion: Mechanical cisternal occlusion with microbeads produces glymphatic dysfunction comparable to that following SAH. In both cases, glymphatic blockage triggers an upregulation of AQP-4, GFAP and IBA-1, consistent with a progressive inflammatory response. These findings indicate that obstruction of waste clearance through the glymphatic system after SAH is significant component of early brain injury and a novel pathway to cerebral edema and neuroinflammation.

SESSION 4 | Spreading Depolarizations in Injured and Normal Brain

Cortical and systemic inflammatory markers after spreading depression in mice

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Introduction: Cortical spreading depression (CSD) induces neuroinflammatory marker expression in rat cortex, in vivo, and hippocampal slice cultures, in vitro. Objectives of our study were (1) To employ non-invasive optogenetics method to induce CSD to study temporal profile of neuroinflammation after SD in mice, (2) to seek the presence of systemic inflammation, and (3) to check whether drug intervention of Dexamethasone and NSAIDs have effect on inflammation.
Methods: C57BL/6 (n=116) and Thy1-ChR2 YFP (n=41) mice were studied. To examine cortical inflammation, 1 or 6 CSDs were induced in one hemisphere using either 1M KCl cotton ball through thinned skull, or optogenetics (Illumination using 470nm LED light source for 10 seconds). CSD was detected either by non-invasive optical intrinsic signal (OIS) imaging or laser doppler through intact skull. For multiple CSD group, mice were sacrificed 1, 2, 4, 12 or 24 hour after first CSD. For single CSD group, mice were sacrificed at 4 hour. Cortical tissue was harvested from ipsilateral and contralateral (control) hemispheres. TNF-α, IL-1β, IL-6, CCL-2, VCAM-1 and ICAM-1 were measured using RT-PCR. In separate cohorts, dexamethasone was administered 15 min prior or 1, 2 or 3 hour after the first CSD and cortical makers were studied at 1 or 4 hours. Ibuprofen was given 15 min prior and markers were studied at 4 hour. To examine systemic changes, 6 CSDs were induced bilaterally, and data compared to sham mice. Mice were either sacrificed at 6 hours to measure CBC and plasma TNF-α, IL-1β, IL-6, CCL-2, VCAM-1 and ICAM-1, or 4 or 18-24 hours to measure spleen weight.
Results: Cortical tissue IL-1β, TNF-α and CCL-2 increased significantly and dramatically. IL-1β rapidly increased 1 hour after CSD (3638% of contralateral) but returned to normal at 2 hours. CCL-2 peaked at 2 hour (783%), and TNF-α at 4 hour (1077%). Changes in ICAM-1 and IL-6 were much smaller. VCAM-1 did not change. A single CSD also increased TNF-α and CCL-2 at 4 hour. Dexamethasone significantly attenuated cortical IL-1β, TNF-α and CCL-2 after CSD. Ibuprofen tended to decrease cortical TNF-α. Systemically, CSDs did not alter plasma inflammatory marker levels, CBC or spleen size.
Discussion: This is the first study reporting inflammatory marker expression changes after CSD in mice and non-invasively using optogenetics. We defined discrete temporal patterns for each inflammatory marker expressed in cortical tissue after CSD. We also for the first time show that dexamethasone attenuates cortical inflammation after CSD, even when given long after CSDs occurred. At time points studied so far, we have no evidence of systemic inflammation after CSD.

Stereological analysis of spreading depression-induced Egr-1 immunolabeled cells, in the rat somatosensory cortex

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Introduction: The zinc finger transcription factor early growth response-1 (Egr-1) is widely expressed in the brain, and regulates a range of cellular processes, including proliferation, growth and neuronal differentiation. More recently, it has been associated with an apoptotic function. Egr-1 expression can be triggered by several factors, but its downstream consequences still need to be better elucidated. Indeed, Egr-1 can be upregulated by cortical spreading depression (CSD). However, there is no detailed quantitative analysis using unbiased stereological methods to investigate potential correlations between the number of CSD episodes and Egr-1 expression in infragranular cortical layers.
Methods: In the present study, we elicited CSD within the left frontal cortex by the focal application of a 2% KCl solution. CSD was recorded at two sites within the left parietal cortex using a pair of Ag–AgCl, agar-Ringer electrodes. Electrophysiological recordings were performed over six hours before the animals were perfuse-fixed. A vibratome-cut anatomical series from both right and left (CSD) hemispheres was generated for each animal and an optical fractionator was used to count Erg-1 positive cells in two distinct experimental groups: low (2 to 5 CSD episodes (mean)) or high (6 to 10 CSD episodes (mean)); a sham group was recorded over the same period but was not stimulated with 2% KCl (zero CSD episodes).
Results: CSD increases Egr-1 expression in a time and event dependent manner in the ipsilateral hemisphere. Surprisingly, while CSD does not cross the midline the elevated expression of Egr-1 was also observed in the contralateral hemisphere in the 'high' group in the infragranular layers after 6 hours of recording. Thus, repeated waves of CSD have the capacity to generate far reaching and more global effects than previously considered likely. The mechanism of contralateral activation is unknown, but we suspect that callosal projections from the depolarized hemisphere are the cause.

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Effects of edema on neuronal excitability and spreading depolarizations after traumatic brain injury.

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Introduction. Edema is a major cause of morbidity and mortality after brain injury, and it occurs during a time when spreading depolarizations are prevalent. We examined the effects of neuronal edema on cellular and network measures of excitability after controlled cortical impact (CCI) TBI, using in vivo whole cell recordings and two photon microscopy. We examined layer 2/3 excitatory neurons in the hindpaw cortex, 1-1.5mm from the edge of a CCI lesion centered on barrel cortex.
Results. 48 hours after injury, Thy1 labeled neurons demonstrated a significant increase in cell volume as expected; however to our initial surprise this change was associated with a decrease in excitability. Intrinsic membrane resistance was decreased, capacitance was increased, rheobase was increased, and the frequency-current curve slope was decreased compared to sham treated animals. On a synaptic level, excitatory post-synaptic currents were reduced, and on a network level up-state area and action potential frequency were both decreased. Moreover, the voltage and calcium responses to sensory stimulation were reduced, and adaptation was enhanced, compared to sham. These changes were reversed by the NKCC1 cation chloride co-transporter inhibitor bumetanide. Thus post-CCI neuronal edema, thought to be associated with increased excitability, is actually associated with its opposite, and reversing the edema increases excitability. However, when spreading depolarizations were induced 48h after CCI, these were of significantly longer duration and associated with greater tissue displacement than in sham animals.
Discussion. We hypothesize that post-TBI neuronal edema may exert protective effects on excitability after TBI, likely due to the effects of neuronal volume on intrinsic excitability characteristics. However when excitable events like SD do occur in an edematous environment, their effects may be more deleterious, perhaps due to the effects of edema on the extracellular space. Further work aims to test these hypotheses.

"Concussion"-like impacts induce spreading depolarizations

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Introduction: It has been estimated that there are 1.6 to 3.8 million sport related concussions per year, in the United States. Concussions are diagnosed by vague behavioral responses, such as loss of consciousness, dizziness, headache, balance abnormalities, and/or difficulties concentrating. It has become clear that multiple concussions can result in progressive degeneration of the brain resulting in chronic traumatic encephalopathy (CTE) and such injuries are now considered to be mild traumatic brain injuries (mTBIs). Proper diagnosis and treatment of mTBIs are severely lacking because we do not fully understand the cellular and molecular effects that occur immediately following a blow to the head.
Methods: To model a concussion-like injury, we used a closed skull electromagnetic impactor model in mice without head restriction. Immediately following the impact, cerebral blood flow (CBF) was non-invasively monitored using laser speckle contrast imaging (LSCI) and neuronal activity was monitored with electrocorticography (ECoG).
Results: Our data indicate that a single closed skull impact results in a propagating wave of hypo-perfusion that coincides with a transient loss of neuronal activity, both of which are associated with spreading depressions (SDs). SDs were confirmed by their wave propagation rates, ECoG recovery, and extracellular potential shifts. CBF was monitored for 90 minutes and compared to the baseline CBF prior to the impact. Our preliminary data indicate that the CBF is reduced by 50% at 30 minutes and 30% at 90 minutes post-impact.
Discussion: Overall, our data suggests that a single impact produces a single SD and CBF could be used as a short-term diagnostic marker and indicator of brain recovery following an impact. Furthermore, our data provide a critical link between SDs and concussions/mTBIs, and suggests that SDs, in part, may play a role in acute behavioral phenotype of concussions.

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Large-conductance Ca^{2+}-activated potassium channels are potently involved in the inverse neurovascular response to spreading depolarization

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Introduction: Spreading depolarizations (SD) contribute to lesion progression possibly by the associated vasoconstriction and progressive reduction of cerebral blood flow (CBF). Our recent work has been driven by the hypothesis, that SD-related vascular smooth muscle cell (VSMC) depolarization is achieved by direct release of K+ from perivascular astrocyte endfeet, at higher than 20 mM concentration. Therefore we set out to determine the role of astrocyte large-conductance Ca2+-activated K+ (BK) channels and the VSMC L-type voltage gated Ca2+ channels (VGCCs) in the mediation of SD-related arteriolar constriction.
Methods: Local field potential (LFP), extracellular K+ concentration ([K+]e) and CBF variations were assessed with electrophysiology and laser-Doppler flowmetry in the cerebral cortex of anesthetized mice (n=15). In other mice, K+ accumulation using a fluorescent K+ indicator (APG-2), and diameter changes of rhodamine-dextran loaded arterioles were visualized synchronously with multiphoton microscopy (n=8). SDs were provoked with 1 M KCl. BK channels were blocked by paxilline (500 nM), while VGCCs were inhibited by nimodipine (100 uM). In live rat coronal brain slices (350 µm, n=8), SDs were triggered by bipolar constant current stimulation.
Results: Arterial constriction (from 16.4±3.2 to 6.7±5.1 µm) in response to SD was coincident in space and time with the drastic, extracellular accumulation of K+, as shown by the increase of APG-2 fluorescence (peak amplitude: 0.14±0.03 ΔF/F). Pharmacological manipulations hampered the [K+]e elevation with SD (32.9±4.4 vs. 29.7±5.4 vs. 37.0±3.5 mM, nimodipine vs. paxilline vs. control). Accordingly, paxilline reduced SD amplitude in vitro (9.1±5.3 vs. 17.2±5.5 mV, paxilline vs. control) and in vivo (11.8±6.2 vs. 19.3±4.5 mV, paxilline vs. control), and virtually diminished the SD-related hypoperfusion (relative amplitude: 2.82±0.1 vs. 24.03±13.23 %, paxilline vs. control). Nimodipine, although less potent, also reduced the magnitude of hypoperfusion (11.33±7.5 vs. 24.03±13.23 %, nimodipine vs. control).
Discussion: We propose that potassium efflux through BK channels – whether at the astrocytic endfeet or neurons – is a central component in SD-related pathophysiology and vasoconstriction. Overall, the data gathered here are highly relevant and translate to neurological disease states (i.e. ischemic stroke and traumatic brain injury), in which SDs reoccur.

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A model of neurovascular coupling with application to cortical spreading depolarization

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Introduction: Cortical spreading depolarizations (CSDs) are slowly propagating waves of neuronal hyperactivation followed by silencing on cerebral cortex, and are related to diseases e.g. traumatic brain injury, stroke, and migraine. The related vascular changes can be either spreading hyperemia or ischemia. Occurrence of ischemia in patients can imply worsening outcome and hence more severe CSD. There is therefore a need to distinguish hyperemia (mild) and ischemia (severe) to guide clinical care. We have developed a mathematical model of neurovascular (NV) coupling during CSD, which can be used to assess the feasibility of using fMRI and near infrared spectroscopy (NIRS) to distinguish hyperemia and ischemia.
Methods: We combine three differential equation-based models in the existing literature in serial, namely, (i) an ion exchange model that propagates and describes the dynamics of ions and neurotransmitters (ii) a NV coupling model that describes the chemical processes triggered by potassium and glutamate intake, and predicts vasodynamics (iii) a hemodynamic model that predicts hemodynamics and blood oxygen level dependent (BOLD) signals. We consider potassium as the main vasoactive factor, whose differential increase in concentration leads to the two CSD cases. The difference is made by changing the cleanup rate of potassium and neurotransmitters in the ion exchange model, mimicking the pump defection during ischemia.
Results: In mild CSD, we observe a maximum cerebral blood flow (CBF) increase of ~70%. In severe CSD, we see a triphasic vascular response (dilation, constriction, and a second dilation). The maximum CBF decrease is ~25% during vasoconstriction, and an entire wave lasts for ~120s. The results agree well with earlier experimental reports qualitatively and quantitatively. The model predicts an increase of oxygenated hemoglobin (HbO) and a decrease of deoxygenated hemoglobin (Hb) concentration in mild CSD. In severe CSD, HbO and Hb show inverse trends in the vasoconstriction phase. This inverse hemodynamic response suggests the feasibility of distinguishing hyperemia and ischemia with NIRS, which measures both HbO and Hb. BOLD signal in mild CSD shows a dip followed by a peak, while in severe CSD a second but smaller peak is also observed. Despite the distinguishability of BOLD, it is less significant than NIRS.
Discussion: Though demonstrated in the special case of CSD, the model has further applications to understanding NV coupling and interpretation of imaging data such as from fMRI. In future work, we will consider other vasoactive factors eg. nitric oxide, and model the oxygen supply dependent feedback effect of vasodynamics.

The role of glutamate uptake in neuronal ion homeostasis: a case study of spreading depolarization

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Simultaneous changes in ion concentrations, glutamate, and cell volume together with exchange of matter between cell network and vasculature are ubiquitous in numerous brain pathologies. A complete understanding of pathological conditions as well as normal brain function, therefore, hinges on elucidating the pathways involved in these mostly interdependent variations. In this study, we develop the first computational framework that combines the Hodgkin-Huxley type spiking dynamics, dynamic ion concentrations and glutamate homeostasis, neuronal and astroglial volume changes, and ion exchange with vasculature into a comprehensive model to elucidate the role of glutamate uptake in the dynamics of spreading depolarization (SD). Our results demonstrate that glutamate signaling plays a key role in the dynamics of SD, and that impaired glutamate uptake leads to recovery failure of neurons from SD. We confirm predictions from our model experimentally by showing that inhibiting astrocytic glutamate uptake using TFB-TBOA nearly quadruples the duration of SD in layers 2-3 of visual cortical slices from juvenile rats. The model equations are either derived from first physical principles of electroneutrality, osmosis, and conservation of particles or a combination of these principles and known physiological facts. Accordingly, we demonstrate that our model can account for several other normal and pathological brain states. Furthermore, our modeling framework provides an opportunity to investigate a range of key variables simultaneously in these states.

The fundamental role of microglia in the induction and propagation of spreading depolarization in the intact mouse brain

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Introduction: The selective elimination of microglia in rat hippocampal slice preparation was shown to elevate spreading depolarization (SD) threshold. Furthermore in a mouse model of focal cerebral ischemia, microglia ablation led to the dysregulation of neuronal Ca^{2+} signaling, and reduced the incidence of SD. Impaired clearance of extracellular potassium ($[K^+]_e$) has long been accepted as a key contributor to the evolution of SD. Since microglia release K^+ as a result of $P2Y_{12}$ receptor activation, we propose that microglial activity may contribute to SD development. Therefore, we set out to resolve whether the presence of microglia is critical for the elicitation and propagation of SD in vivo. Further, we aimed to investigate a possible interaction of microglial $P2Y_{12}$ signaling and $[K^+]_e$ homeostasis with respect to SD. **Methods**: Microglia depletion in adult male C57Bl/6J mice (n=13) was achieved by feeding a chow diet containing the CSF1R antagonist PLX5622 for 3 weeks. $P2Y_{12}$ receptor knock out ($P2Y_{12}$R KO) mice (n=7) and reference groups (n=14) were on control diet. On the day of experiments, two craniotomies were created on the right parietal bone of the animals under isoflurane-anesthesia. Four SDs were triggered by cathodal constant current stimulation or by topical application of 1M KCl in the rostral craniotomy. SD occurrence was confirmed in the caudal window by the acquisition of direct current (DC) potential, $[K^+]_e$ was monitored by ion-sensitive microelectrode. **Results**: The electrical threshold of SD elicitation elevated significantly for recurrent SDs in the microglia-depleted mice with respect to controls (182±119 vs. 85±30 µC). Microglia depletion also altered the DC potential signature of SD, reflected by its attenuated amplitude (18±1.3 vs 20.8±2.7 mV), and shorter duration (20±3.6 vs. 28±9.1 s) with respect to control. In accordance, the amplitude of depolarization was also reduced in the $P2Y_{12}$ R KO group (18.8±1.4 vs 20.8±2.7 mV), but the duration did not deviate from the control. Nonetheless, the hyperpolarization was increased in both groups, indicated by its area under the curve (182±54 and 138±87 vs 70±46 mV x s). $[K^+]_e$ shift with SD was shorter in the microglia depleted group (22.6±4 vs. 34.4±10 s), yet the peak elevation was higher (29.3±6.5 vs. 23±6.1 mM) compared to the controls. However, the genetical knock out of $P2Y_{12}$ receptor gene did not interfere with these parameters. **Discussion**: The data suggest that the presence of microglia lowers the threshold of SD elicitation and makes the brain more prone to SD, probably via sustained clearance of $[K^+]_e$. $P2Y_{12}$ receptor signaling may be partly involved in these mechanisms.

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SESSION 5 | Mechanisms of Spreading Depolarizations

A putative channel that drives spreading depolarization evoked by ischemia

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Ischemic neurons undergo spreading depolarization (SD) within minutes of heart failure, brain injury or focal stroke and can die within minutes. The macro-current that drives SD is well established as inward, non-selective to Na^+/K^+ ions, and reversing near 0 mV (Czeh et al. 1993). Like ischemic SD itself, the current resists blockers of standard voltage- and ligand-gated channels. Identifying this current requires single channel recording but little progress has been made since 1993. In neocortical slices from adult rat, we voltage-clamped membrane patches of pyramidal neurons during oxygen-glucose deprivation (OGD) at 35°C. Cell-attached patches were recorded in the presence of blockers of Na^+, K^+, Ca^{2+}, pannexin and glutamate-related channels. Each blocker was included both in the slice bath and recording pipette. This silenced all spontaneous channel activity within 2 minutes of blockers bathing the slice. During the next 5 minutes of OGD, novel channel opening commenced. The mean unitary current was 1.7 pA at holding potential (h)= -70 mV. Unitary event frequency increased over several minutes of OGD, as did multiple channel openings. More positive h values reversed the unitary current near 0 mV, indicating a Na^+/K^+ conductance. Channel slope conductance was ~28 pS based on unitary pA values from 23 neurons (h= -90 to 50 mV). This channel type clearly resisted the blockers, but what was it? The marine poison palytoxin (PLTX) binds the Na^+/K^+ pump, converting it into an open Na^+/K^+ channel. We have shown that PLTX induces SD in neocortical slices (10 nM in bath). Additional cell-attached recordings with 1 to 10 pM PLTX blockers in the pipette opened a channel similar to that opened by OGD. Moreover our outside-out isolated patch recordings showed that bath-applied PLTX (1 to 10 pM) evoked similar channel opening. Counterintuitively, when an outside-out patch was placed just above a slice, this channel type (or one similar) opened during several minutes of OGD. This suggested release of an endogenous PLTX-like molecule from the stressed slice, a possibility we are currently investigating. We propose that ischemia induces conversion of the Na^+/K^+ pump into an open channel that generates SD, tentatively in response to a released `SD activator` from gray matter.

Potassium channel opener retigabine inhibits spreading depolarization by potentiating voltage dependent NMDAR channel block

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Introduction: Spreading depolarization (SD) is a wave of massive cellular depolarization which slowly spreads through brain tissue, and contributes to the expansion of acute brain injury. NMDAR activation is one of the contributors of the propagating event, and NMDAR antagonists have been shown to inhibit SD in animal and human cortices. Retigabine was originally developed as a new class of antiepileptic drug. The basic antiepileptic mechanism is activation of M-type potassium channels, thereby hyperpolarizing the membrane potential to suppress aberrant discharges. Several studies reported that potassium channel openers can functionally inhibit NMDARs, likely by strengthening voltage dependent blockade of the NMDAR channel by Mg2+. We evaluated 1) whether such functional NMDAR inhibition can influence SD threshold and 2) whether this potassium channel opener also modulates synthetic NMDAR antagonists.
Methods: Pharmacological effects on SD threshold were evaluated using in vitro acute cortical slices and in vivo urethane anesthetized mouse cortex. In both models, SD was evoked by focal KCl applications.
Results: Initial in vitro studies using acute cortical slices showed a concentration dependent SD inhibition by retigabine, and SD was fully and reversibly inhibited at 30μM. A significant elevation of SD threshold by retigabine was also seen in anesthetized mouse cortex at a relatively high but clinically relevant concentration. As hypothesized, the mechanism is at least in part mediated by functional NMDAR inhibition, since SD inhibition by retigabine was completely lost when extracellular Mg2+ was removed in slice experiments. Retigabine also showed a significant augmentation of SD inhibition by synthetic voltage dependent NMDAR channel blockade. A low concentration of the NMDAR channel blocker memantine did not show any inhibitory effect on SD. In contrast, when combined with the potassium channel opener retigabine at subthreshold concentration, memantine showed a significant inhibitory effect on SD.
Discussion: The results suggest that a potassium channel opener can inhibit SD by strengthening the voltage dependent NMDAR channel block by either Mg2+ or a synthetic NMDAR channel blocker. Because the majority of clinically used NMDAR antagonists are voltage-dependent channel blockers (e.g. ketamine, memantine), potassium channel opener might be useful as an adjunct treatment for SD intervention. These results also suggest a potentially altered NMDAR antagonist sensitivity in individuals harboring potassium channel mutations (e.g. KCNQ2/3).

Administration of nimodipine by pH-regulated nanoparticles restrains metabolic burden imposed by SD in global forebrain ischemia

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Introduction: Nanoparticles are emerging carriers of drug delivery, which release drugs in response to specific signals exclusively at injury sites. We have previously demonstrated that spreading depolarization (SD) occurring in the rodent ischemic cerebral cortex initiates remarkable tissue acidosis. For the alleviation of SD-related metabolic burden, here we set out to apply nanoparticles to deliver nimodipine (an L-type voltage-sensitive Ca2+ channel antagonist) in response to decreasing tissue pH in a rat model of cerebral ischemia. This approach was expected to be neuroprotective without undesirable side effects that may be caused by systemic drug administration. **Methods**: Nimodpine (in solution, or associated to chitosan nanoparticles; 100 μM) or its vehicle (alone, or containing nanoparticles) was washed on the exposed brain surface of anesthetized Sprague-Dawley rats (n=35). Both common carotid arteries were permanently occluded (2VO) to create global forebrain ischemia. Recurrent SDs were elicited at 15 min intervals by topical application of 1M KCl. Local field potential, cerebral blood flow (CBF) and tissue pH-variations were recorded from the cerebral cortex. **Results**: Nimodipine in solution significantly increased baseline CBF already before 2VO (131±43 vs. 104±12% nimodipine vs. vehicle). In contrast, nimodipine carried by nanoparticles did not alter baseline CBF (105±16 vs. 107±33 %, nimodipine vs. nanoparticle only) and caused significant CBF elevation only after tissue pH reduction associated with 2VO (pH reduction of 0.23±0.17 units overall; CBF: 60±24 vs. 35±6%, nimodipine vs. nanoparticles only). Nimodipine carried by nanoparticles shortened the duration of both SD itself (54.9±37.1 vs. 106.9±65.5 s, nimodipine vs. nanoparticles only), and the associated tissue acidosis (62.6±30.8 vs. 139.5±64.7 s, nimodipine vs. nanoparticles only). Moreover it enhanced the magnitude of SD-related hyperemia (4543.8±2339.6 vs. 3003.6±1793.7%*s, nimodipine vs. nanoparticles only). **Discussion**: Our data demonstrate that tissue pH-dependent, targeted drug delivery can be achieved in a rodent model of cerebral ischemia, and may curb the metabolic burden imposed by SD on the nervous tissue.

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Vagus nerve stimulation and cortical spreading depression

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Introduction: Vagus nerve stimulation (VNS) acutely suppresses cortical spreading depression (CSD) susceptibility (Chen et al, 2016). Mechanisms of CSD suppression are unknown.
Methods: VNS (1ms pulse of 5kHz sine waves at 25 Hz) was delivered either non-invasively (nVNS) using cutaneous bipolar disc electrodes, or invasively (iVNS) using implanted bipolar hook electrodes. Stimulus trains were generated delivered using a customized stimulator modified from the current gammaCore nVNS device (electroCore LLC, Basking Ridge, NJ). Systemic physiology was monitored during the stimulation. CSD susceptibility was evaluated 40 min after the stimulation last. Experiment 1 determined the optimal nVNS protocol among 1x2-min, 2x2-min 5 min apart, 3x2-min 5 min apart, and 1x6-min. In Experiment 2 examined the effect of proximal or distal vagotomy on iVNS efficacy to suppress CSD. Experiment 3 tested serotonergic (5-HT) and Norepinephrinergic (NE) involvement in VNS effect by using the drugs PCPA (100mg/kg) and DSP-4 (150mg/kg) 3 and 14 days prior to nVNS, respectively.
Results: Among the studied protocols two 2-min stimulation 5 min apart was the most efficient. iVNS was responsible for 57.4% increase in electrical CSD threshold and 22% decrease in KCl-induced CSD frequency when an intact vagus nerve was stimulated. Distal vagotomy did alter the efficacy (55.4% higher threshold and 19% lower frequency). Proximal vagotomy completely abolished iVNS effect on CSD susceptibility. Both lesions (proximal and distal) increased CSD frequency by 10% by themselves. nVNS decreased CSD frequency by 25% and this effect was partially blocked by DSP-4 and PCPA. Two 2-min nVNS provided the optimal efficacy.
Discussion: Our results suggest that central 5-HT and NE pathways mediate VNS suppression of CSD.

SESSION 6 | Treatments for Spreading Depolarizations

Non-invasive suppression of cortical spreading depolarization using current stimulation

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Rational: Cortical spreading depolarizations (CSDs) are waves of electrical silencing in the normal brain activity which propagate across the cortical surface [Leao, J Neurophysiol., 1944]. Recently, CSDs have been shown to be responsible for worsening brain injuries [Hartings et al., Ann Neurol., 2014]. This motivates us to explore possible non-invasive methods to suppress CSD at its early stage of propagation.
Previous works: Commonly used techniques for CSD suppression involve invasive and/or pharmacological methods, i.e. (i) Lesion extraction or decompression after TBI and hemorrhages to remove clotted blood and stop CSDs [Hartings, et al., Ann Neurol., 2014], and (ii) Vasodilating drugs injection such as L-arginine to maintain enough energy and oxygen supplies to the neurons [Scheckenbach et al., Exp Neurol., 2006]. Due to the side effects of surgery and chemical injections in brain, and the time it takes to stop CSDs using these methods, obtaining non-invasive and fast methods of CSD suppression is critical. In this work, we try to answer two questions: 1. What are the physiological mechanisms of CSD propagation? 2. Is it possible to tune some spatiotemporal parameters to suppress CSD waves using available non-invasive and non-pharmacological techniques?
Methods: For simplicity, we use a model of CSD propagation [Tuckwell, AIP, 2008] that is based on reaction and diffusion of ions and neurotransmitters. Based on literature, NMDAR channels play critical role in CSD propagation and suppression [Somjen, Physiol. Reviews, 2001]. Based on this knowledge, we hypothesize that changing in the concentration and/or release rate of excitatory neurotransmitters (e.g. glutamate) could be used to suppress CSDs. In previous work, [Submitted to SfN'18], we have proposed techniques that alter glutamate pump strength to demonstrate suppression. Evidence shows that tDCS stimulation technique can non-invasively change the glutamate concentration in the extracellular space [Pelletier et al., Int J Neuropsychopharmacol., 2014]. We study, using rigorous simulations on Tuckwell's model, whether this change using tDCS technique is sufficient to suppress CSDs.
Results: Our simulation results suggest that changing the glutamate pump strength that decreases the glutamate extracellular concentration by about at least 8% can indeed suppress CSD waves completely. On the other hand, cathodal tDCS can reduce the concentration of glutamate up to 12% [Stagg, et al., J Neurosci., 2009], which is sufficient to completely suppress CSD propagation based on Tuckwell's model. This result remains to be tested through simulations and experiments that account for confounding factors.

SESSION 6 | Treatments for Spreading Depolarizations

Control of spreading depression with electrical fields

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Introduction: Spreading depression or depolarization is a large-scale pathological brain phenomenon related to migraine, stroke, hemorrhage and traumatic brain injury. Once initiated, spreading depression propagates across gray matter extruding potassium and other active molecules, collapsing the resting membrane electro-chemical gradient of cells leading to spike inactivation and cellular swelling, and propagates independently of synaptic transmission.
Methods: Spreading depression was induced in rodent cortical slices via local pressure injection of concentrated potassium chloride, and was measured with intrinsic optical imaging, extracellular electrophysiology and potassium dye epifluorescence.
Results: We demonstrate the modulation, suppression and prevention of spreading depression utilizing applied transcortical DC electric fields. We experimentally observe a surface-positive electric field induced forcing of spreading depression propagation to locations in cortex deeper than the unmodulated propagation path, whereby further propagation is confined and arrested even after field termination. The opposite surface-negative electric field polarity produces an increase in propagation velocity and a confinement of the wave to more superficial layers of cortex than the unmodulated propagation path.
Discussion: These field polarities are of opposite sign to the polarity that blocks neuronal spiking and seizures, and are consistent with biophysical models of spreading depression. Our results define some of the fundamental physics required to interfere with the generation and propagation of SD, and learning how to apply and adapt such physics to clinical therapies appears feasible.

SESSION 7 | Clinical Neuromonitoring

History, evidence and current state of the art of multimodal monitoring in neurocritical care

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Patients with significant neuronal injury caused by trauma, stroke or hemorrhage are frequently sedated or have significant impairment of their neurological function, which limits regular neurological assessment. After acute injury, intracranial hypertension, hypoxia, hyperthermia, spreading depolarization or seizures can trigger complex pathophysiological cascades resulting in secondary brain injury. Therefore, monitoring of brain integrity and function is of utmost importance in order to permit clinicians and researchers to detect, treat and even prevent such critical secondary brain injury. Against this background, continuous monitoring of intracranial pressure, electric activity, cerebral hemodynamics, autoregulation, oxygenation and metabolism has been used to assess tissue integrity by invasive, semi-invasive or non-invasive means. Historically, electrophysiology and intracranial pressure measurement remain first-line parameters for assessment of brain function. Meanwhile, more sophisticated techniques include the measurement of brain tissue oxygenation, metabolites (mainly by microdialysis) and assessment of cerebral hemodynamics, such as resting perfusion or autoregulation. A large variety of these techniques with different modifications have been described and some, like measurement of brain tissue oxygenation, microdialysis and electrocorticography, have proven prognostic relevance. However, no single study provides clear evidence for a benefit of advanced neuromonitoring strategies when compared to conventional monitoring-free treatment and consequently, there remains an ongoing debate on the optimal way of using extended neuromonitoring in critically ill neuro-intensive care patients. Taken together, the history and evidence-based state-of-the-art of multimodal monitoring in severely brain injured patients suggests that there is no single ideal technique for each patient, and that a combination of different monitoring tools and techniques is required for optimized patient care and to prevent complex cascades of secondary brain injury.

Regional temperature, cerebral blood flow and metabolism responses to cortical spreading depolarization in human

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Introduction: We have generated a new multimodal brain monitoring sensor which contains electrode, thermistor and near infra-red spectroscopy (NIRS). Using this sensor we monitored regional temperature, cerebral blood flow and metabolism response to cortical spreading depolarization in patients with severe brain injury including subarachnoid hemorrhage (SAH), infarction and trauma.
Methods: The strip sensor used here consisted of 6 units. One unit included electrocorticography electrode, thermistor and NIRS and total 6 units are arranged in a line on the polymide strip sheet. The length, width and thickness of the sensor were 65mm, 8mm and 20um respectively. We placed this sensor on the brain surface after the decompressive craniotomy. Following surgery, monitoring was continued for 7 to 14 days. The data were collected and analyzed using Powerlab.
Results: We have used this novel sensor for 19 patients so far and there were no apparent adverse effects caused by the sensor. In 5 patients we could detect cortical spreading depolarization (CSD). Three were traumatic brain injury and 2 were SAH. Using the data from those patients, we analyze the temperature, cerebral blood flow and metabolism response to CSD. During CSD, monophasic increase in brain temperature was detected with a high reproducibility. Brain surface temperature rose to a peak increase of 0.03 ± 0.01 ºC on average. Duration of this change (10% maximum amplitude) was 250 ± 74 seconds and it was significantly longer than that of DC shift (=250 ± 74 seconds, P<0.01). Total hemoglobin response showed biphasic pattern, which were initial increase (peak: +0.006 ± 0.002mM, duration: 142.2 ± 43.6 s) and late decrease (minimum: -0.005 ± 0.002mM, duration: 147.5 ± 68.5 s). Tissue oxygen index (=Oxy hemoglobin/ Total hemoglobin x100) was calculated and also showed biphasic pattern: initial increase (peak: +0.32 ± 0.1 %) and late decrease (minimum: -0.46 ± 0.16 %).
Conclusions: We showed the initial results of our new multimodal sensor. Accumulation of data with this devise may help us to understand the pathophysiology of CSD in patients of brain injury.

Brain temperature regulation in poor grade patients with subarachnoid hemorrhage – a multimodal neuromonitoring study

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Introduction: Spreading depolarizations (SDs) are highly active metabolic events. Previous studies indicated that brain temperature (Tbrain) increases by ~0.5°C relative to core body temperature (Tcore) during SDs. The pathophysiologic interactions between brain metabolism and changes in Tbrain are incompletely understood.
Methods: 46 consecutive subarachnoid hemorrhage (SAH) patients with multimodal neuromonitoring were included. Continuous minute-by-minute data of Tcore and Tbrain, cerebral perfusion (cerebral blood flow (CBF), cerebral perfusion pressure (CPP)), intracranial pressure (ICP), were averaged at 1-hour intervals (cerebral microdialysis,CMD; CMD-glutamate, CMD-glucose, CMD-lactate, CMD-pyruvate, CMD-lactate-to-pyruvate ratio (LPR) and CMD-glycerol) for up to 14 days of hospitalization. Brain mitochondrial dysfunction (MD) was defined as a CMD-LPR>30 and CMD-Pyruvate>70 µmol/l. Functional outcome was assessed at 3 months post bleeding using the modified Rankin Scale (mRS) with good outcome defined as mRS≤2. Continuous variables were analyzed using univariate and/or multivariate generalized estimating equation models to account for repeated measurements within patients.
Results: Tbrain (median 37.2°C, IQR 36.6 – 37.8°C) highly correlated with Tcore (median 36.9°C, IQR 36.4 – 37.6°C) (r=0.948, p<0.01). Tbrain was higher than Tcore in 73.7% of neuromonitoring time (median Tdelta +0.18°C (IQR, -0.01 to 0.37°C). Tdelta was higher during normothermia when compared to episodes of fever (>38.3°C, p<0.001). Mitochondrial dysfunction was present in 16% of monitoring time. During these periods, Tdelta was significantly lower (-0.02°C; IQR, -0.2 to 0.1), compared to periods without MD (+0.2°C; IQR, 0.1–0.4°C) (p < 0.001). CPP and ICP were not associated with Tdelta. Tdelta was significantly correlated with CMD-glucose (r = 0.17, p=0.02) CMD-glutamate (r=-0.48; p=0.01), CMD-glycerol (r=-0.40; p<0.01), CMD-lactate (r=-0.39; p<0.001), and CMD-LPR (r=-0.55; p=0.04), but not changes in CBF. A higher Tdelta was moreover associated with a lower risk of vasospasm, DCI, and MD (p < 0.001) and a higher chance of good functional outcome at 3 months (p=0.02). In addition, MD was associated with a worse outcome (p=0.02).
Discussion: Our data indicate that relative elevations of Tbrain are primarily regulated by brain metabolic activity. Preserved mitochondrial activity was associated with higher Tbrain, lower risk for DCI and better neurological outcome. Further studies are needed to investigate metabolic changes during spreading depolarizations following SAH.

Resolving the metabolic signature of SD using dexamethasone enhanced continuous-online microdialysis (coMD)

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Introduction: Spreading depolarisations (SDs) represent a dynamic, intense loss of resting membrane potential and hence represent an overwhelming challenge to the brains ability to repolarize effected cells through metabolism. High time resolution on-line microdialysis has demonstrated in the human brain that SDs are associated with a transient driving down of local extracellular glucose, an increase in lactate and brain potassium providing a signature of the injured brains response to SD. During clusters of SDs the depression of ECF glucose becomes cumulative, potentially providing an index of tissue health. Microdialysis, however has disadvantages, the most significant being that the MD probes are large compared to the mean intercapillary distance. This inevitably leads to a layer of compromised tissue next to the MD probe membrane which can develop over days into a 'walling off' of the probe form the brain tissue. The consequence of this is that the MD probei s less able to detect changes in the brain ECF, particularly when they are dynamic. This study looks at the effects of local application of the anti-inflammatory drug dexamethasone (DEX) on the dynamic metabolic signature detected by mcirdialysis following SD.
Methods: Rats were anesthetized with isoflurane and placed in a stereotaxic frame. Lab made microdialysis probes were inserted acutely into the cortex so that the entire membrane sat within the cortex. SDs were initiated use needle prick via a second skull hole some 4,5 mM from the probe. The microdialysate was analysed as it left the brain using a combination of online microfluidic chips (K+) and rapid sampling microdialysis (glucose). In DEX animals the probes were perfused with low concentrations of dexamethasone. Animals were allowed to recover from anesthesia and returned to their home bowl, and were reanaesthetised at 5 or 10 days to measure the neurochemical response to SD. Post mortem brain tissue was fixed and imaged using immunohistochemistry and fluorescence imaging.
Results: Acutely, DEX improved microdialysis ability to resolve dynamic changes in glucose and K+, giving rise in turn to larger measured responses. These were maintained at 5 days, and still measurable at 10 days, when control animals did not exhibit dynamic changes.
Discussion: We will discuss the relevance of these results for long term monitoring of the human brain.

Spreading depolarization probability with decreasing mean arterial pressure may be explained by disturbed autoregulation

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Introduction: SDs have been implicated in generation of secondary growth in focal ischemia, as well as acute neurological injuries including TBI, SAH, and malignant hemispheric stroke (MHS). Previous studies have established the role of "supply-demand mismatch" as the critical factor in determining the incidence and impact of these secondary SDs. We sought to use high-resolution continuous monitoring data to evaluate the effect of physiologic variables on SD. **Methods**: Patients undergoing craniotomy were enrolled in this prospective observational study. ECoG was recorded and scored with a full band DC amplifier. Continuous blood pressure data from arterial monitoring were exported in one-minute bins and time-linked to ECoG data. A MAP-SD probability relationship was generated by examining the number of MAP recordings with and without SD. Mixed effect logistic regression was used to model these effects using odds ratios and 95% CIs (SAS 9.4). **Results**: 31 patients with TBI (4), SAH (24), and stroke (3) were available for review, 26 of whom had SD. There were 4016 cumulative hours and 416 cumulative SDs. Increased mean arterial pressure (MAP) showed an overall protective effect across the range of 65-120 mmHg. Peak SD probability was around 20% at 65 mmHg and decreased to around 5% at 90 mmHg. SD probability was stable (~5%) with MAP values 90-115 mmHg, before further dropping at 115mmHg (to ~3%). A similar trend was noted for DBP, whereas SBP demonstrated a complex bimodal relationship. Logistic regression confirmed significant associations between MAP (OR = 0.955, 95% C.I. 0.944-0.966) and DBP (OR = 0.947, 95% C.I. 0.933-0.961) with SD. SBP (OR=0.995, 95% C.I. 0.988-1.002, p-value =0.1684) showed no significant association with SD. **Discussion**: These high-resolution data confirm reported associations of MAP with SD probability. Our data suggest that shifted autoregulatory capacity in susceptible regions may explain this shape. Below the threshold of ~90mmHg, there was a nearly linear increase in probability of SD (suggesting decreasing CBF) whereas there was a long flat segment with stable probability up to about 115mmHg (suggesting stable CBF). A small improvement above this threshold offered slight protection, suggesting protective hyperemia. **Conclusions**: These data suggest a threshold for autoregulatory capacity below which probability of SD increases. This may occur at higher MAP (~90mmHg) than the lower threshold of normal autoregulation (~60mmHg) due to the presence of injury. In addition, MAP and DBP seemed to be more reliable predictors of SD than SBP. "MAP push" above this inflection point may help limit secondary SD induced injury in the ICU.

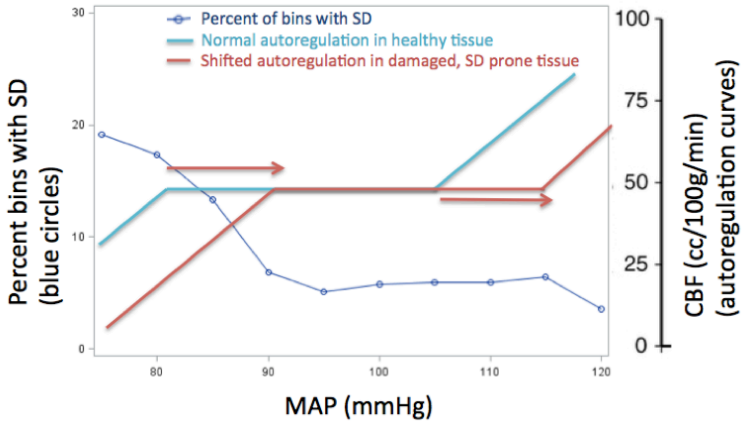

Figure: MAP versus SD probability. The autoregulatory curves indicate the proposed mechanism where the normal curve (light blue), with a lower inflection point around 60-80 mmHg is shifted to the right (red curve), explaining the nearly linear in SD probability below 90mmHg.

Diagnosis anxiety and depression related to severity of traumatic brain injury

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Background: Traumatic brain injury (TBI), according to the World Health Organization, will exceed many diseases as the major cause of death and disability by the year 2020. The aim of the current study was to assessing anxiety, depression and posttraumatic stress disorder across causes and levels of TBI in patients who hospitalized and had any medical care. **Materials and Methods**: The study was done using clinical diagnosis tests: Hospital Anxiety and Depression Scale (HADS). This study examined a subset of patients from a pilot study that covered a 6-months. **Results**: The study included 50 patients, and 66 % were male with 34% female. The median age of the patients was 32.5 years. One-way between groups analysis of variance was conducted to explore the impact of causes and levels of traumatic brain injury, there was statistically significant difference at the HDS in each causes and levels of TBI. **Discussion**: The results of the current study suggest diagnosis mental factors include; anxiety and depression disorder to preventing other mental symptoms after TBI. Knowledge about such risk factors in the development of TBI outcomes provides an opportunity to develop tailored interventions that may prevent or reduce the likelihood of development of outcomes. The severity of injury and situations of incidents leading to the development of neurological, neuropsychological outcomes, to allow for targeted selection of patients for early intervention to prevent symptoms of TBI and other complicated outcomes.

Prognostic value of serially estimated serum procalcitonin levels in traumatic brain injury patients with or without extra cranial injury - A longitudinal observational study.

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Background: Traumatic brain injury (TBI) is lethal and objective tools are required to predict its severity and ultimate outcome to better utilize resources. The application of marker like procalcitonin (PCT) for TBI may be useful. This study was undertaken with primary objective to determine the correlation between serial PCT concentrations with the outcome at discharge or mortality. Secondary objectives were to evaluate correlation with associated extra cranial injuries and complications during hospital stay. **Methods**: 186 TBI patients aged >18yrs admitted to the neuro ICU at the level 1 trauma centre were prospectively enrolled and divided into two groups: TBI with and without extra cranial injuries. Patients were managed according to standard institutional protocol. The PCT values (on days 1, 2 and 5 after trauma), all clinical, microbiological, laboratory data along with all diagnostic, therapeutic interventions with the duration of treatment in the ICU were noted and outcome assessed using GOS-E. Appropriate statistical analysis was done. **Results**: Median PCT level at admission, day 2 and day 5 in TBI patients with extracranial injuries were 3.0, 0.83, and 0.69 ng/ml. Regression analysis of primary mortality with PCT cut-off values at admission (>5.5 ng/ml) and on day 2 (>1.16ng/ml). But for secondary mortality, PCT cut-off values at admission (>2.17 ng/ml), on day 2 (>1.16 ng/ml) and on day 5 (>1.2 ng/ml) were derived significant. However, for primarily CNS cause of mortality PCT cut-off level more than 5.5 ng/ml carried maximum AUC of 75% and for secondary cause (sepsis) of mortality, cut-off values more than 1.2 ng/ml had sensitivity or specificity of 68%. **Conclusion**: Admission PCT of ≥5.5 ng/ml in TBI patients is associated with high risk for mortality and poor outcome. PCT level estimation can be an indispensable tool for outcome assessment in TBI patients with or without extracranial injuries.

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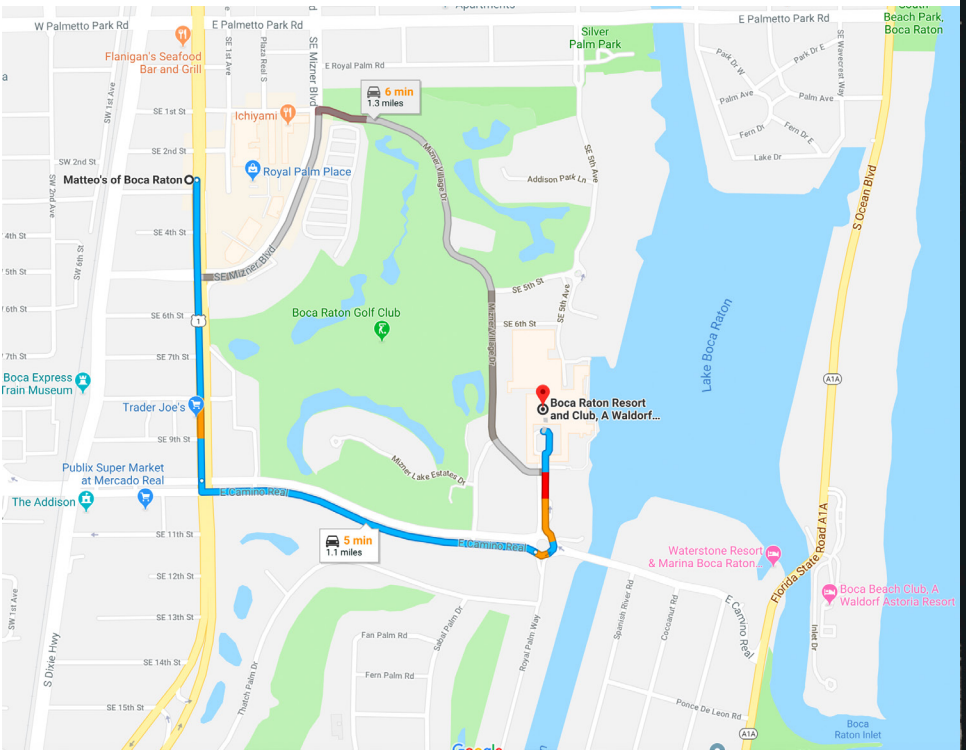
Notes

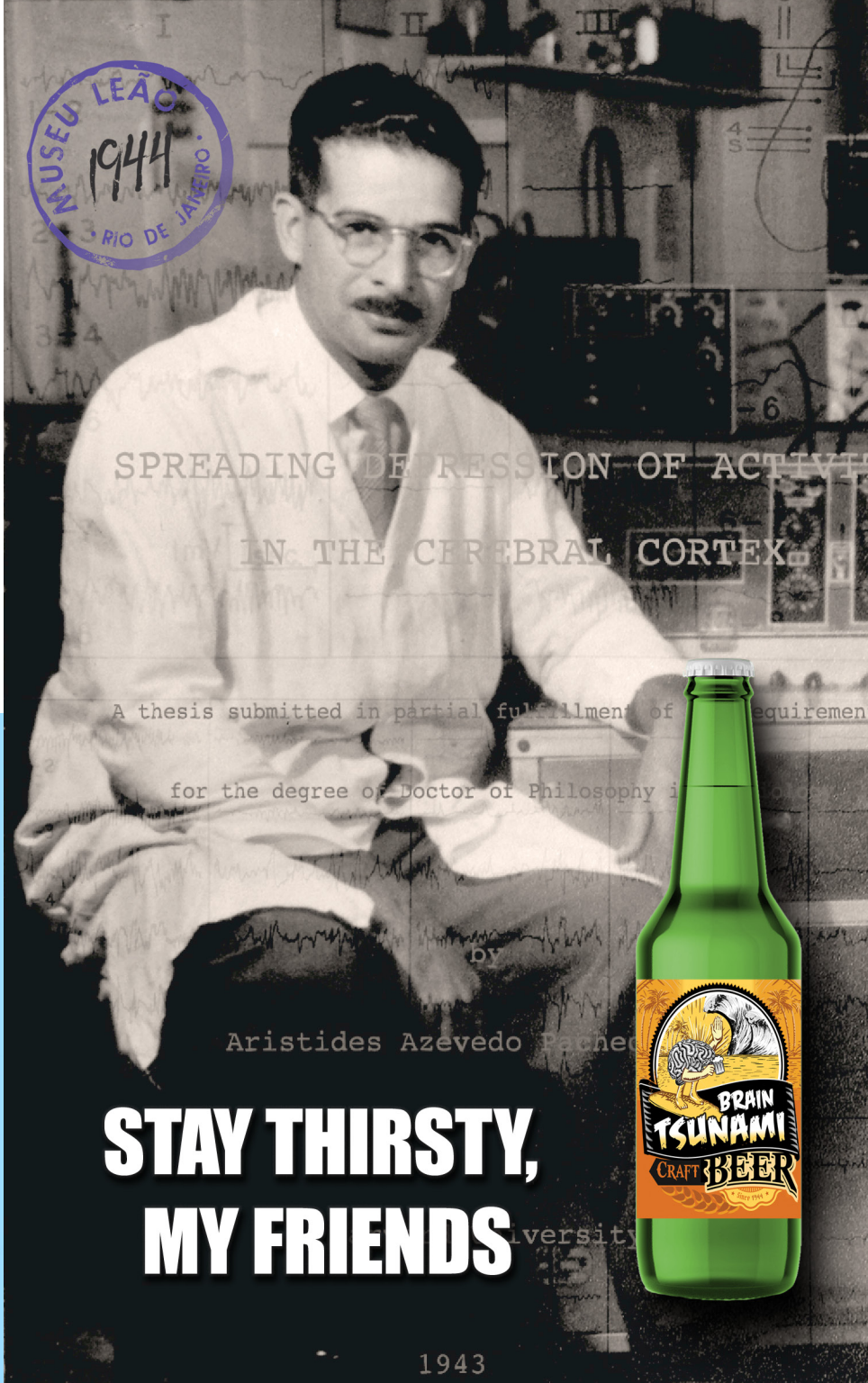
MATTEOS

trattoria • bar

DINNER DIRECTIONS

Matteo's of Boca Raton
233 S. Federal- Highway
Boca Raton, FL 33432
http://bocaraton.matteosristorante.com/
Approx. 6 minute drive or 22 minute walk from Boca Raton Resort & Club





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