iCSD 2023

SZEGED

20 years of COSBID

Co-Operative Studies on Brain Injury Depolarizations

2003-2023

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University of Szeged, Hungary

Welcome to iCSD 2023

On behalf of the Co-Operative Studies on Brain Injury Depolarizations (COSBID), the Local Organizing Committee and Program Committee, we wish you a warm welcome to the **International Conference on Spreading Depolarizations 2023 (iCSD 2023)**, to be held in **Szeged, Hungary between October 2nd 5th, 2023**. The Venue of the meeting will be the HUNGUEST Hotel Forrás, Szeged.

Following the traditions of previous annual meetings of the COSBID group, iCSD 2023 will promote translational research on spreading depolarization in acute brain injury and chronic brain disorders. Discussions about fundamental mechanisms of spreading depolarization as well as ongoing and future applications at the bedside will be discussed. The goal of the iCSD conferences is to provide education on spreading depolarizations and present the latest discoveries within the field.

iCSD 2023 will take place in Szeged, a vibrant university town on the south-eastern border of Hungary, spreading out on both banks of the river Tisza. Szeged hosts four education and research institutions including the University of Szeged, the Biological Research Centre - Centre of Excellence of the European Union, the ELI-ALPS Szeged Laser Research Institute, and HCEMM – Hungarian Center of Excellence for Molecular Medicine. Thousands of academic employees and more than 20.000 university students from all over the world contribute to a lively intellectual environment in the city.

Although an old historical town, Szeged was destroyed by the flood of 1879 and has been rebuilt in the late 19th century almost entirely. The intense reconstruction delivered Neoclassical, Eclecticist and Art Nouveau architecture, and Szeged has become a Hungarian center of Art Nouveau. For nature lovers, Szeged is popular for bird watching, as the reconstruction of former fishponds outside the city resulted in a large and bird-rich wetland. Szeged is also famous for its delicious fish soup known beyond the borders.

We very much look forward to your participation in iCSD 2023 and to welcoming you to Szeged, Hungary!

On behalf of the Co-Operative Studies on Brain Injury Depolarizations and
the Local Organizing Committee,
Yours Sincerely,

Eszter Farkas
University of Szeged, Hungary

Committees

LOCAL ORGANIZING COMMITTEE

Eszter Farkas, Chair (University of Szeged)
Ferenc Bari (University of Szeged)
Ákos Menyhárt (University of Szeged)
Zsuzsa Mező (University of Szeged)
József Tolnai (University of Szeged)

PROGRAM COMMITTEE

Cenk Ayata (Massachusetts General Hospital)
KC Brennan (University of Utah)
Jens Dreier (Center for Stroke Research Berlin & Neurological Hospital, Charité)
Martin Fabricius (Rigshospitalet, Copenhagen)
Jed Hartings (University of Cincinnati)
Sharon Jewel (King's College, London)
Martin Lauritzen (University of Copenhagen)
Britta Lindquist (University of California)
Bill Shuttleworth (University of New Mexico)
Michi Suzuki (Yamaguchi University)
Johannes Woitzik (University of Oldenburg)

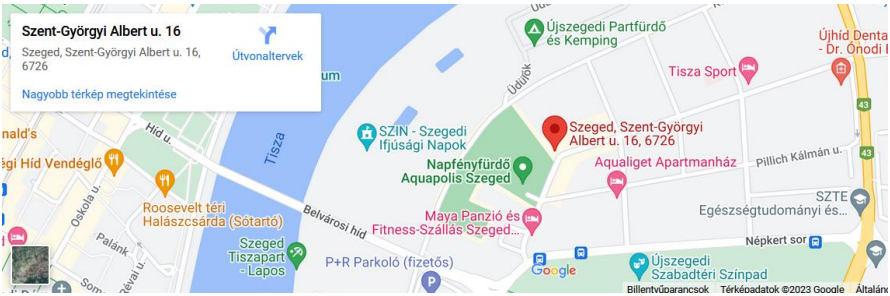
Contact

Conference Secretariat: Zsuzsa Mező
E-mail: icsd.2023@med.u-szeged.hu

General Information

Venue and reception

HUNGUEST Hotel Forrás
Szent-Györgyi Albert u. 16-24
Szeged, Hungary, H-6726



Networking Dinner

Hungi Vigadó
Stefánia
Szeged, Hungary, H-6720

Social Programs

Guided city tour

Unique opportunity to explore the beautiful city of Szeged.

Immerse yourself in the local culture, architecture, and history with a guided tour. Here are the important details for the city tour:

Date: October 4, 17:00 to 18:30, **Meeting Point**: Lobby, Hotel Forrás

Departure: We will start walking from the hotel at 16:30

16:30 - Gathering: Meet in the hotel lobby by 16.15. We will set off for our city exploration on foot.

17:00 - Tour Start: Our friendly guide will lead you through the city, sharing interesting stories about its landmarks.

18:30 - The tour will end by 18:30. You can either return to the hotel with the group or continue exploring the city on your own and walk to the Hungi Vigadó, the location of the networking dinner.

Dress: Dress comfortably and wear appropriate shoes for walking.

Guide: Tour guide of Szeged and Surroundings Tourism Nonprofit Ltd.

Bird watching

Get ready to explore local birdlife and enjoy the outdoors with fellow attendees. The key details are:

Date: October 4, 17:00 to 18:30, **Meeting Point**: Lobby, Hotel Forrás

Transportation: Mini-buses will leave the hotel at 16.30

Program Schedule:

16:30 - Departure: Meet in the hotel lobby. The mini-buses will take you to the bird watching location: Lake Fehér.

17:00 - Upon arrival: Our expert guide will introduce you to the local birds and explain what lays in store for you.

17:15 - Bird Watching: Equipped with binoculars, you will spot various birds with the help of our guide. The program ends at 18:30. The mini-buses will take you back to the hotel.

Dress: Wear comfy clothes and water-proof walking shoes.

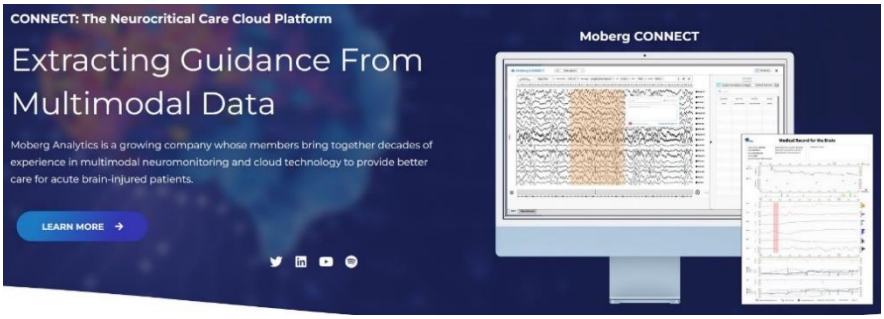
Gear: Binoculars are provided.

Guide: The guide is delegated by Birdlife Hungary (Magyar Madártani és Természetvédelmi Egyesület).

Get ready for a unique bird watching adventure. See you there!

If you have questions, please contact us at icsd.2023@med.u-szeged.hu

Exhibitors


CONNECT: The Neurocritical Care Cloud Platform
Extracting Guidance From Multimodal Data
Moberg Analytics is a growing company whose members bring together decades of experience in multimodal neuromonitoring and cloud technology to provide better care for acute brain-injured patients.
LEARN MORE
Moberg CONNECT


Mespere
LIFE SCIENCES
Nicht-Invasive Messung der hirnvenösen Sauerstoffsättigung (StO2 / RsO2)
L1
69
162
R2
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Sponsors


HCEMM
Translational Medicine
HUNGARIAN NATIONAL LABORATORY
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 739593.


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Presentation guidelines

Poster presentation

Posters should be prepared in A0 size (84.1 x 118.9 cm or 33.1 x 46.8 inches) in a portrait format.

Posters will be on display throughout the entire meeting and should be put up on the poster boards before the Opening remarks on October 3rd.

Poster presenters are asked to introduce their poster at the Poster Power Pitch session (October 3rd). The Poster Power Pitch Session is intended to create interest and attract delegates to the Poster Sessions. The Poster Power Pitch will take place in the lecture room of the meeting. Each presenter will have the opportunity to briefly introduce their poster to all the meeting attendees. Please, prepare a single slide to be projected during your 2-minute talk.

Oral presentation

The time for an oral presentation will be 12 min talk + 8 min discussion, to provide room for as much interaction as possible.

Young Investigator Awards

Two Young Investigator Awards sponsored by the Hungarian Physiological Society will be handed out to acknowledge the best poster and best oral presentations. Presenting authors of abstracts submitted for oral or poster presentations may apply by indicating their eligibility on the Abstract submission form.

The applications of graduate students and young post-doctoral fellows are encouraged. Applicants must be under the age of 35 years or must have earned their PhD degree not earlier than 2017. Presentations will be evaluated by the Members of the Program Committee and the President of the Hungarian Physiological Society. Awardees will receive a certificate of their achievement and a reimbursement of their registration fee to the conference.

Certificate of attendance

Certificate of attendance will be issued upon request placed at the Registration Desk in person, or via email to iCSD.2023@med.u-szeged.hu

Keynote Speakers

Adam Denes

Adam Denes is a principal investigator at the Institute of Experimental Medicine (IEM), Budapest, Hungary. He is heading the Laboratory of Neuroimmunology and the Cell Biology Center in the IEM. Research of his group focuses on the role of microglia in regulating neuronal activity and injury. They also study the mechanisms of neuroinflammation in stroke and other forms of brain injury, as well as the fundamental processes of brain-immune interactions in health and disease. Their recent research revealed the contribution of microglial actions to cerebral blood flow and hypoperfusion.

Jeffrey Noebels

Jeffrey Noebels is a neurologist and Professor of Neurology, Neuroscience, and Molecular and Human Genetics at the Baylor College of Medicine in Houston, Texas. He is heading the Developmental Neurogenetics Laboratory. The principal research strategy of the Laboratory is to apply mutational analysis to learn how genes regulate neuronal excitability and network synchronization within the mammalian central nervous system. Spontaneous and transgenic mutations that express neurological phenotypes in the mouse provide a valuable opportunity to identify excitability genes and examine their role in synaptic plasticity in the developing brain. His work on epilepsy connects directly to the focus of COSBID.

Andrew Carlson

Andrew Carlson is a vascular neurosurgeon/scientist. His work focuses on translational aspects of spreading depolarization including expanding the understanding of how SD may be related to various clinical problems as well exploring approaches to target SD as a novel mechanism to improve clinical outcomes. He first attended COSBID in 2011 and has been a regular contributor for the past decade. He serves on the Editorial board of the Journal of Neurosurgery and is a neurosurgery representative to the multispecialty neurocritical examination and certification committee.

Schedule At-A-Glance

DAY 1, OCTOBER 2, MONDAY		
15:00	18:00	Registration
16:00	18:00	**Introduction to SD**: pertinent issues (questions and answers)
18:00	20:00	Reception
DAY 2, OCTOBER 3, TUESDAY		
8:00	9:00	Registration
8:30	9:00	Opening remarks (Eszter Farkas, Tony Strong)
9:00	10:00	**Keynote lecture I** (Ádám Dénes)
10:00	11:00	**Oral session I**: SD in ischemic and hemorrhagic stroke
11:00	11:30	Coffee break
11:30	12:30	**Oral session II**: SD and cerebral metabolism
12:30	13:30	Lunch
13:30	14:50	**Oral session III**: SD in cerebrovascular and traumatic brain injury states
14:50	15:20	Coffee break
15:20	16:20	Poster Power Pitch (Eszter Farkas)
16:20	17:20	**Poster Session I** (P1-P8)
DAY 3, OCTOBER 4, WEDNESDAY		
9:00	10:00	**Keynote lecture II** (Jeffrey Noebels)
10:00	11:00	**Oral session IV**: Interplay between SD and seizures
11:00	11:30	Coffee break
11:30	12:30	**Oral session V**: Neuronal excitability and network activity in the wake of SD
12:30	13:30	Lunch
13:30	14:50	**Oral session VI**: SD inhibition – the therapeutic benefit of ketamine and nimodipine
14:50	15:20	Coffee break
15:20	16:30	**Poster Session II** (P9-P15)
16:30	18:30	Social program: Guided city tour or Bird watching
20:00	22:00	Networking Dinner Presentation of the Young Investigator Award in poster category
DAY 4, OCTOBER 5, THURSDAY		
9:00	10:00	**Keynote lecture III** (Andrew Carlson)
10:00	11:00	**Oral session VII**: Tissue susceptibility for SD: novel mechanisms
11:00	11:30	Coffee break
11:30	12:30	**Oral session VIII**: Clinical and experimental SD detection: models and methods
12:45	13:00	Presentation of the Young Investigator Award in oral category, Presentation of iCSD 2024, Closing remarks

Program

iCSD 2023, October 2-5, Szeged, Hungary

DAY 1, OCTOBER 2, MONDAY

15:00-18:00 **Registration**

16:00-18:00 **Introduction to SD: pertinent issues (questions and answers)**

Chair: Bill Shuttleworth

18:00-20:00 **Reception**

DAY 2, OCTOBER 3, TUESDAY

8:00-9:00 **Registration**

8:30-9:00 **Opening remarks**

Eszter Farkas, Tony Strong

9:00-10:00 **Keynote lecture I**

Chair: Martin Lauritzen

Microglia modulate neuro-vascular interactions in the brain via purinergic mechanisms and shape central inflammatory responses

Ádám Dénes

10:00-11:00 **Oral session I: SD in ischemic and hemorrhagic stroke**

Chair: Jens Dreier

10:00-10:20 [O1] **Spreading depolarization is a biomarker for infarct growth in malignant stroke**

Christina M. Kowoll, Leonie Schumm, Simeon OA Helgers, Patrick Dömer, Alexandra Gieffers, Coline L. Lemale, Sebastian Major, Christian Dohmen, Gereon R. Fink, Gerrit Brinker, Tilmann von Pidoll, Jens P. Dreier, Nils Hecht, Johannes Woitzik

10:20-10:40 [O2] **Loss of cerebral autoregulation during Spreading Depolarization in a translational model and a clinical study of hemorrhagic stroke**

Francisco Leonardo Ramírez-Cuapio, Renan Sánchez-Porras, Modar Kentar, Pablo Albiña-Palmarola, Roberto Díaz-Peregrino, Jens P. Dreier, Johannes Woitzik, Edgar Santos

10:40-11:00 [O3] **Spreading depolarization following ischemic stroke triggers unique neuronal calcium dynamics and behaviour in freely behaving female mice**

Andrew K.J. Boyce, Yannick Fouad, Cristina Martins-Silva, Renaud Gom, Leo Molina, Tamás Füzesi, Carina Ens, G. Campbell Teskey, Wilten Nicola, Roger J. Thompson

11:00-11:30 **Coffee break**

11:30-12:30	**Oral session II: SD and cerebral metabolism**
	Chair: Britta Lindquist
11:30-11:50	[O4] **Tissue partial pressure of oxygen during spreading depolarization in malignant stroke is associated with outcome** Nils Hecht, Daisy Haddad, Leoni Schumm, Nora Dengler, Patrick Dömer, Max Schrammel, Franziska Meinert, Sebastian Major, Coline Lemale, Jens Dreier, Peter Vajkoczy, Johannes Woitzik
11:50-12:10	[O5] **Long-term effects of spreading depolarizations on collateral vessel growth and hemodynamic impairment after experimental chronic hypoperfusion in mice** Annika Köhne, Patrick Dömer, Simeon OA Helgers, Franziska Meinert, Renán Sánchez-Porras, Johannes Woitzik
12:10-12:30	[O6] **Brain glycogen stores recruitment supports tissue repolarization after spreading depolarizations** Shuting Chen, Baptiste Balança, and Stephane Marinesco
12:30-13:30	**Lunch**
13:30-14:50	**Oral session III: SD in cerebrovascular or traumatic brain injury states**
	Chair: Edgar Santos
13:30-13:50	[O7] **Spreading depolarizations occur after cerebral venous sinus occlusion in the gyrencephalic brain** Renan Sanchez-Porras, Francisco. L. Ramirez-Cuapio, Mildred A. Gutierrez-Herrera, Pablo Albiña-Palmarola, Juan M. Lopez-Navarro, Marcos Suarez-Gutierrez, Roberto Diaz-Peregrino, Diego A. Sandoval-Lopez, Modar Kentar, Johannes Woitzik, Edgar Santos
13:50-14:10	[O8] **A novel model to study spreading depolarizations under cerebral hypoperfusion in the gyrencephalic brain** Lars Wessels, Sebastian Major, Agustin Liotta, Patrick Dömer, Johannes Woitzik, Jens Dreier, Nils Hecht
14:10-14:30	[O9] **Memantine Inhibits Cortical Spreading Depolarizations and Improves Outcome of Repetitive Mild Traumatic Brain Injury** J. Muradov, M. MacLean, L. Wu, A. Friedman
14:30-14:50	[O10] **Multivariate Modeling of Intensive Care Risk Factors for Spreading Depolarizations in Severe Traumatic Brain Injury** Jed A. Hartings, Xinyu Cong, Brandon Foreman, and Roman Jandarov
14:50-15:20	**Coffee break**
15:20-16:20	**Poster Power Pitch**
	Chair: Eszter Farkas

16:20-17:20	**Poster Session I**

[P1] **An in vivo, non-invasive platform to study the impact of repetitive Spreading Depolarisation in awake head fixed mice**
Kağan Ağan, Neela K. Codadu, Daman Rathore, Eduard Masvidal-Codina, Enrique Fernández-Serra, Randy Gyimah, Anton Guimera-Brunet, Rob C. Wykes

[P2] **Occurrence of Spreading Depolarization and impact on delayed infarct progression after malignant hemispheric stroke in C57/bl6 mice**
Anna Zdunczyk, Leonie Schumm, Simeon OA Helgers, Patrick Dömer, Annika Köhne, Xi Bai, Sebastian Major, Jens Dreier, Peter Vajkoczy, Johannes Woitzik

[P3] **Frequency band changes during ischemic stroke, spreading depolarizations and mild hypothermia in gyrencephalic brains**
Roberto Díaz-Peregrino, Modar Kentar, Carlos Trenado, Renán Sánchez-Porras, Pablo Albiña-Palmarola, Johannes Woitzik, Edgar Santos

[P4] **Reperfusion failure after spreading depolarization shapes hemoglobin content in the mouse cortex**
Anna Törteli, Armand Rafael Bálint, Réka Tóth, Péter Makra, Ferenc Bari, Eszter Farkas, Ákos Menyhárt

[P5] **Isoflurane improves cerebral oxygenation during spreading depolarization by lowering the cerebral metabolic rate of oxygen in vitro**
Karl Schoknecht, Mathilde Maechler, Iwona Wallach, Jens P. Dreier, Agustin Liotta, Nikolaus Berndt

[P6] **Cortical spreading depolarization scalp-brain voltage ratios and images from simulated concussion and subarachnoid hemorrhage**
Samuel J. Hund, Benjamin R. Brown, Coline L. Lemale, Prahlad G. Menon, Kirk A. Easley, Jens P. Dreier, Stephen C. Jones

[P7] **Cold Spreading Depolarization (`cold-SD`) in Rodent Brain Slices**
Dominique Hancock, Edwin Kiarie, Peter Gagolewicz Victoria Donovan, R. David Andrew

[P8] **Diversity of cortical activity changes beyond depression during Spreading Depolarizations**
Azat Nasretdinov, Daria Vinokurova, Coline Lemale, Gulshat Burkhanova-Zakirova, Ksenia Chernova, Julia Makarova, Oscar Herreras, Jens P. Dreier, Roustem Khazipov

DAY 3, OCTOBER 4, WEDNESDAY

9:00-10:00 **Keynote lecture II**

Chair: Cenk Ayata

Exploring the Monogenic Borderland of Epilepsy and Spreading Depolarization

Jeffrey Noebels

10:00-11:00 **Oral session IV: Interplay between SD and seizures**

Chair: Rob Wykes

10:00-10:20 [O11] **Characterizing the spatiotemporal patterns of ictal spreading depressions**

Elliot H Smith, Tyler S Davis, KC Brennan, John D Rolston, Punam Sawant-Pokam

10:20-10:40 [O12] **The astrocyte potassium channel Kir4.1 influences seizure and spreading depolarisation susceptibility**

Neela K. Codadu, Eduard Masvidal-Codina, Enrique Fernández-Serra, Randy Gyimah, Hasna A. Boumenar, Yunan Gao, Anton Guimera-Brunet, Rob C. Wykes

10:40-11:00 [O13] **Intravital imaging reveals calcium depletion in the endoplasmic reticulum during cortical spreading depressions following generalized seizures in mice**

Matthew A. Stern, Ken Berglund, Eric R. Cole, Robert E. Gross

11:00-11:30 **Coffee break**

11:30-12:30 **Oral session V: Neuronal excitability and network activity in the wake of SD**

Chair: Daniela Pietrobon

11:30-11:50 [O14] **Changes in the Direct Cortical Response during spreading depolarisations in the injured human brain**

Sharon Jewell, Tomas Watanabe, Jose-Pedro Lavrador, Sascha Freigang, Prajwal Ghimire, Christos Tolias, Clemens Pahl, Martyn Boutelle, Anthony Strong

11:50-12:10 [O15] **A novel local regression approach to analyze functional connectivity following CSD**

Miran Öncel, James H Lai, Sanem A Aykan, Joanna Yang, Tao Qin, Andreia Morais, Andrea Harriott, Sava Sakadžić, Cenk Ayata, David Y Chung

12:10-12:30 [O16] **Voltage-gated calcium channels and glutamate NMDA receptors are both necessary for initiation of cortical spreading depression**

Marina Vitale, Angelita Tottene, Maral Zarin Zadeh, KC Brennan, Daniela Pietrobon

12:30-13:30 **Lunch**

13:30-15:30	**Oral session VI: SD inhibition – the therapeutic benefit of ketamine and nimodipine**

Chair: Martin Fabricius

13:30-13:50 [O17] **S-ketamine for cortical spreading depolarization in patients with severe acute brain injury (KETA-BID): protocol for a randomised, blinded pilot trial**
Trine Hjorslev Andreasen, Markus Harboe Olsen, Christian Gluud, Jane Lindschou, Martin Fabricius, Kirsten Møller

13:50-14:10 [O18] **Mapping Ketamine Modulation of Spreading Depolarisation and Regional Blood Flow Post-Stroke Using Graphene Micro-Transistor Arrays**
Samuel M. Flaherty, A. Eladly, K. Hills, J. Merlini, E. Masvidal-Codina, E. Fernandez, X. Illa, E. Prats-Alfonso, K. Kostarelos, S Allan, J.A. Garrido, A. Guimerà-Brunet, R.C. Wykes

14:10-14:30 [O19] **Nimodipine is protective against spreading depolarization and neuroinflammation**
Rita Frank, István Pesti, Péter Archibald Szarvas, Ákos Menyhárt, Ferenc Bari, Eszter Farkas

14:30-14:50 [O20] **Nimodipine accelerates the restoration of neurovascular coupling after spreading depolarization**
Ákos Menyhárt, Ferenc Bari, Eszter Farkas

14:50-15:20	**Coffee break**
15:20-16:30	**Poster Session II**

[P9] **Ca^{2+}-dependent modulation of astrocytic gap junctional coupling upon brief metabolic stress**
Sara Eitelmann, Katharina Everaerts, Laura Petersilie, Christine Rosemarie Rose* & Jonathan Stephan

[P10] **Blockade of calmodulin-dependent AQP4 trafficking restores neurovascular coupling after stroke and enhances the spreading depolarization coupled hyperemia in mice**
Réka Tóth, Ákos Menyhárt, Eszter Farkas

[P11] **Red Flags for Symptoms of Secondary Spreading Depression in Clinical Practice: SNAIL**
Anders Hougaard

[P12] **The effects of an NO donor on the SD-induced negative ultraslow potential (NUP) after proximal cerebral artery occlusion (PCAO) in rats**
Coline L. Lemale, Baptiste Balança, Sara Simula, Sebastian Major, Jens P. Dreier

[P13] **Modulation of propagation of cortical spreading depolarization by GABAergic neurons.**
Hadi Srour, Martina Simonti, Massimo Mantegazza

[P14] **The impact of the novel sigma-1 receptor agonist S-0758 on somatosensory stimulation and spreading depolarization in cerebral ischemia**
Szilvia Kecskés, Írisz Szabó, Ákos Menyhárt, Eszter Farkas
[P15] **Electrical signaling at the endothelial cell pericyte syncytium during recurrent seizures**
Mirja Grote Lambers, Henrike Planert, Majed Kikhia, Agustin Liotta, Christian Madry, Jörg RP Geiger, Richard Kovács

16:30-18:30 **Social program: Guided city tour or Bird watching**

20:00-22:00 **Networking Dinner**
Presentation of the Young Investigator Award in poster category
Ferenc Bari (Hungarian Physiological Society)

DAY 4, OCTOBER 5, THURSDAY

9:00-10:00 **Keynote lecture III**
Chair: Jed Hartings
You Can't Unsee It
Andrew Carlson

10:00-11:00 **Oral session VII: Tissue susceptibility for SD: novel mechanisms**
Chair: Sharon Jewel

10:00-10:20 [O21] **Spreading depolarization induced plasticity is mediated by a combined potentiation of both AMPAR- and NMDAR- mediated components of the fEPSP**
Jordan E. Weisend, Andrew P. Carlson, Bill Shuttleworth

10:20-10:40 [O22] **Demonstrating Brain Release of an Activator of Spreading Depolarization**
Hellas Julia, Gagolewicz Peter J, Lee Kelly, Ollen-Bittle Nikita, Andrew R David

10:40-11:00 [O23] **Investigating seizure and spreading depolarisation susceptibility in a model of glioblastoma-related epilepsy using graphene-based epidural probes**
Kate Hills, Samuel Flaherty, Aralolaoluwa Ogunrin, Daman Rathore, Neela Codadu, Eduard Masvidal Codina, Enrique Fernandez, Xavi Illa, Thomas Kisby, Anton Guimera Brunet, Kostas Kostarelos, Rob C Wykes

11:00-11:30 **Coffee break**

11:30-12:30	**Oral session VIII: Clinical and experimental SD detection: models and methods**
	Chair: Baptiste Balança
11:30-11:50	[O24] **Towards noninvasive, automated detection and parameter estimation of spreading depolarizations in patients with intact skull using scalp EEG** Alireza Chamanzar, Han Yi Wang, Jonathan Elmer, Lori Shutter, Jed Hartings, Aman B. Patel, Christopher J. Stapleton, David Y. Chung, Eric S. Rosenthal, Pulkit Grover
11:50-12:10	[O25] **Electrocortical activity of the porcine brain during cardiac arrest, resuscitation and return of spontaneous circulation** Alois Schiefecker, G. Putzer, M. Kofler, L. Putnina, J. Wagner, P. Spraider, S. Mathis, J. Abram, D. Pinggera, M. Bauer, B. Glodny, J. Martini, R. Helbok
12:10-12:30	[O26] **A novel platform to investigate seizure and spreading depolarisation interactions using calcium imaging and graphene micro-transistor arrays** Daman Rathore, Smith A, Masvidal-Codina E, Fernandez-Serra E, Rossi LF, Guimera-Brunet A, Timofeeva Y, Wykes RC, Volynski KE
12:45-13:00	**Presentation of the Young Investigator Award in oral category** Eszter Farkas (Hungarian Physiological Society) **Presentation of iCSD 2024** Cenk Ayata **Closing remarks** Program Committee Members


TÜRK NÖROLOJİ DERNEĞİ
TURKISH NEUROLOGICAL SOCIETY
1992
iCSD 2024
International Conference on
Spreading Depolarizations
COSBID and beyond...
13-17 November 2024
Papillon Ayscha, Antalya, Türkiye

Conference abstracts

In chronological order.

K1

Adam Denes
„Momentum" Laboratory of Neuroimmunology, Institute of Experimental Medicine, Budapest, Hungary

Microglia modulate neuro-vascular interactions in the brain via purinergic mechanisms and shape central inflammatory responses

Microglia are key regulators of inflammatory processes in the CNS. Microglial activity is altered in common brain diseases and changes in microglial function have major impact on outcome in experimental models of neurological disorders. However, the underlying mechanisms are not well understood. We have recently identified a novel form of microglia-neuron interaction, which is present in the majority of neurons in mouse and human brain. Somatic microglia-neuron junctions possess specialized nanoarchitecture optimized for purinergic signaling. We show that activity of neuronal mitochondria is linked with microglial junction formation, which is induced rapidly in response to neuronal activation and blocked by inhibition of P2Y12 receptors. As such, an absence of microglia or microglial P2Y12R results in impaired outcome after acute brain injury induced by experimental stroke. Microglia also shape vascular responses via purinergic, compartment-specific actions through which microglia modulate cerebral blood flow, neurovascular coupling and cerebral hypoperfusion. In line with these mechanisms, microglia modulate neuronal and vascular responses associated with spreading depolarization. In addition, altered microglia-vascular interactions are associated with marked perfusion changes in the inflamed brain. Thus, understanding the mechanisms of microglia-neuron-vascular interactions is likely to help the identification of novel therapeutic targets in common neurological disorders.

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O1

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Spreading depolarization is a biomarker for infarct growth in malignant stroke

Introduction Spreading depolarizations contribute to lesion progression after experimental focal cerebral ischemia. Here, we investigated to what extent spreading depolarizations are associated with infarct progression in patients with malignant hemispheric stroke.
Methods In this prospective, diagnostic phase III study, spreading depolarizations were continuously monitored for 3-9 days with electrocorticography after decompressive hemicraniectomy for malignant hemispheric stroke. The number, type, and peak total depression duration of a recording day of Spreading depolarizations were analyzed in the context of infarct progression based on serial MRI.
Results Overall, 62 patients with a mean corrected stroke volume of 289.6 ± 68cm3 were included. Of these, 29/62 (47%) experienced relevant (>5%) infarct progression. To identify patients with a valid electrocorticographic recording above viable peri-infarct tissue, an electrocorticographic activity threshold of 14062µV2 was calculated. This threshold was reached in 44/62 patients (71%) with a mean recording duration of 139.6 ± 26.5 hours and 52.5 ± 39.5 Spreading depolarizations per patient. The number of Spreading depolarizations was similar between patients with and without infarct progression, but patients with progression experienced a significantly longer peak total depression duration of a recording day than patients without (593.8 vs. 314.1 minutes; *p=0.046).
Conclusions Ischemic lesion evolution in malignant hemispheric stroke is frequent and Spreading depolarizations induced depression duration of electrocorticographic activity may serve as an online biomarker for real-time identification of patients most likely to develop secondary stroke progression and may benefit from targeted management strategies.

O2

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Loss of cerebral autoregulation during Spreading Depolarization in a translational model and a clinical study of hemorrhagic stroke

Impairment of cerebral autoregulation (CA) and Spreading Depolarization (SD) occurrence has been observed in patients with intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Indices of cerebrovascular reactivity have proven to be effective tools for the detection of CA disruption. We aimed to evaluate changes in CA during SD in hemorrhagic stroke.

A translational study was conducted on nine swine using an autologous model of ICH. The pressure reactivity index (PRx) and the high-frequency oxygen reactivity index (H-ORx) were calculated through continuous monitoring of mean arterial pressure (MAP), intracranial pressure (ICP), and partial pressure of brain tissue oxygen (PbtiO2). A complementary clinical study was performed on 19 SAH patients. The long-pressure reactivity index (L-PRx) was calculated through continuous monitoring of MAP and ICP. In both studies, an electrocorticographic subdural recording strip was surgically implanted for SD detection. Measurements of all indices were compared before and after SD occurrence.

In ICH swine, 22 SD events evolved spontaneously in 2/3 of the animals. Impairment of CA was detected within 10 min after SD onset. Significant increases in ICP and PbtiO2 were observed within 20 min after SD occurrence. In SAH patients, a total of 277 SDs were detected. An impairment of CA and a significant increase in ICP, tied to the presence of clusters of SD, were observed.

Impairment of CA can be detected during SD development in a translational model of ICH and SAH patients. L-PRx, PRx, and H-ORx are useful tools for the assessment of cerebrovascular reactivity in the period surrounding SD onset.

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O3

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Spreading depolarization following ischemic stroke triggers unique neuronal calcium dynamics and behaviour in freely behaving female mice

Stroke is a leading cause of death and disability globally. During an ischemic stroke, a blocked cerebral blood vessel triggers localized loss of energy substrate and rapid neuronal death in the vessel-fed tissue. Spreading depolarizations (SD) emanate from this anoxic core across the brain. While many studies suggest that SDs are deleterious, some suggest they are benign or even beneficial. Here, we record neuronal Ca^{2+} dysregulation in both the emerging stroke core and in interhemispheric spreading depolarizations in awake, freely behaving mice identifying sex differences in SD-associated Ca^{2+} waves and their impact on behaviour. We use fibre photometry of the Ca^{2+} biosensor GCaMP6f in pyramidal neurons (Thy1-GCaMP6f) through bilateral fibreoptic cannulas dorsal to both hippocampi and measure neuronal Ca^{2+} dysregulation during a focal stroke (generated in one hippocampus via photothrombosis) and contralesional Ca^{2+} waves, linked to SD via paired local field potential recording. While ipsilesional Ca^{2+} dysregulation and associated behaviour are indistinguishable between sexes, female mice have larger and more frequent contralesional SD-associated Ca^{2+} waves. These Ca^{2+} waves induce prolonged exploration in the peri-stroke window. Longitudinal hippocampal deficits are assessed using contextual fear learning. When stroke is evoked immediately after fear memory acquisition, mice present with retrograde amnesia. While most mice who experienced stroke also demonstrate anterograde amnesia, female mice with contralesional SD-associated Ca^{2+} waves show no memory impairment. Here, we introduce a model to record neuronal Ca^{2+} dysregulation and behaviour during stroke in freely behaving mice, highlighting sex-specific differences in SD-associated Ca^{2+} waves and peri-stroke and longitudinal behaviour.

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O4

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Tissue partial pressure of oxygen during spreading depolarization in malignant stroke is associated with outcome

Objective: In the present study, we investigated the influence of SD on brain tissue partial pressure of oxygen ($PtiO_2$) within the peri-infarct tissue of patients suffering malignant hemispheric stroke (MHS).
Methods: This prospective observational study included 25 patients with MHS that underwent decompressive hemicraniectomy (DC) followed by subdural placement of an electrocorticography (ECoG) strip electrode and cortical implantation of a $PtiO_2$ probe within in the periinfarct tissue. Continuous and simultaneous ECoG and $PtiO_2$ recordings were obtained at bedside for 6 days and analyzed for the occurrence of SD and SD-associated $PtiO_2$ changes, as well as their association with clinical outcome at 6 months.
Results: The total simultaneous ECoG and $PtiO_2$ recording time was 2603 hours, during which 796 SDs were detected. During the observation period, the SD-independent $PtiO_2$ baseline changed significantly with an almost linear increase that reached a peak around 100 hours (*p=0.0055), followed by a $PtiO_2$ drop until the end of the monitoring period (*p=0.0048). Baseline $PtiO_2$ did not correlate with outcome (p=0.916). Conversely, 20 out of 25 patients showed SD-associated $PtiO_2$ changes in 363 out of 796 SDs (45.6%), which were categorized as biphasic (222), hypoxic (119) and hyperoxic (22). Among these SD-associated $PtiO_2$ responses, a high occurrence rate, biphasic response pattern and high amplitude correlated significantly with favorable outcome (mRS 1-3) at 6 months.
Conclusion: SD-associated $PtiO_2$ coupling in patients suffering hemispheric stroke appears to be associated with clinical outcome and could reflect the presence of viable and metabolically less impaired peri-infarct tissue.

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O5

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Long-term effects of spreading depolarizations on collateral vessel growth and hemodynamic impairment after experimental chronic hypoperfusion in mice

Introduction The occurrence of spreading depolarizations (SDs) in the injured brain has mainly been linked to secondary neuronal damages. However, experimentally these results are primarily based on examinations of the early postictal phase and do not appropriately translate into clinical experience. To investigate the effects of SDs after chronic hypoperfusion in a later period, we developed an experimental setup for long-term SD-induction in mice.

Methods Chronic hypoperfusion was induced in mice (Thy1-ChR2; 3-5 months) through permanent unilateral occlusion of the internal carotid artery. For chronic SD-induction, a novel wireless optogenetic device operating on near-field power transfer was implanted under the scalp. Its LED was placed onto the cortical surface. The experimental group received a SD-induction every 6 hours over a period of 3 weeks, the control group received the same surgical treatments without SD-induction. The effects of chronic SD-induction were analyzed functionally by regular assessment of neurovascular coupling and reserve capacity, and histologically at the end of the experiment.

Results With the proposed experimental setup we were able to reliably induce SDs during a period of 3 weeks in free-moving animals with wireless stimulation. Animals with chronic SD-induction showed functional and histological alterations compared to the control group. Especially the analysis of the cerebrovascular structure showed increased vessel diameters in the experimental group.

Conclusions The proposed method has the potential to investigate long-term effect of SDs in various pathologies. Contrary to the results of short-term experiments in rodents, our results suggest that SD-stimulation might improve collateral vessel growth and ischemic tolerance.

O6

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Brain glycogen stores recruitment supports tissue repolarization after spreading depolarizations

Introduction: Brain energy stores consist mostly in astrocytic glycogen recruited in ischemic conditions or during physiological episodes of high neuronal activity. Cortical spreading depolarization (SD) is a propagating wave of near-complete depolarization of neurons and glial cells, representing a strong metabolic challenge for the brain tissue. We hypothesized that glycogen would be recruited during CSDs, providing a model to study the functions of glycogen stores in a normal brain.
Method: SDs were recorded in rats anesthetized with isoflurane, using DC ECoG recordings. Glycogen stores were blocked by local administration of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) an inhibitor of glycogen phosphorylase. Brain lactate, glucose, and oxygen concentrations were monitored second by second using enzymatic microelectrode biosensors.
Results: Blocking glycogen stores increased the duration of tissue depolarization after SDs. By contrast, the duration of the spreading depression of activity was left unchanged. SDs induced a transient decrease in cortical extracellular glucose concentration accompanied by lactate release. In the presence of DAB, the glucose decrease lasted longer, and lactate release was diminished, indicating that glycogen recruitment predominantly induced lactate release. Interestingly, in the presence of DAB, intravenous lactate administration could rescue a normal repolarization time, suggesting that lactate released from glycogen stores augmented the energy supply required for tissue repolarization. In addition, changes in brain tissue oxygen pressure were similar in the presence or absence of DAB.
Conclusion: Glycogen stores can be recruited within seconds to provide a boost in energy metabolism in the form of lactate released into the brain interstitial fluid as a supplemental energy source.

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O7

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Spreading depolarizations occur after cerebral venous sinus occlusion in the gyrencephalic brain

Until now, cerebral venous occlusion as an etiology for SD has been only documented in lissencephalic brains. The objective of the present study was to test the reliability of inducing SDs after venous occlusion in the gyrencephalic brain. The occlusion was performed by clipping the middle third of the swine's superior sagittal sinus (SSS). Animals were divided into three groups. According to the assigned group, animals were monitored with electrocorticography (ECoG) alone, ECoG and intrinsic optical signal (IOS) imaging, or ECoG together with laser speckle contrast and oxygen imaging (LSCI). After the experiment's conclusion, TTC (2,3,5-triphenyl tetrazolium chloride) staining was performed to evaluate venous infarct formation. We found that SDs developed after venous sinus occlusion in the gyrencephalic swine brain. SDs could be detected in all methods. The highest SD incidence occurred during the first hour after the occlusion, with a clear decrement in the following hours. In IOS, four different hemodynamic responses were visualized. Tissue TTC analysis did not show thrombosis or venous infarction formation. We described for the first time that SDs develop spontaneously in the gyrencephalic swine brain after SSS occlusion. Our results warrant further investigation in animal models and clinical studies to confirm our results.

O8

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A novel model to study spreading depolarizations under cerebral hypoperfusion in the gyrencephalic brain

Objective: The effect of cerebral hypoperfusion on the development of Spreading Depolarization (SD) has not yet been determined. Here, we developed a novel swine model of endovascular, intracranial vessel occlusion without acute infarction for simulation of reversible cerebral hypoperfusion.

Methods: Twelve female landrace swine were anesthetized and mean arterial blood pressure was targeted at 60-80mmHg. Bilateral iliac artery punctures were performed and two 8F angiographic sheaths were inserted. Using 2D angiographic guidance, balloon catheters were positioned within both carotid arteries directly proximal to the main feeding trunk of the porcine rete mirabilis. Next, the animals were repositioned prone and a bilateral craniectomy was performed. The dura was excised and a Laser Speckle Imaging (LSI) device was positioned for continuous recording of cortical perfusion. With angiographic control, a baseline LSI perfusion measurement (60 min) was obtained, followed by LSI during unilateral (60 min) and bilateral (60 min) occlusion and subsequent reperfusion (60 min).

Results: In 9/12 animals (75%), a total number of 51 SD-associated hemodynamic response patterns were recorded during a recording time of 2.880 hours. The mean SD propagation velocity was 3.2±0.9mm/min across a propagation area of 90±40mm^2. The mean SD numbers were 0.42±1.7 SDs/h at baseline, 0.17±0.39 SDs/h during unilateral occlusion, 2.58±3.5 SDs/h during bilateral occlusion and 1.08±2.8 SDs/h during reperfusion (p=0.058, one way ANOVA).

Conclusion: Endovascular balloon occlusion proximal to the porcine rete mirabilis can reliably trigger SD activity in the gyrencephalic brain, which may help to unravel the pathophysiology of TIA in patients suffering chronic cerebral ischemia.

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O9

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Memantine Inhibits Cortical Spreading Depolarizations and Improves Outcome of Repetitive Mild Traumatic Brain Injury

Cortical spreading depolarizations (CSDs) are common following traumatic brain injury (TBI). We investigated the role of post-traumatic CSDs (PTCSDs) in a closed head impact model and the effect of memantine treatment on CSD characteristics and neurobehavioral outcomes.
In 9-week-old rats (N=20) PTCSDs were recorded *in vivo* electrocorticographically following a moderate TBI. Neurobehavioral assessment was performed (baseline, 1, 24, 48 h post-TBI). Post-impact cerebral blood flow changes were recorded via laser doppler flowmetry. Effects of memantine (10 mg/kg i.p.) on electrically triggered CSDs were investigated in naive (N=40) and TBI animals (N=53) that underwent electrode implantation microsurgery. A randomized controlled trial (RCT) of memantine treatment (i.p. 10 mg/kg; N=16) compared with vehicle (N=15) was conducted to test the neurobehavioral outcomes of repetitive mild TBI (rmTBI). PTCSDs were recorded in 50% of animals following TBI (N=20). Animals, displaying PTCSDs, had marked oligemia, microvascular damage, and lower neurobehavioral scores at 48 h ($p = 0.005$) compared with animals in which PTCSDs were not recorded. Memantine reduced the likelihood of CSDs in response to electrical stimulation by 50-67% in naive (N=40) and TBI-exposed rats (N=53). In the RCT, memantine-treated rats had higher neurological scores following four daily rmTBIs compared to vehicle-controls (9.27/12 (SD 3.08) vs. 5.56/12 (SD 3.05)), $p< 0.001$).
We conclude that PTCSDs are associated with microvascular injury and impaired neurobehavioral outcome. Memantine inhibited CSDs in TBI animals and prevented neurological decline in a repetitive mild TBI model without side effects.

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O10

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Multivariate Modeling of Intensive Care Risk Factors for Spreading Depolarizations in Severe Traumatic Brain Injury

Introduction/Objectives: Several variables that are routinely managed in neurocritical care of acute brain injury have been identified as risk factors associated with higher incidence of spreading depolarizations (SD). Here we sought to investigate these factors in a large patient cohort with an aim toward developing SD prediction models.
Methods: We used data from 82 patients who had SDs on electrocorticography following surgical treatment of traumatic brain injury. Systemic monitoring variables were extracted from hourly nursing charts and blood biochemistry data were linearly interpolated to populate values aligned with hourly SD counts.
Results: In univariate analysis of 7,067 hours, we found that mean arterial pressure (MAP), cerebral perfusion pressure (CPP), brain oxygenation ($P_{br}O_2$), and heart rate were significantly lower when SDs occurred. In >3,300 hours of biochemistry data, SDs were also associated with lower P_aCO_2, higher pH, and higher glucose. Higher F_iO_2, S_aO_2, and P_aO_2 were also associated with elevated SD risk. Each of these relationships was even more pronounced for SDs classified as isoelectric. In multivariate analysis using 1,429 hours with complete data for all physiology and biochemistry variables, lower MAP, heart rate, P_aCO_2, ICP, and higher temperature, S_aO_2, and glucose were independently associated with SD occurrence. The logistical model had an AUC of 0.72, with sensitivity of 58% and specificity of 78%, for predicting hours with SDs.
Conclusions: Results confirm the importance of key systemic variables in SD risk. Future work aims to extend prediction to all patients, and not just those known to have SDs.

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P1

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An in vivo, non-invasive platform to study the impact of repetitive Spreading Depolarisation in awake head fixed mice

Introduction. Anaesthesia and invasive induction mechanisms effect downstream responses to Spreading Depolarisation (SD). We previously reported an optogenetic induction protocol and the ability to electrographically record SDs through the intact skull using graphene micro-transistor arrays (gSGFETs) in awake head-fixed mice. The aim of this study is to characterise the effect of repetitive SDs on behavioural responses and early biomarkers of SD using immunohistochemical techniques.

Methods. Mice were injected with viral vectors to express channelrhodospin in the right motor cortex and to attach headbars. 6 weeks later gSGFET arrays were placed on the skull over the ipsilateral somatosensory cortex. Cameras were focused on eye pupils and limbs. SDs were induced a total of 10 times (interval 10 mins). 2-3 hrs after the 10th SD animals were sacrificed and brains perfused for subsequent immunohistochemical analysis.

Results. Non-invasive optogenetic illumination (10s 10mW blue light) reliably induced SDs, detected through the skull using gSGFET arrays. Preliminary results indicate that SDs were associated with eye pupil dilation, which took longer to recover during repetitive stimulations. The behavioural response to a single SD was subtle, however pronounced freezing, followed by dystonic limb posturing was observed following repetitive SDs. Post hoc immunohistochemistry revealed increased expression of inflammatory biomarkers such as COX2 and IBA-1 in the ipsilateral cortex to SD induction.

Conclusion. This in vivo platform can be used to study SD without the confounders of anaesthesia and invasive induction protocols and can be adapted to study the impact of SDs in different preclinical models of neurological disease.

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P2

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Occurrence of Spreading Depolarization and impact on delayed infarct progression after malignant hemispheric stroke in C57/bl6 mice

Introduction In various experimental models of stroke, spreading depolarizations (SD) have been shown to cause secondary neuronal damage in the initial hours after stroke onset. In contrast, the contribution of SDs to the infarct maturation during later periods remains unknown. In this current study, we analyzed the role of SDs 24 hours after experimental cerebral ischemia, translating to the typical timepoint of SD monitoring in patients. Additionally, the influence of ketamine treatment was investigated.
Methods Permanent focal ischemia was induced by distal occlusion of the left middle cerebral artery in male C57/bl6 mice. 24 hours after middle cerebral artery occlusion, spreading depolarizations were induced with potassium chloride. The neurovascular response was measured by laser speckle contrast analysis. Infarct progression was evaluated by sequential MRI scans. Four study groups were analyzed: control group without SD induction, SD induction with potassium chloride, SD induction with potassium chloride and Ketamine administration.
Results 24 hours after stroke onset spontaneous SDs occurred sporadically and were reliably triggered by potassium chloride application. Ketamine treatment reduced the number and duration of SDs significantly. Induction of SD using potassium chloride application significantly increased stroke volume even 24 hours after stroke onset, which however, could be prevented by ketamine treatment.
Conclusions Induction of SDs with potassium was significantly associated with stroke progression even 24 hours after stroke onset. Therefore, SDs might be a significant contributor for delayed stroke progression. Ketamine might be a possible treatment option to prevent SD induced stroke progression.

P3

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Frequency band changes during ischemic stroke, spreading depolarizations and mild hypothermia in gyrencephalic brains

Objective: To characterize frequency band changes during ischemic stroke, spreading depolarizations (SDs), and mild hypothermia in gyrencephalic brains.

Methods: Left middle cerebral arteries (MCAs) from six hypothermic and twelve normothermic pigs were permanently occluded (MCAo). One hour after MCAo, hypothermia was gradually established at 32°C. ECoG signals from both frontoparietal cortices, where the MCA and anterior cerebral artery (ACA) provide blood supply, were recorded one hour before and 23 hours after the MCAo. Five-minute ECoG epochs were obtained before, 5 min, 4, 8, 12, and 16 hours after MCAo, and before, during, and after SDs. Power spectra of ECoG epochs were decomposed into fast (alpha, beta, and gamma) and slow (delta and theta) frequency bands.

Results: After MCAo, electrodes in the ischemic core registered an immediate decay of the five frequency bands. Electrodes in penumbra reported accelerated drops of fast frequencies but gradual slumps of the slower ones. The ACA electrode experienced the maintenance of all the frequencies until the 12th hour when only gamma remained unchangeable. During the SD analysis in both groups, all the frequency bands underwent a sudden power decay in the MCA and ACA electrodes when the SDs were passing by; meanwhile, just the ACA electrode reported a power recovery of all frequencies when SDs left the recorded area.

Conclusions: A ischemic-core map was created based on frequency band fluctuations. SDs can suppress all the frequency bands. Mild hypothermia neither prevented the power decay during the SD development nor supported the power recovery after SD expansion.

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P4

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Reperfusion failure after spreading depolarization shapes hemoglobin content in the mouse cortex

Introduction: Spreading depolarizations (SDs) trigger vasoconstriction and worsen tissue outcome after acute ischemic stroke (AIS). Our recent study has confirmed that spontaneously occurring SDs are crucial in the evolution of reperfusion failure after AIS. Here we show that in the cortical area invaded by SD, reperfusion failure is associated with decreased tissue hemoglobin content and neuronal necrosis.

Methods: Female and male C57BL/6 mice (n=6) were anesthetized with isoflurane (0.8-1%). Ten minutes baseline was followed by transient (45 min) occlusion of the bilateral common carotid arteries (2VO) and subsequent reperfusion was monitored for 60 min. Cerebral blood flow (CBF) and hemoglobin concentration changes were monitored using green light reflectance and laser speckle contrast imaging. Image analysis and signal processing were performed with custom-made algorithms written in MATLAB. Neuronal necrosis was evaluated in hematoxylin-eosin-stained sections.

Results: In 4 mice SDs (n=6) occurred spontaneously in response to AIS induction during the ischemic period (45 min). Cortical regions invaded by SD displayed reperfusion failure (CBF<60% in 78±11% of total cortical area) and a significant decrease of total hemoglobin concentration (-10.77±3.7 mM). In contrast, cortical hemispheres devoid of SD (n=6) showed successful reperfusion (CBF>60% in 97±3% of total cortical area) and negligible hemoglobin concentration variations (-1.02±3.39 mM). In concert, SD occurrence and reperfusion failure were associated with neuronal necrosis 24 hours after AIS.

Conclusions: Our data substantiate the key role of SDs in the evolution of reperfusion failure despite successful recanalization. We propose the pharmacological inhibition of SD evolution to attenuate reperfusion failure and improve CBF after recanalization.

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P5

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Isoflurane improves cerebral oxygenation during spreading depolarization by lowering the cerebral metabolic rate of oxygen in vitro

Introduction: Spreading depolarization (SD) has been shown to aggravate tissue damage following acute brain injuries. This is thought to be due in part to a mismatch between the supply and demand of energy substrates. Anesthetics reduce energy consumption, yet their effects on cerebral metabolism during SD remain largely unknown.
Methods: We investigated oxidative metabolism during SD induced by focal potassium chloride application in acute rat brain slices. Extracellular potassium ($[K^+]_o$), local field potential (LFP) and partial tissue oxygen pressure ($p_{ti}O_2$) were simultaneously recorded. Cerebral metabolic rate of oxygen ($CMRO_2$) was calculated from recorded vertical $p_{ti}O_2$ profiles using a reaction-diffusion model. By that, we tested the effect of clinically relevant concentrations of isoflurane on $CMRO_2$ during SD and modeled tissue oxygenation for different capillary pO_2 values to simulate hemodynamic responses.
Results: $CMRO_2$ increased ~2.7-fold during SD, which led to transient hypoxia in the slice core despite supply of 95% oxygen. Isoflurane treatment at concentrations known to induce deep anesthesia (3%) did not prevent SD but decreased $CMRO_2$ and peak $[K^+]_o$ and prolonged $[K^+]_o$ clearance, which indicates reduced synaptic transmission and sodium-potassium ATPase inhibition. Modeling of oxygen diffusion for different values of oxygen supply and different $CMRO_2$ values predicted that 3% isoflurane would prevent SD-associated hypoxia for capillary pO_2 levels as low as ~40 mmHg, while only marginal improvements of tissue oxygenation can be expected when capillary pO_2 levels drop to 20 mmHg.
Conclusions: The metabolic effects render isoflurane a promising candidate for pre-clinical studies on neuronal survival in conditions involving SD.

P6

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Cortical spreading depolarization scalp-brain voltage ratios and images from simulated concussion and subarachnoid hemorrhage

Cortical Spreading Depolarization (SD), a propagating depolarization wave in the cerebral gray matter, occurs in severe acute brain injury and, as suggested by experimental studies, in human concussion.

To explore the possibility of noninvasive SD detection, we developed a finite element model to predict scalp voltage changes from a concussive expanding-ring SD (Hund, PMID:35233716). We compared our simulation results with retrospectively evaluated data in aneurysmal subarachnoid hemorrhage (aSAH) patients (Drenckhahn, PMID:22366798). To test the possibly of noninvasive detection, we recorded DC-shifts from ECoG COSBID-coded SDs in a SAH patient with a 1-cm hex-packed 29 electrode array (Jones, iCSD-2021) and produced scalp images.

The ratio of scalp to simulated cortical voltage was 0.074, whereas the ratio from the retrospectively evaluated data was 0.032 (0.031) [median (IQR), n = 161, $p < 0.001$] and of our exploratory data, 0.124 (0.022), n=26. Reconstructed images from virtual scalp detection arrays with 1 cm electrode spacing showed recognizable expanding-ring propagating scalp voltages from a simulated cortical concussive-SD. Electrode spacings of ≥2 cm produced distorted reconstructed images. From the hex-packed array, 24 of 26 ECoG and scalp DC-shift pairs had coefficients-of-determination >0.80 [0.980 (0.001)] and scalp images showed spatial characteristics consistent with noninvasive SD detection.

Differences in the voltage ratios can be attributed to electric-field shape differences between concussive- and aSAH-SDs and between SDs themselves. Our simulation and human study results suggest that concussive SDs can be detected from the scalp and noninvasive SD detection is possible in severe acute brain injury.

Grant support: This project was conducted for CerebroScope, a medical device company developing a scalp DC-EEG system for detecting SDs in severe acute brain injury, concussion, and migraine. This work was partially supported by grants from the: US Public Health Service National Institutes of Health: NS30839; NS30839-14S1; and NS66292 to the SCJ while at the Allegheny-Singer Research Institute; and 5R43NS092181 and 3R43NS092181-02S1 to SCJ for CerebroScope; DFG Deutsche Forschungsgemeinschaft, German Research Council: DFG DR 323/5-1 and DFG DR 323/10-1 to JPD; and BMBF Bundesministerium fuer Bildung und Forschung (Era-Net Neuron EBio2), with funds from BMBF (0101EW2004) to JPD.

P7

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Cold Spreading Depolarization (`cold-SD`) in Rodent Brain Slices

'Chill coma' has been documented in insects when exposed to near-freezing (n/f) temperatures that evoke spreading depolarization (SD). We found that exposure to n/f temperature causes an SD-like event in mammalian higher brain, which we term `cold SD`. SD is a mass wave of cellular depolarization when the Na+/K+ pump fails. SD during ischemia causes neuronal swelling, injury, and death. We hypothesize that cold SD arises from compromised Na^+/K^+ pump function, building from research by Kirov showing neuronal swelling/beading in rodent slices at ~6°C and on our findings that n/f temperature evokes cold SD in rodent slices, based on imaging changes in light transmittance (LT). As bath temperature dropped from 10°C to 3-6°C for ~250 seconds, LT decreased in neocortex coinciding with a slow positive drift in extracellular voltage of 2-3 mV recorded with a KCl pipette. Then, a sudden negative shift of ~3mV coincided with the front passing the pipette, so this is a classic SD event but slower, with less cell swelling compared to OGD-SD. Cold SD slices when slowly warmed, could generate OGD-SD, demonstrating recovery. We conclude 1) preparing rodent slices at n/f temperatures can induce cold SD from which slices recover upon warming; 2) The Gibbs-Donnan equilibrium maintains the chemical and electrical energy differential between the intra- and extracellular compartments. SD can still be generated so long as the pump functions. 3) The brains of certain small species of bat and ground squirrel likely undergo cold SD and recover, much like insects. Months after completing our study, we found a rat study published only in German that strongly supported our findings. (Lehmenkühler, A (1990) - Spreading depression - Reaktionen an der Hirnrinde - Störungen des extrazellulären Mikromilieus).

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P8

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Diversity of cortical activity changes beyond depression during Spreading Depolarizations

Spreading depolarizations (SDs) are implicated in a variety of brain diseases, including ischemic stroke, subarachnoid hemorrhage (SAH), traumatic brain injury, migraine and epilepsy. SDs are classically thought to be associated with spreading depression of cortical activity. Here, we found that SDs in patients with SAH produce variable, ranging from depression to booming, changes in subdural electrocorticographic activity, especially in the delta frequency band. Similar variability has also been observed in high-potassium-induced SDs in rats, and the vertical propagation profile of SDs largely accounted for this variability. Depression of activity at the cortical surface was characteristic of full SDs penetrating all cortical layers. In contrast, partial SDs, confined to the superficial layers, were associated either with little change or even with a boom of activity at the cortical vertex. Electrical activity at the cortical surface during partial SDs was supported by volume conduction of signals from spared delta generators in the deep layers. In addition, partial SDs caused light depolarization and sustained excitation, organized in gamma oscillations in a narrow sub-SD zone. Our study challenges the general concept of homology between spreading depolarization and spreading depression by showing that SDs produce variable, from depression to booming, changes in activity at the cortical surface and in different cortical layers depending on the depth of SD penetration.

K2

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Exploring the Monogenic Borderland of Epilepsy and Spreading Depolarization

Seizures and spreading depolarization are clinically and electrophysiologically distinct, however an emerging genetic overlap of these two episodic neurological disorders offers critical insight into their mechanistic borderland. A small, but growing subset of epilepsy-linked genes also modulate the threshold for slowly propagating spreading depolarization in cortical networks. In these co-morbid models, both loss and gain of function mutations are involved, and in some genes, the clinical distinction is variant-specific. These genetic guideposts help illuminate the indistinct molecular boundaries separating the fast aberrant network synchronization of inherited seizure disorders from the slow, electrically silent, SD-linked aura of complex migraine syndromes.

A forward screen of monogenic mouse epilepsy models is providing additional mechanistic information. One recent intriguing discovery reveals that hemispheric cortical SD thresholds need not always be asymmetric. Conditional Kcnq2 potassium channel deletion responsible for the muscarinic M current in forebrain excitatory neurons not only produces simultaneously bilateral SD events, but also regulates propagation speed and seizure coupling threshold. These features are not uniformly present in the *Kcna1* deletion model, but are phenocopied by Kcnq2 pharmacologic blockade, while Kcnq2 activation elevates the SD threshold *in vitro*. Mutations in *Scn1a* sodium channels generate a different epilepsy/SD syndrome. *Scn1a* gain of function (FHM3) provokes unilateral SD, however these are also seen in a *Scn1a* loss of function (DEE) model, where the rate of spontaneous SD events exceeds that of seizures and is profoundly accelerated by a single episode of hyperthermia that is curtailed by memantine.

Continuing exploration of the genetic underpinnings and pharmacological sensitivity of SD and seizures in monogenic mouse models will broaden our understanding of the molecular control and cellular propagation of this unique depolarizing relative of epilepsy.

O11

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Characterizing the spatiotemporal patterns of ictal spreading depressions

It has been suggested that the depression during and after seizure-like activity is similar to spreading depolarizations (SD) observed in migraine and traumatic brain injury. Notably, electrophysiological recordings in brain-injured patients have shown large, infraslow (DC – 1 Hz) shifts in electrical potentials accompanied by a depression in electrocorticographic activity consistent with SD – these are also often associated with seizures. Importantly, SDs in brain-injured patients are associated with significantly worsen clinical outcomes. Here we sought to better understand the spatiotemporal propagation of these potentials in medically refractory epilepsy patients, by examining the gradients of infraslow (DC – 1 Hz) activity during 19 seizures recorded from 6 patients who were undergoing stereoelectroencephalographic monitoring. While brief bouts of infraslow activity were observed at the beginning of seizures, the largest signal in the infraslow frequency band was associated with seizure termination. We characterized the spread of this large, termination associated infraslow activity throughout the areas sampled in each patient, finding that many exhibited patterns that were 1) consistent within patients, and 2) correlated with other electrophysiological features of the seizure spread. These results relate the spatiotemporal propagation of infraslow activity to seizure spread, termination, and postictal suppression, thereby contributing to a more comprehensive understanding of seizure spread.

O12

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The astrocyte potassium channel Kir4.1 influences seizure and spreading depolarisation susceptibility

Introduction: Kir4.1 is an inwardly rectifying potassium channel expressed in astrocytic processes that surround synapses. It plays a direct role in potassium buffering and an indirect role in glutamate uptake from the synapse. Reduced expression or mis-localisation of Kir4.1 is observed in tissue obtained from epilepsy resections.

Methods: To study the impact of Kir4.1 loss to seizure and spreading depolarisation (SD) susceptibility directly we developed a novel rodent model of temporal lobe epilepsy (TLE) using viral vectors to target cre-recombinase to focally knockout Kir4.1 expression in the hippocampus/cortex of adult flox-mice. Continuous video-telemetry recordings were employed to characterise the development of epileptiform activity and spontaneous seizures. In order to detect concurrently seizures and SDs we used DC-coupled graphene micro-transistor arrays to record both spontaneous and optogenetically evoked-seizures in awake head-fixed mice and to assess the threshold for optogenetic induction of SD.

Results: Spontaneous seizures arise 1-2 weeks post-viral injection (7±2.2 seizures from 7-14 days post-injection; n = 8 mice). In 60% of Kir4.1-cKO mice, SD temporally co-existed with seizures, indicating a high susceptibility for seizure-associated SD in this model. Post-ictal depression was longer following seizures associated with SD compared to seizures alone (recovery period to baseline activity: seizure with an SD, 341.8±169.2 s, n = 3 mice; seizure only, 73.7±28.7 s, n = 2 mice).

Conclusion: Hippocampal knockout of Kir4.1 results in TLE where the majority of seizures temporally co-occur with SD. This is a useful model to investigate the mechanisms underlying, and importance, of seizure-associated SDs.

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O13

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Intravital imaging reveals calcium depletion in the endoplasmic reticulum during cortical spreading depressions following generalized seizures in mice

Introduction/Objectives: Cortical spreading depression (CSD) has been observed following seizures in various animal models and induced CSD has been demonstrated to terminate seizures. However, this mechanism of termination is incompletely understood and defining intracellular differences between seizures and CSD could offer insight to this end. Here we present novel findings on calcium homeostasis during these events.
Methods: We developed a calcium indicator co-expression paradigm to enable simultaneous recording of the cytosol and endoplasmic reticulum (ER). Using AAV delivery we pan-neuronally expressed our constructs in mouse cortex and performed awake intravital two-photon calcium imaging with simultaneous EEG and DC recordings during repeated pentylenetetrazol-induced seizures.
Results: We observed sharp rises in cytosolic calcium during pre-ictal spike-wave discharges and ictal events, while ER calcium remained unchanged. Upon seizure termination, we frequently noted a slow propagating calcium wave with an associated DC shift consistent with CSD. During the negative DC deflection, cytosolic calcium increased and ER calcium decreased, suggestive of calcium induced calcium release (CICR). However, during the positive DC rebound, cytosolic calcium diminished and ER calcium restored. These dynamics were recapitulated during electrically induced CSD, but not during post-ictal phases occurring without CSD.
Conclusions: These findings establish the occurrence of CICR as a distinguishing feature between seizures and CSD. Additionally, while CICR and ER calcium replenishment may be consequences of CSD, their close association with DC shift phase implicate them in playing a more casual role. Thus, we plan to explore the necessity and sufficiency of CICR for CSD and its anti-seizure effect.

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O14

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Changes in the Direct Cortical Response during spreading depolarisations in the injured human brain

Introduction: How neuronal excitability is directly affected by spreading depolarisations (SDs) in the in-vivo human brain is yet unknown. The Direct Cortical Response (DCR) is an electrically evoked potential with exceptional cross-species congruency that provides a measure of neuronal excitability.
Objective: To assess if monitoring the DCR in brain-injured patients could reveal new insight about how SD alters excitability.
Methods: Electrocorticographic electrodes were used for delivery of stimuli and recording of DCRs, the DC-shift and spreading depression in 15 patients. DCRs were elicited via biphasic charge-balanced pulses of <40µC/cm^2/pulse at 0.2Hz. Recordings lasted 6min<5hrs. Features of the DCR were measured semi-automatically and analysed using custom MATLAB scripts.
Results: During DCR monitoring, 105 SDs were captured. Principal findings were: **1)** DCR amplitude fell dramatically during SDs; **2)** Between SDs, DCR amplitude was remarkably stable facilitating objective, reliable measurement of SD duration and burden (measured as AUC); **3)** DCR amplitude fell a median of 2min 51s and up to 10min 38s in advance of the DC-shift; **4)** Discrete DCR components expressed distinct temporal patterns of behaviour during SD.
Conclusions: The findings indicate that **1)** in humans, evoked as well spontaneous activity is interrupted by SD; **2)** a loss of neuronal excitability can be detected minutes before collapse of ion gradients; **3)** specific mechanisms and/or cell populations are involved differentially during the passage of human SD; **4)** the DCR is an ideal method to reliably quantify critical SD properties and may enhance bench to bedside translation, paving the way for development and testing of novel therapies.

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O15

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A novel local regression approach to analyze functional connectivity following CSD

Cortical spreading depolarizations (CSD) are implicated in the pathophysiology of several neurological conditions, including stroke, traumatic brain injury, and migraine with aura. Our previous work has suggested that CSDs induced in one hemisphere using optogenetic stimulation can cause changes in functional networks for up to 20 minutes. We implanted a chronic imaging window over an intact skull in wild-type C57 and transgenic GCaMP mice (GCaMP6f). CSD was induced either with optogenetic stimulation or needle insertion through the olfactory bulb to preserve cortical integrity. Optical resting state functional connectivity (RSFC) imaging was performed under tribromoethanol anesthesia at baseline; during and immediately following CSD; and at 1, 12, and 24 hours following CSD. We found changes in RSFC metrics such as bihemispheric and global connectivity indices, seed-based connectivity, and power of hemodynamic and neuronal fluctuations immediately after a unilateral CSD. We found marked differences in our results when we used a local hemisphere regression which took into account of differences in mean signal within each hemisphere as compared to global regression which treated both hemispheres identically. This work may have implications for the interpretation of functional network analysis following CSD or other lateralizing phenomena.

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O16

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Voltage-gated calcium channels and glutamate NMDA receptors are both necessary for initiation of cortical spreading depression

The mechanisms of initiation of cortical spreading depression (CSD) in the brain of migraineurs remain unknown, and the mechanisms of initiation of experimentally-induced CSD in normally metabolizing brain tissue remain unclear and controversial. Here, we investigated the mechanisms of CSD initiation by focal application of KCl in mouse cerebral cortex slices. High KCl puffs of increasing duration up to the threshold duration eliciting a CSD were applied on layer 2/3 whilst the membrane potential of a pyramidal neuron located near the site of CSD induction and the intrinsic optic signal were simultaneously recorded. This was done before and after the application of specific blockers of NMDA or AMPA glutamate receptors (NMDARs, AMPARs) or voltage-gated Ca2+ (CaV) channels. Inhibiting AMPARs was without effect on CSD threshold and velocity. Blocking either NMDARs or CaV channels completely inhibited CSD initiation by both CSD threshold and largely suprathreshold KCl stimuli, thus showing that both NMDARs and CaV channels are necessary for CSD initiation. Analysis of the CSD subthreshold and threshold neuronal depolarizations in control conditions and in the presence of MK-801 or Ni2+ revealed that the mechanism underlying the ignition of CSD by a threshold stimulus (and not by a just subthreshold stimulus) is the CaV-dependent activation of a threshold level of NMDARs. The delay of several seconds with which this occurs underlies the delay of CSD initiation relative to the rapid neuronal depolarization produced by KCl. Our data give insights into potential mechanisms of CSD initiation in migraine.

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O17

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S-ketamine for cortical spreading depolarization in patients with severe acute brain injury (KETA-BID): protocol for a randomised, blinded pilot trial

Introduction: Cortical spreading depolarizations (CSDs) are pathological depolarization waves in cortex, which in clusters may contribute to secondary brain damage in patients with severe acute brain injury. Ketamine appears to inhibit CSDs both in vitro and in patient series.
Methods: This randomised, blinded feasibility and pilot trial includes adults (≥ 18 years) who undergo craniotomy or craniectomy for severe acute brain injury (traumatic brain injury, aneurysmal subarachnoid or spontaneous intracerebral haemorrhage). During surgery, an electrocorticography (ECoG) strip will be placed adjacent to injured brain tissue. Patients are continuously monitored throughout their stay at the neurointensive and semi-intensive care unit. In case of an CSD, physiological optimization of intracranial pressure, brain tissue oxygen tension ($PbtO_2$), core temperature, and blood glucose will be initiated. Participants developing CSD clusters will be randomised for continuous infusion of S-ketamine or matching placebo in a 1:1 allocation. Participants, clinicians, investigators, and outcome assessors are blinded to treatment allocation. Infusion rates (i.e., dose) and duration of trial medication are adjusted accord to the number of CSDs. Surviving patients are followed up until six months after the injury with recording of functional outcome. The primary outcome is occurrence of CSDs per hour of monitoring after randomization.
Results: The KETA-BID trial aims to examine the efficacy and safety of S-ketamine for CSD in severe acute brain injury, as well as the feasibility of the trial design. This trial will provide new knowledge regarding CSD following severe brain injury as well as the clinical effect of ketamine for these patients.

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O18

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Mapping Ketamine Modulation of Spreading Depolarisation and Regional Blood Flow Post-Stroke Using Graphene Micro-Transistor Arrays

Introduction: Spreading depolarisations (SDs) can induce hypoperfusion in at-risk tissue surrounding the ischaemic core in the post-stroke brain. This inverse haemodynamic response is associated with a prolongation of the SD duration and decreased viability of affected tissue. In contrast to metal-based electrodes, graphene micro-transistor arrays (gSGFETs) enable multisite recordings of SDs without signal attenuation or distortion. This allows spatial mapping and direct correlation of SD waveform to the underlying change in regional cerebral blood flow (rCBF).
Methods: The photothrombotic model was used to create a reproducible, controlled and localised region of cortical ischaemia. A gSGFET array was positioned 0.5 mm from the site of irradiation to cover areas of at-risk penumbra and uncompromised tissue in anaesthetised mice. 30 regions of interest were selected underneath each transistor to directly monitor cerebral perfusion at sites of electrographic recording. Using this experimental set up, we mapped with high spatial resolution SD waveform and rCBF with time post-stroke. Animals received an injection of ketamine (15mg/kg) or vehicle alone i.p. ~10 minutes after the first SD was observed.
Results: In regions close to the site of stroke induction (<1.5mm away), long duration, double peaked SD waveforms coupled to haemodynamic responses which included a period of hypoperfusion were detected in the vehicle treated group. In contrast SDs were shorter in duration, single peaked and coupled with a hyperperfusion only response in animals treated with ketamine, despite a similar underlying perfusion deficit in this region.
Conclusions: Ketamine narrows SD waveform and prevents the inverse haemodynamic response.

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O19

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Nimodipine is protective against spreading depolarization and neuroinflammation

Introduction: Voltage gated Ca^{2+} channels (VGCCs) are widely expressed in the CNS and are implicated in neuronal injury. Nimodipine, a potent vasodilator and VGCC antagonist is effective against spreading depolarization (SD) induced vasoconstriction. However, little is known about the effect of nimodipine on neuronal and glial cells. Here, we aimed to explore the direct action of nimodipine on the nervous tissue.
Methods: Cortical microglia cultures (pure, mixed) from SPRD rats were treated with lipopolysaccharide (LPS;20 ng/ml) and nimodipine (10 µM), alone or in combination. Brain slices from C57BL/6 mice (n=32) were perfused with artificial cerebrospinal fluid (aCSF). After nimodipine (10 µM) incubation, low glucose aCSF and transient anoxia or hypo-osmotic stress were applied to mimic ischemia or edema, respectively. Intrinsic optical signal imaging was used to analyze SD features, transformation index (TI) was calculated to determine microglial activation.
Results: Nimodipine reduced microglial activation in cultures (pure: 3.59±1.7 vs 1.53±0.18; mixed: 2.49±1.07 vs 1.32±0.1 TI, LPS+nimodipine vs LPS). In slices, during edema nimodipine lowered the frequency of spontaneous SDs. In ischemia, nimodipine decreased the SD focus (2.37±0.94 vs 3.38±0.88%, nimodipine vs control), the total cortical area invaded by SD (17.12±8.63 vs 39.88±22.42%, nimodipine vs control) and the propagation velocity of SD (0.19±0.79 vs 1.59±2.29mm/min, nimodipine vs control). Nimodipine reduced microglial activation also in brain slices (8.66± 4.07 vs 5.6±3.29 TI; nimodipine vs control).
Conclusion: Nimodipine was protective against SD and successfully diminished neuroinflammation by decreasing microglial activation. The observed neuroprotective effect was achieved independent of nimodipine's vascular action.

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Nimodipine accelerates the restoration of neurovascular coupling after spreading depolarization

Introduction: Spreading depolarization (SD) is the pathophysiological correlate of migraine aura, leading to spreading depression of activity and long-lasting spreading oligemia. SD also suppresses cerebrovascular reactivity and leaves neurovascular coupling (NVC) reversibly impaired. Here we explored (i) the progressive restoration of NVC and (ii) whether nimodipine treatment accelerated the recovery of NVC during spreading oligemia.
Methods: Male, 4-9-month-old C57BL/6 mice (n = 11) were anesthetized with isoflurane (1%-1.5%). SD was triggered with 1M KCl. Electroencephalogram (EEG) and cerebral blood flow (CBF) were recorded with a silver ball electrode and laser-Doppler flowmetry. The L-type voltage-gated Ca^{2+} channel blocker nimodipine was administered i.p. (10 mg/kg). Evoked potentials (EVPs) and functional hyperemia were assessed under isoflurane (0.1%)-medetomidine (0.1 mg/kg i.p.) anesthesia before, and repeatedly after SD, at 15-min intervals for 75 minutes.
Results: Nimodipine accelerated the recovery of CBF from spreading oligemia (time to full recovery, 52 ± 13 vs. 70 ± 8 min, nimo vs. control) and tendentiously shortened the duration of spreading depression. The amplitudes of EVP and functional hyperemia were reduced and recovered over an hour post-SD. Nimodipine treatment exerted no effects on EVPs but increased the amplitude of functional hyperemia from 20 min post SD (93 ± 11% vs. 66 ± 13%, nimo vs. control). A linear, positive correlation between EVP and functional hyperemia amplitude was skewed by nimodipine.
Conclusions: In conclusion, nimodipine facilitated CBF restoration from spreading oligemia which was linked to a tendency of an accelerated return of neuronal activity and the significant recovery of NVC.

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P9

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Ca^{2+}-dependent modulation of astrocytic gap junctional coupling upon brief metabolic stress

Altered astrocytic coupling has been implicated in the pathogenesis of various neurological disorders, including ischemic stroke. In this condition, the brain's energy demands vastly surpass its availability. While cells in the ischemic penumbra retain the potential for recovery, this process is impeded by spreading depolarizations (SDs), which impose an additional metabolic challenge on the tissue. Moreover, SDs transiently disrupt cellular pH and Ca^{2+} homeostasis, both of which are modulators of gap junctional coupling. If and how astrocytic gap junctional conductance might be altered following SDs is, however, unknown. To address this question, we mimicked SD-like conditions by a 2-minute perfusion with blockers targeting glycolysis and oxidative phosphorylation ("chemical ischemia") in acute neocortical tissue slices of mice. Electrophysiological recording of syncytial isopotentiality revealed that the induction of brief chemical ischemia caused a rapid, partial uncoupling of astrocytes. Employing widefield imaging of ion-sensitive dyes to monitor changes in intracellular pH or Ca^{2+}, we found that the moderate ischemia-induced intracellular acidification was most likely not the primary cause for astrocyte uncoupling. However, dampening large astrocytic Ca^{2+} increases by either removal of extracellular Ca^{2+} or blocking Ca^{2+} influx, prevented uncoupling.

In conclusion, our data indicate that astrocytes subjected to large Ca^{2+} loads during SD-like conditions undergo rapid uncoupling. We propose that disconnecting these astrocytes could serve as a protective mechanism by preventing additional gap junction-mediated Ca^{2+} increases in adjacent healthy astrocytes. Consequently, astrocytic uncoupling could help to restrict and mitigate cellular damage within the penumbra.

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Blockade of calmodulin-dependent AQP4 trafficking restores neurovascular coupling after stroke and enhances the spreading depolarization coupled hyperemia in mice

Introduction: Aquaporin-4 channels (AQP4) are fundamentally involved in edema progression after acute ischemic stroke (AIS). However, genetic deletion of AQP enhanced brain swelling in mouse AIS models and caused adverse repolarization after spreading depolarization (SD). Here we aimed to investigate the effects of inhibiting calmodulin-dependent AQP4 trafficking after AIS on neurovascular coupling (NVC) and on SDs.
Methods: Two sets of experiments were performed on male isoflurane anesthetised C57BL/6 mice (n= 31). In the first set, AIS was induced by the transient (60 min) middle cerebral artery occlusion (MCAO). NVC was tested 3 days post-AIS. In the second set, recurrent SDs were elicited by 1M KCl acutely, for 2 hours in the non-ischemic cortex. In both experimental settings, CBF was measured by laser-Doppler Flowmetry, and neuronal activity was monitored by extracellular electrophysiology. Trifluoperazine (TFP) was administered for calmodulin inhibition.
Results: TFP restored the impairment of functional hyperemia with NVC after AIS (20.65±8.8% vs. 4.01±3.77%; TFP vs. Control). In concert, TFP treated mice displayed greater hyperemia coupled to SD (37.39±17.07 vs. 46.95±25.22%; TFP vs. Control). Interestingly, SD frequency was unaltered (8 vs. 9 SDs; TFP vs. Control), but SD amplitude gradually increased after TFP treatment (18.25±3.37 vs. 14.28±6.17 mV; TFP vs. Control).
Discussion: Astrocyte end-foot swelling has been implicated in the narrowing of the microvascular lumen and the reduction of CBF. In additional experiments we aim to prove that TFP acts through the modulation of AQP4 trafficking and propose it as a therapeutic target to improve CBF after AIS.

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P11

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Red Flags for Symptoms of Secondary Spreading Depression in Clinical Practice: SNAIL

Introduction Clinical symptoms of spreading depression (SD), similar to those of migraine with aura, may arise due to cortical pathology. Distinguishing between primary SD (migraine aura) and secondary SD based on clinical features is both crucial and challenging. Methods Drawing upon clinical features reported in a previously published systematic review of the literature and a series of cases from our own department, we compiled a list of clinical red flags that should raise suspicion of secondary SD. Results Based on 11 cases of definite secondary SD, 39 cases of possible secondary SD from the literature, and 12 cases from our department, we propose the following list of clinical red flags: • Side-locked symptoms of spreading depression (i.e., symptoms consistently occurring on the same side) • Non-visual onset • Atypical characteristics not strictly fulfilling ICHD-3 1.2.1 (International Classification of Headache Disorders, 3rd edition) • Increase in frequency or high frequency of episodes • Late onset (age > 50) Of the cases with a strong causal relation (n=23), all exhibited side-locked symptoms (required to establish causality), 12 had late onset, 9 non-visual onset, 7 increased frequency, and 3 atypical features. In 4 cases, side-locked symptoms were the sole red flag. Eighteen patients reported post-symptom headache. Conclusion We propose a list of red flags suggestive of potentially serious underlying causes for clinical episodes of SD. We recommend that patients presenting with one or more of these features undergo investigations to rule out cortical or cerebrovascular pathology. Further studies are required to validate the utility of this proposed list in clinical practice.

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The effects of an NO donor on the SD-induced negative ultraslow potential (NUP) after proximal cerebral artery occlusion (PCAO) in rats

Spreading depolarization (SD) is primarily a reversible event initiating cytotoxic edema in gray matter. Further along the continuum lies the SD-initiated NUP, the electrophysiological correlate of a developing brain infarct. In tissue at risk of progressive injury, SD causes spreading ischemia (SI). For example, SI occurs when extracellular baseline potassium ($[K^+]_o$) is elevated while the basal NO level is low. SI also occurs after PCAO where the ischemic penumbra might be deprived of NO because NO synthesis requires molecular O_2.

We investigated the effects of intravenous administration of the NO donor SIN-1 in spontaneously hypertensive stroke prone and normotensive Wistar Kyoto rats during PCAO-induced severe ischemia and reperfusion, using the SD-initiated NUP as biomarker for infarct development. Among other parameters, mean arterial pressure (MAP), regional cerebral blood flow (rCBF), brain activity, intracortical direct current (DC) potential and $[K^+]_o$ were continuously recorded.

Interestingly, although SIN-1 reduced MAP, the rCBF level an hour after PCAO was higher in SIN-1 treated rats ($p<0.05$). rCBF negatively correlated with $[K^+]_o$ (adjusted-R^2=0.69). If PCAO triggered a NUP, the areas under the curve for DC and $[K^+]_o$ were lower in SIN-1 treated rats ($p<0.05$). The amplitude of brain activity was greater during reperfusion in SIN-1 treated rats ($p<0.05$).

The NO donor may delay the commitment point based on the behaviors of DC potential, $[K^+]_o$ and the better recovery of brain activity. SIN-1 may be an interesting drug in stroke patients requiring antihypertensive treatment (e.g., acute hypertension in patients treated with rt-PA) as it lowers MAP while increasing rCBF.

P13

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Modulation of propagation of cortical spreading depolarization by GABAergic neurons.

Introduction: We have previously shown that a hyperactivity of GABAergic neurons can initiate cortical spreading depolarization because of spiking-induced extracellular potassium upload. We have proposed that this is a mechanism involved in hemiplegic migraine caused by genetic variants of *SCN1A/*$Na_V1.1$.
Objectives: We have investigated the involvement of GABAergic neurons in CSD propagation speed.
Methods: We have induced CSD in neocortical slices from mouse brain by focal application of 130mM KCl and quantified features of CSD propagation by intrinsic optical imaging and extracellular local field potential (LFP) recordings. We have used cre-lox mouse lines selectively expressing in GABAergic neurons the excitatory opsin *Channelrhodopsin-2* (ChR2) or the inhibitory opsin *Archaerhodopsin* (ArchT) for enhancing or inhibiting, respectively, the activity of GABAergic neurons by optogenetic illumination. Moreover, we have used the GABA-A receptor blocker gabazine to block fast GABAergic synaptic transmission.
Results: Neither enhancement nor inhibition of GABAergic neurons' activity with optogenetic illuminations in control conditions modified CSD propagation speed. Gabazine increased propagation speed. Interestingly, optogenetic enhancement of GABAergic neurons' activity in the presence of gabazine increased the propagation speed more than with only gabazine.
Conclusions: The results are consistent with a scenario in which the activity of GABAergic neurons can modulate CSD propagation with two contrasting effects: facilitation by spiking-induced increase in extracellular potassium and limitation by GABAergic synaptic transmission. The block of GABA-A receptor by application of gabazine discloses the facilitation.

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The impact of the novel sigma-1 receptor agonist S-0758 on somatosensory stimulation and spreading depolarization in cerebral ischemia

Intracellular sigma-1 receptors regulate Ca^{2+} transport between the endoplasmic reticulum and mitochondria and support cell survival under stress. The use of sigma-1 receptor agonists may contribute to the treatment of ischemic stroke. We have examined the effect of the novel sigma-1 agonist S-0758 in a rodent model of ischemic stroke.

Forebrain ischemia was induced by bilateral carotid artery occlusion in male Sprague-Dawley rats anaesthetized with isoflurane (n=21). Local field potential and cerebral blood flow changes were recorded from the cortex exposed in a parietal cranial window. Mechanical stimulation of the entire whisker pad was performed, or spreading depolarization was evoked by topical 1M KCl. Animals were treated with S-0758 administered via a femoral vein cannule during ischemia. Coronal brain sections were prepared for immunohistochemical analysis.

The amplitude of evoked field potentials (EVPs) was similar in the two experimental groups, as was the amplitude of the coupled functional hyperemia. The negative DC shift indicative of SD was significantly smaller in the S-0758-treated group. However, the relative amplitude of the coupled hyperemia was similar to control. Apoptotic cell death labelled by caspase 3 (CC3) immunohistochemistry was counteracted by S-0758, reflected by the reduced number of CC3-positive cells in the hippocampal CA1 region. Further, S-0758 application appeared to rescue GFAP-labeled astrocytes.

The impact of the new compound S-0758 on SD was similar to the previously documented effect of *N,N*-dimethyltryptamine, a natural sigma-1 receptor agonist. Accordingly, sigma-1 receptor agonism may be considered as adjuvant pharmacological therapy in the management of acute cerebral ischemia.

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P15

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Electrical signaling at the endothelial cell pericyte syncytium during recurrent seizures

Neuronal activity-dependent increases in extracellular potassium concentration ($[K^+]_o$) are siphoned to the vasculature by the astrocyte syncytium, acting as a vasodilatory signal for neurovascular coupling. However, $[K^+]_o$ levels > 20 mM can cause vasoconstriction by depolarizing smooth muscle cells and activating voltage-gated calcium channels (VGCCs). Although seizure-associated $[K^+]_o$ changes do never reach this level, we observed a gradual loss of vasodilatory response in capillary pericytes during recurrent seizures, leading to neurovascular uncoupling.

Here we tested the hypothesis that the seizure-associated rise in $[K^+]_o$ might contribute to postictal uncoupling via excessive activation of VGCCs, by obtaining whole cell recordings as well as calcium-imaging from pericytes and astrocytic endfeet during seizure-like activity in hippocampal slice cultures.

Capillary pericytes displayed distinct morphological, dye coupling and electrophysiological properties along the arterio-venous axis. Resting membrane potential in both astrocytes and pericytes was mainly determined by K^+. Seizure-associated depolarization matched the course of changes in $[K^+]_o$ measured with ion-sensitive electrodes. The missing vasotonus was restored using a thromboxane analogue, which depolarized pericytes close to VGCC threshold. However, at the onset of epileptiform activity pericytes rapidly hyperpolarized. This hyperpolarization was not mediated by nitric oxide (NO) but partially reversed with adenosine receptor blockade. While a subset of cells displayed intracellular calcium oscillations, we found no evidence of VGCC-mediated calcium influx, except when activated with a nifedipine analogue.

In conclusion, despite the positive shift in potassium reversal potential, our findings suggest that VGCCs do not significantly contribute to neurovascular uncoupling during recurrent seizures.

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K3

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You Can't Unsee It

The scientific community related to spreading depolarization as a mechanism of brain injury is split into "die-hard devotees" and "dismissers". What creates such a visceral division and how can it be bridged? The experience, beyond raw data, of witnessing SD as an explanation for previously unexplained or poorly explained phenomena has been a turning point for many in the field. This phenomenon of SD as an explanatory mechanism will be discussed in the context of several conditions as it relates to the "A-Ha" moment that links SD to clinical impact or data. Strategies to use divergent thinking to evaluate SD in novel conditions are proposed. In addition, strategies to ensure appropriate rigor before definitively translating promising findings into clinical interventions is discussed.

O21

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Spreading depolarization induced plasticity is mediated by a combined potentiation of both AMPAR- and NMDAR- mediated components of the fEPSP

Prior studies have reported SD-induced synaptic plasticity (SDIP) in brain slices and *in vivo*; however, the underlying mechanisms and characteristics of SDIP remain understudied. We have examined SDIP in a classic model of long-term potentiation (LTP), the CA3->CA1 synapse of hippocampal splices, using a focal KCl stimulus for SD initiation. Field excitatory post synaptic potentials (fEPSPs) and optical recordings monitored functional and structural recovery, and APMPA and NMDA contributions were examined with antagonists of AMPA (NBQX, 10μM) and NMDA (AP5, 20uM; NVP-AAM077, 300nM; TCN-201, 1uM, Ro-256981, 1uM; ifenprodil 1uM) receptors. A single SD induced a persistent epsp potentiation (125.7 ± 8.076% of baseline at 30 minutes post-SD, n=18). Presynaptic excitability (fiber volley) was not significantly enhanced over the same time frame (n=6), and significant paired-pulse ratio decreases (n=18) were consistent with increased presynaptic release probability. The kinetics of epsps (initial slope and decay) also suggested enhancement of both AMPAR and NMDAR mediated components of the compound fEPSP, and isolated NMDAR-mediated fEPSP (using NBQX) were significantly potentiated (155.9 ± 41.164%). Theta-burst LTP (10 trains of 4 pulses (100Hz), 200ms interval) was not further enhanced by SD applied 15 or 45 min earlier (n=10, n=8, respectively). Together, these results imply that SDIP in this model is mediated by enhanced presynaptic glutamate release, independent of fiber recruitment and leads to both NMDA and AMPA receptor activation. It will be of interest to determine further the extent to which this LTP-like mechanism is functionally relevant in a range of pathophysiological brain states.

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O22

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Demonstrating Brain Release of an Activator of Spreading Depolarization

While there are hints in the literature that grey matter may release a substance that activates/promotes spreading depolarization (SD) during metabolic stress, the question has not been rigorously examined. Here we tested aCSF samples that bathed rodent cerebral slices undergoing oxygen-glucose deprivation (OGD) for 10 min at 34^{o}C. We created an SDactivator (SDa) sample by exposing ~12 rodent brain slices to OGD, removing the slices, and replacing O_2 and glucose. This `Post-SD aCSF` evoked SD in normal naïve slices with a 78 to 82% frequency (n=26 slices). In dramatic contrast, `Pre-SD aCSF` bathed the same slices, but before OGD, evoked SD in 0 % of naïve slices (n=18 slices). Freezing did not reduce activity but heating to 100^{o}C lowered SD frequency to 27% (n=24 slices). We could also induce SD in naïve slices when the SDa was released during `Hyperthermic SD` at 44^{o}C. SD persisted in 8 of 8 naïve slices in the presence of the glutamate receptor general antagonist 2mM kynurenate. Thus pH change, released K^{+}, or released glutamate was not responsible for SD activation. These data complement our patch clamp and HPLC data which further support the elevated release of an SDa Post-SD but not Pre-SD. The isolated Post-SD aCSF should serve as a reasonably purified SDa solution, given the absence of cellular disruption/extraction procedures. Understanding of the activity/identity of an endogenous SDa and its molecular mechanisms driving SD will help elucidate novel targets to inhibit recurrent SDs in clinical settings of brain ischemia.

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O23

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Investigating seizure and spreading depolarisation susceptibility in a model of glioblastoma-related epilepsy using graphene-based epidural probes

Glioblastoma (GBM) is the most common and advanced form of primary malignant brain tumour occurring in the adult CNS. GBM growth disrupts the functionality of the peritumoural border (PTB), often resulting in hyperexcitability, i.e. epilepsy and spreading depolarisations (SDs). The development of seizures and presence of SDs have been proposed to actively contribute to tumour expansion.

We developed an immunocompetent mouse model of GBM-related epilepsy (GRE) by stereotactic implantation of GL261 glioma cells into the entorhinal cortex of adult mice. Longitudinal *in vivo* bioluminescence and MR imaging of tumour growth complemented continuous video-telemetry recordings of spontaneous seizures. Post-hoc immunohistochemical analysis of molecular changes within the PTB was conducted. Acute studies implementing graphene micro-transistor arrays (gSGFETs) permitted optogenetic interrogation of seizure and SD thresholds in GRE mice.

Tumour cortical infiltration was associated with the development of spontaneous seizures and epileptiform activity (1.1±1.6 seizures/day). Immunohistochemistry demonstrated changes to glutamate transporter (GLT-1) (tumour:0.03±0.01, PTB:0.14±0.14, contralateral:0.63±0.52 total fluorescence/DAPI) and astrocyte potassium channel (Kir4.1) expression in the PTB. To investigate regional changes in hyperexcitability, we positioned graphene-based micro-transistor arrays epidurally across regions of PTB and healthy tissue to permit acute wide bandwidth DC-coupled recordings. Epileptiform spiking was detected from transistors within the PTB, and spontaneous SDs propagated from the PTB outwards towards healthy tissue. We are currently evaluating the threshold for SD induction within and outside the PTB using optogenetic approaches.

Application of gSGFET technology in our novel model of GRE will allow us to determine the influence of seizures and SDs on GBM progression.

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O24

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Towards noninvasive, automated detection and parameter estimation of spreading depolarizations in patients with intact skull using scalp EEG

Background: Spreading depolarizations (SDs) are a potentially treatable mechanism of secondary brain injury after traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH). Current methods for detection of SDs are based on intracranial recording, an invasive method with limited spatial coverage. Here we establish the feasibility and quantify the performance of noninvasive detection and parameter estimation of SD from scalp electroencephalography (EEG) using advances in deep learning and signal processing.

Methods: We tested the performance of our previously developed WAVEFRONT algorithm on 12 severe TBI patients with a total of 700 SDs who underwent simultaneous scalp EEG monitoring and invasive monitoring from a subdural electrode strip placed on a pericontusional gyrus during decompressive hemicraniectomy (DHC). In addition, we designed an end-to-end Spatial-Temporal Graph Attention Network (STGAT) to explore the feasibility of noninvasive detection and width estimation of SD, and tested it on simulated SDs using different densities of scalp EEG.

Results and Conclusions: WAVEFRONT achieves 74% detection accuracy, with less than 1.5% false alarm rate on real data on patients with DHC. For intact skulls and simulated data, using our deep learning STGAT technique, we succeeded in estimation of the width of simulated SDs for the first time, with less than 11% normalized error using high-density EEG. As an ongoing effort towards noninvasive SD detection in milder head injuries with intact skull, we are applying our method on a dataset from MGH, which involves continuous recordings from TBI and SAH patients with only a burr hole and/or bone flap replacement.

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Electrocortical activity of the porcine brain during cardiac arrest, resuscitation and return of spontaneous circulation

Introduction: During global cerebral ischemia in patients with severe brain injury, electrocorticography (EcoG) showed non-spreading depressions followed by terminal spreading depolarizations (SDs).
Objectives: To investigate EcoG and brain tissue oxygen tension (PbtO2) in experimental cardiac arrest (CA), resuscitation (CPR) and return of spontaneous circulation (ROSC).
Methods: EcoG was analysed in 60 [SAP1] pigs. Propofol and remifentanil were used for general anaesthesia until CA. A subdural strip electrode and a Licox probe (PbtO2 monitoring) were inserted through a burr hole. After 5 minutes of CA (induced by 50Hz alternating current), mechanical CPR was initiated. EcoG was acquired using a biosignal amplifier (g.BSamp) and PowerLab. Data are presented as median and/or interquartile range.
Results: During a total of 155 hours with EcoG-monitoring, all pigs showed a decrease in EcoG-amplitude (559µV to 97µV) following CA, linked to a drop in PbtO2 (10.7 mmHg at baseline to 2.6mmHg; P<0.001). Non-spreading depressions were observed in all pigs within 73-108sec after CA, followed by isoelectric SDs within 20-50sec in 67% (n=40) of pigs. Repolarization waves (900-2200µV), defined as synchronized depolarizations (initial isoelectric, then low-voltage component), were observed in all pigs 52-125sec after CPR onset. PbtO2 and EcoG-amplitudes increased (P<0.001) from 3.4mmHg/191µV after two minutes of CPR to 20.1 mmHg/283µV following ROSC. Thirteen SDs in eleven pigs were observed during 15 hours of resumed circulation.
Conclusion: The tight association between cortical activity and PbtO2 was confirmed by this study. Non-spreading depressions followed by isoelectric depolarizations and reperfusion waves were a consistent pattern. The clinical relevance of SDs following ROSC needs further investigations.

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A novel platform to investigate seizure and spreading depolarisation interactions using calcium imaging and graphene micro-transistor arrays

Introduction: Spreading depolarisations (SDs) and seizures can co-exist and there are complex spatiotemporal interactions between the two phenomena. The impact of this is currently not well understood with some suggesting that it is a physiological way to terminate seizures, whereas others argue that seizure-associated SD increases the risk of death post-seizure. The events leading to SD initiation in epileptic tissue remain poorly characterised. Previous studies have typically been restricted to electrode recordings from few sites, limiting the ability to resolve spatial and temporal relationships.

Methods: We employed bilateral widefield calcium imaging and transparent graphene micro-transistor arrays in awake head-fixed mice. Epileptiform activity was induced following focal blockade of $GABA_A$ receptors. Due to the ability to localise event onsets using imaging, we were able to perform detailed characterisation of the spatiotemporal interactions between seizures and SD. We constructed an automated SD-specific imaging and electrophysiology analysis toolbox using Python.

Results: There is heterogeneity in the spatiotemporal profile of SD with respect to epileptiform activity and seizures. We are evaluating biomarkers (electrographic and calcium dynamic based) recorded from the site of SD onset prior to the SD initiation to determine whether these can provide insight into the mechanisms by which SDs arise in an epileptic network. We characterised the extent to which SD is able to suppress subsequent pathological activity when it co-occurred during different types of epileptiform activity; focal or generalised seizures, and status epilepticus.

Conclusion: Our experimental platform and analysis tools have the flexibility to provide novel insight into seizure-SD dynamics.

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