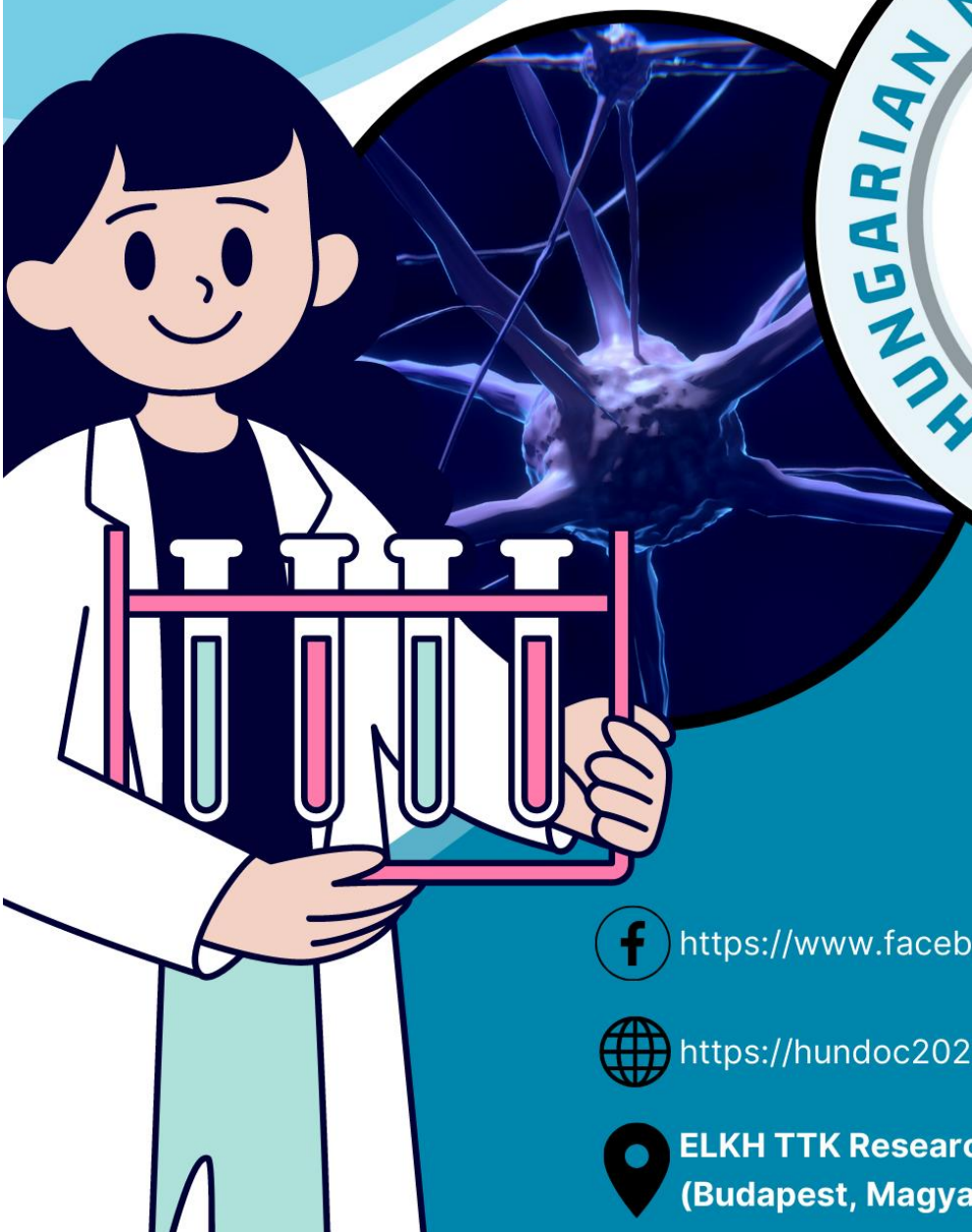
31JAN
2023

HuNDoC

6th Hungarian Neuroscience Meeting for Undergraduate Students, Graduate students and Young Postdocs



HUNGARIAN NEUROSCIENCE MEETING 2023 - 6TH

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ELKH TTK Research Centre for Natural Sciences (Budapest, Magyar Tudósok Körútja 2, 1117)

OUTLINE

INVITATION

Dear Colleagues and Fellow Students,

We are excited to welcome you to the sixth **Hungarian Neuroscience Doctoral Conference for Undergraduate Students, Graduate Students and Junior Post-Docs**. The conference will be held on the 31st of January 2023 in Budapest, as a satellite event preceding the joint meeting of the Hungarian Neuroscience Society (MITT) and the Austrian Neuroscience Association (ANA).

HunDoC offers a friendly and relaxed environment with the opportunity to get to know your peers, form new collaborations, find new ideas or even new solutions to an existing issue. You can also participate in workshops that aim to help you navigate through the ever-shifting landscape of academia. So grab your miniposter or your presentation slides and come join us!

We hope that HunDoC proves to be an exciting and successful experience that will accompany you across your scientific journey.

See you there!

The Organizing Committee

GENERAL INFORMATION

Date: 31 January 2023, Budapest, Hungary

Venue: Research Centre for Natural Sciences, Budapest, Magyar Tudósok Körútja 2, 1117

Organizers:

Emília Bősz, Institute of Experimental Medicine and Janos Szentagothai Doctoral School of Neurosciences

Christina Miskolczi, Institute of Experimental Medicine and Janos Szentagothai Doctoral School of Neurosciences

Paula Mut-Arbona, Institute of Experimental Medicine and Janos Szentagothai Doctoral School of Neurosciences

Acknowledgment

HunDoC 2023 is supported by the Buzsáki Fund

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PANDEMIC RESTRICTIONS

In accordance with the current pandemic situation, wearing a face mask is **optional** at the HunDoC. However, we strongly encourage participants to take appropriate measures to prevent any potential infection.

Depending on the situation these rules are subject to change, so please make sure to check this page for possible updates before you visit the conference.

VENUE

Research Centre for Natural Sciences

(Eötvös Loránd Kutatási Hálózat Természettudományi Kutatóközpont)

Address: Budapest, Magyar Tudósok Körútja 2, 1117

Approaching of the venue

Public transport:

Bus 107: BudaPart (stop Egyetemváros - A38 hajóállomás)

SCIENTIFIC PROGRAM

Scientific program

Our program includes one plenary lecture by Dr. Éva Mikics, two sessions of oral presentations (including elevator speech presentations) by the selected speakers and a midday poster session. In the afternoon, each registered attendee can participate in the career forum and the mental health workshop. All sessions and the two workshops will take place at the Research Centre for Natural Sciences (Budapest, Magyar Tudósok Körútja 2. 1117).

Please note that the official language of the conference is English. All presentations must be prepared accordingly.

Oral presentations

Presenters selected for oral presentation must prepare a 10-minute presentation with a slideshow (preferred format: PowerPoint). For the lecturers, computer presentation facilities will be provided. Lecturers are kindly asked to give their presentations on a USB stick to the technician before the morning or the afternoon session. Any special needs (e.g. the use of own laptop) should be discussed in time with the technician.

We ask the presenters to keep the time limits strictly.

An audience award for the best presentation will be assigned at the end of the conference.

Elevator speech presentations

Presenters selected for elevator speech presentation must prepare a 3-minute presentation with ONE slide (preferred format: PowerPoint or pdf). For the presenters, computer presentation facilities will be provided. Presenters are kindly asked to give their presentations on USB stick to the technician before the morning or the afternoon session. Any special needs (e.g. the use of own laptop) should be discussed in time with the technician.

We ask the presenters to keep the time limits strictly.

An audience award for the best elevator speech presentation will be assigned at the end of the conference.

Poster session

All registered participants, who submitted an abstract, must prepare a miniposter (A4 size), except for those who were selected for oral presentation. Poster presenters will be assigned to groups of 4-6 and each participant will present their work to the others in the group in a less formal manner. Ideal miniposters are not shrunk versions of regular scientific posters. Keep text as little as possible, present the most essential data only. Keep in mind that there might be significant differences in scientific background and career stage among group members within each group.

The miniposter session will take place at 13:35 for 90 minutes. During this time, all participants should present their poster in the group. Please respect other group members' time: try to save time for others to present their work and leave room for discussion.
Digital posters are permitted, but technical support (e.g. tablets) for these will not be provided.

Workshops
There will be two different thematic workshops in the afternoon. For detailed description of each workshop, please visit the Workshop section.

SOCIAL EVENT

The evening social event will take place at Grund in a reserved space for HUNDOC 2023 conference attendees only. This event starts at 20:00.

The HUNDOC 2023 Covid-19 restrictions are all applicable for the social event.

Venue website:

https://agrund.hu/

Address:

1082 Budapest, Nagytemplom str. 30

PROGRAM OVERVIEW

8.00-9.00	**Registration**
9.00-9.15	Welcome speech
9.15-10.00	Invited speaker Dr. Eva Mikics (Institute of Experimental Medicine)
10.00-10.20	Coffee break
10.20-11.35	Oral presentations and elevator speeches I
11.35-12.45	Lunch
12.45-13.35	Workshop I Career Forum
13.35-15.05	Miniposter session
15.05-15.35	Coffee break
15.35-16.50	Oral presentations and elevator speeches II
16.50-17.40	Workshop II What makes you bulletproof? - How to cope with stress using resilience?
17.40-18.00	**Closing remarks**
20.00	**Social event at Grund**

DETAILED PROGRAM

08:00 – 09:00 - Registration

09:00 – 09:15 - Welcome speech

09:15 – 10:00 - Invited speaker

Dr. Éva Mikics (Institute of Experimental Medicine)

Prefrontal mechanisms transmitting behavioral consequences of early-life social adversities

10:00 – 10:20 - Coffee break

10:20 – 11:35 - Oral presentations and elevator speeches I

10:20 - Dávid Keller: Control of social grooming by a thalamo-preoptic neuronal pathway

10:35 - Maissa Ben Mahmoud: Morphological and electrophysiological maturation of human neurons derived from induced pluripotent stem cells

10:50 - Zsófia Pálffy: What and how affects the perception of bistable visual stimuli in a volatile environment?

11:05 - Anikó Szecskó: Investigation of viral PepH3 peptide-functionalized nanoparticles on a culture model of the Blood-Brain-Barrier

11.15. Elevator speeches

- Petra Kovács: Speech processing in multi-talker situations: The role of speaker similarity
- Ákos Babiczky: Interconnectivity of the segregated cortico-thalamo amygdalar pathways
- Melinda Rácz: PlatypOUs—A Mobile Robot Platform and Demonstration Tool Supporting STEM Education
- Réka Bod: Automated detection of spontaneous population activity on human in vitro recordings

11:35 – 12:45 - Lunch

12:45 – 13:35 – Workshop I: Career Forum featuring Dr. Balázs Hangya, Dr. Zoltán Varga, Márton Mayer and Dr. Viktor Kis

13:35 – 15:05 - Miniposter Session

15:05 – 15:35 - Coffee break

15:35 – 16:50 - Oral presentations and elevator speeches II

15:35 - Anna A. Abbas: Study the effect of Cariprazine in induced neurons directly reprogrammed from fibroblasts in Huntington's disease patients

15:50 - Anna Virág Bakacsi: Multisensory signal association by glutamatergic and GABAergic tecto-thalamic cells

16:05 - Bodó Angelika: Application of Multiple AAV Serotypes and Experimental Setups for Inhibition of Food Intake by Silencing LHA Using DREADD Technology

16: 20 - Teadora Tyler: Single cell composition and signaling in the human caudate nucleus – focus on the opioid pathway

16.35. Elevator speeches

- Olivér Nagy: Higher-order thalamic nuclei facilitate the generalization and maintenance of spike-and-wave discharges of absence seizures
- Olha Shchur: Firing statistics of neuron with autapse
- Melinda Erika Gazdik: Differential regulation of static firing responses vs. synaptic integration in physiologically distinct classes of subiculum neurons
- Adrienn Szabó: Enhanced food intake and abnormal deiodinase mRNA expression pattern in the triple transgenic Alzheimer's disease model mice

16:50 – 17:40 – Workshop II: What makes you bulletproof? - How to cope with stress using resilience? by Dr. Viktor Kis

17:40 – 18:00 - Closing remarks

20.00 – Social event at Grund

Plenary lecture – Dr. Éva Mikics

Prefrontal mechanisms transmitting behavioral consequences of early-life social adversities

Childhood and the adolescent period represent time windows during which brain regions modulating social behavior undergo major network reorganization. Adverse social experience during these sensitive periods can lead to disrupted maturation of such brain regions, especially the prefrontal cortex, known for its extended developmental trajectory. In this talk, I will present our work on behavioral changes induced by early-life social adversities in rodent models and demonstrate underlying network, cellular and synaptic impairments within the prefrontal cortex. Finally, we will review the role of neural plasticity-related cortical mechanisms that transmit such behavioural deficits and that may be targeted in the treatment of abnormal aggression and social deficits.

oral presentations

Group I: Behaviour and Network

Control of social grooming by a thalamo-preoptic neuronal pathway

Dávid Keller[1,2], Tamás Láng[1], Melinda Cservenák[2], Gina Puska[2,3], János Barna[1], Fanni Dóra[1, 2,4], Miklós Palkovits[4], Valery Grinevich[5], Árpád Dobolyi[2]

1 Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology, Budapest, Hungary
2 Hungarian Academy of Sciences, Eötvös Loránd Research Network, and Eötvös Loránd University, Department of Physiology and Neurobiology, MTA-ELTE Laboratory of Molecular and Systems Neurobiology, Budapest, Hungary
3 University of Veterinary Medicine Budapest, Department of Ecology, Budapest, Hungary
4 Semmelweis University, Human Brain Tissue Bank, Budapest, Hungary
5 Central Institute of Mental Health, University of Heidelberg, Department of Neuropeptide Research in Psychiatry, Mannheim, Germany

Social touch is an essential component of communication. Little is known about the underlying pathways and mechanisms. The hypothalamus is a major regulatory center of rodent social behavior. It is also likely to be involved in the control of instinctive behaviors in humans. It is conceivable that ascending sensory pathways carrying information on social touch might project directly to the hypothalamus. Here, we discovered a novel neuronal pathway from the posterior intralaminar thalamic nucleus (PIL) to the medial preoptic area (MPOA) is involved in control of social grooming.

First, we determined the effect of chemogenetic stimulation of PIL neurons on social interactions between familiar adult female rats. Activity-dependent tagging of PIL neurons was performed in rats experiencing physical social contacts. The selective chemogenetic stimulation of the preoptic area-projecting PIL neurons was performed using double viral injections and also by CNO administration directly into the preoptic area.

We found that neurons in the PIL and MPOA were naturally activated by physical contact between female rats and also by chemogenetic stimulation of PIL neurons. Chemogenetic activation of these neurons increased social grooming between familiar rats as did selective activation of the PIL-MPOA pathway. Neurons projecting from the PIL to the MPOA express the neuropeptide parathyroid hormone 2 (PTH2) and central infusion of its receptor antagonist diminished social grooming. We showed its increased expression in the PIL in response to social interaction. Finally, we showed similarity in the anatomical organization of the PIL-MPOA circuit in the rat and human brain.

We propose that the discovered PIL-MPOA neuronal pathway facilitates physical contacts in both rodents and human. Therefore, the pathway as well as the PTH2 neuropeptide and its receptor should be investigated in the future in disorders where deficits in direct social interactions are found, such as autism spectrum disorder.

Support: New National Excellence Program and Doctoral Student Scholarship Program of the Co-operative Doctoral Program of the National Research, Development and Innovation Office, Excellence Program of the Semmelweis University, EFOP-3.6.3-VEKOP-16-2017-00009, the National Brain Program of the Hungarian Academy of Sciences 2022 (NAP3) and OTKA K134221.

What and how affects the perception of bistable visual stimuli in a volatile environment?

Zsófia Pálffy[1], Kinga Farkas[2,3], Gergő Orbán[4] and Bertalan Polner[5]

1 Budapest University of Technology and Economics, Department of Cognitive Science, Faculty of Natural Sciences, Budapest, Hungary
2 Semmelweis University, Department of Psychiatry and Psychotherapy, Budapest, Hungary
3 Research Centre for Natural Sciences, Institute of Cognitive Neuroscience and Psychology, Budapest, Hungary
4 Wigner Research Centre for Physics, Department of Computational Sciences, Budapest, Hungary
5 Eötvös Loránd University, Department of Clinical Psychology and Addiction, Institute of Psychology, Faculty of Education and Psychology, Budapest, Hungary

Introduction. Perception can be understood as inference combining precision-weighted sensory information with prior expectations. Here, we manipulate prior expectations by associative learning and investigate the effect of cue modality. We explore intra- vs. inter-individual variance.

Methods. In our experiment, participants (N=29) indicated the perceived direction of illusory motion of dot pairs (640 trials) twice, with a one-week delay. A visuo-acoustic cue preceded the target stimulus and probabilistically predicted the direction of the motion. In 30% of the trials, motion direction was ambiguous, and in half of these trials, the auditory and the visual dimension of the cue predicted opposing directions. We calculated intra-class correlation coefficients (ICCs) for all measures.

Results. The impact of associative learning on perceptual decisions was evidenced by slower responses to less predictable, relative to more predictable non-ambiguous stimuli and by the increased rate of cue-congruent decisions on ambiguous trials. When the visual and the auditory dimensions of the cue predicted conflicting directions of motion on ambiguous trials, decisions were mostly congruent with the prediction of the acoustic dimension. Furthermore, we found substantial inter-individual variability with relatively low intra-individual differences ($0.8 < ICCs$).

Summary. Overall, priors based on auditory information seem to have a stronger weight during the perception of illusory visual motion. There are temporally stable differences between participants.

Future directions. In addition to the aggregated measures, we are currently working on computational modelling of trial-wise learning during the experiment, by fitting the LATER model with various levels of complexity to reaction time data, where beliefs (e.g. cue-target associations) are represented as probability distributions. Furthermore, the observed temporal stability opened up novel research directions: neuroimaging and assessing symptoms in psychiatric patients thought to be related to suboptimal inference mechanisms.

Group II: Development

Morphological and electrophysiological maturation of human neurons derived from induced pluripotent stem cells

Maissa Ben Mahmoud[1], Anikó Rátkai[1], Kristina Rita Bauer[1], Attila Szücs[1], Katalin Schlett[1], Krisztián Tárnok[1]

1 Institute of Biology, Department of Physiology and Neurobiology, Budapest, Hungary

Human neurons derived from induced pluripotent stem cells (h-iPSC-N) offer a valuable and reliable model to understand the physiological aspects of neuronal development and disease. To determine age-dependent neuronal characteristics of h-iPSC-Ns more precisely, we aimed to analyze the timescale of neuronal maturation by following electrophysiological and morphological parameters for more than 10 weeks.

Neuronal excitability and physiological properties were analyzed using the whole-cell current clamp technique. In the early stages of neuronal differentiation, h-iPSC-Ns exhibited passive behavior, manifested as simple RC-responses or as small 'spikelets' and high membrane resistance. From the 4th week of culture, cells expressed well-developed action potentials. Furthermore, membrane resistance and rheobase decreased, indicating the gradual increase of neuronal intrinsic excitability. The frequency and amplitude of excitatory postsynaptic currents (EPSCs) measured in voltage clamp showed similar behavior indicating the formation of functional neuronal network.

As patched cells were filled with biocytin, further morphological and immunocytochemical analyses were carried out on the recorded cells. Maturation of the dendritic arborization was investigated by Sholl analysis. Our results indicated a time-dependent change, represented by the appearance of long and bifurcated processes. Cells showing a high number of synaptic inputs in patch clamp measurements were found to be labeled with the postsynaptic marker Shank2 and presynaptic Synapsin I. Spontaneous synaptic activity was further proved by Fluo-3 AM Ca-imaging in 4, 6, and 8 -week-old h-iPSC-N cultures, where h-iPSC-Ns were highly active during the 4 and the 6 weeks of maturation, overall they manifest partially synchronized network activity.

Taken together, neuronal progenitor cells derived from human-induced pluripotent stem cells differentiate into mature neurons in a reliable and reproducible manner. The uncovered progression of differentiation events validates the usability of the model system and gives us a powerful tool to plan targeted experiments in different stages of neuronal maturation.

Supported by Gedeon-Richter Plc. grant RG-IPI-2020-TP14/025 to K.T., by the National Brain Research Programs (2017-1.2.1-NKP-2017-00002) to KS, by ANN_135291, the VEKOP-2.3.3-15-2016-00007 grants supported by the National Research, Development and Innovation Office, by the ELTE Thematic Excellence Program 2020 (TKP2020-IKA-05) to KS, the ÚNKP-22-3 New National Excellence Program of the Ministry for Culture and Innovation from the source of the National Research, Development and Innovation Fund.

Group III: Neurodegenerative Disorders and Injury

Study the effect of Cariprazine in induced neurons directly reprogrammed from fibroblasts in Huntington's disease patients

Anna A. Abbas[1], Karolina Pircs[1,2], Judit Mária Molnár[3], Idris János Jimoh[3], Lea Danics[1], Balázs Kis[1], Lajos Kemény[4], Zoltán L. Veréb[4], Anikó Göblös[4], Roger A. Barker[5], Johan Jakobsson[2]

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3 Semmelweis University, Institute of Genomic Medicine and Rare Disorders, Budapest, Hungary
4 University of Szeged, Szeged, Hungary
5 University of Cambridge, Cambridge, United Kingdom

Huntington's disease (HD) is an incurable autosomal dominant progressive neurodegenerative disease (ND). The role of the dopaminergic system in the development of HD symptoms is crucial, as the central dopaminergic pathways are overactive in HD. Dopaminergic overactivity can be reduced by several drugs. However, their effect on psychiatric symptoms is limited. Moreover, the management of apathy and cognitive symptoms is still a challenge in HD. Cariprazine, a third-generation antipsychotic, acts as a dopamine D3 and D2 receptor agonist. Previous results have shown positive effects in HD patients following treatment with cariprazine. Clinical trials have shown positive effects on some psychiatric symptoms, such as depressed mood, apathy and cognitive function, following cariprazine treatment in patients with early HD. In addition, cariprazine also improved dopamine imbalances in the prefrontal cortex. Given the human-and age-specificity of the disease, induced neurons directly reprogrammed from patient fibroblasts serve as a human-relevant, donor-specific model that preserves the transcriptomic and epigenetic properties of the donor.

In this project, we aim to investigate the effects of cariprazine in a novel in vitro model system of HD using donor-derived, aging-induced neurons. Our aim is to understand the putative beneficial effects of cariprazine in HD patients and to better understand the mechanism of action focusing on autophagy.

Using a reverse translational strategy, we applied cariprazine treatment directly on reprogrammed induced neurons derived from fibroblasts of 5 ctrl, 5 HD drug naïve and 5 cariprazine-treated HD patients. Immunocytochemistry (ICC) followed by high-content automated microscopy (HCS) was used for detection.

Cariprazine-preferentially responsive donor HD-iN neurons were shown to be effective in preliminary experiments based on changes in neuronal complexity. Further studies are ongoing to investigate the putative underlying autophagy. we hypothesize that the abnormal neurite morphology and neurite-specific impairment of subcellular autophagy described above will be positively altered following cariprazine treatment.

Investigation of viral PepH3 peptide-functionalized nanoparticles on a culture model of the Blood-Brain-Barrier

Anikó Szecskó[1, 2], Mária Mészáros[1], Gergő Porkoláb[1, 2], Vera Neves[3], Marco Cavaco[3], Beatriz Simões[3], Catarina Chaparro[3], Miguel A.R.B. Castanho[3], Mária A. Deli[1], Szilvia Veszelka[1]

1 Biological Research Centre, Institute of Biophysics, Biological Barriers Research Group, Szeged, Hungary
2 University of Szeged, Doctoral School of Biology, Szeged, Hungary
3 Universidade de Lisboa, Instituto de Medicina Molecular, Faculdade de Medicina, Lisbon, Portugal

Drug delivery to the CNS is limited by blood-brain barrier (BBB), which is mainly composed the endothelial cells of brain capillaries. Nanoparticles (NPs) are promising new tools to increase the transfer of drugs across the BBB. The advantage of vesicular NPs is that they increase the penetration of cargo molecules across biological barriers and by decorating their surfaces with appropriate ligands they are suitable for targeted drug delivery. The aim of this study was to investigate the PepH3 peptide, isolated from the capsid protein of Dengue virus alone, and as a targeting ligand of NPs to elevate the cargo penetration across the BBB.

In our experiments, we used Quasar570 labeled PepH3 and prepared PEGylated PepH3-targeted NPs loaded with the Texas-Red bovine serum albumin (TR-BSA) or single-domain antibody (sdAb) against amyloid beta peptide as cargo. The physico-chemical properties of NPs, such as particle size, polydispersity index and surface charge were measured by dynamic light scattering. The encapsulation efficiency was detected by spectrofluorimeter or western blot. The effect of PepH3 alone and PepH3-targeted NPs on the viability of primary rat brain endothelial cells was monitored by impedance measurement.The cellular uptake of PepH3 and PepH3-targeted NPs were visualized by confocal microscope. We investigated the entry of the peptide and peptide-targeted nanovesicles into cells and their penetration across the culture model of the BBB with spectrofluorimeter.

The mean diameter of untargeted and N-PepH3 particles was between 100-120 nm, respectively. The NPs have slightly negative surface charge and relatively narrow size distribution.The encapsulation efficiency of TR-BSA cargo was ~35 %, in the case of sdAb loaded NPs it was ~70%. PepH3 had no effect on the viability of RBEC and was rapidly taken up by RBEC cells supported by the visualization and cellular uptake studies. PepH3 peptide alone and PepH3-targeted NPs with TR-BSA cargo had significantly higher penetration across the BBB model compared to marker molecule or non-targeted NPs. Although, the penetration of sdAb cargo across the model was not measurable, high amount of sdAb was detected in primary rat brain endothelial cells after the permeability measurements.

Our results proved that PepH3 is a good candidate to be used as a peptide for targeted brain delivery of therapeutic biomolecules.

This work was funded by research grant 2018-2.1.15-TÉT-PT-2018-00013. A.S. was supported by ÚNKP-22-3-SZTE-458, Gedeon Richter Plc Centenarial Foundation. S.V. was supported by Premium-2019-469 and OTKA-FK 143233. M.M. was supported by PD 138930, Richter Plc Centenarial Foundation and NTP-NFTÖ-21-B-0228. G.P. was supported by the National Academy of Scientist Education (FEIF/646-4/2021-ITM_SZERZ), Stephen W. Kuffler Research Foundation, Richter Plc. Centennial Foundation and ÚNKP-22-3-SZTE-446.

Group IV: Sensory and Motor systems

Multisensory signal association by glutamatergic and GABAergic tecto-thalamic cells

Anna Virág Bakacsi[1,2], Péter Berki[1,3], Aletta Magyar[1,3], Sándor Borbély[1], Kinga Kocsis[1,4], Ferenc Mátyás[1,5]

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3 Semmelweis University, János Szentágothai Doctoral School of Neurosciences, Budapest, Hungary
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In an ever-changing multisensory environment, the brain plays an important role in recognizing and integrating the relevant behavioural stimuli. As these are essential for survival, the underlying network level processes must be fast and precise.

During fear conditioning, an associated memory trace is formed when a conditioned stimulus (CS) appears alongside an affective (unconditioned) stimulus (US). The anatomical basis for this CS-US pairing includes a network in which these two types of information can converge on a single neuron. Our recent findings have revealed that this could occur in a tecto-thalamic circuit, at the level of the LA-projecting calretinin-expressing lateral thalamic (CR+LT) cells (Barsy B., Kocsis K. et al. 2020). The tectal part of this circuit is formed by the paired structures of the midbrain, the inferior (IC) and the superior colliculus (SC). The superficial SC neurons can convey visual, while the intermediate and deep SC cells transmit multisensory information; however, their exact role in associative learning is largely unknown.

In order to investigate these tecto-thalamic circuits, first, we used classical and viral tracing techniques in combination with immunohistochemical approaches in mice. We show that both colliculi are able to form synaptic contact on the same CR+LT cell involving glutamatergic and GABAergic collicular cells. Next, we investigated response properties of local and CR+LT-projecting SC cells driven by unimodal (visual, auditory and somatosensory-pain) and complex signals with optogenetic and electrophysiological approaches. We found that multisensory signals rather than the unimodal one altered the activity patterns of both glutamatergic and GABAergic cells; however, with different time course. While the glutamatergic cells responded faster and showed elevated firing rates for a short time, the GABAergic cells had longer latencies but for a longer timeframe. This could indicate a complex network mechanism between the different SC cell types and the CR+LT cells. In conclusion, complex synaptic transmissions by SC-LT routes can contribute to the fast signal integration during associative fear learning process and promote survival.

This work was supported by the Hungarian Scientific Research Fund NKFIH-FK 135285 (SB), FK144583 (SB), K138836 (FM) and KKP126998 (FM), by the New National Excellence Program of the Ministry for Culture and Innovation from the source of the National Research, Development and Innovation Found ÚNKP-20-5-ÁTE-3 (FM); ÚNKP-22-2-III-ELTE-539 (AVB) and by ELKH SA-SA-48/2021 (FM).

Group V: Techniques

Application of Multiple AAV Serotypes and Experimental Setups for Inhibition of Food Intake by Silencing LHA Using DREADD Technology

Bodó Angelika[1,2,3], Bali Zsolt Kristóf[1,4,3], Nagy Lili Veronika[1,4,3], Kovács Péter[5,6], Kitka Tamás[5], Hernádi István[1,4,3]

1 University of Pécs, Grastyán Translational Neuroscience Research Centre, Pécs, Hungary
2 University of Pécs, Medical School, Pécs, Hungary
3 University of Pécs, Szentágothai Research Centre, Pécs, Hungary
4 University of Pécs, Faculty of Sciences, Pécs, Hungary
5 Vascular Research Group, Budapest, Hungary
6 The Pennsylvania State University, Department of Biomedical Engineering, PA, United States

Introduction: Designer Receptors Exclusively Activated by Designer Drugs (DREADD) is a novel chemogenetic technology where genes of modified human receptors, without any endogenous ligands, are expressed. However, these receptors can be reversibly activated or silenced by specific actuators, small molecules selectively binding to their DREADDs and not to any naturally occurring receptors, showing minimal off-target effects, thus making DREADD a powerful tool that can be widely applied in basic research and preclinical drug development.

Aims: In our preliminary experiments we measured the effects of silencing DREADDs on food consumption as a simple endpoint to compare the effects of different expression vector serotypes, administration routes and actuators to choose the most robust experimental design for future experiments.

Methods: We injected adeno-associated expressional virus vectors (AAV5 or AAV9) expressing the gene of modified human M4D(Gi) cholinergic receptor, or PBS into the LHA of rats. We examined dose-response curves of Clozapine-N-oxide (CNO) and deschloroclozapine (DCZ) after subcutaneous (s.c.) or per os (p.o.) administration in a food-intake paradigm. Rats were fasted for 16 h before the experiments, then, after re-feeding, we measured food consumption in the first 30 min and in every hour over an 8-hour long period. To conclude about the time-course of the actuator's effectiveness, intermediate dose of DCZ was injected s.c. at 16, 3, 1 or 0.5 hours prior to re-feeding time.

Results: All three doses of CNO administered s.c. and DCZ either s.c. or p.o. reduced food-intake measured at 30 min and 8 h time points both in the AAV5 and AAV9 groups but were ineffective in the PBS group. AAV5 and AAV9 injected animals consumed more food in the first 30 min when DCZ was given at 16 h prior compared to 0.5 or 3 h pre-treatment time point. All animals maintained their body weight between experiments, so the inhibitory effect was transient and solely caused by the actuators. The successful cellular integration and expression of both vector serotypes was post-mortem confirmed by fluorescent microscopy.

Discussion: We have shown the feasibility of DREADDs for reversible inhibition of food-intake, also, DCZ was proven as a more potent actuator compared to CNO. We aim to apply multiple titres and volumes of AAV vectors to investigate possible neurotoxic side-effects before applying the technology for further experiments resembling cognitive decline.

This project was funded by the Thematic Excellence Program 2021 Health Sub-programme of the Ministry for Innovation and Technology in Hungary, within the framework of the EGA-16 project

of the University of Pécs and by the sponsorship of Vascular Venture Ltd. This research work was conducted with the support of the National Academy of Scientist Education Program of the National Biomedical Foundation under the sponsorship of the Hungarian Ministry of Culture and Innovation.

Single cell composition and signaling in the human caudate nucleus – focus on the opioid pathway

Teadora Tyler[1], Arpad Dobolyi[2,1], Zdravko Petanjek[3], Istvan Adorjan[1]

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2 Eötvös Loránd Tudományegyetem, Budapest, Hungary
3 University of Zagreb, Croatian Institute for Brain Research, Zagreb, Croatia

Introduction: Single cell/nucleus RNA sequencing (scRNAseq; snRNAseq) opens new horizons in the research of complex neuropsychiatric disorders – illnesses in which a broad range of cell types are affected due to intricate alterations in the web of cellular, molecular and genetic networks. For a comparative study, a set of good quality control tissue is essential.

Methods: In a pilot study, one control caudate nucleus (CN) sample was processed by snRNAseq. The raw base call matrices were initially filtered and analysed with Seurat, and later – as quality was found good – integrated with 5 control CN samples from another study (Lee et al, 2020). Principal component analysis and clustering was done with Seurat. After identifying clusters based on known marker genes, CellChat package was used to predict ligand-receptor based signaling between cell types.

Results: Samples from different origin integrated well. Striatal cell types expected based on previous studies were identified. Other than general pathways such as cell adhesion molecule networks, CellChat also revealed more cell type-specific pathways. For example, between subtypes of medium spiny neurons (opioid pathway, largely consisting of interactions of enkephalin and opioid mu and delta receptors), interneurons and medium spiny neurons (tachykinin, reelin), interneurons and endothelial cells (pleiothropin, a secreted signaling cytokine), or astrocytes and other cells (ANGPTL).

Conclusion: Here we tested whether we can use control samples from Lee et al (2020) together with our sample as one, united control cohort. The results suggest that the integrated set of control samples is sufficient for further analysis.

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elevator speech

Speech processing in multi-talker situations: The role of speaker similarity

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Speakers with perceptually similar voice should be harder to segregate in multi-talker situations. However, while the dissimilarity of voices may help their segregation, the same variable may also affect sustained selective attention. Thus, the overall effect of voice similarity on following one voice in the cocktail party situation may either be beneficial or detrimental. To tease the two effects apart, we collected electrophysiological (EEG) and behavioral data while 22 healthy young adults listened to two concurrent speech streams consisting of either 1) identical, 2) similar, 3) dissimilar, or 4) opposite-gender speakers. Functional brain connectivity and behavioral results suggested that, while speaker similarity hinders auditory stream segregation, dissimilarity hinders selective attention by making the speech stream to be ignored more distracting. The problem to be solved by the speech processing system in multi-talker situations is thus different depending on the level of perceived speaker similarity.

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Interconnectivity of the segregated cortico-thalamo amygdalar pathways

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The amygdala with its afferent and efferent connections has long been implicated in a wide range of emotion regulating processes, such as associative fear learning. According to the classical model, the basolateral amygdalar complex governs these functions by combining various thalamic and cortical inputs and conveying them to the central amygdala.

However, fine details of these thalamic and cortical afferent pathways, have not been elucidated yet. For example, it has not been directly tested yet whether these thalamic and cortical inputs converge or segregate within the amygdala. Furthermore, the precise nature of how thalamo-cortical afferents and intra-amygdalar pathways are connected is also yet to be described.

Therefore, first, we constructed a biologically relevant molecular map of the mouse amygdala to precisely delineate different amygdala subnuclei. We used this map as an anatomical basis for any further investigation.

Next, using adeno-associated viral vectors, we labelled major thalamic and cortical neuron populations projecting to the amygdala, and directly compared their innervation patterns. Our results demonstrated that both midline and lateral thalamic, as well as medial prefrontal and temporal cortical sources innervate different amygdala subnuclei in a rather non-overlapping manner. These results were further confirmed by in-vivo electrophysiological findings showing different activation patterns after optical stimulation of different thalamic afferents in the amygdala.

Ultimately, we labelled all major amygdala subnuclei with the combination of classical retro- and anterograde microinjections and conditional viral tracing to map intra-amygdalar connections and found a rather complex network within the amygdala. These results somewhat contradict the classical linear information flow model highlighting a serial lateral-basal-central pathway in the amygdala.

Taken together, we demonstrated with combination of anatomical and electrophysiological tools that thalamo-cortical afferents are mostly segregated within the amygdala. We further described a complex network of different amygdala subnuclei in contrast to previous studies. Our results together suggest that information processing in the amygdalar circuitry might be more complex than previously supposed.

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Higher-order thalamic nuclei facilitate the generalization and maintenance of spike-and-wave discharges of absence seizures

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Spike and wave discharges (SWD), generated by the cortico-thalamo-cortical (CTC) network, are pathological, large amplitude oscillations and the hallmark of absence seizures (ASs). SWD begin in a cortical initiation network in both humans and animal models, including the genetic absence epilepsy rats from Strasbourg (GAERS), where it is located in the primary somatosensory cortex (S1). The behavioural manifestation of an AS occurs when SWD spread from the initiation site to the whole brain, however, the mechanisms behind this rapid propagation remain unclear. Here we investigated beyond the principal CTC network, in higher-order (HO) thalamic nuclei (lateral posterior (LP) and posterior (PO) nuclei), their diffuse connectivity and known facilitation of intracervical communication make these nuclei candidates to support SWD establishment and maintenance. In freely moving GAERS, multi-site LFP in LP, PO and multiple cortical regions revealed a novel feature of SWD: during SWD, cortical regions far from S1, become transiently unsynchronized from the ongoing rhythm, named SWD-breaks. Inactivation of HO nuclei with local muscimol injections or optogenetic perturbation of HO nuclei activity increased the occurrence of SWD-breaks and the former also increased the SWD propagation time from S1. The neural underpinnings of these findings were explored further by recording from single units of PO which uncovered two previously unknown grous of excitatory neurons based on their burst firing dynamics at SWD-onset. A tonic to burst switch at SWD-onset was shown to be an important feature as the change was less exaggerated during non-generalized events (i.e. SWD that remained local to S1), additionally, one group of neurons showed a reverse of this switch during SWD-breaks, demonstrating the importance of this firing pattern throughout the SWD. To conclude, the results of these experiments converge on the conclusion that multiple HO thalamic are utilized at SWD onset and contribute to cortical synchrony throughout the discharge.

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Firing statistics of neuron with autapse

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Recent experimental evidence showed that, in neocortical layer V, parvalbumin-expressing basket cells and pyramidal cells often form functional autapses. Excitatory autapses promote bursting and coincidence detection while inhibitory ones enhance spike timing precision on the milisecond scale and provide important mechanism of disinhibition. We studied analytically the impact of both excitatory and inhibitory autapses on neuronal activity. Assuming that interspike interval distribution of a neuron without autapse is known, we calculated firing statistics of the same neuron with autapse. Our results indicate that depending on the autaptic time delay, the spike regularity can lower or rise in comparison with the case of the neuron without autapse.

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Enhanced food intake and abnormal deiodinase mRNA expression pattern in the triple transgenic Alzheimer's disease model mice

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Alzheimer's disease (AD) is an age-related neurodegenerative disease with progressive memory decline, which could be aggravated by other factors such as abnormal hypothalamic–pituitary–thyroid (HPT) axis [1]. Transgenic AD mouse models are promising tools in understanding the underlying mechanisms.

We compared male, 8-month-old triple transgenic (3xTg-AD) mice to age-matched controls, as the appearance of pathological hallmarks is expected at 6-month. First, the animals' body composition was studied by magnetic resonance imaging, while food and water consumption and respiratory exchange ratio were recorded in metabolic cages for 24 hours. Next, since the HPT axis greatly affects metabolism, its key enzymes were examined that play a decisive role in the central nervous system. So, deiodinase mRNA expression pattern was measured using qPCR in pituitary gland and in the mediobasal hypothalamus (MBH).

The 3xTg-AD mice had increased food and water consumption and showed higher respiratory exchange ratio compared to age-matched controls. Paradoxically, a lower body fat percentage was detected in them, while their energy expenditure showed no difference between the two groups. The type 1 and 2 deiodinase increased in the pituitary gland without any difference in the type 3 deiodinase. However, in the MBH a decrease of the type 2 deiodinase was detected.

In summary, we have found higher nutrient requirement in 3xTg-AD mice, which greatly influenced their body composition. Alterations in deiodinase expression at critical parts of the HPT might influence the basal metabolic rate contributing to the observed changes. Our results further strengthen the idea that AD is a metabolic disease [2].

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Primary topic: Neurodegenerative Disorders and Injury (POE)
Secondary topic: Other (POE)

Automated detection of spontaneous population activity on human in vitro recordings

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Introduction: Discerning various events on electrophysiological recordings may reveal a fair amount of knowledge about synchrony-generating principles. Considering the vastness of data available for this purpose, as well as the time-intensive and experience-dependent nature of the analysis workflow, application of machine learning-aided technologies is welcome for this task. Although several analogous algorithms were set up for the investigation of interictal events, none of them attempted to detect physiologically occurring hypersynchronous events. We ventured on creating artificial neural networks that distinguish spontaneous synchronous population activity (SPA) from background with an accuracy and robustness comparable with manual analysis.

Materials and Methods: Data were collected by a 24-channel laminar microelectrode from human neocortical slices inferential to patients either or not displaying epileptic signs. Manual analysis identified 53 962 SPAs, based on which 0.1 s-long epochs were generated from 3 neighboring channels where event amplitudes were the highest. Similarly, long, although eventless epochs were generated from baseline activity (n= 113 588). Before feeding data in the neural networks, a proper randomization and a 70-20-10% partition of training-validation-testing datasets took place. Neural network architectures relied on 1D- and 2D-convolutional, recurrent (LSTM) and dense layers.

Results: Overall fitness of the artificial neural networks was evaluated by the following metrics: binary accuracy ([true positive nr. + true negative nr.] / total entries), precision (true positive nr. / [true positive nr. + false positive nr.]) and recall (true positive nr. / [true positive nr. + false negative nr.]), the loss function chosen was binary crossentropy. After 30 epochs of training and validation, the neural network employing 1D-convolutional layers performed on the testing dataset as follows: accuracy=0.849, precision=0.752, recall=0.793. We plan to improve performance metrics by applying scheduled learning rates.

Conclusion: By the implementation of artificial neural networks, identification of SPAs benefitted from decimated inter-observer variability and substantial time reduction during analysis. This latter feature encourages our method to be assessed on similarly recorded human in vivo data, with the promise to detect SPAs unprecedentedly in this context.

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PlatypOUs—A Mobile Robot Platform and Demonstration Tool Supporting STEM Education

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Introduction: in an interdisciplinary project, students at Semmelweis University and Óbuda University developed a mobile robot platform that uses electrophysiological signals as control instructions. The aim of the project was to create a mobile robot system for educational purposes (to be featured in a robot operating system programming course at Óbuda University) and to facilitate interaction between different research fields (robotics and health sciences) and students from different levels of education (i.e. from bachelors to doctoral studies).

Methods: the hardware is based on an Intel mini-PC, has differentially driven wheels and is equipped with wheel encoders, a LIDAR, a depth camera and an inertial measurement unit (containing an accelerometer and a gyroscope). As signal acquisition device, a portable wireless electroencephalography headset (a MindRove arc) is utilized. The robot can be controlled to make a 90° turn to the right, to go forward or stop. A graphical user interface collects sample sequences corresponding to each command and trains a support vector machine-based classifier to differentiate between the samples.

Results: regarding sample prediction accuracy (during preliminary tests), our system could achieve 86.67%; in a real-world pattern following task, an average error of 12.39% was encountered.

Conclusion: The initial tests have deemed our proof-of-concept system useable but further validation is required to prove its real-world feasibility.

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Differential regulation of static firing responses vs. synaptic integration in physiologically distinct classes of subiculum neurons

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The subiculum is a part of the hippocampal formation and it has an essential role in processing neuronal signals emanating from the hippocampus proper and forwarding it to different cortical and subcortical brain regions.

The principal cells of the subiculum, the pyramidal cells can be divided into two categories based on their firing profiles: regular and bursting types. In previous studies, researchers mostly utilized traditional electrophysiological methods to investigate the functional properties of these cells. However, our group explores the integrative properties of neurons in the subiculum by exposing them to various types and intensity of simulated, computer-synthesized synaptic inputs (dynamic clamp). In such scenario we can investigate their firing output, spike timing reliability and precision under various types of in vivo-like activity including theta- or gamma-oscillations.

We performed the present experiments on acute brain slices from mice, in whole-cell patch-clamp configuration. First we performed conventional current step protocols to assess the standard physiological properties and static excitability of subiculum neurons. Next, we applied simulated synaptic currents on the same cells. During dynamic stimulation, we elicited firing responses of the cells driven by simulated synaptic bombardment.

Comparison of responses from static vs. dynamic stimulation revealed differential regulation of neuronal excitability and weak correlation between total spike counts observed under static vs. synaptic-type inputs. Additionally, the firing responses of regular and bursting neurons differed in a stimulation intensity dependent manner not readily expected from the static responses.

Our results confirm the previous data measured in hippocampal cell cultures and it can serve as a further help to the better understanding of the effects of voltage-dependent ionic currents in neurons that regulate synaptic integration.

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mini-poster session

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- Szonja Bianka Plesz: Decreased Lactobacillaceae abundance in the gut microbiota of a 'three-hit' schizophrenia rat model (Wisket)
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- Ammar Alomari: Involvement of the centrally projecting Edinger-Westphal nucleus in a mouse model of migraine.
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- Joanna Sandle: Group I metabotropic glutamate receptor-mediated modulation of excitatory synaptic transmission shows interneuron specificity in the human neocortex
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- Olívia Mária Huszár: Automated eye-blink artefact removal from electroencephalogram (EEG) recordings using image processing techniques
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- Máté Tóth: Developing a portable, customizable, single-channel EEG device for homecare and validating it against a commercial EEG device

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- Victoria Lyakhova: The Lateral Septum and its multifaceted role in anxiety
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- Husamalddin Alhour: Resting-state functional connectivity correlates of mental fatigue
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- Ildikó Szöts: Spatial profile of calcium transients evoked by backpropagating action potential in human cortical pyramidal dendrites
- Péter Berki: Microglial behaviour in acute slice preparations
- Gábor Farkas: Modelling the intracellular biochemical mechanisms of long-term potentiation in a CA1 pyramidal cell spine head
- Sára Sáray: Automated and systematic validation of models of hippocampal neurons against electrophysiological data

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- Farah Yaseen: Mapping Mossy cells Synaptic Projections
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MINIPOSTERS – ABSTRACTS

Group 1

Sociogenomic study of the rodent nervous system

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Although social behavior is common in mammals, including humans, its hormonal and genetic basis is not established yet. Social touch, the need for the presence of a partner, is a major component of social interactions. A comprehensive understanding of social behavior should include molecular analysis of brain mechanisms. Correlating gene expression levels and their molecular functions with behavioral analysis is still challenging due to the complexity of behavioral regulation and accompanying physiological changes. There are regions that are involved in the formation of different forms of behavior, thereby forming a node in terms of the regulation of behaviors. One such node is the medial prefrontal cortex, which is the subject of this study. The aim of the present study was to use RNA sequencing methods to identify genes present in the rat medial prefrontal cortex in order to determine RNA level changes between groups of male rats kept socially or solitarily for 3 weeks.

The social behaviour of rats was measured using 3 chamber test and a direct social interaction test. Their anxiety-like behaviour was measured by the elevated plus maze test and the open field test. Forced swimming test was used to assess the depression-like behaviour of the animals. More than 30 genes differed between the groups according to criteria of log2FC > ±1 and adjusted p-value < 0.05. We measured 5 genes with RT-PCR, which were all validated. These validated genes differentially expressed between the groups were Ndst4, Rgs9, HTr2c, Pdyn and Lrrc10b. The level of these genes decreased as a result of social isolation. Based on the known functions of the genes, HTr2C and Rgs9 are of particular interest as they may play an important role in depression and social behaviour.

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A translational model of comorbid anxiety and depression

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Anxiety and depression are the most prevalent and burdening mental diseases, and, in 50% of patients they co-occur. Patients with comorbid anxiety and depression (CAD) have more severe and persistent symptoms, and their pharmacotherapy is less successful. To treat this clinical subgroup more effectively, we need to understand the neurobiological, emotional and cognitive traits behind this difference. However, to date, there are no established rodent models of CAD. We therefore aimed to create a mouse model with high clinical translational validity, then examined whether cognitive factors play a role in comorbidity, and finally tested differences in sensitivity to anxiolytics.

Using naive adult male mice, we performed a multi-sampling behavioural battery to identify stable traits, involving 3 anxiety and 3 depression tests repeated 3 times with each animal, and a depression model, the Learned Helplessness test (LH). With machine learning predictions, the test battery was reduced to the Light-Dark anxiety test (LD), the Forced Swim coping test (FST), and the LH. Using these 3 tests, we can reproducibly characterise a distinct subpopulation of animals that stably show high trait anxiety, high passive coping, and high learned helplessness, which could serve as a translational model of comorbidity.

To examine if there were any differences in the underlying cognitive factors behind the distinct subpopulations, we exposed a new population of mice to an automated home-cage system (IntelliCage), where animals were tested in cognitive tasks for 3 months. The highly anxious, highly passive and helpless subpopulation was also present in this cohort. Retrospectively, compared to other subgroups showing active coping strategies or low anxiety, comorbid animals showed significantly worse performance in spatial learning tasks, were more impulsive and had worse cognitive flexibility in delay discount tasks. Moreover, the comorbid population showed an adverse reaction to treatment with the anxiolytic agent buspirone.

In conclusion, with machine learning-based reduction of an extensive test battery, we developed a translational model of CAD. Moreover, we showed that comorbid animals a priori show worse cognitive properties and differ in sensitivity to anxiolytics. Further examining the neurobiological background of these could help in developing more effective pharmacotherapy for CAD patients.

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Excitability changes in prefrontal cortical networks in a rat model of autism

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The experiments focused on brain excitability and plasticity changes in autism spectrum disorder model rats. People diagnosed with ASD exhibit impairment in social interactions and communication skills as well as repetitive behaviours. Underlying this triad of impairments, changes in neural network connectivity and excitability can be observed in several brain areas.

Experiments carried out by our group focused on the prefrontal cortex, an area, which is connected to a wide variety of functions, among others, the interpretation of others' emotions and the evaluation of social situations.

Valproate was administered to rat dams on the 12th day of pregnancy. Pups were subjected to behavioural tests at postnatal days 3-45, to observe the expected delayed development and autistic traits. Acute brain slices were prepared from 6-week-old and 3-month-old offspring of both sexes. To investigate network functions, evoked field potentials were recorded in the prefrontal cortex. Basic excitability was tested with input-output curves. To test network plasticity, long-term potentiation was induced with two different protocols (1 or 4 stimulation trains of 100Hz). Excitability of individual neurons was tested with patch clamp recordings.

Valproate treatment evoked significant delays in postnatal development and impaired social behaviour. According to preliminary electrophysiological results, the amplitude of evoked potentials' early component was lower, while late component amplitude was higher in treated 6-week-old males compared to controls, indicating an altered circuit excitability. The results also pointed out, that there is a significant sex difference between the threshold of excitation of the treated 6-week-old male and females. LTP efficacy did not differ significantly.

Intracellular recordings revealed that cells in the treated 6-week-old females were more excitable compared to their control peers, based on the finding that the membrane resistance increased and the rheobase decreased. The excitability difference was observed in the 6-week-old males due to the membrane potential becoming more positive, but the resistance of the membrane decreasing. The difference of the valproate treated and control animals diminished in the 3-month-old groups.

Further investigation is needed to increase the sample numbers in each treatment group. Testing network sensitivity by recording epileptiform activity is also planned.

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Decreased Lactobacillaceae abundance in the gut microbiota of a 'three-hit' schizophrenia rat model (Wiske)

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Growing evidence suggests that the gut-brain axis may play an important role in the development of neuropsychiatric disorders. The connection between the pathogenesis of schizophrenia and the gut microbiome is barely detected. Lactobacillaceae is the most abundant family of microorganisms in the gastrointestinal tract related to intestinal health. Recently, their beneficial role in cognitive impairments has been proven in both preclinical and clinical studies. Wisket rats generated by 'three-hit' (post-weaning isolation rearing, ketamine treatment, and behavior-based selective breeding) show several schizophrenia-like behavioral phenotypes, like impaired sensory gating, cognitive, memory, altered social behavior, and decreased pain sensitivity. Our aim was to determine the gut microbiome alteration in a 'three-hit' schizophrenia rat model (Wisket).

Twelve-week-old male, control, and Wisket rats were involved in the study (n=6-12/group). The composition of fecal microbiota was assessed by deep sequencing of bacterial 16S rRNA. Alpha diversities were quantified by using the Shannon index, and principal component analysis was used for visualizing the microbiome composition.

Regarding the alpha diversity, there were no significant differences between groups. Microbiome analysis demonstrated significant differences in gut microbial composition at certain taxa. Lactobacillaceae also showed a strong trend towards reduction ($p<0.01$, $q=0.07$) including the reduction of Lactiplantibacillus, Lactobacillus, and Limosilactobacillus at the genus level in Wisket animals compared to control groups.

These results may suggest that the cognitive impairment observed in Wisket rats may correlate with the decreased Lactobacillaceae abundance. However, to correlate these results with the behavioral findings, further studies are required to increase the number of cases.

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Transcriptomic and functional comparison of IPSC-derived in vitro hippocampal neurons from a schizophrenia patient and isogenic controls

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Introduction: Our research group investigates neurodevelopmental disorders using induced pluripotent stem cell (IPSC) based in vitro models. Earlier we established induced pluripotent stem cell lines from a schizophrenic patient, carrying a functionally relevant mutation in the ZMYND11 gene. Moreover we have managed to generate isogenic cell lines by introducing the patient specific mutation into a healthy cell line, or by correcting the mutation in the patient-derived cell line, using CRISPR genome editing. These IPSC lines were differentiated into PROX-1 positive dentate gyrus granule neurons, as to our current understanding the hippocampus may play a pathogenic role in schizophrenia [1].

Methods: We used an in vitro differentiation protocol yielding PROX-1 positive dentate gyrus granule cells. [2] We carried out bulk RNA sequencing from neural progenitor cells and hippocampal neurons. Based on the transcriptomic differences, we planned several functional assays to validate these results, including calcium imaging and multi-electrode array measurements.

Goals: Our hypothesis is that the ZMYND11 mutation causes changes in neuronal differentiation, resulting in altered gene expression and altered connectivity and reactivity of neurons.

Results: Based on RNA sequencing, genes involved in neural differentiation and neural function, were overexpressed in the mutant cell lines. In functional measurements we expect to see accelerated differentiation and network formation, and increased reaction to glutamate in the mutant cell lines.

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Group 2

Speech processing in multi-talker situations: The role of speaker similarity

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Speakers with perceptually similar voice should be harder to segregate in multi-talker situations. However, while the dissimilarity of voices may help their segregation, the same variable may also affect sustained selective attention. Thus, the overall effect of voice similarity on following one voice in the cocktail party situation may either be beneficial or detrimental. To tease the two effects apart, we collected electrophysiological (EEG) and behavioral data while 22 healthy young adults listened to two concurrent speech streams consisting of either 1) identical, 2) similar, 3) dissimilar, or 4) opposite-gender speakers. Functional brain connectivity and behavioral results suggested that, while speaker similarity hinders auditory stream segregation, dissimilarity hinders selective attention by making the speech stream to be ignored more distracting. The problem to be solved by the speech processing system in multi-talker situations is thus different depending on the level of perceived speaker similarity.

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Simple visual stimuli lead to poorer retrieval and generalization in audiovisual associative learning

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Acquired equivalence learning, is a form of associative learning where the subject learns that two or more stimuli have the same outcome, and for this reason they are equivalent to each other. Primarily the basal ganglia and the frontal lobe circuits are responsible for learning the associations, and the hippocampus takes part in retrieval and generalization. The purpose of our research was to investigate the effect of less complex visual stimuli on acquired equivalence learning and the connected memory processes in visual and audiovisual paradigms.

Our volunteers took two tests: a visual and an audiovisual one. In the visual test (Polygon) they made associations between four grayscale circles and four simple polygons (triangle, square, rhombus and concave deltoid). These visual stimuli are less simple because they do not contain color information compared to the original Rutgers Acquired Equivalence Test. They have less emotional and semantic content. In the audiovisual test (SoundPolygon) the subjects associated the same polygons (mentioned earlier) with four distinct sounds.

We analyzed the data from 127 healthy adult subjects. We did not find significant difference between the two tests in performances and reaction times during the acquisition phase. On the contrary, the performance was significantly poorer in retrieval and generalization in the audiovisual SoundPolygon test than in the visual Polygon test.

Our results suggest that simple visual stimuli had no significant influence on association forming in audiovisual learning, and that association building is probably independent from the modality of the stimulus. However, simple visual stimuli has a negative impact on the performances in retrieval and generalization in the audiovisual test, in contrast to our former results, where complex visual stimuli could slightly improve these memory processes.

Identifying transfer learning in the reshaping of inductive biases

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Transfer learning is a critical hallmark of human intelligence that has been frequently pitted against the capacities of artificial learning agents. Yet, the computations relevant for transfer learning have been little investigated in humans. Here we follow an analytical paradigm that allows tracking individual learning day-by-day and identify signatures of the transfer of knowledge. From a Bayesian learning perspective, updating the prior over possible inventories that can be recruited for interpreting data is the key for efficient transfer of knowledge. We investigate two consequences of this computation: 1, Expediting the acquisition of new internal models; 2, Flexible parallel maintenance of multiple internal models. We reverse-engineered the internal models of individuals in an implicit sequence learning paradigm from their response times. We used a non-parametric version of the Hidden Markov Model, the infinite Hidden Markov model to infer individual internal models. Participants were trained on a non-trivial visual stimulus sequence (alternating serial reaction times, ASRT) without being aware of the higher-level structure of the task. After multiple days of training, a new sequence was introduced while the high-level statistics of the stimulus structure remained the same. This paradigm allowed us to investigate whether participants merely learned the specific sequence of the task stimuli, or they could incorporate the higher-level (structure-related) characteristics of the task. Our results show that above the acquisition of the stimulus statistics our participants were also able to update their priors. Acquisition of the new sequence was considerably sped up by earlier exposure but this enhancement was specific to individuals showing signatures of abandoning initial inductive biases. Enhancement of learning was reflected in building up a new internal model. We found internal models were automatically switched when the sequences were interchanged. Further investigation of internal models revealed that the behavior is rather a reflection of subjective beliefs, than the simple representation of the ground truth stimulus sequence. Our results also prove that subjects are able to construct an inventory of internal models and alternate between them automatically depending on the requirements of the environment.

The effect of visual stimulus complexity on the performance in audiovisual equivalence learning

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Equivalence learning is one kind of associative learning, where two discrete and often different stimuli are linked together, if they share the same outcome. The Rutgers Acquired Equivalence Test (RAET) is a computer based learning paradigm, where the subjects make associations between visual stimuli (drawn faces and fishes). Based on this paradigm, we developed two audiovisual learning tests. In both tests the antecedent stimuli were different distinct sounds. In the SoundFace test the consequents were four drawn faces from the RAET (features: age, sex and hair color), and in the SoundFish four different colored fish from the RAET, all same in size and shape. In the present study we compared the learning performances of healthy volunteers between the two audiovisual tests. The aim of the study was to investigate whether there is any difference between the performances when the antecedents (face) or consequents (fish) from the RAET had to associate to the same four sounds. We compared the performance in stimulus pair learning, retrieval and generalization of the previously learned equivalence to new but predictable pairings. The performance was significantly poorer in the SoundFish in all compared parameter and the response times were also longer. Our results suggest that the complexity of the visual stimuli affects the audiovisual associative learning effectiveness. Additionally, the semantic meanings and emotional contents of the faces could also facilitate these learning processes.

Group 3

Different projections from the medial prefrontal cortex inhibit social behaviors

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Our previous results indicated that preoptic area inputs from thalamic neurons promote social interactions in rats. In the present study, we addressed the effect of prefrontal cortical projections to the preoptic area as compared to the actions of corticothalamic projections from the medial prefrontal cortex (mPFC).

We expressed Cre recombinase in neurons projecting to the medial preoptic area (MPOA) of the hypothalamus using retrogradely spreading adeno-associated virus (AAV) followed by the injection of an AAV expressing designer receptors exclusively activated by designer drugs (DREADD) into the infralimbic and prelimbic cortices of the mPFC. Tracing of the fluorescent protein in the construct indicated that the MPOA projecting mPFC neurons also project to other subcortical sites including the accumbens nucleus, the septal nuclei and the medial amygdaloid nucleus. In a separate experiment, an AAV using the calcium/calmodulin-dependent protein kinase II (CaMKII) promoter to drive DREADD expression was injected into the same part of the mPFC. Neuronal tracing revealed that these neurons project only to thalamic nuclei, the paratenial, mediodorsal, submedius as well as reticular thalamic nuclei. Chemogenetic activation by clozapine-N-oxid injection, validated by c-Fos expression in mPFC neurons, indicated that both types of mPFC projection neurons inhibited social preference measured in the three chamber test compared to previous and subsequent days vehicle injection. In turn, direct social interactions were only inhibited by activation of the corticothalamic projections. We ruled out the contribution of changes in anxiety-like behavior to the observed changes in social interaction by demonstrating that the behavior of the animals was not altered in the elevated plus-maze test in response to chemogenetic stimulation.

The results indicate that subcortically projecting mPFC outputs inhibit social motivation while corticothalamic projections, which include further activation of the mPFC via thalamocortical projections inhibit social motivation as well as direct social interactions.

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Interconnectivity of the segregated cortico-thalamo amygdalar pathways

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The amygdala with its afferent and efferent connections has long been implicated in a wide range of emotion regulating processes, such as associative fear learning. According to the classical model, the basolateral amygdalar complex governs these functions by combining various thalamic and cortical inputs and conveying them to the central amygdala.

However, fine details of these thalamic and cortical afferent pathways, have not been elucidated yet. For example, it has not been directly tested yet whether these thalamic and cortical inputs converge or segregate within the amygdala. Furthermore, the precise nature of how thalamo-cortical afferents and intra-amygdalar pathways are connected is also yet to be described.

Therefore, first, we constructed a biologically relevant molecular map of the mouse amygdala to precisely delineate different amygdala subnuclei. We used this map as an anatomical basis for any further investigation.

Next, using adeno-associated viral vectors, we labelled major thalamic and cortical neuron populations projecting to the amygdala, and directly compared their innervation patterns. Our results demonstrated that both midline and lateral thalamic, as well as medial prefrontal and temporal cortical sources innervate different amygdala subnuclei in a rather non-overlapping manner. These results were further confirmed by in-vivo electrophysiological findings showing different activation patterns after optical stimulation of different thalamic afferents in the amygdala.

Ultimately, we labelled all major amygdala subnuclei with the combination of classical retro- and anterograde microinjections and conditional viral tracing to map intra-amygdalar connections and found a rather complex network within the amygdala. These results somewhat contradict the classical linear information flow model highlighting a serial lateral-basal-central pathway in the amygdala.

Taken together, we demonstrated with combination of anatomical and electrophysiological tools that thalamo-cortical afferents are mostly segregated within the amygdala. We further described a complex network of different amygdala subnuclei in contrast to previous studies. Our results together suggest that information processing in the amygdalar circuitry might be more complex than previously supposed.

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The geometry of hippocampal representations in different virtual reality tasks

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It is well-established that the hippocampus is critical for successful completion of spatial memory tasks by rapidly forming a sparse spatial code. The hippocampal code is also modulated by other, non-spatial variables but how this modulation develops during learning is poorly understood.

Here we analyzed data from two-photon Ca2+ imaging experiments monitoring the activity of CA1 pyramidal neurons in Thy1 mice expressing GCaMP6s in two different experiments. First, in a contextual go/no-go task animals learned to collect water reward by licking in the hidden reward zone in one of two virtual corridors that differed in their non-spatial (color or pattern) visual cues. Second, in a spatial learning task, the animals collected water reward by licking at the right location in either of two corridors containing rich spatial cues. To test the properties of the population level representation of environmental variables we performed static naive Bayesian decoding on the inferred spike data.

We found that in the contextual go/no-go task early during learning, when the animals behaved similarly in the two corridors, the neuronal activity also did not distinguish them. Specifically, we could decode the position of the animals in both corridors but not the corridor identity. As the animals learned the task an accurate representation of corridor identity emerged. In most animals the representation of corridor identity generalized well, i.e., a decoder trained at one position could predict the corridor identity in most other positions. The representation of position flexibly adapted to the task, becoming more accurate in the rewarded corridor, but less accurate in the unrewarded corridor.

In the spatial learning task both corridor identity and position were accurately encoded. However, even after behavior was relatively stable, the accuracy of the encoding increased with experience. Importantly, while here the code of position and corridor identity did not generalize, the relative distance from reward generalized well across the two corridors.

We conclude that hippocampal representations are highly flexible adapting to the structure of the task. The emerging geometry of the representations allows the generalization of task-relevant variables, such as reward or context.

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Perinatal asphyxia causes ADHD-like phenotype changes and excitatory- inhibitory imbalance in rats

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Aims: Perinatal asphyxia (PA) represents a great burden on healthcare systems worldwide as it is one of the leading causes of neonatal mortality and a heavy contributor to neurodevelopmental disorders. Still, the underlying mechanisms of asphyxia-induced long-term brain injury remain elusive to date, hindering clinicians in applying targeted therapy and emphasizing the need for a more veritable preclinical approach. In our study we aimed to explore the neuropsychiatric outcome and putative neurobiological mechanisms of PA in rodents, using a novel non-invasive model.

Methods: 7 days old male Wistar rat pups were treated with an asphyxia-inducing special gas mixture (4% O2, 20% CO2) for 15 minutes in normothermic conditions. For the profiling of the behavioural consequences caused by the PA insult, rats were subjected to comprehensive motor, emotional and cognitive testing from infancy through adulthood. To address the behavioural alterations on a histological level, confocal and STORM microscopy were performed in relevant brain regions.

Results: PA resulted in prefrontal cortex-dependent attention deficits in an operant learning-based paradigm and impaired inhibitory control function in the go/no-go task, suggesting ADHD-like behavioural changes. Long-term immunohistochemical staining revealed a permanent shift of the excitatory/inhibitory balance in the prefrontal cortex of asphyctic animals, demonstrated by significant changes in vesicular glutamate transporter and vesicular GABA transporter ratio, which was confirmed by STORM imaging as well.

Conclusion: Our study shows that PA results in lasting local histological changes in the prefrontal cortex, paralleled by marked region-dependent behavioural deficits, suggesting a strong pathophysiological link between early-life hypoxic- ischaemic injury and later-manifesting psychiatric disorders.

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Group 4

Neuropeptide mediated effects of thalamic neurons on the lateral septum in suckling rodents

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Parathyroid hormone 2 (PTH2) is a neuromodulator involved in the central control of maternal adaptations. PTH2 is maternally induced in the brain during the early postpartum period, most significantly in the posterior intralaminar thalamic nucleus (PIL). We aimed to determine the involvement of thalamic PTH2-positive projections in maternal activation of the lateral septum (LS). First, we mapped the inputs of the LS by retrograde neural tracer. The tracer injected animals were also mapped for c-Fos activation in response to pup exposure. We found activation in several brain regions already described in maternal care. However, only the neurons of the PIL showed c-Fos expression and sent projection to the LS, as well. PTH2-containing fibers projecting from the PIL to the LS was confirmed by using distinct pathway tracing methods combined with immunohistochemistry in suckling dams. PIL PTH2-expressing neurons especially project to the ventral subdivision of the LS (LSv). PTH2 action on septal neurons was suggested by the presence of PTH2 receptor (PTH2R) positive terminals in the area where PTH2-positive fibers are located. We also addressed whether suckling-related stimuli activate neurons in the LSv, too. We used pup-deprivation method in rat mothers and confirmed that the number of activated LSv neurons is significantly higher in suckling rat dams following pup exposure compared to control mothers with complete pup-deprivation. The level of activated neurons was significantly lower in those dams who received only pup-related vocal, visual and olfactory but not physical stimuli compared to suckling mothers, but still elevated when compared to totally pup-deprived mothers. We showed by both confocal and electron microscopies that PTH2-positive terminals closely apposed c-Fos activated septal neurons and form synaptic connection with them. In conclusion, lateral septal activation pattern of mother rats suggests that both non-physical and suckling-related stimuli from the pups contribute to neuronal activation. As PIL neurons are activated after pup exposure and PTH2-positive terminals innervate activated LS neurons, it is suggested that PIL PTH2 neurons take part in somatosensory input mediation to the LS.

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Afferents of the paraventricular thalamic nucleus (PVT) and the role of PVT in stress induced behavioral alterations

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Severe acute stress could lead to the emergence of psychiatric disorders, such as acute stress disorder (ASD), which is characterized by avoidance, hyperarousal and negative mood, and occurs in the initial month after the traumatic event.

The calretinin expressing cells in the paraventricular thalamic nucleus (PVT/CR+) form a critical hub between brainstem and forebrain areas and play an essential role in fear, anxiety and stress regulating circuit operations. In this study we tested whether the post-stress activity of PVT/CR+ neurons, following exposure to a natural stressor (fox odor, 2MT), contributes to the emergence of ASD like phenotype. We examined how post-stress optogenic inhibition (SwiChR) of the PVT/CR+ neurons affects locomotion, nesting behavior, stress hormone levels and c-Fos activity at the projection areas of PVT/CR+ neurons. We also investigated, which areas send GABAergic and glutamatergic inputs to PVT/CR+ cells and to what extent do these inputs converge or segregate in the PVT. We used retrograde and anterograde virus labeling in vGLUT2-Cre, VGAT-Cre and VGLUT2-Cre/vGAT-Flp double transgenic mouse lines and analyzed the PVT projecting cells and their fibers in the PVT by fluorescence and confocal microscopy after immunohistochemical staining.

We found that post-stress photoinhibition (1 hour) of PVT/CR+ cells prevented the acute stress induced changes including increased locomotor activity, disturbed nesting behavior, elevated corticosterone levels and increased c-Fos expression in the PVT/CR+ neurons and their projection areas. We also found that the origins of GABAergic and glutamatergic subcortical inputs to PVT largely segregate. Afferents from these subcortical centers selectively innervated PVT/CR+ cells and overlapped significantly in PVT. In contrast, cortical inputs segregated from subcortical inputs and they innervated the peripheral part of the nucleus.

Collectively, our findings indicate that PVT/CR+ neurons integrate excitatory and inhibitory information from numerous structures related to stress and salience, and the post-stress activity of PVT/CR+ neurons is critical in the emergence of ASD-like phenotype. We found, that post-stress inhibition of PVT/CR+ neurons is sufficient to prevent these changes.

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Higher-order thalamic nuclei facilitate the generalization and maintenance of spike-and-wave discharges of absence seizures

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Spike and wave discharges (SWD), generated by the cortico-thalamo-cortical (CTC) network, are pathological, large amplitude oscillations and the hallmark of absence seizures (ASs). SWD begin in a cortical initiation network in both humans and animal models, including the genetic absence epilepsy rats from Strasbourg (GAERS), where it is located in the primary somatosensory cortex (S1). The behavioural manifestation of an AS occurs when SWD spread from the initiation site to the whole brain, however, the mechanisms behind this rapid propagation remain unclear. Here we investigated beyond the principal CTC network, in higher-order (HO) thalamic nuclei (lateral posterior (LP) and posterior (PO) nuclei), their diffuse connectivity and known facilitation of intracortical communication make these nuclei candidates to support SWD establishment and maintenance. In freely moving GAERS, multi-site LFP in LP, PO and multiple cortical regions revealed a novel feature of SWD: during SWD, cortical regions far from S1, become transiently unsynchronized from the ongoing rhythm, named SWD-breaks. Inactivation of HO nuclei with local muscimol injections or optogenetic perturbation of HO nuclei activity increased the occurrence of SWD-breaks and the former also increased the SWD propagation time from S1. The neural underpinnings of these findings were explored further by recording from single units of PO which uncovered two previously unknown grous of excitatory neurons based on their burst firing dynamics at SWD-onset. A tonic to burst switch at SWD-onset was shown to be an important feature as the change was less exaggerated during non-generalized events (i.e. SWD that remained local to S1), additionally, one group of neurons showed a reverse of this switch during SWD-breaks, demonstrating the importance of this firing pattern throughout the SWD. To conclude, the results of these experiments converge on the conclusion that multiple HO thalamic are utilized at SWD onset and contribute to cortical synchrony throughout the discharge.

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Validation and modulation of seizure activity in a novel genetic absence epilepsy model
Safiye Chalyshkan

(Abstract not supplied.)

Group 5

Anatomical comparison of hippocampal HS and OLM interneurons using SEM array tomography

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The hippocampal formation of the mammalian brain is essential in learning and memory processes. Its main output neurons are the pyramidal cells, which are innervated by different types of GABAergic neurons, including the somatostatin-positive hippocampo-septal (HS) and oriens-lacunosum moleculare (OLM) interneurons. To fully understand hippocampal network mechanisms, we need precise interneuron models, for which we need their physically and morphologically accurate dendritic parameters. Electrical conductance of neuronal processes depend on several factors, e.g. the surface area of dendritic segments, the local volume of cytosol of dendritic segments, the latter of which is strongly affected by the local volume of their mitochondria. The density and number of excitatory/inhibitory inputs on the different types of dendrites of these neurons are also important, because they control the computational ability of these dendritic segments and the neuron as a whole. We investigated, whether synaptic coverage is different in different regions, like on somata, on different types of dendrites along the dendritic tree, and on the branching points. Using array tomography with scanning electron microscopy (SEM), we reconstructed two different types of GABAergic somatostatin-positive neurons labeled using viral and retrograde BDA tracing: the HS and the OLM interneurons. After the precise calibration of tissue shrinkage/dilatation during tissue processing, we measured the above mentioned real-life parameters along the dendritic tree and the soma. Using double immunolabeling, we also revealed the densities and sizes of inhibitory and excitatory synapses. Our results show highly variable parameters along the dendritic tree that need to be incorporated into precise models of the hippocampal network.

Anatomical characterization of principal neurons in the basolateral amygdala

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Amygdala refers to a cluster of structurally distinct nuclei in the brain including the basolateral complex (BLA) and the central amygdala (CeA). The former region consists of the lateral (LA), basal (BA) and basomedial (BMA) nuclei. In spite of many studies focusing on local information processing within the circuits of these areas, the features of amygdalar principal neurons (PNs) remained elusive. Here, we combined neuroanatomical, electrophysiological and tracing techniques to determine the single-cell features of the PNs.

Using a mouse reporter line for in vitro experiments, we found that cholecystokinin (CCK) expression defined two groups of spatially segregated PNs both in the LA and BA. PNs in the CCK+ part of the LA had small somata and short dendrites which matched to their passive and active membrane properties, while PNs in the CCK- subnuclei of the LA and BA had similar single-cell features. Importantly, the dendritic arbors of PNs were restricted to the subnuclei defined by the CCK expression. Based on post hoc reconstruction of 21 PNs labelled in vivo using juxtacellular technique we defined groups of BA and LA PNs with different morphological patterns, considering their soma location, the characteristics of the axonal and dendritic arbors, and their projections sites. For instance, two distinct units were distinguished within the BA: a lateral posterior one that typically projects to the CeA, and a medial-anterior one that does not, forming a separate functional unit communicating with other brain areas. The collaterals of PNs in the two functional BA units were further investigated using viral tracing approaches, which highlighted e.g. the prefrontal cortex and the dorsomedial striatum as target sites of the CeA-avoiding PNs.

In summary, our results uncovered the diverse input and output properties of principal neurons in the LA and BA that help to define the information flow within the basolateral amygdala networks.

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Differential regulation of static firing responses vs. synaptic integration in physiologically distinct classes of subiculum neurons

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The subiculum is a part of the hippocampal formation and it has an essential role in processing neuronal signals emanating from the hippocampus proper and forwarding it to different cortical and subcortical brain regions. The principal cells of the subiculum, the pyramidal cells can be divided into two categories based on their firing profiles: regular and bursting types. In previous studies, researchers mostly utilized traditional electrophysiological methods to investigate the functional properties of these cells. However, our group explores the integrative properties of neurons in the subiculum by exposing them to various types and intensity of simulated, computer-synthesized synaptic inputs (dynamic clamp). In such scenario we can investigate their firing output, spike timing reliability and precision under various types of in vivo-like activity including theta- or gamma-oscillations. We performed the present experiments on acute brain slices from mice, in whole-cell patch-clamp configuration. First we performed conventional current step protocols to assess the standard physiological properties and static excitability of subiculum neurons. Next, we applied simulated synaptic currents on the same cells. During dynamic stimulation, we elicited firing responses of the cells driven by simulated synaptic bombardment. Comparison of responses from static vs. dynamic stimulation revealed differential regulation of neuronal excitability and weak correlation between total spike counts observed under static vs. synaptic-type inputs. Additionally, the firing responses of regular and bursting neurons differed in a stimulation intensity dependent manner not readily expected from the static responses. Our results confirm the previous data measured in hippocampal cell cultures and it can serve as a further help to the better understanding of the effects of voltage-dependent ionic currents in neurons that regulate synaptic integration.

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Detection of synaptic connectivity using voltage imaging

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Recent advancements in genetically encoded voltage indicators (GEVIs) present an opportunity to describe the synaptic properties at the level of individual neurons within a large network. Voltron, a newly developed GEVI, is fast and sensitive enough to detect both subthreshold potential changes and action potentials. We used spontaneous action potentials of Voltron-expressing neurons in acute slices to detect presynaptic activity to which the responses of several potential postsynaptic cells were correlated in a large area within the hippocampus. I will demonstrate one example experiment in a mini-poster format. Indeed, this all-optical approach is sufficient to detect several synaptic connections within a single experiment, in which we imaged about 50-100 neurons.

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Noxious stimulus-responsive neurons in the dorsal tegmentum of the midbrain

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The ventral periaqueductal grey (vPAG) is a part of the dorsal tegmentum of the midbrain incorporating the ventrolateral PAG and dorsal raphe nucleus. The vPAG plays a critical role in controlling anxiety, fear memory formation, autonomic processes and most particularly, it is involved in descending modulation of pain processing. It has been shown that different neuron types, such as dopaminergic and serotonergic cells are part of this circuitry – besides the glutamatergic and GABAergic neurons – however their exact functions remained unclear. Additionally, malfunctioning of the circuit operation in the vPAG contributes to several neuropsychiatric disorders, the treatment of which is still a great challenge. Therefore, understanding the functional properties of neurons in this region can be critical in proposing new therapeutic approaches.

Here we used the juxtacellular recording technique to monitor the spiking activity of single neurons in urethane-anesthetized mice in response to noxious stimulation, and post-hoc immunocytochemistry to identify the recorded cell types. We distinguished functionally different neurons in the vPAG. Analysing the firing features and neurochemical content of the recorded neurons, we found that dopaminergic neurons can be separated into two groups based on their response latency and vasoactive intestinal polypeptide content, suggesting their different involvement in noxious stimulation processing. Further, we revealed that serotonergic neurons are heterogeneous and can be clustered into five groups based on their responses upon noxious stimulation. Our current results show that the firing of the monoaminergic neurons in the vPAG circuitries is distinctly modified by noxious stimuli, implicating their different contribution to pain processing in this clinically important brain region.

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Group 6

Effects of sumatriptan on P2X7 purinergic receptor-mediated signaling in an amphetamine-induced acute mania mouse model

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Acute mania is a phase of bipolar disorder. Symptoms include, among others, elevated mood, fast talking, engaging in risky behaviours, overconfidence in abilities and intense energy. Understanding the disorder and identifying new drug targets could be an important step forward in the treatment of this still far from resolved condition. Dysfunction of purinergic signalling plays a role in the pathophysiology of acute mania. The P2X7 receptor (P2X7R) affects neurotransmitter release and mania-like behaviour in mouse models.

In our research we investigated amphetamine-induced hyperactivity in wild-type (WT) and P2X7R gene knockout (P2X7KO) mice using open field (OF) and elevated plus maze (EPM) tests, and changes in c-Fos expression in striatum using immunohistochemistry.

In behavioural assays, the serotonin 5-HT1A/1B/1D receptor agonist sumatriptan and the P2X7R antagonist JNJ47965567 reduced amphetamine-induced hyperlocomotion in WT mice, whereas sumatriptan had no effect in P2X7KO mice. However, co-administration of sumatriptan and JNJ47965567 did not affect hyperactivity in WT mice. C-Fos expression was increased by amphetamine in both WT and P2X7KO mice.

Our results suggest that sumatriptan inhibits mania-like behavior in mice and that P2X7R plays a role in mediating its modulatory effect, thus sumatriptan may be effective not only in the treatment of migraine but also in the treatment of mania.

Involvement of the centrally projecting Edinger-Westphal nucleus in a mouse model of migraine.

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Background: Urocortin1 (UCN1)-immunoreactive neurons of the centrally projecting Edinger-Westphal (EWcp) nucleus are recruited by acute pain stress. The EWcpprojects to several pain sensitive centers including the spinal trigeminal nucleus (SpV), that plays a key role in the protopathic afferentation in migraine. Interestingly, the EWcp is involved in the regulation of the circadian rhythm, hormonal changes, stress exposure, pain and inflammation, that are known to induce migraine in susceptible individuals. Therefore, here we aimed at investigating the possible role of EWcp nucleus in the neurobiology of migraine.

Methods: A calcitonin gene-related peptide (CGRP) injection model of migraine was applied in C57BL6J mice. Light-dark box test was performed to validate the migraine-like state. In the EWcp, the neuronal activity was measured by FOS immunohistochemistry, and the Cgrp receptor and Ucn1 mRNA as well as UCN1 peptide expression was tested by RNAscope in situ hybridization combined with immunofluorescence. In the SpV, we searched for urocortinergic fibers juxtaposed to corticotropin-releasing hormone receptor (Crhr1 and Crhr2) mRNA expressing cells.

Results: CGRP treatment increased the time spent in the dark compartment of the light-dark box device suggesting the development of migraine-like state associated with photophobia in mice. The number of FOS positive neurons, the magnitude of Ucn1mRNA expression and UCN1 peptide content in the EWcp/UCN1 neurons was increased upon CGRP treatment. We proved the presence of Cgrp receptor mRNA in the EWcp. Crhr1 and Crhr2 mRNA-containing SpV cells were seen to recieve urocortinergic afferentation.

Conclusion: EWcp urocotinergic neurons are recruited by in CGRP-induced migraine-like state. The increased Ucn1mRNA expression and UCN1 peptide content of EWcp neurons in migraine, moreover, their possible connection to CRHR1 and/or CRHR2-positive SpV cells strongly suggest their regulatory role in headache control.

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Brainstem reticular formation regulates reward experience

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Reward-seeking behavioral strategies are essential for effective decision-making. Yet the involvement of the brainstem is still unclear. Using viral tract tracing in transgenic mice, we found a previously unrecognized gamma-aminobutyric acidergic (GABA) cell population in the brainstem that regulates reward, because their optogenetic stimulation induced both acute and conditioned place preference in mice. Monosynaptic retrograde rabies tracing experiments revealed their inputs from several behavior modulating subcortical structures. These brainstem GABAergic cells do not express typical brainstem neuronal molecules like acetylcholine, serotonin, parvalbumin, calbindin, calretinin or relaxin. However, their vesicular GABA transporter-positive axonal terminals establish GABAA-receptor and gephyrin containing synapses in the epithalamic lateral habenula (LHb) that is actively involved in modulating reward expectations. These results suggest that a novel LHb targeting brainstem GABAergic pathway has a role in reward processing by inhibiting the avoidance generating LHb cells.

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Chemogenetic evidence that posterior intralaminar thalamic neurons modulates aggressive behavior in rats

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In a previous study, we established the activation of the posterior intralaminar thalamic (PIL) neurons during social interactions between adult female rats. In this study we focused on the role of PIL in intermale aggressive behavior. For manipulation of PIL neurons, adeno-associated virus was stereotaxically injected into the PIL. The virus expressed DREADD fused with mCherry in the infected cells. Excitatory and inhibitory DREADDs were used, activated by clozapine-N-oxide (CNO). Behavioral tests were recorded during the chemogenetic manipulation. After perfusion of the animals, we verified the injection sites and performed histological analysis. We identified the brain areas activated by aggressive behavior using c-Fos method. We found neuronal activation in the infralimbic cortex, medial preoptic area (MPOA) and the lateral septum. To induce aggression, the animals were separated at an early age. The behavioral tests were performed at the age 5 month. On the first day of the experiment, vehicle was injected to the animal. We performed aggressive behavioral test, where an unfamiliar intruder was placed in the subject animal's cage resulting in an aggressive response. On the second day, the same test was repeated starting 1,5 hours after CNO administration. Chemogenetic stimulation significantly decreased aggression and increased the duration of positive valance contact, while inhibiting the PIL resulted in the increase of aggression and decreased the duration of positive valance contact. Based on the results, PIL neurons may participate in the regulation of aggressive behavior conveying sensory inputs from the conspecific to higher brain areas.

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Group 7

The role of microglia-mediated mechanisms in the modulation of cerebral blood flow

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Microglia, the main resident immune cells of the brain parenchyma are key regulators of inflammatory processes in the central nervous system. Despite the broad implication of microglial actions in shaping neuronal function in health and disease, their role in cerebral blood flow (CBF) remained vaguely defined. The aim of the study was to investigate the mechanisms of microglia-vascular interactions in order to understand the possible role of microglial actions on cerebral blood flow modulation. Formation of contacts between microglia and other cell types in the neurovascular unit was assessed by in vivo two-photon imaging and high resolution anatomy (confocal microscopy, immunoelectron microscopy and electron tomography), using the microglia-specific marker, P2Y12 receptor. CBF changes in the circulation were measured by Functional Ultrasound and Laser Speckle Contrast Imaging through the intact skull bone, in real time. The role of microglial actions were investigated via elimination of microglia by PLX5622, by using P2Y12R-/- and Cx3Cr1-/- mice, or blocking P2Y12R signalling in microglia by PSB-0739 injected into the cisterna magna. Cortical hypoperfusion was induced by repeated, transient unilateral common carotid artery occlusions. Whisker stimulation or visual stimulation was used to investigate neurovascular coupling in the barrel or in the visual cortex, respectively. Our anatomical data show that microglia dynamically contact different levels of the vascular tree in vivo and form direct purinergic contacts with the cells of the neurovascular unit (NVU) including endothelial cells, astrocytes, pericytes and vascular smooth muscle cells in both the mouse and the human brain, which shape CBF. We found that through these interactions microglia modulate CBF via purinergic actions during neurovascular coupling, hypercapnia-induced vasodilation and cerebrovascular adaptation to hypoperfusion. Our data also show that microglia may be able to sense different perfusion-related changes in the NVU and interact with different cell types in a compartment-specific manner. Our findings demonstrate that microglia should be considered as an important modulatory cell type involved in physiological and pathological alterations of cerebral blood flow and understanding their actions may facilitate the discovery of novel treatment opportunities in common neurological disorders.

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Examination of the density of macro- and microglia coverage of the blood-brain barrier in human patients with focal cortical dysplasia-associated epilepsy

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Around 20 percent of people with epilepsy suffer from focal cortical dysplasia (FCD). It is a neurodevelopmental disorder. FCD type II cases are characterized by impaired cortical lamination, the appearance of various abnormal cell types (including glial cells), and gliosis. The blood-brain barrier (BBB) is a unit that separates the blood from the brain tissue. It contains many cells, such as microglia, astrocytes, pericytes, and endothelial cells. Several studies have revealed the BBB is often impaired in humanepileptic patients and animal models of epilepsy. Therefore, we wanted to investigate whether changes in glial elements at the BBB are present in FCD.

In the current study, we have investigated the brain tissues of six control and six epileptic patients, taken from Brodmann's areas 38 (temporal pole) and 46 (dorsolateral prefrontal cortex). The control ones were post-mortem (post-mortem interval: 2-5 hours) perfused brains, while the epileptic samples were surgically removed. We have applied multiple immunofluorescent microscopy to study the astrocytes, blood vessels, and microglia in the same sections. Astrocytes were immunostained for glial fibrillary acidic protein (GFAP), microglia for IBA1 (ionized calcium-binding adapter molecule 1), and blood vessels with lectin. We have examined the intensity of the immunolabellings around the lectin-labelled blood vessels in a confocal fluorescence microscope.

Our results have shown a significant increase in the intensity of GFAP-immunolabelling, which is a sign of gliosis. However, the intensity of IBA1-positive microglia did not change. With further experiments, we would like to understand the complex changes of the BBB in FCD, so we can learn more about this disease and later compare it to other types of epilepsy.

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Spreading depolarization disrupts neurovascular coupling after global cerebral ischemia in mice

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Introduction: Neurovascular coupling (NVC) is weak or absent upon acute ischemic stroke (AIS). The mechanistic basis of NVC dysfunction might be the evolution of spreading depolarization (SD), that causes vasoconstriction and lesion progression in AIS. Here, we show that SD occurrence disrupts functional hyperemia during NVC despite reperfusion after AIS.

Methods: Male C57BL/6 mice (n=11) were anesthetized with isoflurane (0.6-1.2%). A baseline of 10 min was followed by a transient (45 min) bilateral common carotid artery occlusion (2VO) and a subsequent 60 min reperfusion. Cerebral blood flow (CBF) variations were captured using laser speckle contrast imaging (LASCA). After 60 min reperfusion, NVC function was evaluated under isoflurane (0.1%)-medetomidine (0.1 mg/kg) anesthesia by whisker stimulation (~2Hz). SHAM operated animals served as control.

Results: Low CBF (<20%) early under ischemia favored spontaneous SD evolution (CBF <20% vs. >30%, SD vs. no SD; 16 SDs in 9 mice). SDs occurred in both hemispheres (bilateral) in 7, and in one hemisphere (unilateral) in 2 mice. In concert, functional hyperemia was diminished in 7, and was unilaterally intact in 2 mice (hyperemia amplitude: 8.73±3.01 vs. 17.16±6.21 %; bilateral vs. unilateral). The amplitude of unilaterally intact functional hyperemia was comparable to SHAM mice (17.16±6.21 vs. 16.71 %, unilateral vs. SHAM).

Discussion: Our data demonstrate that SD evolution impairs NVC after AIS. SD is known to trigger vasoconstriction, called spreading oligemia that might diminish NVC function. We propose the pharmacological attenuation of spreading oligemia to improve NVC function after AIS.

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Group 8

A Quantitative Study of Cannabinoid Receptor1-Immunopositive Perisomatic Input of Principal Cells in Focal Cortical Dysplasia Type IIB in Human Epileptic Patients

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Focal cortical dysplasia (FCD) is one of the most common causes of drug-resistant epilepsy. TypeII FCDs are characterized by the appearance of impaired cortical lamination and abnormal cell types, including dysmorphic neurons, balloon cells, and abnormal glial cells. As many studies have revealed, the defects of the perisomatic inhibitory system may play a role in the development of seizures. Therefore, we wanted to investigate whether changes in perisomatic inhibitory inputs are present in FCD. In our previous temporal lobe epileptic and FCD cases enhanced parvalbumin-immunopositive perisomatic input was found. These conditions may increase the synchronous firing of cells and seizure probability. Therefore, we wanted to investigate, whether cannabinoid receptor type1 (CB1R)-immunopositive perisomatic innervation has been changed in FCD cases, too.

For the quantitative measurements, FCDIIB surgical samples were compared to controls with short post-mortem delay (2-5h, perfusion fixation). The current study was performed on FCD samples with distinguishable layers. The perisomatic terminals contacting principal cells were reconstructed in 3D with CB1R-NeuN immunostaining in a confocal fluorescent microscope.

The pathological pattern of our FCD patients (FCDI-II-III) was heterogeneous from mostly control-like tissue to disorganized cortical layers and many abnormal cells. Perisomatic input FCDIIB cases were examined with CB1R immunostaining and quantified by NeuN-CB1R double immunostaining in confocal fluorescent microscope.

In most cases, there were numerous dysmorphic neurons with particularly dense inhibitory input in the FCD samples. Quantitative measurements are still in progress, but despite the individual variations, our preliminary results and observations show that the CB1R-immunopositive synaptic coverage of principal cells is larger in FCD cases.

It is unclear whether the amount of inhibitory elements is changing due to an adaptive mechanism balancing the abnormal synchronous firing in FCD patients, or is a prior pathological alteration that is further increasing by the seizures. To be noted, both PV- and CCK-, CB1R-expressing basket cells may be involved in the enhancement of perisomatic inhibition. The reorganization of the perisomatic inhibitory system could further increase the chance of seizure formation in both cases. Thus, these alterations may be a general mechanism of abnormal network activity.

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Group I metabotropic glutamate receptor-mediated modulation of excitatory synaptic transmission shows interneuron specificity in the human neocortex

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Activation of group I metabotropic glutamate receptors (mGluR) in the brain mediates changes in neuronal excitability, synaptic transmission, and network activity of cortical circuits. Influence of mGluRs on neural activity in the neocortex has been linked to learning-related plasticity, brain state-modulation as well as various human neurological disorders but studies investigating their effect in human brain are scarce. We performed intracellular recordings from synaptically-connected glutamatergic pyramidal cell-to-GABAergic interneuron pairs in layer 2/3 of human neocortical slices to study the effect of group I mGluR activation on these neurons and their synaptic communication. We found that activation of group I mGluRs by agonist (S)-3,5-dihydroxyphenylglycine (DHPG) modulated interneurons in subtype-dependent manner. We observed depression of excitatory synaptic transmission strength in non-fast-spiking adaptive firing interneurons whereas most fast-spiking basket cells and axo-axonic cells exhibited potentiation of their synaptic excitatory input by the agonist. Parallel experiments in Wistar rat showed DHPG-mediated strengthening of glutamatergic input to fast-spiking basket cells. Our results demonstrate cell type-specific modulation of human neocortical neurons and their synaptic excitation by group I metabotropic receptor activation.

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Microglia-endothelial interactions in vascular and leukocyte responses

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Microglia, the main immune cells of the brain have been found to closely associate with the vasculature and to modulate vascular responses. We have characterized microglia distribution along the vascular tree and show that microglial association with different types of vessels reflect their functional properties. Microglia form physical contacts with cells of neurovascular unit (NVU), like pericytes and perivascular macrophages. To investigate the early inflammatory response on the microglia-vasculature interface, we developed a chronic systemic inflammation model with mice receiving three times i.p. LPS injections 24h apart. Chronic systemic inflammation was associated with altered microglial morphology (increased soma volume and reduced process ramification), increased vascular coverage and reduced hypercapnia-induced vasodilatory response as measured by Laser Speckle Contrast Imaging (LSCI). Chronic LPS treatment also triggered leukocyte recruitment that was most apparent in the cerebral cortex and the striatum. The recruited cells, mainly neutrophil granulocytes and monocytes were found trapped in blood vessels or transmigrated into the brain parenchyma. We used magnetic resonance imaging together with specific superparamagnetic micro-sized particles of iron oxide (MPIOs) targeting endothelial VCAM-1 to detect early endothelial activation in vivo, which markedly increased after the last shot of LPS. We found that elimination of microglia reduces leukocyte recruitment upon systemic inflammation, which was also observed in mice lacking microglial IL-1α or IL-1β indicating a role of microglia in central leukocyte recruitment. Surprisingly, absence of IL-1α and IL-1β in IL-1 IL-1αβ KO mice was associated with increased monocyte and reduced neutrophil recruitment into the brain. Thus, microglia and microglial IL-1 emerge as important contributors to systemic inflammation-related leukocyte recruitment into the brain, while central and systemic IL-1 may have complex, site specific actions on central leukocyte recruitment.

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Optimization of culture conditions for the co-culture of human endothelial cells, pericytes and brain organoids

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Blood-brain barrier (BBB) forms a dynamic interface between the blood and the central nervous system (CNS). The BBB protects the brain and provides oxygen and nutrients for the neuronal cells, but these protective mechanisms also restrict the entry of pharmaceutical drugs into the brain limiting the treatment of CNS diseases. Cell culture models are essential to investigate cerebral drug delivery. The latest trend among the induced pluripotent stem cell (iPSC) based technologies is the formation and use of human brain spheroids and organoids. Brain organoids have been used in drug discovery but so far they were not combined with in vitro BBB models.

Our aim was to (1) create and optimize a new, complex cell culture model by the co-culture of an in vitro human BBB model and human midbrain organoids, and to (2) examine the barrier integrity of the BBB model in the presence of midbrain organoids.

For modelling the BBB, a co-culture of human stem cell derived endothelial cells and brain pericytes was used (Cecchelli et al., 2014; PMID: 24936790). Human midbrain organoids were created from iPSCs from healthy people and Parkinson's disease patients (Nickels et al., 2020; PMID: 32534166).

The following culture conditions and experimental steps were optimized: (i) the maintenance and characterization of the organoids in our laboratory, (ii) the appropriate number of organoids used in the co-culture, (iii) the timing of the start and the length of the co-culture, and (iv) the best ratio of the BBB and the organoid cell culture media. The cellular composition of the brain organoids was characterized by immunostaining. The barrier integrity of the BBB model was investigated in the presence of midbrain organoids by the measurement of transendothelial electrical resistance and permeability for fluorescent markers. The morphology of brain endothelial cells was examined by immunostaining for tight junction proteins.

We successfully optimized the culture conditions of the human BBB model with midbrain organoids. Appropriate BBB maturation and integrity was observed in the presence of brain organoids. A variation of this new co-culture model system was already successfully used in our lab for nanoparticle penetration experiments (Veszelka et al., 2022, PMID: 35056983). Our future aim is to adapt this static co-culture model to our dynamic lab-on-a-chip device (Walter et al., 2016, doi: 10.1016/j.snb.2015.07.110; Santa-Maria et al, 2021, PMID: 33563079).

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Group 9

EEG Spectral Parameters of Sleep Regulation

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In the frequency domain the electroencephalogram (EEG) signal can be decomposed into two components: an aperiodic background activity described by a 1/f function and periodic perturbations superimposed on the background activity. An index of the aperiodic activity is the spectral slope derived by curve fitting over the log-log transformed power spectrum, reflecting on the ratio of slow to fast oscillations. The present study investigates the spectral slope computed using the fooof (fitting oscillations & one over f) algorithm on an animal model (Mus musculus, C57BL/6 and 129S4/SvJae hybrids). The mice were exposed to a 9 day-long sleep deprivation paradigm with baseline, sleep deprivation, and recovery phases. The spectral slope appears to adequately capture the homeostatic sleep regulatory adjustments related to prolonged wakefulness and the subsequent compensation. Furthermore, the spectral slope quantifies more accurately the neural changes caused by sleep deprivation relative to the classical band/bin-wise approaches (within the slow wave range in the current case), and also reflects on the high inter-individual variability of neurophysiological signals.

A grounding model for LFP measurements in anesthetized cat experiments

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Measuring electrophysiological recordings from inside the brain is mandatory for several hypothesis checkings. Having low amplitude levels and a non-ideal amplifier sets other signal sources could highly interfere with the measure targets, especially when they make the amplifier clip. A possible source of these noises is non-suppressed common-mode noises. They could decrease either by enhancing the amplifying instrument or providing a lower impedance direction for the causing energy. As the subject is not a perfect electric conductor, a simple ground clip might not be enough for this purpose. In this presentation, a model will be shown and a possible solution from the model with its results.

Reliability of resting-state EEG networks

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Functional connectivity (FC) has attracted major attention in the previous years as a tool that characterizes coordinated interaction between functionally specialized brain areas. A large number of studies investigated the reliability of FC, most commonly using fMRI data. However, fMRI FC captures functional relations on a timescale of seconds, while research relies on EEG for shorter time-scales. The present study focuses on the reliability of FC networks as measured with resting-state EEG rhythms (0.5-80 Hz) on a large sample of young healthy adults (N = 201; mean age = 22.4 +/- 3.1). Reliability was tested both within subjects and across groups with varying sizes, comparing different FC methods (based on phase synchronization and amplitude envelope correlation, with and without spatial leakage correction), epoch lengths (1-9 s) and frequency bands (delta, theta, alpha, beta, gamma). The data revealed that FC metrics not corrected for spatial leakage show high, but spurious reliability that is mainly influenced by the characteristics of the tested subject and the analysis pipeline, not by true neural interactions. However, these FC metrics were shown to be superior for personal identification compared to their spatial leakage corrected counterparts. The effect of epoch length and frequency showed FC method-dependent patterns. The results can provide guidance for FC estimation in future studies and for meta-analyses.

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Ictal heterogeneity in the awake striatum

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Absence seizures are sudden and brief lapses of consciousness characterized by synchronized, bilateral spike and wave discharges (SWDs). Although generated in cortico-thalamo-cortical system the role of basal ganglia circuits in the generation of SWDs has been recently proposed in animal models of absence epilepsy and supported by the consistent finding of ictal changes in functional fMRI BOLD signals in the basal ganglia of patients with absence epilepsy. Most of the investigations studying ictal basal ganglia neuronal activity have been performed in anaesthetized preparations that could influence the ictal entrainment of various BG neurons. Thus, we monitored the activity of identified BG neurons in drug-free preparations in order to fully understand the involvement of BG circuits in absence seizures. The activity of striatal neurons in awake stargazer mice was very heterogeneous ranging from ictal firing rate increase through lack of entrainment to decrease. Generally, medium spiny neurons were characterized by sparse activity and a lack of apparent mean firing rate changes between ictal and interictal periods. However even in neurons which seemingly lacked ictal firing rate changes the activity was related to individual cycles of the SWDs. Fast spiking neurons were able to change both the mean firing rate and firing mode from tonic firing to rhythmic bursting during SWDs. Ongoing experiments are aiming to elucidate the ictal activity of other neuronal populations in the basal ganglia nuclei. Our results revealed heterogeneous ictal activity in striatal neurons coupled to SWDs on multiple timescales.

Group 10

Optimal conditions for recording retroaxonal barrage firing in hippocampal interneurons

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The term barrage firing (BF) refers to the persistent firing of neurons that outlasts the long stimuli that trigger them. Action potentials generated during BF originate from the axon. This phenomenon has been observed in hippocampal and the neocortical interneurons. Intriguingly, in contrast to typical neuronal operations, BF allows independent axonal output without dendritic integration of input. However, the mechanisms of barrage firing are not yet fully understood.

As an undergraduate student my goal is to better understand BF in hippocampal interneurons using patch clamp recordings in acute slices. Currently, I am investigating whether BF occurs in different hippocampal regions and strata with similar probability, and whether sensitivity of BF depends on the recording temperature. Furthermore, I am exploring potential correlations between the age of the animals and the occurrence of BF. I would like to present my preliminary data from these experiments as a miniposter at the HunDoc.

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Firing statistics of neuron with autapse

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Recent experimental evidence showed that, in neocortical layer V, parvalbumin-expressing basket cells and pyramidal cells often form functional autapses. Excitatory autapses promote bursting and coincidence detection while inhibitory ones enhance spike timing precision on the milisecond scale and provide important mechanism of disinhibition. We studied analytically the impact of both excitatory and inhibitory autapses on neuronal activity. Assuming that interspike interval distribution of a neuron without autapse is known, we calculated firing statistics of the same neuron with autapse. Our results indicate that depending on the autaptic time delay, the spike regularity can lower or rise in comparison with the case of the neuron without autapse.

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Nimodipine exerts a neuroprotective effect against spreading depolarization independent of cerebral circulation

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Introduction: Nimodipine is an L-type voltage gated Ca2+ channel (VGCC) antagonist and a potent cerebral vasodilator. In preclinical models of cerebral ischemia, nimodipine mitigates the deleterious impact of spreading depolarizations (SDs). It remains to be explored whether the beneficial effect of nimodipine is achieved by the improvement of perfusion, or a potential direct action on the nervous tissue. Here we evaluate direct nimodipine action on SD in live brain slice preparations.

Materials and methods: Coronal brain slices prepared from C56BL/6 mice (n=16) were perfused with artificial cerebrospinal fluid (aCSF). First, we determined the kinetics of nimodipine (10 µM) saturation with liquid chromatography-tandem mass spectrometry (LC-MS) and found that 30 min incubation leads to full saturation of brain slices. Accordingly, after 30 min nimodipine incubation, low glucose aCSF (5 mM) and transient anoxia (1 min) were applied to elicit SD. Intrinsic optical signal imaging was used to analyze SD features, TTC staining was carried out to assess tissue injury.

Results: Nimodipine reduced the focal area of SD (3.38±0.88 vs. 2.37±0.94 %, control vs. nimodipine), decreased the total cortical area affected by SD (39.88±22.42 vs. 17.12±8.63 %, control vs. nimodipine) and curtailed the propagation velocity of SD (1.59±2.29 vs. 0.19±0.79 mm/min, control vs. nimodipine). Furthermore, nimodipine reduced the tissue injury by elevating the number of TTC stained particles (3.52±1.52 vs. 4.48±1.45 particle/1000 µm2, control vs. nimodipine).

Conclusion: Taken together, nimodipine exerted direct neuroprotection against the detrimental effect of SD, irrespective of its vascular action. In further experiments, we aim to administer nimodipine by using pH sensitive nanoparticles in our in vitro ischemia model. This method could yield a novel therapeutic approach in the clinical therapy of ischemic stroke.

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Subcellular localization of the calcium channel Cav2.3 in cultured hippocampal neurons

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Voltage-gated Ca2+ (Cav) channels mediate Ca2+ influx in living cells and are necessary for essential physiological functions such as muscle contraction, regulation of gene expression as well as neuronal activity (e.g., excitation-contraction coupling, learning, and memory). In particular, Cav2 channels are highly expressed in the central nervous system (CNS) and play an important role in the mammalian brain. They are involved in pre- and postsynaptic functions and are critical regulators of synaptic transmission. Especially, Cav2.3 (α1E), which belongs to the R-type class of Cav channels, is involved in neuronal development as well as synaptic plasticity and, compared to the other Cav channels, shows the strongest expression in mouse hippocampus and cultured hippocampal neurons. Nevertheless, little is known about the subcellular localization of Cav2.3 in neurons of the CNS. Here, we aim to investigate the role of Cav2.3 in hippocampal neurons, particularly its subcellular localization. To this end we are employing primary cultured hippocampal neurons, transfected with HA-epitope tagged α1 subunit of calcium channels, immunofluorescence staining, and high-resolution microscopy. For a quantitative comparative analyses, the well-characterized L-type channel Cav1.2 is used as control. Fluorescence microscopy of live-cell-labelled hippocampal neurons revealed a clustered localization of Cav2.3 channels in the neuronal plasma membrane of somata, dendrites, and axons. The somato-dendritic labelling pattern is similar to the previously characterized expression patterns of the L-type channels Cav1.2 and Cav1.3. Compared to Cav1.2, Cav2.3 channels show a significantly higher expression in dendrites and axons. Preliminary experiments suggest a presynaptic localization of Cav2.3 in synaptic boutons and a postsynaptic localization in dendritic spines of excitatory glutamatergic neurons, which will be analysed in relation to pre- and postsynaptic proteins (e.g., synapsin, vGlut1, PSD-95). Taken together, our results show a pre- and postsynaptic localization pattern of Cav2.3 channels, which is further supported by its proposed roles in synaptic transmission and postsynaptic calcium signalling.

Gesellschaft für Forschungsförderung Niederösterreich

Group 11

Development of an induced pluripotent stem cell-based organoid model for investigating the molecular mechanisms of cerebellar ataxia

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The cerebellum is important for processing motor and sensory information. Due to its continoued development during the post-natal period, it is vulnerable to a number of pathological processes, for example to different type of ataxias. Spinocerebellar ataxias (SCA) represent a group of ataxias with a diverse range of neurological disorders, mainly characterised by the loss of motor co-ordination. Recently it has been discovered that pathological pathways of different genetic sub-types of SCA can overlap and they affect not only Purkinje cells, but also other cell types of the cerebellum, such as Bergmann glia cells. Since the development of the human cerebellum is completely different from that of the mouse cerebellum, it is essential to use human model systems to study both developmental biological and neurodegenerative changes. The human induced pluripotent stem cell (hiPSC)-derived cerebellar organoid system contains the disease relevant cell types in a tissue-like organization and therefore can provide a relevant model for investigating the molecular mechanisms of ataxias affecting the human cerebellum. First we developed a reproducible differentiation protocol for the generation of a hiPSC-derived organoid model of the cerebellum, which also enables the production of cerebellar organoids from hiPSC lines created from patients with SCA. The cell types found in the organoids on days 21, 35 and 50 of the differentiation were characterized by immunocytochemical methods, using markers specific to the developmental stages of the cerebellum. We showed that Kirrel2-positive Purkinje progenitors appear already on day 35, from which Calbindin-positive Purkinje neurons develop by day 50. By optimizing the culture conditions, the later developing astroglial cells were already detectable on the 50th day. In order to prove that the model is also suitable for detecting pathological changes, we treated the organoids with IL-1β, capable of inducing ataxia in mice. IL-1β treatment increased the expression level of the autophagy marker P62, as detected by western blot. In order to find out whether this change occurred in a cell-specific manner, we examined P62 in organoid sections together with neuronal and astroglial markers. Overall, it can be concluded that we have created an organoid model of the human cerebellum, which is suitable for examining cell-specific pathological changes and can serve as a platform for the development of therapies targeting them.

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AgRP neurons modulate exploratory behavior during calorie restriction

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In the last century human life expectancy has considerably increased in most developed and developing countries. Healthy life expectancy however, is rising at a much slower pace, which ultimately leads to an increase in age-associated diseases. It is now evident, that there is a growing need for simple and efficient methods to tackle these maladies at symptomatic, behavioral and physiological levels.

Caloric restriction (CR) has been known for decades to prolong healthy life span in mammals. CR has many beneficial effects in the short- as well as long-term, including delay in onset and reduction in incidence of many chronic diseases. Despite the considerable effort to decipher the underlying mechanisms involved in these processes, how CR exerts its effects is still ill-defined.

Hypothalamic agouti-related peptide (AgRP) and neuropeptide Y-expressing neurons have a crucial role in driving food intake, but also in modulating complex, non-feeding behaviors. AgRP neurons are exclusively located in the arcuate nucleus of the hypothalamus and together with POMC neurons they form the basis of the melanocortin system, a collection of CNS circuits regulating energy balance. Using multiple mice model-systems with impaired AgRP neuronal functions, we show here that CR promotes the activity of AgRP neurons in the brain, and that perturbation of AgRP neuronal function leads to impaired behavioral responses to CR. We also characterized the adaptive response of AgRP neurons to CR and we sought to determine whether AgRP neurons might be important for the adaptive response of mice to CR.

Our findings highlight the pivotal role of the AgRP neurons during CR in regulation of complex behaviors, and show that AgRP neurons are critical for complex behavioral adaptations to CR.

Investigation of viral PepH3 peptide-functionalized nanoparticles on a culture model of the Blood-Brain-Barrier

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Drug delivery to the CNS is limited by blood-brain barrier (BBB), which is mainly composed the endothelial cells of brain capillaries. Nanoparticles (NPs) are promising new tools to increase the transfer of drugs across the BBB. The advantage of vesicular NPs is that they increase the penetration of cargo molecules across biological barriers and by decorating their surfaces with appropriate ligands they are suitable for targeted drug delivery. The aim of this study was to investigate the PepH3 peptide, isolated from the capsid protein of Dengue virus alone, and as a targeting ligand of NPs to elevate the cargo penetration across the BBB.

In our experiments, we used Quasar570 labeled PepH3 and prepared PEGylated PepH3-targeted NPs loaded with the Texas-Red bovine serum albumin (TR-BSA) or single-domain antibody (sdAb) against amyloid beta peptide as cargo. The physico-chemical properties of NPs, such as particle size, polydispersity index and surface charge were measured by dynamic light scattering. The encapsulation efficiency was detected by spectrofluorimeter or western blot. The effect of PepH3 alone and PepH3-targeted NPs on the viability of primary rat brain endothelial cells was monitored by impedance measurement. The cellular uptake of PepH3 and PepH3-targeted NPs were visualized by confocal microscope. We investigated the entry of the peptide and peptide-targeted nanovesicles into cells and their penetration across the culture model of the BBB with spectrofluorimeter.

The mean diameter of untargeted and N-PepH3 particles was between 100-120 nm, respectively. The NPs have slightly negative surface charge and relatively narrow size distribution. The encapsulation efficiency of TR-BSA cargo was ~35 %, in the case of sdAb loaded NPs it was ~70%. PepH3 had no effect on the viability of RBEC and was rapidly taken up by RBEC cells supported by the visualization and cellular uptake studies. PepH3 peptide alone and PepH3-targeted NPs with TR-BSA cargo had significantly higher penetration across the BBB model compared to marker molecule or non-targeted NPs. Although, the penetration of sdAb cargo across the model was not measurable, high amount of sdAb was detected in primary rat brain endothelial cells after the permeability measurements.

Our results proved that PepH3 is a good candidate to be used as a peptide for targeted brain delivery of therapeutic biomolecules.

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Investigation of adherence and permeation of bacteriophages through culture models of biological barriers

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The human body is colonized by several microorganisms, including bacteriophages, which have impact on the human microbiome and thus on our health. Interacting with mucosal surfaces, phages can permeate epithelial cell layers and spread throughout the body (including brain), creating an intra-body phageome. The mechanism and function of these intra-body phages are still largely unknown. Our aim was to investigate the adherence and permeation of phages isolated from human samples in the in vitro intestinal epithelial barrier and the blood-brain barrier models. Phages were filtrated and pooled of faecal samples of healthy patients. T4 and K1F phages were applied as reference phages. The Caco-2 cell line was used as the intestinal barrier model, the blood-brain barrier model was established by the co-culture of human brain endothelial cells and brain pericytes using culture inserts. Non-adherent phages were collected from the upper, luminal compartment of the barriers; while phages that crossed the barriers were collected from the lower, abluminal compartment. Cells of the barriers were lysed to extract phages sticked in the cells. All samples were sequenced, and the contigs of phage origin were determined. The glycocalix layer of Caco-2 cells were removed by neuraminidase. The phagocytosis of phages were blocked by cytochalasin D, an inhibitor of actin polymerization. Phages within the cells were visualized by SYBR gold stain using confocal microscopy. Different pattern of human-associated phages got through the intestinal barrier and the BBB. Phages that could enter but not cross the cells were identified in both barriers. The neuraminidase treatment decreased the number and variety of adhered phages to the Caco-2 cell layer. SYBR gold-stained T4 and K1F phages were visualized in both Caco-2 cells and brain endothelial cells. but K1F showed a low uptake. The endocytosis of T4 phages was reduced by cytochalasin D, indicating a phagocytotic mechanism. Some of the human-associated phages are able to cross the in vitro intestinal and the blood-brain barrier models. Phages from the upper/lower compartment or the cell lysate show different distribution in the different barriers. The identification of domains of human-associated phages that influence the adherence and permeation through the barriers, needs further investigation. Application of participating domains on therapeutically potential phages could support the development of phage therapy.

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Group 12

All-optical synaptic connectivity mapping using Voltron

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A long-standing goal in neuroscience is to understand synaptic connectivity between individual cells that underlies function-specific neuronal activities. Patch clamp electrophysiology provides a powerful tool for revealing unitary synaptic connections with high temporal resolution. However, the spatial resolution of this method is limited to only a few potential connections. To overcome the limitations of this traditional method we sparsely expressed a new genetically encoded voltage indicator (GEVI), the Voltron in the hippocampus. Using fluorescent voltage imaging, Voltron allows the detection of a large number of unitary synaptic connections in acute slice preparations.

Voltron was injected into the hippocampus using rAAV vectors in rats and expressed for 4-8 weeks. Acute hippocampal slices were made and incubated with a fluorescent dye (JF549) which covalently binds to the Voltron protein in the membrane. The Voltron allows the detection of small voltage fluctuations in a large number of neurons using epifluorescent illumination and a fast CMOS camera with high spatial (375x235 µm) and temporal (1kHz) resolution. Typically, hundreds of Voltron+ neurons are visible, and we recognized that several cells are spontaneously active and elicit action potentials (APs) which can be detected with high fidelity using all-optical method. The spontaneous APs can be used as presynaptic activity of different cells which enhances the chance of detecting several unitary synaptic connections in one slice using only optical techniques. Furthermore, the persistence of Voltron signal after fixation allowed us to map the identity of imaged neurons using posthoc immunolabelling.

Thus, using Voltron it is possible to detect multiple synaptic connections in a large pool of neurons and is suitable for detailed mapping of synaptic connectivity.

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Automated detection of spontaneous population activity on human in vitro recordings

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Introduction: Discerning various events on electrophysiological recordings may reveal a fair amount of knowledge about synchrony-generating principles. Considering the vastness of data available for this purpose, as well as the time-intensive and experience-dependent nature of the analysis workflow, application of machine learning-aided technologies is welcome for this task. Although several analogous algorithms were set up for the investigation of interictal events, none of them attempted to detect physiologically occurring hypersynchronous events. We ventured on creating artificial neural networks that distinguish spontaneous synchronous population activity (SPA) from background with an accuracy and robustness comparable with manual analysis.

Materials and Methods: Data were collected by a 24-channel laminar microelectrode from human neocortical slices inferential to patients either or not displaying epileptic signs. Manual analysis identified 53 962 SPAs, based on which 0.1 s-long epochs were generated from 3 neighboring channels where event amplitudes were the highest. Similarly, long, although eventless epochs were generated from baseline activity (n= 113 588). Before feeding data in the neural networks, a proper randomization and a 70-20-10% partition of training-validation-testing datasets took place. Neural network architectures relied on 1D- and 2D-convolutional, recurrent (LSTM) and dense layers.

Results: Overall fitness of the artificial neural networks was evaluated by the following metrics: binary accuracy ([true positive nr. + true negative nr.] / total entries), precision (true positive nr. / [true positive nr. + false positive nr.]) and recall (true positive nr. / [true positive nr. + false negative nr.]), the loss function chosen was binary crossentropy. After 30 epochs of training and validation, the neural network employing 1D-convolutional layers performed on the testing dataset as follows: accuracy=0.849, precision=0.752, recall=0.793. We plan to improve performance metrics by applying scheduled learning rates.

Conclusion: By the implementation of artificial neural networks, identification of SPAs benefitted from decimated inter-observer variability and substantial time reduction during analysis. This latter feature encourages our method to be assessed on similarly recorded human in vivo data, with the promise to detect SPAs unprecedentedly in this context.

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In vivo calcium imaging of neuronal activity in the mouse visual cortex during electrical microstimulation with high-density flexible multi-shank probes

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Sensory neuroprostheses use electrical microstimulation through implanted neural interfaces with the aim to restore sight or hearing. Although this field showed great progress in recent years, there are still gaps in our knowledge on how to precisely target and activate specific neurons or neuron populations by intracortical microstimulation. To improve the stimulation resolution, an evident solution would be to increase the number of stimulation sites as well as to decrease the size of electrodes. However, increasing the volume or the number of devices implanted into the brain tissue will inherently result in more tissue damage and complications. Another, less invasive way to provide more precise control of neuronal activity without increasing the number of electrodes could be the application of advanced stimulation patterns (e.g., current steering, dynamic stimulation). In this pilot study, we developed flexible multi-shank probes containing multiple small electrodes to assess the effects of advanced electrical microstimulation strategies on cortical activity obtained using in vivo two-photon calcium imaging. The shanks of polyimide probes had a cross-section of 20 × 70 µm² (thickness × width), a length in the range of 700 to 1200 µm and were located at a fixed distance of 150 to 200 µm from each other. The rectangular iridium oxide electrodes (20 × 30 µm²) spread along the width and length of each shank, creating a grid with distances varying from 15 µm to several 100 µm. The fabricated probes were implanted into the visual cortex (V1) of Thy1 -GCaMP6f transgenic mice anesthetized with ketamine/xylazine. The cavity of the craniotomy was filled with biocompatible silicone to reduce brain pulsations. Here, we show the preliminary results of the first implantations where we used a two-photon laser scanning microscope (laser wavelength between 820 and 920 nm) to image the calcium activity in layer 2/3 of the visual cortex next to the probes. Imaging (raster scanning at 31 Hz) was performed through a 20x water immersion objective with a numerical aperture of 1, providing a field of view of 550 µm × 550 µm. Our future plans are to study the effects of various advanced stimulation patterns on the activity of the visual cortex and to determine promising stimulation strategies with the aim to improve the resolution of state-of-the-art visual cortical prostheses.

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Chronic functional ultrasound imaging of freely moving cats combined with optogenetics

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Perception and behavioral commands are computed by neuronal circuits organized into brain-wide networks. How the activity of distinct cell types is contributing to brain-wide network dynamics remains not well understood. We combine functional ultrasound imaging (fUSI) with optogenetic stimulation to reveal the network of brain regions functionally activated during a visuomotor task in freely behaving cats. Here, we present a novel modular chronic neural interface for monitoring and manipulating neural activity. The interface allows us to perform mesoscale measurements with fUSI in freely behaving animals, at an order of magnitude better spatiotemporal resolution than conventional fMRI can provide. Monitoring the effect of optogenetic perturbation may give causal proof on the role of cortical and subcortical cell types in visually guided behavior. Thus, our method could provide insight into the functional organisation of the networks governing behavior in freely-moving large animal species.

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Group 13

Age-related neuronal autophagy changes in induced neurons directly reprogrammed from adult human dermal fibroblasts

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Human lifespan continues to climb, this will result in an aging society with its own problems. One of them is the increase of neurodegenerative diseases (ND) due to age, however we know little about the connection of age to these diseases. One of the promising targets of interest is autophagy in neurons. It was shown that autophagy declines with age in neurons.

Autophagy is an evolutionary conserved lysosomal degradation pathway that ensures the cytoplasmic homeostasis. Deficits in autophagy have been linked to decreased mitochondrial biogenesis and trafficking, oxidative stress, increased apoptosis and ATP deficit, which have been implicated in neurodegenerative diseases like Parkinson's and Alzheimer's disease.

Modeling human aging in a lab so far was challenging, especially neuronal aging as donor neurons were not readily available. iPSC-s solved some of the availability issues, however due to the process of rejuvenation they are not the best candidate to model aging.

In this project we will use an induced neuronal model (iN) to follow the changes in autophagy during neuronal aging. We will use an all-in-one self-inactivating lentivirus to directly reprogram donor fibroblasts into neurons. The advantage of this methodology is that iNs maintain age (and disease)-related signatures of the donor cells as direct reprogramming bypasses the intermediary cell rejuvenation step inevitable in other approaches such as iPSC.

We will convert 50 healthy sex matched human dermal fibroblasts iNs from different ages. We will use immunostaining combined with high content automated microscopy to monitor the conversion efficiency, purity, cell number and neuronal morphology using neuronal markers like MAP2 and TAU. Afterwards, we will measure the expression of different autophagy markers during basal and starvation conditions (LC3, p62, LAMP1, BECN1). We will also monitor proteomic and transcriptional changes of autophagy using mass spectrometry and RNA-seq. We will combine our data to establish the relation of age to autophagy.

Quadruple-transgenic mice model of Alzheimer's disorder, with Aβ1-42, pTau deposition, and cholinergic neuron specific Cre expression

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Introduction: Alzheimer's disease is the most common type of cognitive dementia, which is among the top 10 leading causes of death in the world. The most affected neurocircuit in AD patients is the cholinergic system, therefore, it is a common target in AD therapy. The exactrole of the cholinergic system in AD is still unknown.

Aim: Our aim was to create a genetical mouse model, that represents the progression of AD, in form of Aβ1-42 plaques, pTau aggregates and cognitive impairments, while at the same time expresses the Cre recombinase enzyme specifically in cholinergic neurons. The presence of this enzyme will give us the opportunity to manipulate this system more selectively. However, we have to confirm the usefulness of the model first.

Material and methods: Two strains were cross-bread in multiple steps: B6;129-Tg(APPSwe,tauP301L)1Lfa Psen1tm1Mpm/Mmjax) as 3xTg-AD and B6;129S6-Chattm2(cre)Lowl/J as ChAT-Cre. After genotyping, a colony, homozygote for all four genes (PSEN1, APPSwe, tauP301L and Cre as 3xTg -ChAT-Cre) was created. To test the functionality of the Cre enzyme a stimulating DREADD virus (AAV8-hSyn-DIO-hM3Dq-mCherry)was injected unilaterally into the nucleus basalis magnocellularis (NBM) and clozapine-N-oxide-induced c-Fos activation was compared between the two hemispheres. Further immunostaining confirmed the expression of mCherry (i.e. DREADD) in ChAT positive cells as well as the appearance of the pathological hallmarks (Aβ1-42 and pTau).

Results: DREADD was expressed in the NBM in overlap with ChAT. Aβ1-42 plaques (hippocampus, prefrontal cortex, amygdala) and pTau aggregates (hippocampus, amygdala) were detected only in the 3xTg-ChAT-Cre and not in ChAT-Cre controls.

Conclusions: The newly created animals have a functional Cre recombinase enzyme in cholinergic cells. Additionally, the animals showed the pathophysiological hallmark of AD in specific brain areas. Thus, this strain seems to be appropriate for further studies.

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Enhanced food intake and abnormal deiodinase mRNA expression pattern in the triple transgenic Alzheimer's disease model mice

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Alzheimer's disease (AD) is an age-related neurodegenerative disease with progressive memory decline, which could be aggravated by other factors such as abnormal hypothalamic–pituitary–thyroid (HPT) axis [1]. Transgenic AD mouse models are promising tools in understanding the underlying mechanisms.

We compared male, 8-month-old triple transgenic (3xTg-AD) mice to age-matched controls, as the appearance of pathological hallmarks is expected at 6-month. First, the animals' body composition was studied by magnetic resonance imaging, while food and water consumption and respiratory exchange ratio were recorded in metabolic cages for 24 hours. Next, since the HPT axis greatly affects metabolism, its key enzymes were examined that play a decisive role in the central nervous system. So, deiodinase mRNA expression pattern was measured using qPCR in pituitary gland and in the mediobasal hypothalamus (MBH).

The 3xTg-AD mice had increased food and water consumption and showed higher respiratory exchange ratio compared to age-matched controls. Paradoxically, a lower body fat percentage was detected in them, while their energy expenditure showed no difference between the two groups. The type 1 and 2 deiodinase increased in the pituitary gland without any difference in the type 3 deiodinase. However, in the MBH a decrease of the type 2 deiodinase was detected.

In summary, we have found higher nutrient requirement in 3xTg-AD mice, which greatly influenced their body composition. Alterations in deiodinase expression at critical parts of the HPT might influence the basal metabolic rate contributing to the observed changes. Our results further strengthen the idea that AD is a metabolic disease [2].

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P2Y12 receptors - master regulators of microglial physiology

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More and more attention is directed to microglia, the brain's main immune cell, which plays essential roles in brain homeostasis, while being involved in several pathological processes. In order to fulfil their diverse tasks, microglia need to communicate with neurons and other brain cells in a very dynamic and efficient way. To achieve this, microglia make physical contacts with different brain cells. Indeed, motile microglial processes have been shown to constantly and dynamically probe their environment, and form contacts with other cellular compartments for shorter or longer periods to fulfil their roles. However, our understanding of the regulation of microglial process motility is incomplete. The involvement of microglial P2Y12Rs in baseline surveillance and microglial morphology is controversial. Several studies suggested that these receptors are only necessary for the recognition of injury sites. However, our preliminary data suggested the possible role of P2Y12R-dependent purinergic signaling in baseline microglial responses and surveillance activity, therefore we aimed to investigate the importance of this receptor under physiological conditions. To explore the role of P2Y12Rs we applied acute pharmacological inhibition or genetic receptor deletion. Microglial motility was assessed with high resolution anatomy and in vivo imaging and receptor distribution was tested using super-resolution microscopy.

Our results show that acute inhibition or genetic deletion of P2Y12R leads to robust changes in the speed of process movement and in the travelled distance by single microglia processes. Disruption of P2Y12R function resulted in altered microglial surveillance of neurons and microglial morphology. Genetic deletion of P2Y12R affected cortical microglial cell numbers, distribution homogeneity and observed different compensatory effects in the knockout animals.

Our results confirmed that P2Y12Rs play an essential role in the basic physiological functions of microglia, also affecting microglia-neuron interactions. Disturbance of P2Y12R signaling hinders microglial surveillance, and renders these cells unable to fulfil their homeostatic roles. These results help us to better understand the complex regulation of microglial motility and surveillance, and might facilitate the establishment of new therapeutic approaches in a broad range of neurological disorders.

Group 14

Glucose sensor development – optimizing an electrochemical method for preclinical research

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INTRODUCTION

Measuring metabolic processes in the brain with adequate temporal resolution is crucial to understand its function. Previous studies showed that glucose drinking may deeply influence the behaviour of an animal. Therefore, we hypothesized that brain glucose metabolism, especially in the prefrontal cortical area containing glucosensor cells, plays a crucial role in the development of psychiatric disorders. To test this hypothesis we must have a suitable device for brain sugar measurement.

METHOD

Glucose-oxidase, a specific glucose degrading enzyme, bound to the surface of an electrode will generate hydrogen-peroxyde, which induces a current proportional to the glucose concentration. It is measurable by periodically interrupted amperometry, which ensures high sensitivity and a low detection limit. After testing the microelectrodes in vitro, in vivo measurements were carried out in rats. In vivo glucose or insulin were administered intraperitoneally or via a jugular cannula to manipulate endogenous glucose homeostasis and subcutaneous tissue glucose levels were followed by a commercially available continuous glucose-monitoring (CGM) sensor. The CGM is insufficient for targeting the thin cortex (too flexible, too much electrode surface area and measurement only from 2 mmol/l), but it provides a reliable way to follow glucose levels peripherally.

RESULTS

We successfully optimized the size, lifetime and sensitivity of our electrode, which made it suitable for brain measurement in contrast to the commertial sensor. Selectivity was successfully ensured by an electropolymerized meta-phenylenediamine ultrathin grid-like layer. This acts as a size exclusion layer (SEL), because the potentially interferring electroactive species such as ascorbic acid cannot penetrate it due to its size. Central and peripheral measurements showed the same response to manipulations (glucose or insulin injections).

DISCUSSION

This biosensor can contribute to the understading of the metabolic aspects of psychiatric disorders, therefore, to improve the efficacy of the therapy. The knowledge gained during development of the biosensor will open a new window for applying this electrochemical method to other projects and animal models. Building a small hand-held potentiostat is also under investigation. A reliable portable device would simplify the setup, which will provide a more optimal environment for the animal experiments.

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Assessment of neutralizing factors against engineered adeno-associated virus serotypes in preclinical species

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Adeno-associated viruses (AAVs) are gaining increasing importance for both basic science and gene therapy applications. However, a major obstacle to AAV-based gene therapy is the high prevalence of neutralizing antibodies and factors in the human population. These neutralizing effects can reduce or completely inhibit the expression of the transgene upon systemic delivery. One strategy to overcome the pre-existing immunity barrier is capsid engineering. Engineered variants can have a tissue-specific bias in their tropism and may also evade pre-existing neutralization in hosts that have already been infected previously with a natural serotype.

We establish a generic assay to quantify the degree of neutralization in blood serum samples. Using samples from subjects previously infected with AAVs, we quantify their immune response upon re-infection with another serotype. Our results demonstrate that engineered serotypes are better choices for gene therapy due to both better tissue tropism and lower evoked immune response.

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Methylated cyclodextrin derivatives decrease trpv1 and trpa1 ion channel activation and mitochondrial function in chinese hamster ovary cells

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Transient Receptor Potential Ankyrin 1 (TRPA1) and Vanilloid 1 (TRPV1) are nociceptors involved in pain sensation and neurogenic inflammation. These non-selective ion channels are expressed in special cholesterol-rich membrane domains (lipid rafts) of primary sensory neurons and peripheral nerve endings, where TRP activation is aided by the lipid environment. Targeting protein-lipid hydrophobic interactions is a promising way to reveal analgesic compounds with novel mechanism of action. Cyclodextrins (CDs) are cyclic oligosaccharides that form inclusion complexes with cholesterol, depleting them from lipid rafts. We described that lipid raft disruption by Methyl-β-CD (MCD) inhibits TRP ion channel activation and has analgesic effect in mouse models.

Four methylated CD derivatives (Randomly methylated β-CD: RAMEB; isomeric mixtures of Heptakis (2,6)-di-O-methyl β-CD: DIMEB-50 and DIMEB-95; Heptakis (2,3,6)-tri-O-methyl β-CD: TRIMEB) were tested in respect of their cytotoxicity (24-hour treatment, chinese hamster ovary (CHO) cells) with CellTiter-Glo® Luminescent Cell Viability Assay.

To reveal the effect of 24-hour CD treatment on mitochondrial function of CHO cells MitoTracker™ Red CMXRos fluorescent dye was used in laser scanning confocal microscopic experiments.

To detect alterations of receptor activation after CD treatment radioactive 45Ca-uptake measurements were performed on CHO cells stably expressing TRPA1 and TRPV1 receptors.

In CellTiter-Glo® Luminescent Cell Viability Assay the order of cytotoxicity was the following: RAMEB (3 mM) < TRIMEB ≤ DIMEB-50 (1 mM) < DIMEB-95 (0.75 mM).

Significantly decreased mitochondrial functioning was detected with MitoTracker™ Red CMXRos fluorescent labeling after 24-hour CD treatment in case of all derivatives, except DIMEB-50.

All of the investigated CDs were able to inhibit the 45Ca-uptake in TRPA1 and TRPV1 receptor-expressing CHO cells in a concentration dependent manner, except DIMEB-50 in case of TRPA1 ion channel.

Besides showing that methylated derivatives have different characteristics in respect of cytotoxicity, we revealed that they seem to cause mitochondrial dysfunction and are able to inhibit TRPA1 and/or TRPV1 channel activation, presumably via lipid raft disruption. Our plan is to further investigate the safety and lipid raft disrupting ability of CD derivatives, furthermore to evaluate the possible analgesic effects of the safest and functionally most active CD derivatives in mouse pain models.

Intracortical effects of continuous infrared neural stimulation

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Infrared (IR) neuromodulation is an area of research that has been ongoing for more than a decade. It has shown many experimental results that have consistently confirmed the importance of temperature as a state variable in neuronal function. Many studies have described how it is possible to stimulate or block conduction in peripheral nerve preparations by IR radiation. Because IR stimulation can inhibit neural activity, research so far predicts its use in the treatment of neurodegenerative diseases, such as epilepsy. However, this must be preceded by examinations elucidating the biophysical background of the IR stimulation effect mechanism.

In our experiments, we investigated the effect of brain tissue temperature modulation on cortical activity in rats anesthetized with ketamine/xylazine (n=5). Our system included a flexible electrocorticogram that could measure intracranial EEG signals on at least 32 channels and tissue temperature on at least 8 channels during the acute experiments. In addition, a high-density Neuropixels silicone probe was implanted to obtain neural activity from all cortical layers. The inhibition and excitation of neurons were achieved by spatially localized delivery of IR radiation through an integrated optrode device implanted close to the silicon probe located in the neocortex. This device can also record extracellular electrophysiological signals on 16 channels besides delivering IR light. During the experiments, the continuous IR light was delivered for 4 minutes, then turned off for 4 minutes, and this was repeated 5 times.

To determine the effects of IR neuromodulation, single units were extracted from the high-density cortical recordings from minimum 230 neurons per animal. Changes in the firing rates of single neurons were examined in the five animals during stimulation trials. The temporal change in firing rate was investigated and compared in the superficial and deep cortical layers, and they were compared between subsequent trials as well. In addition, to investigate the changes in neural functions, the percentage of neurons inhibited and excited by IR stimulation was determined in all six cortical layers. We also investigated how the firing rate of different types of neurons, such as pyramidal cells and interneurons, changes during IR stimulation, based on preliminary results. With this analysis, we can obtain more precise information about the propagation of the IR stimulation-evoked signals in the cortex.

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Groups 15

PlatypOUs—A Mobile Robot Platform and Demonstration Tool Supporting STEM Education

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Introduction: in an interdisciplinary project, students at Semmelweis University and Óbuda University developed a mobile robot platform that uses electrophysiological signals as control instructions. The aim of the project was to create a mobile robot system for educational purposes (to be featured in a robot operating system programming course at Óbuda University) and to facilitate interaction between different research fields (robotics and health sciences) and students from different levels of education (i.e. from bachelor's to doctoral studies).

Methods: the hardware is based on an Intel mini-PC, has differentially driven wheels and is equipped with wheel encoders, a LIDAR, a depth camera and an inertial measurement unit (containing an accelerometer and a gyroscope). As signal acquisition device, a portable wireless electroencephalography headset (a MindRove arc) is utilized. The robot can be controlled to make a 90° turn to the right, to go forward or stop. A graphical user interface collects sample sequences corresponding to each command and trains a support vector machine-based classifier to differentiate between the samples.

Results: regarding sample prediction accuracy (during preliminary tests), our system could achieve 86.67%; in a real-world pattern following task, an average error of 12.39% was encountered.

Conclusion: The initial tests have deemed our proof-of-concept system useable but further validation is required to prove its real-world feasibility.

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Deep learning-based spike sorting on edge TPU

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The ever-increasing number of recording sites of silicon-based probes imposes a great challenge for detecting and evaluating single-unit activities in an accurate and efficient manner. Currently separate solutions are available for high precision offline evaluation and separate solutions for embedded systems where computational resources are more limited.

We propose a spike sorting system that is deep learning based, utilizing both unsupervised and supervised paradigms to learn a general feature embedding space and be able to detect neural activity in raw data and predict their feature vector for sorting. The proposed system is built in such a unique way that the model can be trained on multiple, versatile datasets at once, offering greater generalizability than previous deep-learning-based models.

We demonstrate that the proposed model does not only reaches the accuracy of current state-of-art offline spike sorting methods, but has the unique potential of being able to run on artificial intelligence specific chips designed for edge computing (edge TPUs). The herein demonstrated system paves the way to the integration of deep learning-based spike sorting algorithms into wearable electronic devices, which will be a crucial element of high-end brain-computer interfaces.

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Automated eye-blink artefact removal from electroencephalogram (EEG) recordings using image processing techniques

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Introduction: Cortical electrical activity is captured by electroencephalogram (EEG) measurements. It can be beneficial for a deeper understanding of many neurological and psychiatric disorders. Our research focuses on eye-blink artefact removal and automated filtering during the pre-processing of EEG recordings that were taken on both healthy people and neurological or psychiatric patients.

Methods: In order to identify the origin of the eye-blink artefact on topoplots, independent component analysis (ICA) was first applied. These artefact components from the topoplots, which primary source is in the frontal lobe, have to be removed in the following stages. With this selection, the position of the source as well as the direction of the frontlines originating from the source were both taken into consideration. This was accomplished by implementing image processing techniques.

Results: Our method allowed the objective filtering of eye-blink components and their automated elimination in the open-source MNE-Python environment, which is able to see and analyze neurophysiological data, without the arbitrary setting of subjective thresholds. 60 EEG samples were used to test the program, and of them, 44 (73.3%) had all undesired artefacts totally eliminated. In the remaining recordings, blinking was only partially filtered out in 11 instances (18.3%) and the program made a mistake in choosing the right noise component in 5 instances (8.3%).

Discussion: According to our first results, the method's basic idea is acceptable, and the software can be usable, but it still needs to be improved. We want to increase the efficiency of the current software to at least 90%. We think that by using our software, we can process EEG signals much more quickly and minimize subjective inaccuracies brought on by the previously partly manual pre-processing.

Development of an automated behavioral training framework for cats

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For decades, human vision has been modeled with cats, a large-animal species having sharp vision and a rich spectrum of eye motions. In behavioral experiments, training and readout requires unbiased and efficient protocols. We revisit a classical behavioral setup, the jump stand, used to test visual behavior in cats. We build an automated, data-rich jump-stand environment for testing visual functions. Several sensors and actuators are used to interact with the subject. Our immediate goal is to determine the visual acuity of healthy and deprived cats in a two-alternative forced choice task. Our results may reintroduce a docile, highly visual large-animal species offering a rich, controllable behavioral repertoire.

Developing a portable, customizable, single-channel EEG device for homecare and validating it against a commercial EEG device

Máté Tóth

(Abstract not provided.)

Group 16

The Lateral Septum and its multifaceted role in anxiety.

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The Lateral Septum (LS) plays an important role in controlling emotional states such as anxiety, aggression, and also controls social behaviors, presumably in a sex-dependent manner. Despite the relatively sizeable amount of experimental data supporting these LS functions, the mechanistic understanding of how LS regulates these processes is hindered by a series of contradicting results. Although the LS is thought to contain exclusively GABAergic cells, we found that a fraction of LS cells express cholinergic neuronal markers. In this study, we try to understand the function of this specific neuronal population named LS cholinergic cells (LSCNs), using LSCN-specific viral expression of optogenetic actuators combined with behavioral testing.

Using the Open Field Test and the Light-dark Box to assess anxiety levels, our preliminary results show that stimulation of the LSCNs has an anxiogenic effect in male, and an anxiolytic effect in female mice, which might explain contradictory results in existing literature regarding LS function. Since traditional fiber optogenetics obstruct the usability of other paradigms, such as the Elevated Plus Maze or sociability tests, due to physical constraints on the animals exerted by optic cables, we started to adopt wireless optogenetics to overcome this limitation. In the future, we aim to expand our investigations with an array of techniques, including optogenetic inhibition, fiber photometry, electrophysiology, and anatomy in order to better understand this critical yet enigmatic structure.

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Excessive fructose intake aggravates inflammation and may lead to brain damage in a mouse model of obesity

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Western diet increases the prevalence of obesity, which is an important risk factor for many chronic diseases. White adipose tissue secretes pro-inflammatory cytokines and adipokines leading to a low-grade, systemic inflammation. This phenomenon seems to have a key role in the development of different diseases, however the cellular and molecular mechanisms are not completely understood. In this study we show that high-fat diet (HFD) induces inflammation and metabolic alterations throughout the body, and that the symptoms are particularly severe when the HFD is combined with increased fructose intake (HFD+F).

During the experiment, we used three groups of mice: an HFD-fed group, an HFD+F-fed group, and a normal chow-fed control group. Body weight of the HFD-fed mice was significantly higher than that of the control animals, however this increase was even greater in the HFD+F group. We found similar changes in liver weight, while we confirmed the hepatic steatosis by hematoxilyn-eosin staining. Moreover, signs of glucose intolerance were only seen in mice fed with HFD+F. Using qPCR we showed, that gene expression levels of certain pro-inflammatory cytokines were elevated in response to HFD, showing an even higher increase in the HFD+F mice. Interestingly, doublecortin immunostaining of brain sections revealed a strong increase in neurogenesis in the case of certain animals treated with HFD+F. Possibly this process is a compensatory mechanism responding to a diet-induced brain damage, which could explain the lower brain weight in the HFD+F group.

Our findings confirm that obesity negatively affects the function of several organs; not only the white adipose tissue, but also the liver and the brain. In addition, the Western diet, which is a combination of high-fat and high-fructose intake, leads to more severe inflammation and metabolic disturbances. Our research may contribute to the better understanding of the cellular and molecular mechanisms behind the harmful effects of our lifestyle, which may facilitate the therapeutic treatment of obesity-related disorders in the future.

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Unexpected effects of neuropeptide QRFP administration into the lateral hypothalamic area

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Severe feeding disorders, such as overweight, obesity and, on the other hand, anorexia, are getting progressively spread all over the world. Understanding the complex hunger/satiety regulating mechanism has a crucial role in the management of these metabolic disturbances.

RFamide-related peptides are known to be involved in the regulation of feeding and body weight in rodents, avians, and humans. The pyroglutamylated RFamide peptide (referred to as QRFP) acts as an endogenous ligand of the previously orphan G protein-coupled receptor GPR103. By means of immunohistochemical methods QRFP synthesizing neurons and binding sites were identified in the hypothalamus, an important feeding regulation center. Previous data suggest that QRFP has a tendency to increase food consumption following i.c.v. administration, especially intake of food with high-fat content.

In our experiment male Wistar rats received microinjections of QRFP (100, 200 ng) or an equimolar dose of neuropeptide Y1/neuropeptide FF receptor antagonist BIBP 3226 into the lateral hypothalamic area (LHA). Following the treatment, liquid food (milk) intake was measured over a 60-minute period. QRFP administration into the LHA decreased food consumption, while receptor antagonist BIBP 3226 prevented the anorexigenic effect of the peptide.

These findings indicate that QRFP acts directly on the hypothalamic NPY and NPFF systems to modify feeding and mechanisms of hunger and satiety.

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Thalamocortical circuits in motor learning

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The thalamus has been classically seen as the final relay station of sensory information toward the cortex. Recent knowledge however suggests that it is actively involved in cortical functions. All cortical areas receive thalamic input, which carries not only sensory information but is essential for maintaining cortical function. The role of thalamocortical circuits has been demonstrated in many cortical computations.

Thalamic inputs are divided into driver and modulator types. The basis for this division is their effects on relay cells. These inputs differ in many properties, such as size, site of origin, electrophysiological properties and electron microscopic structure. Many thalamic nuclei receive driver inputs from layer 5 pyramidal cells of the cortex (L5) and modulator inputs from L6. The properties and effects, of drivers with cortical origin, have only been investigated in sensory areas.

The influence of frontal cortical areas on the thalamus, which plays a central role in the preparation and learning of goal-directed movements, is still poorly understood. In our study, we investigated the morphology and behavioral impact of L5 driver inputs from the secondary motor cortex (M2) in the ventromedial nucleus (VM).

To investigate the anatomy of the pathway, we injected GFP-containing virus into RBP4-cre mice (L5-specific strain), in the M2 and primary sensory cortical area (S1) and measured the maximum cross-sectional area of the boutons in the VM and posterior nucleus area on confocal images. Boutons originating from the M2 were significantly smaller, compared to those of S1 origin.

To investigate the effect of the pathway on behavior, we injected ArchT-containing virus into the M2 region of RBP4-cre mice and axon terminals were inhibited in the VM region. The effect of L5 inhibition in VM was investigated in open field, in place aversion test, and during locomotion training on a horizontal wheel.

Inhibition of the pathway did not affect the animals' movement in open field and didn’t provoke place aversion. On the other hand, animals receiving L5 inhibition in VM spent less time on the wheel, proportionately less time running and their average speed was lower at the end of the learning period.

These data show that M2 L5-VM corticothalamic pathway is morphologically distinct from those in sensory areas and is required for motor learning. This raises the possibility of synaptic plasticity in this connection.

Group 17

The effect of migraine on visually and multisensory guided associative learning and related memory processes in childhood

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Cognitive performance may deteriorate during migraine attacks, but little is known about the long-term effects of the disease on cognitive functions. In our work, we aimed to compare the visually and audio-visually guided associative learning abilities of pediatric patients suffering from migraine.

In our research the visually guided Rutgers' acquired equivalence learning test, as well as our self-developed audiovisual so-called the Sound Face test were used to investigate association learning in pediatric migraineurs. The performance in the learning phase, where feedback-based matching of different images or images and sounds has to be mastered, depends primarily on the functioning of the basal ganglia frontal cortex loop pathways. The test phase, when already learned pairs must be recalled without feedback, or new pairs must be inferred based on previous associations (generalization), is primarily related to the functioning of the hippocampus-mediotemporal lobe. Error ratios in the different stages of the task (learning, recall, generalization) and the number of repetitions required for learning were examined and measured. In our study, we used the results of 30 children with migraine and 30 healthy children matched in age, gender and intelligence.

The population of migraineurs does not perform worse in any of the studied learning parameters, neither in the visual nor in the audiovisual test, compared to the control group. In contrast, the children in the control group formed associations more efficiently ($p=0.006$) and learned the pairings with fewer repetitions ($p=0.002$) in the multisensory paradigm than in the visual paradigm. However, this multisensory facilitation was not observed in the migraine group.

In our previous studies on an adult population, patients with migraine showed significantly worse performance in the learning and generalization stages of the visually guided test compared to healthy controls. However, we did not find such a clear correlation in the case of children with migraine either during the visually or audio-visually guided equivalence learning. However, the multisensory facilitation described in the control group of healthy children is absent in children with migraine, which may be a sign of the beginning of cognitive changes already expressed in adulthood.

Ethical permit: Reg. No. 27/2020-SZTE

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Resting-state functional connectivity correlates of mental fatigue

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Mental fatigue arises during prolonged cognitively-taxing tasks, leading to performance decrements, time-on-task effects (ToT), and declines through rest or incentives. Although mental fatigue is ubiquitously experienced in daily life and its adverse consequences are documented in a variety of settings, its neurocognitive correlates remain uncertain. This study used the prolonged version of the psychomotor vigilance task (PVT) to induce fatigue and resting-state functional MRI (rs-fMRI) to investigate functional connectivity (FC) correlates of the ToT effect and the motivation effect (monetarily rewarding participants after fatigue induction) in 74 healthy young adults. Fatigue scores (change in mean reaction times between the blocks of PVT) were extracted as a measure of overall performance. Fatigue-resistant (n=25) and fatigue-sensitive (n=24) subjects were separated based on fatigue scores. A data-driven, multi-variate pattern analysis (MVPA) was used to derive suitable seeds (4) for later seed-to-voxel analysis -post hoc analysis- to analyze FC patterns. Behaviourally, subjects showed strong ToT drops in performance, as assessed by increasing reaction times as the test progressed. Extra monetary reward positively affected PVT performance in fatigued subjects. Our rs-fMRI results showed changes in FC in task-related brain regions and non-related regions. Specifically, we found TOT-related connectivity changes between the first two seed regions and areas in the frontal, parietal and temporal regions indicative of sensorimotor and cognitive systems, as well as in the insula and anterior cingulate cortex. Increased connectivity between our first seed and the dorsolateral prefrontal cortex was positively correlated with performance improvement due to the reward effect.

Early language intervention and IQ of children with non-syndromic oral clefts

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Introduction: Children with non-syndromic oral clefts are at higher risk for developmental difficulties, and speech and language are commonly affected developmental domains. The aim of the current study was to explore if early interventions for language and speech have positive effects on later cognitive outcomes in this patient population.

Methods: A combined retrospective/prospective-comparative study was carried out at the Department of Pediatrics of the University of Pécs (Hungary). The participants were between 6 and 16 years old. The study consisted of a self-designed demographic questionnaire and an IQ test (WISC-IV).

Results: A total of 41 children with non-syndromic oral clefts and 44 age-matched controls participated in the study. Children of the cleft group were examined by pedagogical professional services and required special education plans significantly more often than controls ($p<.001$ and $p=.02$, respectively). Participants of the cleft group who received early speech and language therapy score higher on the Verbal Comprehension Index ($p=.005$). Full-Scale IQ score was also higher for cleft participants who received therapy, however not significant but borderline ($p=.08$).

Conclusion: Early language and speech interventions for children with non-syndromic oral clefts may have a positive effect on verbal skills and overall cognitive development. Children with oral clefts with atypical developmental patterns seem to catch-up with their peers and perform similarly next to well-timed early interventional programs. Future longitudinal studies examining baseline cognitive functioning of infants are needed to provide a more conclusive evidence of the effects of interventional programs on language development in these patients.

Group 18

Spatial profile of calcium transients evoked by backpropagating action potential in human cortical pyramidal dendrites.

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Backpropagating action potentials play important role in synaptic plasticity, dendritic excitability and compartment specific intracellular Ca2+ dynamics. Signal propagation in human dendrites shows potentially species and dendritic region specific properties and we asked whether action potential backpropagation in human dendrites follows a uniform or a segment regulated pattern. We studied human cortical layer 2/3 pyramidal apical dendrites in acute brain slices with somatic whole-cell stimulation and simultaneous dendritic two-photon Ca2+ imaging. Single action potentials produced detectable Ca2+ influx in segments of apical dendrites up to 270 µm from the soma of human pyramidal neurons. Evoked Ca2+ signals showed a stereotyped spatial profile along dendrites: the amplitude of the Ca2+ transients increased with distance from the soma, reached the maximum level on the dendritic region 50-100 µm from the soma then decreased towards the distal dendritic regions of primary and higher order dendrites. Non-specific blockage of Ca2+ channels and blockade of voltage-gated Na+ channels significantly reduced and completely abolished Ca2+ transients, respectively. Various Ca2+ channel types contributed to the Ca2+ signals as shown by selective blockade with N-type, L-type, T-type, or R-type Ca2+ channel subtypes. These results suggest a booster region in primary dendrites of human pyramidal cells for backpropagation induced Ca2+ influx in the dendritic tree.

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Microglial behaviour in acute slice preparations

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Microglia, the main immune cells of the central nervous system (CNS) have long been known for their remarkable sensitivity to tissue disturbance or injury, but its implications to the interpretation of results from ex vivo models of the CNS have remained largely unclear to date. To this end, we have followed the course of microglial phenotype changes and contribution to neuronal network organisation and functioning in acute brain slices prepared from mice, widely used to study the physiology of the brain from nanoscale events to complex circuits. We found that upon acute slice preparation, microglial cell bodies dislocate and migrate towards the surface of slices, alongside with rapidly progressing morphological changes and altered interactions with neurons. This is accompanied by gradual depolarization and downregulation of P2Y12 receptors, which are instrumental for microglia-neuron communication. Quantitative post-embedding immunofluorescent labelling reveals time-dependent increase in the number of excitatory and inhibitory synapses upon slice preparation in the cerebral cortex, which are markedly influenced by microglia. In line with this, the absence of microglia diminishes the incidence, amplitude and frequency of sharp wave-ripple activity in hippocampal slices. Collectively, our data suggest that microglia are not only inherent modulators of complex neuronal networks, but their specific actions on network reorganisation and functioning must be taken into account when learning lessons from ex vivo models of the CNS.

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Modelling the intracellular biochemical mechanisms of long-term potentiation in a CA1 pyramidal cell spine head

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Hippocampal CA1 pyramidal neurons are one of the most comprehensively studied cell types in connection with synaptic plasticity, the underlying mechanism of learning and memory. Synaptic plasticity is the activity-dependent modification of the strength of synaptic transmission. The most extensively studied form of plasticity is long-term potentiation (LTP); the long-lasting increase in the strength of synapses that lasts from hours to days, or even longer.

Besides the biophysical features of neurons, intracellular biochemical signaling pathways also contribute to the formation of complex neuronal functions such as synaptic plasticity. A detailed computational model of plasticity-related subcellular signaling cascades was used to investigate the underlying molecular machinery of LTP. The model contains the main signaling pathways that were reported to take part in the formation, maintenance, and expression of hippocampal LTP: the calcium/calmodulin-dependent protein kinase II (CaMKII), the protein kinase A (PKA) and the protein kinase C (PKC) cascades. Parameters of the model were fit to experimental data derived from hippocampal Schaffer collateral synapses. The parameters were optimized with the Neuroptimus optimization software using the Neuroscience Gateway (NSG) which enablesthe access and usage of high-performance supercomputers containing popular computational neuroscience tools and environments. The fitted models describe the experimental data properly, making possible further investigations.

The expression of synaptic plasticity often emerges as changes regarding the total synaptic conductance of AMPA receptors that is determined by the subunit composition, the phosphorylation state, and the number of these receptors in the synaptically active membrane. The induction of the subcellular cascades results in altered total AMPA receptor conductance which can be investigated at the level of subunits and affecting molecules. After the analysis of the fitted models, different components were identified that shape LTP. These components act on different timescales using various mechanisms mediated by the interactions of the cascades.

The detailed biochemical model can be used to study the mechanisms of different forms of plasticity, the roles and contributions of the molecular pathways, individual molecular species, and the effects of different induction protocols and various neuromodulations.

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Automated and systematic validation of models of hippocampal neurons against electrophysiological data

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Anatomically and biophysically detailed data-driven neuronal models are useful tools in understanding and predicting the function of the different cell types of the brain. However, most of these models have been built to capture a few selected properties of the real neuron, and it is often unknown how they would behave under different circumstances, or whether they can be used to successfully answer different scientific questions. The collaborative approach of model development requires extensive validation test suites which enables modelers to evaluate their models against experimental observations according to standardized criteria and to explore the changes in model behavior at the different stages of its development. Applying automated tests also facilitates optimal model re-use and co-operative model development by making it possible to learn more about models published by other groups with relatively little effort.

Initially we addressed this issue by developing an open-source Python test suite, called HippoUnit (Sáray et al., 2021; github.com/KaliLab/hippounit) for the automated and systematic validation and quantitative comparison of the behavior of models of the hippocampal CA1 pyramidal cells against electrophysiological data. We applied HippoUnit to test and compare the behavior of several different hippocampal CA1 pyramidal cell models available on ModelDB (github.com/KaliLab/HippoUnit_demo).

Currently we are extending this test suite by adding new tests for the validation of other important hippocampal cell types. These cover the somatic behavior and signal propagation in dendrites of basket cells and CA3 pyramidal cells. We are also developing further tests for the CA1 pyramidal cells, including one that validates the Ca2+ spikes triggered in the apical dendrites by synaptic inputs, and the burst firing induced by them on the soma. Furthermore, to broaden the range of neuronal behaviors that can be targeted during automated fitting of model parameters we are integrating the tests of HippoUnit into our open-source neural parameter optimization tool, Neuroptimus (formerly Optimizer - github.com/KaliLab/optimizer) as cost functions during optimization.

By presenting these results we hope to encourage the modeling community to use more systematic testing during model development, in order to create neural models that generalize better, and make the process of model building more reproducible and transparent.

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Group 19

Mapping Mossy cells Synaptic Projections

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Intro: mossy cells are the major excitatory cellular group in the hilus of the hippocampus. They have immense longitudinal connections with the granule cells (GC) and interneurons of the dentate gyrus (DG), hence, they play a key role in the DG function and circuitry. Additionally, mossy cells can project to local GCs and distant ones, and these may contribute differently to hippocampal functions. Therefore, the precise mapping of mossy cells projections to individual neurons is essential to reveal how these enigmatic cells contribute to associative memory function and temporal epilepsy.

Aims: Using all-optical recordings and specific viral strategy we aim to extensively investigate local, ipsi- and contralateral projections of mossy cells in the dorsal and ventral hippocampus.

Methods: In order to map projections' specific connections, we will use a viral strategy to express Channelrhodopsin in a spatially restricted population of mossy cells and their axons. These axons will be stimulated optogenetically in a rat brain slice, where DG neurons express Voltron, a genetically encoded voltage indicator. The Voltron will enable us to detect postsynaptic connections in response to Channelrhodopsin-mediated stimulation of mossy cell axons in the region.

Temporal disparity of action potentials triggered in axon initial segments and distal axons in the neocortex

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Neural population activity determines the timing of synaptic inputs, which arrive to dendrites, cell bodies and axon initial segments (AISs) of cortical neurons. Action potentials in the AIS (AISAPs) are driven by input integration, and the phase preference of AISAPs during network oscillations is characteristic to cell classes. Distal regions of cortical axons do not receive synaptic inputs, yet experimental induction protocols can trigger retroaxonal action potentials (RAAPs) in axons distal from the soma. We report spontaneously occurring RAAPs in human and rodent cortical interneurons that appear uncorrelated to inputs and population activity. Network linked triggering of AISAPs versus network independent timing of RAAPs of the same interneurons result in disparate temporal contribution of a single cell to in vivo network operation through perisomatic and distal axonal firing.

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Investigating the role spines play in synaptic integration

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The dendrites of cortical pyramidal cells bear spines which receive most of the excitatory synaptic input, act as separate electrical and biochemical compartments, and play important roles in signal integration and plasticity. In this study, we aimed to develop fully active models of hippocampal pyramidal neurons including spines to analyze the contributions of nonlinear processes in spines and dendrites to signal integration and bursting.

We developed morphologically and biophysically detailed models of CA1 pyramidal cells. We considered multiple attributes of the cell determined by experiments, including the biophysics and distribution of ion channels, as well as the different electrophysiological characteristics of the soma and the dendrites. For systematic model development, we used two software tools developed in our lab: the Neuroptimus software for the automated parameter fitting, and the HippoUnit package to validate these results.

We also investigated ways to reduce the computational complexity of models of spiny neurons without altering their functional properties. In the optimized models we did not explicitly model dendritic spines but adjusted the membrane properties with a surface-correction factor (F-factor) that takes into account the membrane area of the spines.

To explore the role of spines in dendritic behavior, synaptic integration and somatic bursting we compared three different cases with the help of the HippoUnit's Oblique Integration and Pathway Interaction tests: the original optimized models where we only used the F-factor, then we explicitly modelled those spines that receive excitatory synapse, moved the synapses to the spine heads, while the rest of the spines were implicitly taken into account by appropriate changes in the membrane properties using the F-factor. Last, we explicitly modelled all spines that exists on our morphology, and excitatory synapses were connected to the spine heads in that case as well. We also investigated the effect of active and passive spines, leading to 6 individual cases on 20 optimized models.

This approach enables a comprehensive computational investigation of the role spines play in synaptic integration, the possible mechanisms underlying dendritic spikes and activity-dependent synaptic plasticity in hippocampal pyramidal neurons.

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Electrophysiological performance of flexible polymer-based neural probes in acute rodent experiments

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In this study, we developed two types of single-shank polyimide-based neural probes with different recording site layouts and validated their acute electrophysiological performance in rodent models. These flexible spiral probes have a 3.9-mm-long, 75 to 300-µm-wide and 10-µm-thick tapered, implantable shank which contains 24 linearly placed gold microelectrodes with a diameter of 20 µm and center-to-center distance of 150 µm. Two probe variants (edge-site layout with recording sites located at the edge of the probe shank, and center-site layout with sites placed in the middle of the shank) were fabricated to assess and compare their electrophysiological performance. The probes could be connected via a Zero Insertion Force (ZIF) connector and a custom-made ZIF-to-Omnetics adaptor to the Intan RHD2000 recording system. Impedance measurements performed in vitro in physiological saline solution showed that the recording sites had an average impedance magnitude of 221 kΩ at 1 kHz (n=117 sites). To compare the signal quality provided by the two probe variants (edge vs. center), we implanted them into neocortical and hippocampal areas of anesthetized rats and mice. To aid the insertion of the flexible probes into the brain tissue, on the one hand, we removed the dura mater over the targeted brain area. On the other hand, the probe shank was either fixed to a silicon shuttle using a small amount of polyethylene glycol, or was inserted without a shuttle but after cutting a small opening into the pia mater. During the acute in vivo experiments, we recorded good-quality local field potentials (LFPs) as well as single- and multi-unit activity with both probe types. In terms of LFPs, we were able to monitor cortical slow waves and hippocampal gamma activity with the implant. Furthermore, in both animal models, we detected spike amplitudes over 100 µV and recorded the activity of multiple well-isolated single units simultaneously. A detailed comparison of the signals recorded with the two probe types will be presented, including the single unit yield, spike amplitude and signal stability. Our future plans are to chronically implant the polyimide probes in rodents to evaluate their long-term electrophysiological performance as well as the brain tissue response in the vicinity of the probe shank.

The research leading to these results has received funding from the Hungarian National Research,Development and Innovation Office (PD134196 to R.F., TUDFO/51757-1/2019-ITM to R.F. and I.U.) and from the Deutsche Forschungsgemeinschaft (DFG, Grant EXC 1086 to P.R.). B.Á. is was supported by the New National Excellence Program of the Ministry for Innovation and Technology (ÚNKP-22-1-I-PPKE-59). R.F. was supported by the Bolyai János Scholarship of the Hungarian Academy of Sciences.

Workshops

Workshop 1: Career Forum

Am I prepared for a career in neuroscience? What are the ups and downs of this life? Should I choose academic or industrial research? How much will I earn? Do I have the chance to have a family?

Should I consider working abroad?

If You ever wondered about any of these questions, then the career forum is for You. In this workshop, invited speakers of different scientific backgrounds and at different career stages will share their insight and experience in a less formal manner.

Participants are encouraged to ask relevant questions directly from the speakers during the forum. Questions can also be submitted anonymously before the conference via a google form that can be found **here**.

Get to know our invited speakers below!

Dr. Balázs Hangya - Having the vague idea of being interested in human genetics, I decided to submit my application to the med school after my highschool years. Throughout my first year I learned two things: first, modern genetics was not really what I imagined - something like Mendel growing peas in the monastery garden. Second, I was missing math, more precisely, the need of using logic and reason - med school impressed me more like an extensive declarative memory exercise. Thus, I enrolled in the math program (then a 5-year program, before the introduction of BS and MS) in parallel with the med school. While intensive, I really enjoyed this, and soon found myself performing undergrad research ('TDK') in a neuroscience lab where data analysis (would be called data science these days) expertise was needed.

From here, my academic path was relatively straightforward: after graduating from med school, I started a PhD in neuroscience (while finishing the math program with a specialization in probability theory and statistics). I then spent nearly five years as a postdoc at Cold Spring Harbor Laboratory in the US, to return to Hungary as a young PI in 2016, when I established my lab with support from the Academy (Momentum starting grant) and the EU (ERC Starting Grant). Eight years into independence, I'm considered a so-called 'mid-career' neuroscientist...

Dr. Zoltán Varga - I started my studies as a biologist student due to my affection for wildlife. At the university, I found out that the core of such interest is more about understanding complex phenomena piece by piece than fandom for a particular animal species. This realization has led me to experimental research, and my faculty's focus has led me to behavioural science. One of my teachers told me that if I want both of these, that is what they call neuroscience, and he has contacts with KOKI if I am interested.

I have worked at KOKI on stress neurobiology from undergrad to postdoc. In the last 13 years, I had fewer grants than submissions and fewer papers than projects, but I'm still rather motivated than burned out and feel I have the best job on earth. Despite being satisfied with my career, I am

considering a postdoc position abroad and moving with my family, which is frankly terrifying. I am really into destructive topics like "from what point is it considered pathological to fear the change", "do I need to be a top scientist to be happy", or the classical "science is broken, it has to be repaired".

Márton Mayer - I have a bachelor's degree in Biology from the University of Veterinary Medicine and a master's degree in Neurosciences from Eötvös Loránd University. In the beginning of my studies, I joined the Institute of Experimental Medicine and started working as a student researcher. I spent a large part of my time in the lab contributing to significant scientific discoveries and successful research projects. After graduation, I decided to continue as a PhD student, so I began to work more independently on the topic of my doctoral program, studying the cholinergic system.

After years of scientific research as a full-time job, recently I made a sharp turn and started working as an application scientist at a company developing medical devices. Currently, my aim is to finish my thesis and doctoral studies and to pursue a career in the healthtech industry.

Dr. Viktor Kis - Throughout my life, I have been guided by two things: learning new things and then passing them on to others. The love of learning and reading was instilled in me by my maternal grandfather when I was a small child. Teaching, and through this, the feeling of self-efficacy, that I am able to convey my knowledge to others in an understandable and enjoyable way touched me when I was in high school. This way of thinking has accompanied me throughout my life so far.

I graduated from Eötvös Loránd University in 2009 as a biologist. From 2009 to 2018, I initially worked at ELTE and later at the Institute of Experimental Medicine (KOKI) as a teacher and researcher. I taught for seven years, and during that time I had the pleasure of teaching more than a thousand students. After the academic world, my interest gradually shifted towards business, consultancy and psychology. I worked as a sales representative at Unicam Hungary Ltd. for 3 years. I was responsible for the sales, support and installation of state of art Hitachi electron microscopes in Hungary. Meanwhile I completed the mental health specialist postgraduate course at Semmelweis University.

The fact that I changed my career plans many times reflects my proactive approach, that I realized that I need to develop in the areas mentioned above in order to be able to flourish in my life. These changes were often difficult, but at the same time I gained a lot of knowledge and experience, which made me very tough and resilient.

Workshop 2: Mental Health

Dr. Viktor Kis - What makes you bulletproof? - How to cope with stress using resilience?

In my talk, I will present the mental superpower called resilience. I will discuss in detail the characteristics of the resilient character, and the so-called resilience competencies. The most important message of my talk is that the resilience competencies are built on each other, their order is not accidental, and that these competencies can be developed.