JOINT NEUROSCIENCE MEETING OF THE HUNGARIAN NEUROSCIENCE SOCIETY (MITT) & THE AUSTRIAN NEUROSCIENCE ASSOCIATION (ANA)

2023

DETAILED PROGRAM AND POSTER ABSTRACT BOOK

1-3 FEBRUARY, 2023, BUDAPEST

Detailed Program

Wed, 1 Feb 2023

09:15 - 09:30 Opening ceremony (Isabella Sarto-Jackson and Zoltán Nusser)

09:30 - 10:30 Plenary lecture I.

Marlene Bartos (Albert Ludwigs Universität Freiburg Institute for Physiology, Department of Physiology, Freiburg, Germany)

DENTATE GYRUS CIRCUITS FOR ENCODING, RETRIEVAL AND DISCRIMINATION OF EPISODIC MEMORIES

10:30 – 11:10 Coffee break

11:10 – 12:55 Symposium I.

NEURAL CONTROL OF SOCIAL BEHAVIOR

Chair: Arpad Dobolyi

(Department of Physiology and Neurobiology, Eötvös Loránd University, Budapest, Hungary) Shlomo Wagner

(Department of Neurobiology, Faculty of Natural Sciences, University of Haifa, Haifa, Israel) NEURAL CORRELATES OF SOCIAL DECISION MAKING IN MICE

Árpád Dobolyi

(Department of Physiology and Neurobiology, Eötvös Loránd University, Budapest, Hungary) THE CONTROL OF SOCIAL BEHAVIOURS BY THALAMO-PREOPTIC PROJECTIONS

Françoise Muscatelli

(Laboratory of Perinatal Imprintings and Neurodevelopmental Disorders, Institut de Neurobiologie de la Méditerranée (INMED)-INSERM, Marseille, France)

EARLY LIFE OXYTOCIN IMPRINTING SHAPES THE NORMAL AND PATHOLOGICAL SOCIAL BRAIN

Attila Tóth

(Department of Physiology and Neurobiology, Eötvös Loránd University, Budapest, Hungary) SLEEPING MOTHERS – SLEEP AND WAKEFULNESS DURING THE REPRODUCTIVE CYCLE IN FEMALE RATS

Petra Varró

(Department of Physiology and Neurobiology, Eötvös Loránd University, Budapest, Hungary) FUNCTIONAL ALTERATIONS OF CORTICAL NETWORKS IN A RAT MODEL OF AUTISM

12:55 – 13:55 Lunch

13:55 – 15:40 Symposium II.

NEUROMODULATION OF NEURONAL NETWORKS IN COGNITION AND BEHAVIOR

Chairs: Balazs Hangya (Institute of Experimental Medicine, Budapest, Hungary) & Sarah Melzer (Medical University Vienna, Center for Brain Research, Vienna, Austria) **Armin Lak**

(Oxford University, Department of Physiology, Anatomy and Genetics, Oxford, UK) DOPAMINERGIC CIRCUITS FOR PERCEPTUAL DECISIONS

Isabel Beets

(KU Leuven, Animal Physiology and Neurobiology, Leuven, Belgium) DECODING THE NEUROPEPTIDERGIC CONNECTOME AND MODULATION OF LEARNING IN *C. ELEGANS*

Sarah Melzer

(Medical University Vienna, Center for Brain Research, Vienna, Austria) NEUROPEPTIDERGIC MODULATION OF CORTICAL CIRCUITS FOR FEAR MEMORY Tommaso Patriarchi

(University of Zürich, Institute of Pharmacology and Toxicology, Zürich, Switzerland) A NEXT-GENERATION OPTICAL TOOLKIT TO STUDY NEUROMODULATORY FUNCTIONS AND SIGNALING

15:40-18:00 Posters and Coffee

(in which the coffee will be available e.g. from 15:40 - 16:40)

18:00 – 19:00 Plenary Lecture II: Buzsaki lecture

Adam Kepecs (Washington University School of Medicine, Department of Neuroscience, Washington, USA)

A CROSS-SPECIES APPROACH TO THE NEURAL BASIS OF EMPATHY AND PROSOCIALITY

Thu, 2 Feb 2023

09:30 - 10:30 Plenary lecture III.

Christian Keysers (Netherlands Institute for Neuroscience and University of Amsterdam, Netherlands) A CROSS-SPECIES APPROACH TO THE NEURAL BASIS OF EMPATHY AND PROSOCIALITY

10:30 – 11:10 Coffee break

11:10 – 12:55 Symposium III.

COMPUTATIONAL PRINCIPLES OF NEURAL CIRCUITS

Chairs: Wiktor Młynarski (Institute of Science and Technology Austria, Klosterneuburg, Austria) & Balazs Ujfalussy (Institute of Experimental Medicine, Department of Biological Computation, Budapest, Hungary)

Wiktor Młynarski

(Institute of Science and Technology Austria, Klosterneuburg, Austria) SHARED COMPUTATIONAL PRINCIPLES OF SENSORY ADAPTATION AND ATTENTIONAL MODULATION

Gergő Orbán

(Computational Systems Neuroscience Lab, Wigner Research Centre, Budapest, Hungary)

GEOMETRY OF TASK-REPRESENTATION IN THE VISUAL CORTEX

Jean-Pascal Pfister

(Institute of Neuroinformatics, ETH, Zurich, Switzerland, Department of Physiology, University of Bern, Bern, Switzerland)

NONLINEAR FILTERING AS A UNIFYING PRINCIPLE FOR SYNAPTIC PLASTICITY

Heloisa Chiossi

(Institute of Science and Technology Austria, Klosterneuburg, Austria) HIERARCHICAL VARIABLE REPRESENTATION IN THE HIPPOCAMPUS SUPPORTS COMPLEX TASK LEARNING

Guillaume Hennequin

(Neural Dynamics and Control Group, Computational and Biological Learning Lab, Department of Engineering, University of Cambridge, Cambridge, UK) NEURAL NETWORKS THAT LEARN TO PLAN EXPLAIN HUMAN BEHAVIOR AND HIPPOCAMPAL REPLAY

12:55 – 13:55 Lunch

13:55 – 15:40 Symposium IV.

TIMING IS NOT EVERYTHING: MEDIAL SEPTUM FUNCTIONS BEYOND THETA GENERATIONS

Chairs: Viktor Varga (Subcortical Modulation Research Group, Institute of Experimental Medicine, Budapest, Hungary) & Sanja Mikulovic, (Research Group Cognition and Emotion, Leibniz Institute for Neurobiology, Magdeburg, Germany)

Sanja Mikulovic

(Research Group Cognition and Emotion, Leibniz Institute for Neurobiology, Magdeburg, Germany) WHAT DOES MEDIAL SEPTUM AND THE SONG "I LIKE TO MOVE IT" HAVE IN COMMON?

Peter Petersen

(University of Copenhagen, Copenhagen, Denmark) HOW THE BRAIN NAVIGATES IN SPACE AND TIME: ROLES AND MECHANISMS OF THE THETA RHYTHM

Balazs Hangya

(Lendulet Laboratory of Systems Neuroscience, Institute of Experimental Medicine, Budapest, Hungary)

THE MEDIAL SEPTUM MODULATES HIPPOCAMPAL OSCILLATIONS BEYOND THE THETA RHYTHM

Antal Berenyi

(Lendulet Oscillatory Neuronal Networks Research Group, Department of Physiology, University of Szeged, Szeged, Hungary) NOVEL THERAPEUTIC TARGETS FOR ELECTRICAL STIMULATION IN EPILEPSY – THE MEDIAL SEPTUM AND BEYOND

15:40 – 18:00 Posters and Coffee (in which the coffee will be available e.g. from 15.40 - 16.40)

18:00 – 19:00 Plenary lecture IV.

Otto Loewi Award Lecture

Noelia Urban

(IMBA - Institute of Molecular Biotechnology of the Austrian Academy of Sciences) Local and systemic regulation of adult neurogenesis

Pioneer in Austrian Neuroscience Award 2023

Alois Saria (Medical University Innsbruck)

20:00 – 24:00 Gala dinner

Fri, 3 Feb 2023

09:30 - 10:30 Plenary Lecture V.

Asya Rolls (Rappaport Institute for Medical Research Technion, Israel Institute of Technology, Haifa, Israel) IMMUNOCEPTION: NEURONAL REPRESENTATION AND REGULATION OF IMMUNITY

10:30 – 11:10 Coffee break

11:10 – 12:55 Symposium V. ORAL PRESENTATIONS SELECTED FROM ABSTRACTS

12:55 – 13:55 Lunch

13:55 – 15:40 Symposium VI.

NEURAL CIRCUITS SUPPORTING NETWORK OPERATIONS

Chairs: Bálint Lasztóczi (Division of Cognitive Neurobiology, Center for Brain Research, Medical University of Vienna, Vienna, Austria) and Judit Makara (Laboratory of Neuronal Signaling, Institute of Experimental Medicine, ELRN, Budapest, Hungary)

Judit Makara

(Laboratory of Neuronal Signaling, Institute of Experimental Medicine, ELRN,

Budapest, Hungary)

DENDRITIC CA2+ SPIKES SUPPORT DIVERSE COMPUTATIONS BY HIPPOCAMPAL

PYRAMIDAL CELLS

Márton Rózsa

(MTA-SZTE Research Group for Cortical Microcircuits, Department of Physiology, Anatomy, and Neuroscience, University of Szeged, Szeged, Hungary) TEMPORAL DISPARITY OF ACTION POTENTIALS TRIGGERED IN AXON INITIAL SEGMENTS AND DISTAL AXONS IN THE NEOCORTEX

Jake Watson

(Institute of Science and Technology Austria, Klosterneuburg, Austria) CELL-SPECIFIC WIRING ROUTES INFORMATION FLOW THROUGH HIPPOCAMPAL CA3

Bálint Lasztóczi

(Division of Cognitive Neurobiology, Center for Brain Research, Medical University of Vienna, Vienna, Austria) PATHWAY SPECIFIC REGULATION OF INFORMATION TRANSFER BY HIPPOCAMPAL NEUROGLIAFORM CELLS

15:40 – 18:00 Posters and Coffee

(in which the coffee will be available e.g. from 15.40 - 16.40)

18:00 – 19:00 Plenary lecture VI.

Christine Heim (Berlin)

NEUROBIOLOGICAL CONSEQUENCES OF EARLY-LIFE STRESS: FROM MECHANISMS TO NOVEL APPROACHES FOR THE DEVELOPMENTAL PROGRAMMING OF LIFELONG HEALTH

19:00 – Closing remarks, announcement of poster prize winners

POSTER ABSTRACTS

Day 1 Poster

ID:101

Control of social grooming by a thalamo-preoptic neuronal pathway

Dávid Keller, Tamás Láng, Melinda Cservenák, Gina Puska, János Barna, Veronika Csillag, Imre Farkas, Dóra Zelena, Fanni Dóra, Stephanie Küppers, Lara Barteczko, Ted B. Usdin, Miklós Palkovits, Mazahir T. Hasan, Valery Grinevich, Arpád Dobolyi

Dávid Keller (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology, Budapest, Hungary), (Hungarian Academy of Sciences, Eötvös Loránd Research Network, and Eötvös Loránd University, Department of Physiology and Neurobiology, MTA-ELTE Laboratory of Molecular and System Neurobiology, Budapest, Hungary) Tamás Láng (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology, Budapest, Hungary) Melinda Cservenák (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) Gina Puska (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), (University of Veterinary Medicine Budapest, Department of Ecology, Budapest, Hungary) János Barna (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology, Budapest, Hungary) Veronika Csillag (Institute of Experimental Medicine, Laboratory of Endocrine Neurobiology, Budapest, Hungary) Imre Farkas (Institute of Experimental Medicine, Eötvös Loránd Research Network, Department of Behavioral and Stress Studies, Budapest, Hungary) Dóra Zelena (Institute of Experimental Medicine, Eötvös Loránd Research Network, Department of Behavioral and Stress Studies, Budapest, Hungary), (Institute of Physiology, Medical School, University of Pécs, Szentágothai Research Centre, Centre for Neuroscience, Pécs, Hungary) Fanni Dóra (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology, Budapest, Hungary), (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), (Semmelweis University, Human Brain Tissue Bank, Budapest, Hungary) Stephanie Küppers (Central Institute of Mental Health, University of Heidelberg, Department of Neuropeptide Research in Psychiatry, Mannheim, Germany) Lara Barteczko (Central Institute of Mental Health, University of Heidelberg, Department of Neuropeptide Research in Psychiatry, Mannheim Germany) Ted B. Usdin (National Institute of Mental Health, NIH, Systems Neuroscience Imaging Resource, Bethesda, United States) Miklós Palkovits (Semmelweis Universify, Human Brain Tissue Bank, Budapest, Hungary) Mazahir T. Hasan (Achucarro Basque Center for Neuroscience, Laboratory of Brain Circuits Therapeutics, Leioa, Spain) Valery Grinevich (Central Institute of Mental Health, University of Heidelberg, Department of Neuropeptide Research in Psychiatry, Mannheim, Germany) Arpád Dobolyi (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)

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 areaprojecting 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 Cooperative 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.

Poster ID:201 Effects of cohousing mice and rats on stress levels and the attractiveness of dyadic social interaction in C57BL/6J and CD1 mice and Sprague Dawley rats

Gerald ZERNIG, Hussein GHAREH, Helena BERCHTOLD

Gerald ZERNIG (Medical University Innsbruck, Pharmacology, Innsbruck, Austria) Hussein GHAREH (Medical University Innsbruck, Pharmacology, Innsbruck, Austria) Helena BERCHTOLD (Medical University Innsbruck, Pharmacology, Innsbruck, Austria)

Rats may kill mice. Therefore it is standard practice in many research animal housing facilities – despite often very limited space - to separate mice from rats (i.e., the predators) to minimize stress for the mice. We tested the effect of cohousing on the stress levels of mice from either the C57BL/6J (BL6) or the CD1 strain and Sprague Dawley rats by quantifying their fecal corticosterone and metabolites (FCM) concentration and investigated how cohousing impacts a behavioral assay, i.e., conditioned place preference for mouse-mouse or rat-rat social interaction. Mice from the BL6 strain (but not CD1 mice) that were cohoused with rats had significantly increased FCM concentrations, indicative of higher stress levels. In contrast to their elevated stress levels, the attractiveness for contextual cues associated with mouse-mouse social interaction even increased in rat-cohoused mice, albeit nonsignificantly. Thus, cohousing BL6 mice and rats did not impair a behavior of BL6 mice that had proved to be sensitive to social factors, especially handling by humans, in our laboratory. Our findings suggest that the effect of cohousing rats and mice on their stress levels and behavior might be less clearcut than generally assumed and might be overriden by conditions that cannot be controlled, i.e., different deliveries. Our findings can help to use research animal housing resources more efficiently. Publication: Zernig, Ghareh, Berchtold, 2022, Biology (Basel) 11, 291.

Supported by Austrian Ministry of Science, Research and Economy grant grant BMFWF-80.110/0001-WF/V/3b/2017

Poster

ID:301

Sociogenomic study of the rodent nervous system

Vivien Csikós, Rashmi Kumari, Fanni Dóra, Arpád Dobolyi

Vivien Csikós (Eötvös Loránd University, Department of Physiology and Neurobiology, Molecular and Systems Neurobiology, Budapest, Hungary) Rashmi Kumari (Eötvös Loránd University, Department of Physiology and Neurobiology, Molecular and Systems Neurobiology, Budapest, Hungary) Fanni Dóra (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology, Budapest, Hungary) Arpád Dobolyi (Eötvös Loránd University, Department of Physiology and Neurobiology, Molecular and Systems Neurobiology, Budapest, Hungary) and Neurobiology, Molecular and Systems Neurobiology, Budapest, Hungary)

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 $log2FC > \pm 1$ 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.

Support: New National Excellence Program (ÚNKP 22 3) for VCs, NKFIH OTKA K134221 and MTA NAP2022-I-4/2022 (NAP 3) for AD, and the TKP2020-IKA-05.

Poster ID:102

Different projections from the medial prefrontal cortex inhibit social behaviors

Luca Darai, Dávid Keller, Árpád Dobolyi

Luca Darai (Eötvös Loránd University, Department of Physiology and Neurobiology, Budapest, Hungary) Dávid Keller (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology, Budapest, Hungary), (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) (Eötvös Loránd University, Department of Physiology and Neurobiology, Budapest, Hungary)

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 adenoassociated 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.

Support: HAS NAP2022-I-3/2022 NAP3 and NKFIH OTKA K134221, and EFOP-3.6.3-VEKOP-16-2017-00009.

Poster ID:202

Day 2

Female, but not male, mice favor prosocial choices

Klaudia Misiołek, Marta Klimczak, Magdalena Chrószcz, Łukasz Szumiec, Anna Bryksa, Karolina Przyborowicz, Jan Rodriguez Parkitna, Zofia Harda

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Prosocial behaviors are defined as actions that benefit others. Unlike in humans, where literature is pointing to increased prosociality in women, there are limited data on the effect of sex on prosocial behaviors in laboratory animals. Most rodent studies on empathy have focused on only one sex, several studies examined both females and males, but the results considering sexdifferences appear inconclusive. Therefore, we investigated the frequency of prosocial choices in adult C57BL/6 mice towards familiar conspecific in a food-motivated prosocial choice task, where focal animal chooses between selfish and mutual reward. We found that females, but not males, significantly favor prosocial choices. It was proposed that prosocial behavior is directly motivated by empathy as well as the rewarding effects of social interactions, together termed the "camaraderie effect"1. Hence, to explain the observed sex differences in prosocial behavior, we assessed rewarding effects of social contact in conditioned place preference task and sensitivity to altered emotional state of the conspecific (hungry/relieved vs. neutral) in affective state discrimination task. We observed that females and males similarly prefer to spend time on bedding associated with social cues and prefer to interact with a partner in altered emotional state. Our results provided evidence that propensity for prosocial behavior might be sexdependent in mice and seems to be independent of sensitivity to social reward and empathy-like capacity. Recently, Scheggia and colleagues have shown that prosocial behaviors in mice are highly dependent on sex. However, they observed that male mice are more prosocial than females, which is at odds with our results2. This discrepancy may emerge from the differences in construction of the experimental setup. They proved that tactile social contact is crucial for developing bias towards prosocial choices2. In our experiment transparent, perforated partition was used between focal and stimulus animal, to allow access of visual, auditory and olfactory cues. However because of the small size of the perforations the direct social contact was very restricted, which could be insufficient to induce establishment of prosocial preferences. Therefore, further research is necessary to draw definitive conclusions regarding sex-differences in prosocial behaviors. 1Lahvis GP, 2017. Curr Top Behav Neurosci 30:127–157 2Scheggia D et al., 2022. Nat Neurosci 25:1505-1518

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Poster ID:302

Day 3

Development of an automated behavioral training framework for cats

Gaspar J. Schliszka, Domonkos Horvath, Sarolt K. Gintner, Julio Loera, Klaudia Csikos, Klaudia Spitzer, Attila B. Dobos, Daniel Hillier

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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.

This work was supported by the Lendület ("Momentum") Programme of the Hungarian Academy of Sciences to DH as well as by project no.129120 that has been implemented with the support provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, financed under the FK18 funding scheme.

Poster ID:103

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

Tamás Láng, Dávid Keller, Árpád Dobolyi

Tamás Láng (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology,, Budapest, Hungary) Dávid Keller (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology,, Budapest, Hungary), (Hungarian Academy of Sciences, Eötvös Loránd Research Network, and Eötvös Loránd University, Department of Physiology and Neurobiology, MTA-ELTE Laboratory of Nolecular and Systems Neurobiology, Budapest, Hungary) Árpád Dobolyi (Semmelweis University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology,, Budapest, Hungary), (Hungarian Academy of Sciences, Eötvös Loránd University, Department of Anatomy, Histology and Embryology, Laboratory of Neuromorphology,, Budapest, Hungary), (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), (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), (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)

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.

Support was provided by Doctoral Student Scholarship Program of the Co-operative Doctoral Program of the Ministry of Innovation and Technology financed from the National Research,Excellence Program of the Semmelweis University,Gedeon Richter Plc. Centenary Foundation,EFOP-3.6.3-VEKOP-16-2017-00009,NKFIH-4300-1/2017-NKP_17,OTKA K134221,ÚNKP-22-2-I-23 NEW NATIONAL EXCELLENCE PROGRAM OF THE MINISTRY FOR CULTURE AND INNOVATION FROM THE SOURCE OF THE NATIONAL RESEARCH, DEVELOPMENT AND INNOVATION FUND

Poster ID:203

Day 2

Activation of the social decision-making and social-stress network in valproate-treated, autism-model mice

Róbert Gergely Kemecsei, Viktória Horváth, András Csillag, Gergely Zachar

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The Autism Spectrum Disorder (ASD) is a lifelong neurodevelopmental disease that is extensively prevalent, and males are multiple times more affected than females. ASD, at any degree of severity, is clinically characterized by social behaviour impairments, mainly involving difficulties in non-sexual social situations. Exposure to specific agents, such as valproic acid (VPA) during pregnancy, have been linked to ASD. In the current experiment we used the VPA-mouse model of ASD, investigating neuronal activation in the nuclei of the social decision-making network (SDMN) and nuclei that has regulator effect on the SDMN in juvenile male mice in various social settings. The efficacy of VPA treatment was validated by three-chamber sociability test, commonly accepted for measuring the ASD-like behavioural phenotype. c-Fos immunohistochemistry was performed in control and VPA-treated individuals in order to capture snapshots of the momentary activity of cells of the SDMN during three types of social situation: mice were kept with familiar companion (1); separated from familiar companion and kept isolated for one day (2); separated for one day and then reinstated to familiar cagemates (3). Certain brain regions of the SDMN showed marked differences according to social situations and embryonic treatments: e.g.: nucleus accumbens (NAcc) and ventral tegmental area (VTA), which plays a major role in the mesolimbic reward system, showed increased activity after the reinstatement in VPA treated mice in contrast to the control individuals. Such a difference in the activity is most likely not independent from those we found also in the medial habenular nucleus (mHb). The mHb plays role in the regulation of stress through the connection to intependuncular nucleus (IPN) and also connected to the SDMN through the interfasciculate nucleus of VTA. Exposure to valproic acid most likely disrupts the SDMN and, therefore, affects the social interactions from early postnatal development, further hindering the acquisition of normal social behaviour.

Poster ID:303

The role of prefrontal somatostatin interneurons and neurotrophin signaling in stress coping

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Adequate coping with environmental challenges are essential for survival and adaptation. Accordingly, basic stress coping styles (passive vs active) are regulated by conserved brain mechanisms. Alterations of this circuit results in susceptibility for affective disorders characterized by shifts towards passive coping (avoidance, inactivity, depressive symptoms). Significant evidence show alterations of prefrontal networks under these conditions, particularly somatostatin (SST) interneurons and neurotrophic signaling (BDNF), however, causal pathogenetic mechanisms are not clarified. In the present study, we aimed to investigate the causal role of BDNF signaling (in SST neurons) in the development of passive coping. We used a developmental model, i.e. SST neuron-specific knockout of the tyrosine receptor kinase B (TrkB) receptors by crossing sst-ires-cre and TrkBflox/flox transgenic mouse lines (SST-TrkB-CKO). First, we assessed cognitive, affective and coping behaviors in a detailed behavioral test battery. Next, we confirmed our behavioral findings in a second cohort of mice and expanded our investigations with brain sampling in order to investigate whole brain activity changes using immunolabeling of c-Fos and SST as markers followed by automated brain atlas alignment and quantification method. We found that TrkB dysfunction in SST neurons resulted in significantly enhanced active coping indicated by reduced immobility in the Forced swim, Tail suspension and Back tests. We identified associated brain activity changes in several brain regions including the amygdala, hippocampus and sensory systems. Our findings suggest that neurotrophin hypo-signaling in SST interneurons significantly shapes cortical network activities resulting in altered coping behavior. These mechanisms may contribute to pathological shifts in coping such as observed in depression and anxiety disorders.

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Poster

ID:104

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 nonoverlapping 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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Poster ID:204

Day 2

Ovariectomy-induced cognitive alterations in female mice - an IntelliCage study.

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The ovariectomized (OVX) rodent model is most widely used for studying the influence of estrogen deprivation on memory and executive functions. However, the results of these studies are inconsistent, in that the memory and executive functions of OVX rodents shows either impairment or no change. These inconsistent outcomes increase the difficulty of researching neurochemical mechanisms and evaluating drug efficacy. The aim of our study was to investigate the effects of estrogen deprivation on memory and executive functions after OVX using an automated home-cage system called IntelliCage, which promises a better reproductivity of the results than manual evaluation. A total of 16 female mice were ovariectomized or shamoperated (9/7 per group) 3 weeks before the experiment and then we implanted radiofrequency transponders to each female mice under isoflurane anesthesia. The animals lived together in the IntelliCage with freely available food supply in the center. However, drinking water was available only in the four corners, with programmable accessability by opening/closing of the doors. We examined spatial working memory, behavioral flexibility, impulse control and attention of ovariectomized and age-matched control female mice with various pre-programed behavioral tests adapted to IntelliCage. After OVX, impairments in memory and cognitive functions were found the first time using an automatic monitoring system. These results may contribute to the development of new therapies aimed at reversing the cognitive decline observed after menopause. Funding: NKFIH OTKA K134221 and MTA NAP2022-I-4/2022 (NAP 3) and Eötvös Loránd University Thematic Excellence Programme.

Conflict of interest: The authors declare that they have no conflict of interest.

Poster

ID:304

Increased astrocytic synchronization promotes memory consolidation

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The involvement of astrocytes in oscillatory brain activity, both in physiological (e.g. slow wave activity) and pathophysiological processes (e.g. epilepsy) is supported by a growing body of evidence. By exploring various molecular interactions between neuronal and astrocyte networks, we have previously shown that inhibition of astrocytic synchronization by the blockade of astrocytic gap junctions suppresses slow wave activity (SWA) in rats in vivo (Szabó et al. 2017) and inhibits epileptiform activity in acute hippocampal slices (Vincze et al., 2019), suggesting a causal role of astrocytes in neuronal synchronization at various frequencies. Since SWA is known to be heavily involved in memory formation, we investigated whether manipulation of astrocytic synchronization by activation or inhibition of gap junctions may influence memory performance in the novel object recognition (NOR) memory test. We demonstrate that the working memory of rats can be enhanced by activating astrocytic gap junctions using trimethylamine (TMA) and can also be impaired by blocking them with an astrocyte-specific connexin 43 (Cx43) antibody. Furthermore, we investigated the effects of gap junction activation and inhibition on the level of network activity. Electrophysiological measurements performed in freely moving rats have shown that TMA increased, while the Cx43 antibody decreased the time spent in SWA, corresponding to their effects in NOR tests. In addition, high-frequency imaging of both astrocytes and neurons showed that astrocytic synchronization at various frequencies (0.5 - 20)Hz) can be observed at the cellular level, simultaneously with the same frequency oscillations measured in the electrophysiological measurements. We believe that large-scale synchronization in the astrocyte network through gap junctions plays a previously unrecognized, essential role in higher cognitive functions and may open up new avenues in the therapy of cognitive disorders.

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Poster ID:105

Day 1

Effect of embrional valproic acid treatment on social behavior and brain activation of domestic chicks (gallus gallus)

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Embryonic exposure to valproic acid (VPA) is known to produce sociability deficits, in several vertebrate species, resembling human autistic phenotypes. Chicks of Galliform birds, known to display complex social behaviour, recently have been used to study the autistic phenotype caused by embryonic valproic acid (VPA) exposure. Our question was whether there is any change in the neuronal activation (measured by c-Fos immunohistochemistry) after various social stimulations in VPA treated chicks. The secondary goal was to evaluate a potentially new pharmacological model of autism using the environmental contaminant, deltamethrin. Here, domestic chicken eggs were injected with sodium valproate (200 µl of 35 µmol/l solution) or with vehicle (distilled water) and deltamethrine (1.5mg/kg) on the 14th day of incubation. After hatching, the chicks were tested for sociability, and social memory before and after social isolation. Our findings confirm previous studies, reporting an adverse effect of VPA on embryonic development, including a tendency for aborted or delayed hatching and, occasionally, for locomotor disorders in a small percentage of birds. The most prominent finding was attenuation of sociability of VPA-exposed birds. Social memory of familiarized individuals is not yet formed in chicks at this age. Although deltamethrin treatment caused minor changes in behaviour, it did not cause a behaviour pattern similar to VPA, it was not associated with a decrease in sociability and vocalization. There is probably no direct association between deltamethrin and the incidence of autism. It seems that embryonic deltamethrin treatment is not an appropriate chemical model for autism. Several brain regions of the social decision-making network (SDMN) showed differential expression of c-Fos according to the social environment and according to the embryonic treatment.

Poster ID:205

Alpha7 nicotinic acetylcholine receptor agonist PHA-543613 effectively reverses cognitive deficits of aged rats in the psychomotor vigilance task

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Recently, we developed a rat version of the psychomotor vigilance task (PVT), a cognitive paradigm that is widely used in human neuropsychological screening. Our aim was to introduce a simple method with high translational potential for the purpose of behavioural pharmacological testing of cognitive enhancer compounds. Rats were trained to respond to a randomly appearing visual stimulus (delay varied between 0 and 5 s) with a fast lever-press. First, we compared the reaction time and accuracy (number of errors) of responses of aged (>30 m. o.) and young adult (12-16 m. o.) rats in the PVT. Aged rats showed obvious deficits in the PVT as they responded significantly slower to the stimuli and made more errors (such as premature responses) than young adult rats. Next, aged rats were acutely treated with different doses of alpha7 nicotinic acetylcholine receptor agonist PHA-543613 (0.3-3.0 mg/kg), and we found that the cognitive enhancer compound effectively and dose-dependently improved the reaction time of the aged rats in the PVT. Quantitative PCR and ELISA measurements in post-mortem brain samples showed that the cognitive deficit of aged rats was accompanied by higher mRNA and protein expression of proinflammatory cytokines such as interleukin-1 beta and tumor necrosis factoralpha. In conclusion, the rat PVT is suitable for the preclinical screening of potential cognitive enhancer compounds. Our results confirmed that aging may cause similar deterioration of psychomotor performance in rats as in humans and the poor behavioural performance is also associated with neuroinflammation in rats. PVT results also confirmed that the alpha7 nicotinic receptor is a promising target for further development of cognitive enhancer compounds.

Poster ID:305

Day 3

Brain-wide activity mapping deciphering anatomical code in trauma vulnerability

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Post-traumatic stress disorder (PTSD) is a psychiatric condition after traumatic life events occurring in a subpopulation that develops a persistent set of biological symptoms. Key features of PTSD are the impaired fear extinction and generalisation of fear to safe contexts. Extinction is orchestrated by coordinated operations of several brain regions. Major candidates (i.e. prefrontal cortex, amygdala) have been implicated, however, unbiased large-scale assessments are needed to discover complex networks regulating fear extinction. Pre-trauma differences in behaviour may be a predisposing factor for developing PTSD. To differentiate individuals that are prone or resistant to PTSD, we performed a wide behavioural test battery on adult male Long-Evans rats before a footshock-induced traumatic experience. We discerned subjects based on their freezing response in a safe/altered context four weeks later (i.e. their fear generalisation and extinction). Upper and lower quartiles were identified based on safe context performances as vulnerable and resilient groups and their whole-brain activity patterns were compared and contrasted using complex statistical methods. We compared the two groups based on immunohistochemical labelling with the neuronal activity marker c-Fos. Whole-brain mapping using delineations from the Waxholm Space Atlas identified numerous cortical and subcortical regions distinguishing the investigated groups. The presented model may help understand complex network alterations underlying PTSD and imply new therapeutic targets in the future.

Poster ID:106

Day 1

High concentration posttraumatic sucrose exposure diminished recent but not remote fear memories in mice

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Failure to extinct traumatic memories can result in the development of neuropsychiatric disorders like post-traumatic stress disorder. Previous studies concluded that consuming sucrose may positively impact the stressed brain. For studying the molecular mechanism transgenic mice strains would be suitable, but so far the beneficial effect of sucrose in mice was not confirmed. Thus, we investigated the impact of various concentrations of sucrose solution on the traumainduced freezing behavior of mice. A short electric footshock was used as trauma and the symptoms were detected 24h (recent) or 14 days (remote) later in the trauma context as well as with trauma-cues. First, the mice were habituated for 3 days to 2%, 16% or 32% sucrose, which per se did not influence their freezing behavior. Then, after the trauma half of the mice got sucrose, while other half drunk water for 24-hour. Exposing mice to a 16% and 32% sucrose significantly reduced freezing behavior 24-hour, but not 14-days after trauma. However, 2% was ineffective. Thus, we could confirm that high energy intake (but not the sweet taste) right after trauma may modify the recent, but not remote fear memories. Further studies required for clarifying the details (e.g. necessary time-window). Our findings could shed new light on the significance of sucrose in the relief of early symptoms of stress thereby suggesting a cheap, widely available treatment option.

Poster ID:206

The tachykinin hemokinin-1 mediates behavioural alterations in a chronic variable mild stress mouse model

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The Tac4 gene-derived tachykinin hemokinin-1 (HK-1) is present in several brain regions related to anxiety, stress and pain, as well as in the hypothalamo-pituitary-adrenal axis, but little is known about its functional relevance in stress-related disorders. Therefore, here we investigated its involvement in chronic variable mild stress-evoked nociceptive, locomotor and memory alterations. In order to evoke depression-like condition in C57BI/6 wildtype (WT) and Tac4 genedeleted (Tac4-/-) mice, two different (a 30–180-min-long and a 12-hour-long) paradigms of variable stressors (cold environment or tilted cage or immobilisation or darkness during the light cycle and wet bedding or isolation or group holding) were performed every day for 3 weeks. Touch sensitivity was assessed with aesthesiometry, anxiety and locomotor activity in the lightdark box (LDB) and open field (OFT), memory functions in novel object recognition (NOR) test. Adrenal weights were measured at the end of the experiment. Non-stressed Tac4-/- mice spent significantly less time in the lit compartment of the LDB, in the central zone of the OFT, and they showed decreased motility compared to WTs. The mild stress paradigms did not induce mechanical hyperalgesia and any significant behavioral and memory alterations in WT mice at the end of the third week, but adrenal weights were increased compared to non-stressed controls. Stressed Tac4-/- mice developed significant mechanical hyperalgesia, and they spent remarkably more time in light and showed increased mobility in the LDB and OFT. Stress-induced adrenal weight increase observed in the WT group was absent in Tac4-/- animals. Since HK-1deficient mice show increased stress-related behaviours, this tachyninin is suggested to mediate defensive mechanisms against stress-induced vulnerability. Identification of its targets and signaling pathways might open new directions in anxiety and depression research.

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Poster ID:306

Functional hemispheric asymmetry of medial habenula is associated with fear expression via modulation of GABAB receptor signaling in mice

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The habenula is a phylogenetically conserved bilateral brain structure known to modulate negative emotions. The functional and structural differences between bilateral brain areas are collectively summarized by the term "left-right asymmetry" and are hypothesized to play a key role in behavior and cognition. Although habenular asymmetry is prominent in several vertebrate species, such as zebrafish, there is no evidence for left-right asymmetry in the mammalian medial habenula (MHb). To investigate the asymmetry in synaptic transmission in the MHb to the interpeduncular nucleus (IPN) pathway in mice, we performed electrophysiological recordings using acutely cut 1-mm thick brain slices coupled with targeted electrical stimulation of left or right MHb-derived axons. Using paired-pulse stimulation with 50 ms inter-stimulus interval (n=53 cells) and 50-Hz high-frequency stimulation (n=11 cells), we discovered that the probability of neurotransmitter release from left MHb terminals was significantly lower than that of right MHb terminals. Furthermore, activation of presynaptic GABAB receptors (GBRs) using the GBR agonist baclofen (1 μ M) potentiated the release from left MHb terminals significantly stronger than that from right MHb terminals resulting in an equalization of synaptic strength of left and right terminals (n=30 cells, left: 952.9 ± 153.6 %, right: 543.4 ± 68.49 % increase in EPSC amplitude). Next, we selectively suppressed left or right cholinergic MHb neurons using stereotaxic injection of floxed inhibitory DREADDs-expressing AAV into 8-12 weeks old male ChATCre mice and performed cued fear conditioning. Chemogenetic inhibition of left but not right MHb significantly decreased the expression of auditory cue-conditioned fear memory (n=8 mice, left: 43.04 ± 1.3 % freezing; right: 51.97 ± 2.68 % freezing). Finally, we conditionally knocked out GBR in the left or right MHb via Cre-expressing lentivirus injection into the 8-12 weeks old male GBR1-floxed mice and repeated the cued fear conditioning experiment. Surprisingly, knocking-out GBR in the left but not in right MHb significantly decreased the amount of fear expression (n=7-8 mice, left: 40.27 ± 3.53 %; right 57.45 ± 4.86 %, respectively). Our study provides the first evidence for a functional asymmetry of the MHb-IPN pathway in mammals and its involvement in fear behavior. Moreover, the side-specific inhibitory effect of this pathway on fear expression is mediated by GBR signaling.

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Poster ID:107

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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Poster ID:207

Day 2

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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Day 3

AgRP neurons modulate exploratory behavior during calorie restriction

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Calorie restriction (CR) can prolong a healthy life span in mammals. The underlying mechanisms involved in this process are ill-defined. Using multiple mice models 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.

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Day 1

Prolactin-releasing peptide (PrRP) and depressive-like behaviour in rats

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INTRODUCTION Nowadays, a growing number of nutritional, metabolic and psychological disorders are associated with stress. More and more research results confirm that the RFamide peptides - especially the prolactin-releasing peptide (PrRP) - can play a role in the regulation of stress responses. In the present experiments importance of PrRP was examined in development of depression-like symptoms, a known stress-related psychopathology. PrRP was identified as an endogenous ligand of the GPR10 receptor, but PrRP binds with high affinity to the NPFF2 receptor as well. METHOD Fifteen minutes forced swimming test (FST) was used to induce depression-like symptoms in male rats. On the next day the animals' behaviour was analysed during a 6-min FST, and based upon the time spent in immobility resilient (low level) and vulnerable (high level) group was formed beside a control, non-FST group. At the end of the experiments frozen brain samples were taken for mRNA measurement by rtPCR. RESULTS Due to the food intake-regulatory role of PrRP as well as the disturbed food-intake of depressed patients first we examined the ventromedial hypothalamus (VMH), the well-known satiety center. Although there was no difference between the three groups in the PrRP as well as in NPFF2 receptor mRNA levels, but the GRP10 mRNA level was significantly higher in resilient than in vulnerable group. The paraventricular hypothalamic nucleus, and the A1 cell group in the brainstem are the most important centrums of the stress-adaptation, being implicated in the hypothalamic-pituitary and sympathoadrenomedullary axis, respectively. Moreover, the amygdala, a known center of emotion also showed depression-related alterations in PrRP and its receptors' level as well. Conclusion Our results support that PrRP might play an important role in the development of stress-related psychological symptoms, primarily depression. Increase receptor synthesis might lead to enhanced PrRP regulatory tone in the VMH with the aim to compensate the stress-induced changes. However, different brain areas may have different roles, so systemic treatment will not necessarily be effective.

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Day 2

Microglia monitor, protect and nurture neurons via somatic purinergic junctions

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Microglia are the main immuncompetent cells of the CNS and the sole myeloid cells that reside in the parenchyma. Recent studies have shown that microglia are indispensable for neurodevelopment and brain homeostasis beyond their inflammatory functions, but the exact sites mediating these effects have remained unclear. In line with previous studies elaborating on the importance of interactions between microglial processes and synapses, we have recently shown that specific sites on neuronal somata also exist in both the mouse and the human brain, allowing the dynamic monitoring and assistance of neuronal function by microglia. Using state-of the art methodology, we have revealed that somatic microglia-neuron junctions possess specialized nanoarchitecture optimized for bi-directional communication. We have also shown that microglia react to neuronal activity via these "hot-spots", while brain injury-induced changes at somatic junctions trigger a robust microglial neuroprotection in the adult brain via microglial P2Y12 receptors. Since developmental microglia-neuron interactions remained elusive to date, we hypothesised, that somatic junctions could also enable microglia to fulfill their developmental roles. In adults, somatic junctions are characterized by neuronal mitochondria, mitochondrionassociated-membranes, vesicles and exocytosis-promoting Kv2.1-protein clusters are accumulated at the junctions, opposed by microglial P2Y12R-clusters. We found that microglial processes also form specialized nanoscale contacts with the cell bodies of developing and immature neurons throughout embryonic, early postnatal and adult neurogenesis. These early developmental contacts are highly reminiscent of adult somatic purinergic junctions: their formation and maintenance depends on functional microglial P2Y12Rs, while the deletion of P2Y12Rs causes an aberrant cortical cytoarchitecture both during development and in adulthood. Collectively, our results suggest that microglial processes at these junctions are in ideal position to monitor and protect neuronal functions in both the healthy and injured brain, and also represent an important interface for microglia to modulate prenatal, early postnatal and adult neurodevelopment. These results also indicate the importance of the cellular-domain-specific direct microglia-neuron communication in the developing brain and in adult neurogenic niches.

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Poster ID:308

Gating changes explain increased dihydropyridine sensitivity of human pathogenic CACNA1D voltage-gated calcium channel mutations

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Background: Germline missense variants in the Cav1.3 α1-subunit (CACNA1D) cause a severe neurodevelopmental disorder with or without endocrine symptoms. Mutations enable channel gain-of-function, most of them by shifting steady-state inactivation (SSI) and activation towards negative potentials. Such mutants (e.g. A749T, S652L, F747S) exhibit increased sensitivity for clinically available dihydropyridine (DHPs, e.g. isradipine) Ca2+ channel blockers, which may therefore be used for personalized symptomatic off-label treatment. Aims: We investigated in detail the voltage-dependence of isradipine inhibition of wildtype (WT) and mutant Cav1.3 channels to test if the enhanced DHP sensitivity of mutant channels can be explained by the more negative SSI of mutant channels. This would be predicted by the modulated receptor hypothesis (MRH) if isradipine binds to the inactivated channel conformation of Cav1.3 with higher affinity as previously described for cardiac Cav1.2 channels (Bean BP, PNAS 1984;81:6388). Methods: Human wild-type (WT) Cav1.3 α1-subunits and the pathogenic A749T variant were heterologously expressed in HEK-293T cells with β 2a and α 2 δ 1 subunits and tested for isradipine sensitivity by 50 ms pulses (0.1 Hz) from various holding potentials (HP, -89 - -27 mV). Results: A749T significantly shifted the half-maximal voltage of SSI by 18.8 mV (p<0.0001) towards negative potentials in comparison to WT. At -89 mV holding potential A749T displayed 1.4-fold higher sensitivity towards isradipine (IC50: 97.7 nM) than WT (IC50: 135.8 nM, p=0.0007). This difference increased at more depolarized HPs at -59 mV to 2.1-fold (A749T: IC50=26.2 nM; WT: IC50=56.2 nM, p<0.0001) and at -54 mV to 2.4-fold (A749T: IC50=17.3 nM; WT: IC50=41.6 nM, p<0.0001) increase. As predicted by the MRH, at HP providing substantial SSI in both constructs, IC50s strongly decreased and were no longer significantly different (10%: A749T: IC50=6.22 nM; WT: IC50 = 6.55 nM, p=0.2254; 20%: A749T: IC50=2.12 nM; WT: IC50=3.94 nM, p=0.0681). Measured IC50 values closely followed the predictions by the MRH assuming an isradipine Kd of 135.8 nM for resting and a Kd of 0.7 nM for inactivated states. Conclusion: Voltage-dependent isradipine inhibition of WT Cav1.3 and its A749T variant can be explained by preferential inhibition of inactivated channel states. Therefore, more pronounced SSI at a given holding potential can account for higher isradipine sensitivity of A749T in comparison to WT.

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Poster ID:109

A two-pool vesicle release mechanism in medial habenula terminals underlies GABAB receptor-mediated potentiation

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Activation of presynaptic GABAB receptors (GBRs) reduces neurotransmitter release at most synapses. The only known exception is the synaptic connection from the medial habenula (MHb) to the interpeduncular nucleus (IPN). At these synapses, presynaptic GBR activation causes a several-fold increase in neurotransmitter release (Bhandari et al., 2021, eLife 10:e68274) but the mechanisms underlying this enigmatic potentiation remain elusive. We measured postsynaptic currents in response to 10-Hz electrical stimulations of mouse MHb axons in IPN neurons in 1mm thick slices at room temperature. Our electrophysiological results indicate that application of the GBR agonist baclofen (1 μ M) induces a transition from a tonic to a phasic neurotransmitter release mode at a physiological stimulation frequency. This transition was accompanied by a 4.1 ± 0.6-fold increase in readily releasable vesicle pool size in MHb terminals (n=16 recordings from 4 mice) and mirrored by a 3.5 ± 0.4 -fold increase in the density of docked synaptic vesicles at the presynaptic active zone (n=18 synapses, 3 mice; measured by "Flash and Freeze" electron microscopy). Tonic and phasic release vesicles have different coupling distances and express distinct vesicle-associated molecular markers, synaptoporin and CAPS2, respectively. Synaptoporin mediates augmentation of tonic release and CAPS2 stabilizes readily releasable vesicles during phasic release. A newly developed "Flash and Freeze-fracture" method revealed selective recruitment of CAPS2 to the active zone during phasic release. Thus, we propose a twopool mechanism underlying the GBR-mediated potentiation of release from MHb terminals.

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Poster ID:209

Distribution profile and ratio of Cav2 channels and the plasma membrane Ca2+-ATPase in cerebellar and hippocampal neurons

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In central neurons, calcium (Ca2+) signaling controls a variety of fundamental processes and reaction pathways including the release of neurotransmitters and hormones, regulation of enzymatic activities and excitability, excitation-transcription coupling, and neurite outgrowth. All these processes are switched on by an influx of Ca2+ into the cytosol of dendritic and axonal compartments of neurons, partially through voltage-activated Ca2+ channels (Cav), and they are switched off by the concerted action of various Ca2+ transporters that extrude Ca2+ ions from the cytoplasm. In neurons, one of the most abundant proteins responsible for Ca2+ clearance is the plasma membrane Ca2+-ATPase (PMCA), which transports Ca2+ to the extracellular space using ATP. Here, we combined the high-resolution sodium dodecyl sulfate-digested freezefracture replica labeling (SDS-FRL) immunoelectron microscopy with quantitative analysis of immunoreactivity for Cav2.1 (P/Q-type) channel, Cav2.2 (N-type) channel, and PMCA to determine the distribution pattern, density, and ratio of Cavs and transporter in the cerebellar Purkinje cell dendrites and parallel fiber varicosities, as well as in dendritic shafts of hippocampal CA1 pyramidal cells and in Schaffer collaterals. Conclusions: 1. Both Cav2.1 and Cav2.2 channels are predominant on presynaptic localization. 2. Surface density of PMCAs appears differential in the pre- and postsynaptic compartments with highest density in dendritic shafts of Purkinje cells. 3. Dendritic compartment: the postsynaptic Cav2:PMCA ratio appeared 1:20 on the Purkinje dendritic shafts and 1:10 on CA1 pyramidal cell dendrites. This suggests the preferential role of PMCAs in the regulation of dendritic Ca2+ signaling. PQ:N:PMCA on Purkinje dendrite shafts: 15:0:249 p/µm2 (1:20) PQ:N:PMCA on CA1 pyramidal dendrites: 8:7:135 p/µm2 (1:10) 4. Boutons: in the presynaptic compartment the Cav2:PMCA ratio was 10:1 on the cerebellar parallel fiber varicosities, whereas on Schaffer-collaterals 30:1 was found. This suggests other comechanisms in the fine regulation of axoplasmic Ca2+ concentration. PQ:N:PMCA on parallel fiber varicosities: 213:76:30 p/µm2 (10:1) PQ:N:PMCA on CA1 Schaffer collaterals: 496:239:23 p/µm2 (30:1)

Poster ID:309

HCN channels at the somatic membrane ensure rapid input–output function of human neocortex fast-spiking interneurons

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Accumulating evidence indicates that there are substantial species differences in the properties of mammalian neurons, yet theories on circuit activity and information processing in the human brain are based heavily on results obtained from rodents and other experimental animals. This knowledge gap may be particularly important for understanding the neocortex, the brain area responsible for the most complex neuronal operations and showing the greatest evolutionary divergence. Here we examined differences in the electrophysiological properties of human and mouse fast-spiking GABAergic basket cells, among the most abundant inhibitory interneurons in cortex. Analyses of membrane potential responses to current input, pharmacologically-isolated somatic leak currents, isolated soma outside-out patch recordings, and immunohistochemical staining revealed that human neocortical basket cells abundantly express

hyperpolarizationactivated cyclic nucleotide-gated cation (HCN) channel isoforms HCN1 and HCN2 at the cell soma membrane, whereas these channels are sparse at the rodent basket cell soma membrane. Antagonist experiments showed that HCN channels in human neurons contribute to the resting membrane potential and cell excitability at the cell soma, accelerate somatic membrane potential kinetics, and shorten the lag between excitatory postsynaptic potentials and action potential generation. These effects are important because the soma of human fast-spiking neurons without HCN channels exhibit low persistent ion leak and slow membrane potential kinetics, compared with mouse fast-spiking neurons. HCN channels speed up human cell membrane potential kinetics and help attain an input-output rate close to that of rodent cells. Computational modeling demonstrated that HCN channel activity at the human fast-spiking cell soma membrane is sufficient to accelerate the input-output function as observed in cell recordings. Thus, human and mouse fast-spiking neurons exhibit functionally significant differences in ion channel composition at the cell soma membrane to set the speed and fidelity of their input-output function. These HCN channels ensure fast electrical reactivity of fast-spiking cells in the human neocortex.

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Poster ID:110

Day 1

$CaMKII\alpha\ promoter-controlled\ circuit\ manipulations\ target\ both\ pyramidal\ cells\ and\ inhibitory\ interneurons\ in\ cortical\ networks$

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A key assumption in studies of cortical functions is that excitatory principal neurons, but not inhibitory cells express calcium/calmodulin-dependent protein kinase II subunit α (CaMKII α) resulting in a widespread use of CaMKII α promoter-driven protein expression for principal cell manipulation and monitoring their activities. Using neuroanatomical and electrophysiological methods we demonstrate that in addition to pyramidal neurons, multiple types of cortical GABAegic cells are targeted by adeno-associated viral vector (AAV) carrying the CaMKII α -Channelrhodopsin 2-mCherry construct. We show that the reporter protein, mCherry can visualize a large fraction of different interneuron types, including parvalbumin (PV), somatostatin (SST), neuronal nitric oxide synthase (nNOS) and neuropeptide Y (NPY)-containing GABAergic cells, which altogether cover around 50% of the whole inhibitory cell population in cortical structures. Importantly, the expression of the excitatory opsin Channelrhodopsin 2 in the interneurons effectively drive spiking of infected GABAergic cells even if the detectability of reporter proteins is ambiguous. Thus, our results challenge the use of CaMKII α promoter-driven protein expression as a selective tool in targeting cortical glutamatergic neurons using viral vectors.

Poster ID:210

Investigating the expression of kynurenine aminotransferase-2 in primary cell cultures

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Aims: Kynurenic acid (KYNA) plays an important role in neuroprotection and neuromodulation due to its broad-spectrum receptor modulatory effects. In many neurodegenerative and psychiatric disorders, abnormal levels of KYNA have been observed. KYNA production is catalyzed by enzymes called kynurenine aminotransferases (KATs). From the four identified KAT isoforms KAT-2 is described as the major biosynthetic enzyme of KYNA both in the murine and the human brain. The treatment of diseases affected by abnormal KYNA levels requires the manipulation of the kynurenergic system. Since KAT-2 can regulate KYNA levels, it could be advantageous to study the cell-type-specific expression of the enzyme. Previous studies found that in the rat brain KAT-2 is expressed only in astrocytes. In the mouse brain, however, KAT-2 expression was observed in neurons too. We aimed to further investigate the cell-type-specific expression of KAT-2 in mouse brain-derived cells. Methods: We established primary neuronal, astrocyte, and microglial cell cultures isolated from mouse brains. KAT-2 expression was analyzed using fluorescent immunohistochemistry. Neuronal, glial, and microglial markers were used to identify each cell type. Results: High levels of KAT-2 expression were observed in all three groups studied, further confirming previous results that described the presence of the enzyme outside astrocytic cells. Expression of the protein is most prominent in the cytoplasmic region of the cells but can also be observed in the primary branches. Conclusions: The present study is the first to provide data about cell-type-specific expression of KAT-2 in mouse brain-derived primary cell cultures. These results are hopefully supporting future pharmacological and kynurenergic manipulation studies, that aim to regulate abnormal KYNA levels.

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Day 3 Cellular neuroscience

Poster ID:310

Single cell composition and ligand-receptor based signaling within the human caudate nucleus

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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 celltype-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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Poster ID:111 Dual activation of mu and delta opioid receptors by new oxymorphone analogues produces effective antinociception without the risks of antinociceptive tolerance and physical dependence in mice

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Opioids are highly effective painkillers for the treatment of moderate to severe pain. Chronic use of opioids is associated with analgesic tolerance, physical dependence and addictive potential. They mediate their pharmacological effects via activation of the opioid receptors, mu (MOR), delta (DOR) and kappa (KOR). The MOR is the primary target for the therapeutic analgesic effect, but also for the development of severe side effects. Currently, intensive research focuses on developing new, innovative strategies to mitigate the deleterious opioid-related side effects. Multitarget pharmacology is a promising strategy to discover effective and safer analgesic drugs. Bifunctional ligands with an activity at multiple opioid receptors gained a particular interest over the years, as they can produce additive analgesic effects through binding synergistic targets on the pain pathways at different levels (peripheral, spinal and supraspinal). In this study, we report on in vitro and in vivo profiles of two new oxymorphone analogues that emerge as bifunctional MOR/DOR agonists effective in mouse pain models with reduced liabilities for opioid-related side effects after chronic subcutaneous (s.c.) administration. Radioligand binding studies showed the new oxymorphone derivatives to display very high affinities (picomolar to subnanomolar range) to the MOR and DOR (rat brain) and to the KOR (guinea-pig brain). In the [355]GTPyS functional assays, they were very potent and full agonists to the human MOR and DOR and partial agonists to the human KOR. In vivo, both oxymorphone analogues were highly effective as antinociceptives in mouse models of acute thermal nociception (tail-flick test), and significantly inhibited pain behavior in a model of inflammatory pain (the formalin test). Their antinociceptive effect was reversed by selective MOR (β -funaltrexamine) and DOR antagonists (naltrindole), but not by the KOR antagonist (nor-BNI), demonstrating the involvement of MOR and DOR to the antinociceptive action. Chronic s.c. treatment of mice did not lead to the development of antinociceptive tolerance. The potential for physical dependence was determined using the naloxone-precipitated withdrawal, with none of the new oxymorphone analogues inducing withdrawal syndrome. Dual activation of the MOR and DOR by the new oxymorphone analogues produces effective antinociceptive effects without the CNS-mediated risks of antinociceptive tolerance and physical dependence.

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Poster ID:211

Day 2

Antinociceptive efficacy of selective kappa-opioid receptor agonists HS665 and HS666 in chronic inflammatory pain without inducing anxiety-like behavior in mice

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Effective chronic pain treatment remains an unmet medical need as the currently available analgesics are either ineffective or have multiple and severe adverse effects. The kappa-opioid receptor (KOR) has a central role in modulating neurotransmission in central and peripheral neuronal circuits that subserve pain and other behavioral responses. While activation of the KOR does not produce dependence, euphoria or leads to respiratory suppression, it induces dysphoria, sedation, anxiety and psychotomimesis. Our group has developed two diphenethylamines, HS665 and HS666, as highly selective KOR agonists with a G protein-biased KOR agonist profile. HS665 (full agonist) and HS666 (partial agonist) displayed potent antinociceptive effects in mouse models of acute pain and visceral pain, with reduced centrallymediated KOR liabilities (aversion and sedation/motor impairment) after subcutaneous (s.c.) administration in mice. In this study, we report on the antinociceptive activity of HS665 and HS666 in a model of chronic inflammatory pain as well as their liabilities on anxiety-like behavior and spontaneous locomotor activity in mice after s.c. administration. Additionally, in vitro functional KOR activity of HS665 and HS666 in mouse striatum was investigated. Both, HS665 and HS666 efficiently reversed thermal hyperalgesia (the Hargreaves test) in mice with Complete Freund's Adjuvant-induced paw inflammation in a time- and dose-dependent manner, with a long duration (up to 6-7 hours) of the antihyperalgesic effect. Antinociception was reversed by the selective KOR antagonist nor-binaltorphimine demonstrating a KOR-dependent mechanism of action. Particularly, both KOR agonists showed a favorable side effect profile as no anxiogenic behavior and no alteration in spontaneous locomotion were observed in the elevated plus maze test. In the [35S]GTPyS binding assay, HS665 and HS666 stimulated G protein signaling in striatal membranes from wild-type mice, whereas no stimulation was measured in striatum of KORknock-out mice. In summary, we show that the selective KOR agonists HS665 and HS666 are effective antinociceptives in experimental chronic inflammatory pain and display a favorable benefit/side effect ratio regarding CNS-mediated KOR side effects. Targeting the KOR represents a promising strategy for an improved treatment of chronic pain conditions.

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Day 3 Poster

ID:311

Intranasal application of the neuropeptide alarin leads to c-fos activation

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Alarin is a neuropeptide derived by alternative splicing of GALP. It regulates physiological functions incl. feeding behavior, energy and glucose homeostasis, body temperature and reproduction. Accumulating evidence indicates that alarin is an initiator of obesity. Alarin alters acute food intake in lean rats/mice upon intracerebroventricular injection. Here, we tested intranasal administration of alarin as a minimal invasive route of peptide delivery. Our aim was to elucidate whether the blood-brain barrier (BBB) can be bypassed and to determine potential activation of immediate early gene c-fos in the brain. In a long-term model we investigated whether intranasal alarin application is safe without major side effects. Lean C57BL/6 mice were treated with a single dose of 10, 20 and 30 nmol alarin in 5% α -cyclodextrine or vehicle and compared to untreated controls (short-term model). After transcardial perfusion, brains were excised, cryoprotected and cut sagitally. Immunofluorescence staining was performed on freefloating tissue sections against c-fos. Images were acquired using Olympus slide scanner VS120. To examine whether long-term application of alarin is safe and its effects on food intake/body weight in lean and obese C57BL/6 mice, mice were fed with a 60% fat diet to induce obesity or a 10% fat control diet. After habituation, 10nmol alarin or vehicle was intranasally applied on a daily basis for 4 weeks. Changes in behavior, appearance, social interaction of mice and alterations in body and adipose tissue weight and toxic effects were monitored. Here we demonstrate that intranasally applied alarin can bypass the BBB as short-term application of alarin resulted in dose-dependent c-fos activation in various brain regions, particularly the hypothalamus, the central control of feeding and energy homeostasis. Low-dose intranasal alarin (10nmol) did not alter body weight, appearance or social behavior of mice neither in the shortnor in the long-term model. In the long-term model body and adipose tissue weight was unaltered in obese and lean mice vs. controls. Short- and long-term intranasal application of alarin was proven to be safe without major side effects on appearance and behavior of mice. Intranasal application of alarin represents a minimal invasive route of application and was found to bypass the BBB as shown by c-fos activation in the brain. Further studies will be performed to explore the modes of action of intranasally applied alarin.

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Poster ID:112

Day 1

Molecular mechanisms and physiological importance of a novel interaction between Kv channels across families

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Background: Voltage-gated K+ channels (Kv) allow K+ flux over the plasma membrane in response to depolarization and are usually formed by a tetramer of four related family members. Four of the Kv families (i.e., Kv5, Kv6, Kv8 and Kv9) are electrically silent when assembled as homomers and have therefore been termed silent Kv (KvS). Interestingly, KvS co-assemble with Kv2 subunits, which leads to properties different from homomeric Kv2 channels. This Kv2-KvS coassembly constitutes the only yet known example for heteromerization of subunits across Kv families. As Kv7 subunits exhibit a higher sequence homology to KvS than to all other families, an interaction of Kv7 with KvS – in analogy to Kv2-KvS interactions – is probable. Hypothesis: Kv7 and KvS subunits co-assemble into functional channels (i.e., with all subunits contributing to the channel's pore), leading to modified channel properties in different excitable cells types. Methods: Using a combination of molecular, biological, biochemical as well as electrophysiological techniques, we will (1) determine (co-)expression of different Kv and KvS subunits in dorsal root ganglia, hippocampus and heart tissue using RT-qPCR and RNAscope in situ hybridizations, (2) investigate excitability and network differences in KvS knockout mice using single-cell patch-clamp recordings and multielectrode-array recordings, and (3) probe physiological relevance of KvS subunits by applying sensory and cognitive behavioral tests in KvS knockout mice. Discussion: This project will deliver significant insights into the mechanisms underlying a novel interaction between members of different Kv channel families, challenging a central theorem on the formation of functional Kv channels. It will further help to develop new treatment options against KvS-dependent pathologies by evaluating the therapeutic potential for repurposing specific channel agonists or gene-therapeutic strategies.

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Towards an understanding of cell type dynamics in an animal model for chronobiology and light

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Background: Whereas mammalian brains are largely considered to be differentiated, postmitotic organs, the central nervous system of non-mammalian animals exhibits significant cellular plasticity. Often, this plasticity correlates with the timing of reproduction. We explore the marine annelid worm Platynereis dumerilii as an important system for studying the link between neuronal diversification and endogenous timing mechanisms. We have previously shown that sexual maturation is accompanied by transcriptional changes in the brain and that, like numerous other physiological functions and behavior, maturation is governed by the worm's monthly timing system, which is entrained by moonlight. Methods: To understand the changes occuring in the brain during maturation, we are developing a time-resolved single cell atlas of the Platynereis brain. We employ a combination of single-cell RNA-sequencing, state-of-the-art in situ hybridization and proliferation detection assays. Moreover, we analyze wildtype worms at different stages of maturation, as well as knock-outs of the photoreceptor l-cry, which serves as a signal interpreter and duration decoder of sun-versus moonlight in the context of monthly clock entrainment. Results: The brain atlas provides insight into the plasticity of brain cell type composition over time. Owing to a novel method for integration of large sequencing datasets, we are able to easily highlight not only the differences between cell types, but also between different states that a cell of one type can assume. This allows us to reveal several types of neuronal cells with transcriptomic profiles that change with the progression of maturation in the worm. Moreover, we identify key genes with transient expression specific to immature and premature animals, including an uncharacterized photoreceptor and a neuropeptide, hypothesizing their putative roles as a signal co-interpreter and a signaling molecule. Further, we demonstrate that specific tissues in the brain display disproportionately high growth rates in maturing animals, such as the retina and the neurosecretory niche, the two expression domains of I-cry. Our atlas adds a novel dimension to the phenotype of delayed reproduction onset in I-cry mutants, exploring the phenotype on a brain cell type level. Finally, this work opens a door for further testing of the connection between maturation and brain dynamics, capitalizing on the well characterized hormonal control of sexual maturation.

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Poster

ID:312

Optical recording of unitary synaptic connections using Voltron

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Patch clamp electrophysiology is fundamental for revealing synaptic connections between individual cells because it provides excellent temporal resolution, resolves each presynaptic action potentials (APs) and postsynaptic events, and allows the anatomical identification of the pre- and postsynaptic cells. However, this labor-intensive method can access only a few potential connection within an experiment. We are adapting an in vitro voltage imaging method with the Voltron sensor that allows measuring a large number of unitary synaptic connections while retaining the major advantages of conventional recordings. Voltron was sparsely expressed for 4-8 weeks using rAAV vectors in rats. Acute hippocampal slices were incubated with a fluorescent dye (JF549) that binds to the Voltron protein allowing epifluorescent imaging at high temporal rate (1 kHz) in a large field of view (375x235 µm). We use two approaches for optical detection of synaptic connections. In the first, the presynaptic cell is patch clamp-recorded, allowing the precise control of individual APs and trains, while we image a large region, where potential postsynaptic cells express Voltron. Typically, hundreds of Voltron- expressing cells were visible and we detected up to ten connections in single experiments. Some of these were verified in subsequent patch clamp recordings. Major optimization steps included adjusting the optimal density of cells by virus dilution, and adjusting general conditions, such as imaging temperature. Due to the large amount of data, dedicated analysis scripts were also needed. Importantly, because the Voltron labeling is preserved after the fixation, the imaged cells can be identified using immunolabelling. As presynaptic cells were labeled with biocytin via the patch pipette, we could also follow their axons near the responding cells. In the second approach we use only optical measurements. We recognized that spontaneous APs are readily detected in Voltron signal, which can be used as presynaptic references for postsynaptic responses. By simple combinatorics, this approach greatly enhances the chance of detecting connections, as we usually isolate several spontaneously active cells in our slices. At the same time, this all-optical synaptic analysis also offers all the advantages of Voltron imaging described above. Thus, Voltron imaging is a promising tool to better understand synaptic mechanisms because it reliably detects synaptic connections.

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Day 1

Nimodipine reduces LPS-induced microglial activation in primary mixed and isolated microglia cell culture

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Background: Microglial activation is an early response to brain ischemia which can induce neuroinflammation. Intracellular Ca2+ concentration changes regulate microglial activation. Here we tested whether the pharmacological inhibition of L-type voltage-gated Ca2+ channels suppresses microglial activation. Materials and methods: Primary mixed cell cultures and isolated microglia cultures were prepared from the cortex of neonatal Sprague Dawley rats. On day 9, the plated cells were treated with lipopolysaccharide (LPS; 20 ng/ml) or nimodipine (an L-type VGCC blocker) alone (5-10-20 μM), or in combination with LPS for 24 h. Microglial activation was evaluated by Iba1 immunolabeling (degree of arborization expressed by a transformation index -TI) and Western blot analysis, and the visualization of phagocytotic activity with fluorescent microbeads. Results: Microglia displayed decreased area, perimeter and TI in response to the LPS challenge, indicative of amoeboid transformation and activation. When the LPS-challenged cell cultures were treated with nimodipine, significantly more ramified cells were seen already at the lowest concentration (1.89±0.41 and 3.1±0.91, TI, LPS vs. nimodipine). Increased Iba1 signal intensity in Western blot analysis confirmed microglial activation due to LPS treatment, which was decreased particularly by 10 and 20 µM nimodipine (108.3±20.1 and 77.2±8.49 vs 213.4±29.7 integrated optical density, nimodipine 10 and 20 μM vs LPS). Control microglia engulfed a few microbeads (3.9±6.1 bead/cell). In contrast, LPS challenge increased microglial phagocytic activity (22±20 bead/cell), which was significantly attenuated by nimodipine (6±10 bead/cell). Conclusions: Nimodipine is used to alleviate vasospasm in acute cerebrovascular conditions. Our data suggest that nimodipine may also be applicable in neuroinflammatory conditions including dementia, where neurodegeneration is believed to be linked to neurotoxic microglial activation.

HCEEM

Poster ID:213

Dynamic rearrangement of active zones at hippocampal mossy fiber boutons during synaptic plasticity

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Synaptic transmission depends on a sophisticated complex of proteins that are involved in neurotransmitter release from presynaptic active zone (AZ) (Südhof, 2013, Neuron 80: 675–690). As a consequence, dynamic changes within AZs can result in alterations in the structure and function of synapses during synaptic plasticity. Although recent study elucidated the potential link between physiological and morphological properties of synapses during plasticity (Vandael et al., 2020, Neuron 107: 509–521), the molecular basis remains unknown. The current work aims to correlate structural and physiological data, thus, establishing the mechanisms governing shortterm potentiation (STP) in mouse hippocampus. Hence, we combined chemical potentiation, by the adenylyl cyclase activator forskolin (FSK, 50 μM), paired recording of mossy fiber boutons (MFBs) to CA3 pyramidal neuron (PN) synapses, freeze-substitution of acute hippocampal slices, and freeze-fracture replica immunolabeling (FRIL) of calcium channels (Cav2.1) and the synaptic priming protein (Munc13-1). First, we found that during cSTP both readily releasable pool (RRP) and release probability (Pr) increased (RRP: control -1.05 ± 0.12 nA vs. cSTP -2.55 ± 0.36 nA, p < 0.01, here and below Wilcoxon signed-rank test; Pr: control – 0.15 ± 0.02 vs. cSTP – 0.20 ± 0.03 , p < 0.05; n = 7 pairs). Similarly, we found that the docked vesicle pool increased after cSTP induction (number of docked vesicles per 100 nm AZ profile length: control -0.8 ± 0.04 (n = 159 AZs) vs. cSTP $- 1.2 \pm 0.07$ (n = 149 AZs), p < 0.01). Finally, FRIL revealed that the mean number of clusters of Munc13-1 in the MFB AZs significantly increased from 2.4 ± 0.1 in control to 3.0 ± 0.2 clusters during cSTP (119 and 78 AZs respectively, p < 0.01). In addition, the mean nearestneighbor distance between calcium channels and Munc13-1 proteins decreased after FSK application (control – 49.1 ± 2.5 nm vs. cSTP – 38.5 ± 1.5 nm; p < 0.001). Altogether, our results indicate a marked correlation between the size of RRP, the docked vesicle pool, and the number of clusters of the priming protein Munc13-1 at MFBs. In addition, we show a possible link between Pr and structural coupling distance at MFBs. Finally, we show that exactly this expansion of releasable vesicles together with an increase in Pr determines cSTP at the MFB-CA3 PN synapses.

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Poster ID:313

Species dependent and developmentally regulated connectivity shapes information storage in the hippocampal CA3 cell network

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CA3–CA3 recurrent synapses are crucial for learning and memory. Previous studies showed that synaptic connectivity between CA3 pyramidal neurons (PNs) is sparse, but endowed with nonrandom connectivity motifs (Guzman et al., 2016, Science 353, 1117–1123). Whether these rules are conserved across species, and how they emerge during development has not been determined. We recorded octuples of CA3 PNs (3487 tested connections total); unitary synaptic responses were measured in the current- and voltage-clamp configuration. Under identical conditions, connectivity was higher in mice than in rats (~postnatal day P21). In rats, connection probability was 0.99% for CA3–CA3 and 0.75% for CA3–CA1 synapses, whereas in mice, it was 2.7% for CA3–CA3 and 1.23% for CA3–CA1 synapses (P < 0.004 and 0.52, respectively). As the number of cells is higher in rats than in mice (~330,000 versus ~100,000 CA3 neurons; Boss et al., 1987, Brain Res 406, 280–287), our results suggest an inverse relation between cell number and connectivity. Next, we tested connectivity among CA3 PNs in mice at three different developmental stages, P7–8, P18–25, and P45–50. Average connectivity was developmentally down-regulated, with connection probability values of 3.31%, 2.7%, and 1.01%, suggesting pruning of CA3-CA3 synapses. Furthermore, connectivity motifs increased during development, from 1 to 1.5 and 3.2 above the chance level (P < 0.23, 0.058, and 0.04, respectively). Thus, nonrandom connectivity motifs emerge during network development. To explore how these connectivity rules affect network function, we implemented different connectivity values and cell numbers into a biologically inspired full-scale model of pattern completion (Hopfield, 1982, PNAS 79, 2554–2558; Guzman et al., 2016, Science 353, 1117–1123). Storage capacity increased linearly with cell number and connection probability in the low number limit, but saturated in the high number limit. Thus, sparse connectivity may optimize the storage of information in the hippocampal CA3 network.

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Poster ID:114

Day 1

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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Poster ID:214

Day 2

Cut load labelling by different gap junction permeable dyes reveals physical property dependent alternation in direct connectivity of inner neuronal cells in the mammalian retina

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Vision is our most critical sense. The retinal neurons have a complex neuronal network highly dependent on the gap junctional (GJ) connections that directly link the cells thus serving visual perception. It has previously been shown that the extent of interconnectivity can be monitored by cut loading (CL) of GJ permeable tracers in the photoreceptor and outer plexiform and nuclear layers. However, it is still ambiguous if the same technique can unravel the multitude of interconnected cells and cell types in the inner retina. The bystander neighbours of the primarily labeled cells are interdependent from each other not only by electrical means but also by cellular survival and death markers. The transjunctional movement of various substances is highly dependent on the junctional conductance by the distance tracers travel from the injury site as well as the number of labelled cells observed in the vicinity of CL location. We aimed to label the inner layers of the retina with the classical neuronal tracer Neurobiotin (NB) as well as to show the differential labeling patterns of further new GJ permeable dye candidates (Serotonin, 5,7-Dihidroxytriptamine- Hydrobromide, NB-esther). We utilized the Parvalbumin-tdTomato mouse, where 8 ganglion cell types and sporadically labelled amacrine cells of different types have been identified previously thus serving the morphological characterisation of cells in our experiments. In addition to control tests, we also utilized the GJ blocker Meclofenamic acid (MFA) to visualize the cohort of neurons along the CL site that were tracer loaded primarily. Differences in control and MFA-treated tracer movements will indicate the efficacy of various tracers in partaking in any transjunctional diffusion. Such transjunctional tracer movement will be monitored for ganglion- amacrine-, and bipolar cells separately. Expectedly, the different physical (molecular weight and shape) and chemical (charge, moiety) parameters of various tracers will result in their differential movement across the electrically coupled neuronal arrays. Such differential spreading of molecules may underlie a similar selective transjunctional diffusion of medications thus exploiting the bystander effect on the clinical setting.

Poster ID:314

Day 3

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 potential initiation in the AIS (AIS-APs) is driven by input integration, and the phase preference of AIS-APs 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 (RA-APs) in axons distal from the soma. We report spontaneously occurring RA-APs in human and rodent cortical interneurons that appear uncorrelated to inputs and population activity. Network linked triggering of AIS-APs versus input independent timing of RA-APs 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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Poster ID:115

Functional perspectives of Tarpy2 peptide as a molecular tool in the oligomerization of a repurposed retrotransposon protein, Arc

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Arc, the activity-related cytoskeletal protein, is an early gene product and the analog of the retrotransposon Gag protein. There are several studies revealing the pivotal role of Arc in longterm memory trace formation. Arc participates in synaptic plasticity and Arc KO mice show memory deficits. Recently, it was discovered that Arc, similarly to Gag protein, is able to form capsid-like structure encapsulating RNA, and the capsids are able to move from one cell to another. One of our aims was to develop capsid isolation methods allowing the collection of a large amount of capsids for mRNA sequencing. The other aim was to develop peptides to prevent capsid formation for analysis of the functional role of the Arc capsid form. In the present study, we show isolated capsids of Arc from brain tissue samples which were validated by electron microscopy. Since it is known that Arc binds the Tarp protein family, particularly Tarpy2, we synthetized a peptide (RIPSYR) having the sequence of the Tarpy2 Arc binding motif. We demonstrated that this peptide is able to bind the N-lobe region of recombinant Arc and several proteins in cortical synaptosome lysate by magnetic bead-based assay. Using MS-based protein identification, we revealed four proteins that bind to Tarpy2 peptide with at least 2.5 fold abundances compared to negative control samples. Three of them, Marcks, Basp1, and Gap-43, participate in the generation of filopodium and in the control of synapse size. The same peptide is predicted to inhibit capsid formation because of aspecific protein binding site of Arc is involved in the oligomerization of Arc.

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Poster ID:215

Day 2

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 μ m 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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Poster ID:315

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

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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 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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Poster ID:116

Day 1

The subtype selective RGH-397 inhibits the function of α 5 GABAA receptors with slow off-kinetics and shows efficacy in animal models of cognitive impairment

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The majority of fast inhibitory neurotransmission mediated by the GABAA receptor in the mammalian brain. Inhibiting of the function of α 5 subunit containing GABAA receptor (α 5 GABAAR) could result in restoring the normal neuronal activity in the pathologic processes of cognitive impairment. Chemical optimization of novel naphthyridine derivatives resulted in RGH-397 a subtype-selective negative allosteric modulator (NAM) of α 5 GABAARs. Here we show the in vitro and in vivo characterisation of this compound. Displacement assays were performed using the benzodiazepine site radioligand [3H]Ro15-1788. Cell membranes were prepared from HEK-293 cells stably expressing human α 5 β 3 γ 2, α 1 β 3 γ 2 and α 2 β 3 γ 2 GABAARs. Receptor function was investigated using automated and manual whole-cell patch clamp. Effect on the activity of pyramidal cells was tested on the CA1 region of rat hippocampal slices. For in vivo characterisation RGH-397 was orally applied to rats in the novel object recognition paradigm after subchronic administration of phencyclidine (PCP) and in the neonatal PCP-impaired social recognition test, where neonatal saline-treated, group-housed rats were compared to PCPtreated, isolated animals. RGH-397 potently displaced [3H]Ro15-1788 with Ki values of 4.1±1.3, 221±26 and 161±38 nM for α 5 β 3 γ 2, α 1 β 3 γ 2 and α 2 β 3 γ 2 GABAARs, respectively; and could be characterized by kon of 0.341±0.138 (nM-1x min-1) and a residence τ of 2.0±0.2 min for α 5 β 3 γ 2 GABAARs. The compound inhibited the current mediated by α 5 β 3 γ 2 GABAAR with an IC50 of 330 nM and a maximal effect of 41% with relatively slow off-kinetics when compared to the reference compound basmisanil; while showed no significant inhibition of $\alpha 1\beta 3\gamma 2$ and $\alpha 2\beta 3\gamma 2$ GABAAR currents. RGH-397 (at 10 μ M) caused only 10% inhibition on the population spike amplitudes and no epileptogenic effect was observed in rat hippocampal slices, probably due to the lack of α 1 GABAAR inhibition. RGH-397 proved to be efficacious in rat in vivo tests: it produced a significant reversal of a PCP-induced cognitive impairment in the NOR test at 10 mg/kg and restored the preference for new juveniles of PCP-treated-isolated animals (at 3 mg/kg). RGH-397 is a potent and selective NAM of $\alpha 5\beta 3\gamma 2$ GABAARs. It shows relatively slow offkinetics both in displacement and functional studies. The long-lasting action of RGH-397 on GABAARs might be advantageous for in vivo effectiveness. RGH-397 shows in vivo efficacy in animal models of cognitive impairment.

Poster ID:216

Sclareol is a low-potency non-selective inhibitor of Cav1.3 and Cav1.2 Ltype Ca2+ channels

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Backgound: A recent study proposed sclareol, a bicyclic diterpene alcohol, to be a Cav1.3 subtype-specific blocker with neuroprotective properties in a mouse PD model. Indeed, a growing body of preclinical evidence is linking Cav1.3 L-type Ca2+ channel-mediated oscillatory dendritic Ca2+-transients in vulnerable substantia nigra dopamine neurons (SN DA) to their selective cell death in Parkinson's disease (PD). Therefore, the selective pharmacological inhibition of Cav1.3 channel activity may provide neuroprotection in early PD. Currently available Ca2+-channel blockers are also potent inhibitors of Cav1.2 L-type channels, which explains doselimiting hypotensive side effects in PD patients. Aim: Our aim was to investigate the Cav1.3selectivity of sclareol in whole-cell patch-clamp experiments. Isradipine, a non-selective potent Ca2+ channel blocker, was used as a control. Methods: Whole-cell patch-clamp recordings were performed in HEK-293 cells stably expressing β 3 and α 2 δ 1 subunits together with either Cav1.3S (C-terminally short variant) or Cav1.2 α 1-subunits. Various pulse protocols were employed to study potential voltage-dependent (holding potentials, HP, -89 or -59 mV, 50 ms square pulses, 0.1 Hz) and inhibition during command voltages mimicking the SN DA neuron action potential (2.5 Hz). Results: At -89 mV HP sclareol inhibited Cav1.2 (IC50: 12.2 μM) and Cav1.3S (IC50: 16.9 μ M) with similar IC50s (p = 0.49), more than 100 times higher than the IC50 for isradipine under the same conditions (Cav1.3S IC50: 135.8 nM). Moreover, the percentage of remaining Cav1.3S currents with 10 µM sclareol was not significantly different when cells were depolarized from -89 mV HP (65.2%) in comparison to -59 mV HP (63.9%; p = 0.89). Sclareol's potency and selectivity was also similar during stimulation using a SN DA-like activity pattern (percentage remaining current, 10 µM: Cav1.3S: 59.2 %, Cav1.2: 48.8 %), suggesting that it is non-selective for Cav1.3 and does not act in a voltage- and frequency-dependent manner. Conclusions: By using various stimulation protocols we show that sclareol is neither a subtype-selective nor a potent blocker of heterologously expressed Cav1.3 channels. The previously reported neuroprotective effects of sclareol in a mouse PD model is therefore likely due to effects on other signaling pathways.

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Poster ID:316

Day 3

Calretinin-immunopositive interneurons of the caudate nucleus and dorsolateral prefrontal cortex in primate brain evolution

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Calretinin-immunopositive interneurons represent a major class of interneurons both in the caudate nucleus and dorsolateral prefrontal cortex. Their impairment has recently been demonstrated in autism spectrum disorder and schizophrenia. The diversification of calretinin-immunopositive interneurons in primate evolution has been reported by transcriptomic and neurohistological studies. Nevertheless, no comprehensive investigation has been carried out regarding the topography of calretinin subclasses and their functional diversity in closely related non-human primate species. Our study aims to harness the opportunity provided by the Primate Brain Collection and reveal differences and similarities in the distribution of calretinin subtypes in more than 10 primate species. The current work will help our understanding of the trends in human brain evolution and disease mechanisms of autism spectrum disorder and schizophrenia.

Poster ID:117

Morphological and physiological features of chandelier cells in the prefrontal cortex recorded in two transgenic mouse lines

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Chandelier cells (ChCs) that are present only in cortical structures selectively form synapses on the axon initial segments (AISs) of principal cells (PCs) – the site of action potential generation. Although these GABAergic cells are in the position to control the spiking of their postsynaptic partners in the most powerful way, investigating their characteristics has been technically limited. However, recent advances in more specific ChC labeling techniques allow us to study the diversity within the ChC population in more detail. Here, we compared anatomical and electrophysiological features of ChCs sampled in the medial prefrontal cortex (mPFC) of the Nkx2.1-Cre and PVeGFP mouse lines. By performing whole-cell recordings from ChCs in acute prefrontal cortical slices prepared from the two transgenic mouse lines, we found that ChCs labeled with the two approaches differed both in their passive and active membrane properties. Our paired recordings revealed that ChCs of the Nkx2.1-cre line evoke unitary inhibitory postsynaptic currents (uIPSCs) in PCs with significantly slower kinetic properties, but the shortterm dynamics of these synapses are similar to those recorded from the PVeGFP mouse line. Filling recorded ChCs with biocytin enabled us to analyze their morphological properties post hoc. The distribution of axons and dendrites of ChCs sampled in the two transgenic mouse lines showed some differences between layers, indicating potentially distinct input and output features. Additionally, we observed that the length of innervated AISs or the percentage of AISs targeted in a given area by the ChCs are comparable, but ChCs in the Nkx2.1-cre line establish fewer boutons on individual AISs. Taken together, these results show that ChCs in the mPFC show anatomical and electrophysiological differences in their inhibitory connections. The variability of ChC properties in prefrontal cortical microcircuits might be an important factor in the control of local network operation.

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Poster ID:217

Neuronal-specific septin-3 is connected to autophagy in neurons

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In synapses that are prone to immune-mediated pruning, C1q, the first component of the classical pathway of the complement system of innate immunity, is attached to the synaptic membrane. In these tagged synapses an elevated level of neuronal-specific septin-3 can be observed. The amount of surface-bound C1q and presynaptic septin-3 show positive correlation, however, the role of septin-3 remains elusive. Here, we show that septin-3 participates in neuronal autophagy, through binding ATG8 autophagy protein homologs LC3B and GABARAPL2. In primary neurons, the co-localization of septin-3 and LC3B is elevated during chemical-induced autophagy in primary neurons, also, the changes in levels of septin-3 follow the levels of the autophagy marker p62 in chemically enhanced and blocked autophagy experiments. In electron microscopy study, we detected septin-3 attached to ATG8 positive autophagic membranes in mouse brain slices. Based on our results, we propose that elevated septin-3 levels indicate ongoing or impeded autophagy in synapses targeted to pruning.

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Poster ID:317

Chemosensor TRPA1 modifies T lymphocyte activation *in vitro* and influences CD4+/CD8+ T lymphocyte ratio *in vivo*

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Transient Receptor Potential Ankyrin 1 (TRPA1) is a non-selective cation channel involved in sensation and sensitization to a plethora of inhaled, touched or orally consumed irritating cysteine-reactive agents and also endogenous mediators of oxidative stress such as nitric oxide, hydrogen peroxide, and inflammatory signals. TRPA1 has been reported to influence neuroinflammation accompanied by feedback mechanisms, macrophage and also lymphocyte function, but its complex role is still controversial in immune cells.

We reported earlier by analyses of immune phenotype and activation characteristics of TRPA1deficient mice (knockout—KO) generated by targeted deletion of the pore-loop domain of the ion channel, that the absence of functional TRPA1 modified CD4+/CD8+ thymocyte ratios, diminished CD4/CD8 rates, and B cell numbers in the KO mice in vivo. Lower cytokine (IL-1 β , IL-6, TNF- α , IL-17A, IL-22, and RANTES) secretion was observed in KO lymphocytes, but basal intracellular Ca2+ level and TcR-induced Ca2+ signal did not differ significantly between WT and KO in T lymphocytes originated from lymphatic organs.

The aim of our present studies was to investigate endogenous TRPA1's role in TcR-mediated activation of peripheral lymphocytes in vitro, by analysing potent selective small TRPA1 agonist JT010 on the activation of T and B lymphocytes isolated from peritoneal cavity of mice. A concentration-dependent significant inhibitory effect of JT010 could be observed on TcR-induced Ca2+ signal of peripheral T lymphocytes and CD4+ T lymphocytes, while JT010 neither modified peritoneal B cell activation nor ionophore ionomycin stimulated elevation of intracellular Ca2+ level.

Though TRPA1 proved not to be a key regulator of TcR (anti-CD3 only) stimulated calcium signaling in our earlier studies, its function negatively modulated T lymphocyte but not B lymphocyte activation. Our results indicate that modulation of TRPA1 receptor/channel by an agonist/agent may lead a more complex, cell type-, localization- (environment-, stage-) specific effect on immune cell activation, then signaling through elevation of intracellular Ca2+level by opening the Ca2+/cationic channel.

Poster ID:118

Day 1

Synthetic peptide designed based on the Arc binding epitope of the TARP γ -2 protein inhibit the switch from earliest phase of LTP to later phase

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Arc, the activity-regulated cytoskeleton-associated protein is known to be a key regulator of the late phase of LTP. Here, we studied an Arc binding peptide derived from the Arc binding motif of TARP y-2 protein to uncover its effect on LTP. Previously, using magnetic nano-bead affinity precipitation experiments, we revealed that the peptide binds to 3 proteins (BASP1, GAP43, MARCKS) that are members of the molecular network of filopodium initiation and synapse enlargement processes already known to be involved in synaptic plasticity. We tested the potential inhibitory effect on neuronal development of branches of neurons in primary cell cultures treated with the TARP y-2 Arc binding peptide. Then, we performed a short LTP model using high frequency stimulation and theta burst stimulation models of LTP in anesthetized rats and we measured the effect of different doses on LTP. We found, that right after the stimulation, the initial phase of LTP develops, however, after 5 min, the LTP attenuates and returns to the baseline. The effect was dose-dependent and a 750 micromolar dose proved to be the most effective. Our data-based hypothesis is that modulation of filopodia, axon, and dendrite growth in neurons could be inhibited by this short peptide. Such an inhibition, by separating the early steps from the late phase events, could explain the observed effects on the attenuation of LTP. Based on these results we propose that the synthetic peptide, based on the Arc binding motif of TARP y-2, might be a valuable research tool for studying the initial steps of LTP development.

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Poster ID:218

mRNA expression of two neuronal markers and a potential target for pain relief in the Trigeminal Ganglion of rats with inflammation-induced orofacial pain

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Introduction: Orofacial pain disorders are among the most severe pain syndromes involving the head, face and neck. Apart from dental caries and periodontal diseases, the majority of them is caused by musculoskeletal and neuropathological diseases. The hypothalamic nonapeptide oxytocin binds and activates its receptor in primary sensory neurons of the peripheral sensory system, where it is thought to have an antinociceptive effect. This study used an animal model of inflammation-induced orofacial pain to examine the gene expression of the oxytocin receptor (OTR), c-Fos, an indicator of neuronal activity, and α -calcitonin gene-related peptide (α CGRP), a characteristic neurotransmitter of a significant portion of the trigeminal afferents. Material and methods: Carrageenan (100 μ l, 2% w/v) was unilaterally injected into the vibrissal pads of male and female (nullipara, non-lactating) adult Wistar rats (8-10 weeks old). Mechanical hypersensitivity was checked by Ugo BasileÒ Orofacial Stimulation Test and RT-qPCR was performed to analyze the levels of OTR, c-Fos, and CGRP mRNA (CALCA) expression in TGs 24 hours after injection. Results: The orofacial operant tests established that the mechanical thresholds significantly decreased in both male and female rats one day after the carrageenan administration. The qPCR analysis revealed greater fold changes in the c-Fos (mean±S.E: 9:3.9±0.19; ♂:3.55±0.18) and CALCA (9:2.84±0.13; ♂:3.39±0.47) expression levels of mRNA in the TGs adjacent to the injection site, and a moderate rise in the expression of the OTR mRNA (♀:1.52±0.07; ♂:1.49±0.07) was seen in comparison to untreated controls. Conclusion: An inflammatory substance injected into the orofacial area stimulates the peptidergic neurons in the TG, as evidenced by the rise in CGRP and c-Fos mRNA expression. Furthermore, we think that oxytocin can affect the intensity of pain that inflammation-triggered nociceptive neurons transmit by enhancing their signaling capacity due to elevated OTR expression. Since the outcomes in the animal model mirror those in humans, they may aid in the planning and development of novel OTR-focused treatments for the alleviation of orofacial pain.

Day 3 Poster

ID:318

β subunits of GABAA receptors form proton gated ion channels

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GABAA receptors are pentameric ligand-gated anion channels (pLGIC) permeable to chloride and bicarbonate. These receptors mediate fast signal transmission in the central nervous system (CNS) as well as periphery. While the Gloeobacter violaceus ion channel (GLIC) is a prokaryotic pLGIC homologue being gated upon proton application, protons as agonists have not been shown to activate GABAA β receptors. We describe, for the first time, direct activation of homopentameric GABAA β 3, β 2 and β 1(S265N) receptors by protons in a concentrationdependent manner (pH50 is in the range 6 - 6.3). Steady-state activation and desensitization of β homomeric GABAARs revealed significant window currents at physiological pH suggesting the possibility that a significant fraction sojourns in an open state. In order to identify the location of putative proton activation site(s) we mutated the protonable residues in the pore forming transmembrane region (TM2) of β 3 GABAAR. Mutation of H267A completely prevented channel activation by acidification and, simultaneously, induced significant picrotoxin sensitive baseline currents indicating an increased open probability. Furthermore, the introduction of histidine (G331H) and glutamate (A334E) in homologous positions of the proton insensitive GABAAR r1 subunit transfers proton-dependent gating, thus highlighting the role of this interaction in proton sensitivity. This is also supported by molecular dynamics simulations indicating that protonation of H267 increases formation of hydrogen bonds between E270 and H267 leading to a pore stabilising ring formation and accumulation of Cl- within the transmembrane pore. Deprotonation of H267 is accompanied by a general broadening of the transmembrane pore and expulsion of Cl-. Our findings warrant studies on the molecular base of proton dependent gating and a potential physiological and pathophysiological impact of this novel channel type.

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Poster ID:119

Day 1

Activity dynamics of hippocampal CA1 pyramidal neurons during virtual navigation

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The hippocampus plays a critical role in spatial and episodic memory by creating and storing unique representations of visited environments as activity patterns of principal neurons tuned to specific locations. However, the generation, consolidation and use of hippocampal spatial representations during learning and navigating in environments under variable cognitive demands is incompletely understood. To investigate the development and flexible reorganization of spatial tuning of hippocampal CA1 pyramidal cells (CA1PCs), we implemented a virtual spatial navigation paradigm for head-fixed mice allowing two-photon imaging of Ca2+ activity in CA1PCs. Transgenic Thy1-GCaMP6s mice were implanted with a hippocampal imaging cannula and a head plate for head fixation. Water-restricted mice were trained to collect water rewards at specific locations in two visually different virtual environments. We recorded behavioral parameters (speed, licks) and imaged GCaMP6s-mediated Ca2+ signals in hundreds of CA1PCs over consecutive days, including during 1) initial learning, 2) switches between randomly varied or continuous blocks of presented environments, and 3) exposure to a novel environment. Mice were able to efficiently differentiate between the two virtual corridors and learn the location of the reward zone in both, as demonstrated by speed and lick selectivity. As mice became expert in the task, the ratio of spatially tuned neurons increased, especially near and in the reward zones. We observed gradually developing selective representations of familiar environments, which became more stable and decorrelated from each other. Switching to a simpler task version (blocks of corridors) resulted in stronger decorrelation of the two corridor representations. In turn, exposure to a novel environment disrupted the animals' behavior and led to global remapping. Our results indicate refinement of CA1 coding dynamics during learning and in response to subtle and robust changes in the environment and task structure.

Poster ID:219

Antiepileptic effect of the GABA precursor putrescine in early termination of seizures

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Endogenous anticonvulsant mechanisms are prosperous and still-evolving approaches to prevent recurrent seizures and may serve as the basis for novel original therapeutics. We previously revealed that uptake of Glu during seizures triggers GABA release from astrocytes through GAT-3 transporter and this negative feedback mechanism effectively shortens seizure duration. Here, we looked at whether enhancing the Glu-GABA exchange mechanism in astrocytes by using the astrocytic GABA precursor putrescine (PUT) could be useful in treating both convulsive and nonconvulsive seizures. We observed that PUT application dose-dependently shortened seizure-like events (SLEs) in the low-[Mg2+] in vitro model of temporal lobe epilepsy, where increasing the PUT concentration further lowered the average SLE duration compared to the control. Importantly, this antiepileptic PUT effect was not observed when SNAP-5114, a specific blocker of astrocytic GAT-3 transporter was present. Instead, SLE duration in the presence of PUT and SNAP-5114 significantly increased compared to PUT application alone demonstrating that PUT reduces seizure duration by increasing glial GABA release through the Glu-GABA exchange mechanism. Moreover, in the presence of PUT, the decreasing high frequencies, characteristic to the tonic phase of SLEs were totally absent, indicating that PUT specifically impacts depolarization-induced tonic desynchronization. We also observed that PUT produced a significant depression of spontaneous depolarizing potentials (dSPs). The inhibitory synaptic potentials (hSPs), on the other hand, were unaffected, suggesting that the PUT-derived GABA acts on extrasynaptic receptors In summary, PUT shortens SLEs by increasing desynchronization. Since PUT is a major source of glial GABA and we previously demonstrated significant GABA release in response to Glu uptake, it is suggested that the astroglial Glu-GABA exchange mechanism plays an important role in limiting ictal discharges, potentially opening up novel pathways to control seizure propagation and generalization.

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Poster ID:319

Day 3

Motor neuron and spinal interneuron diversity scale up during frog metamorphosis

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Frog metamorphosis captures simple swimming and complex tetrapod limb movement in one organism. Tadpoles first engage in periodic undulatory swimming (NF 37-38); then switch to constant free-swimming (NF 47-50); and finally, to four-limbed movements such as walking, hopping, and scratching (NF 57-adult). We aim to capitalize on this unique metamorphic behavioral switch to determine how spinal neuron diversity differs for swimming and walking. We focus our analysis on motor neurons (MNs) and V1 interneurons (V1s), a class of spinal inhibitory interneurons that modulate motor neuron firing. We find MN and V1 number and transcriptional heterogeneity scale up with the complexity of behavior. The larval tadpole spinal cord contains a largely uniform population of medial motor column MNs and associated V1s. With the emergence of free swimming, MNs and V1s double in number and begin to diversify in their transcriptional profile, acquiring MN populations equivalent to the mouse hypaxial and preganglionic motor columns and V1 subpopulations equivalent to clades. Finally, at metamorphosis, limb motor column neurons are added, and V1 number and diversity increase dramatically, with the same transcriptional V1 clade and subclade diversity observed in froglets as in the developing mouse. Our work maps MN and V1 molecular properties onto swim and limb behavior during frog metamorphosis, defining how transcriptional diversity scales up with behavioral complexity. We additionally demonstrate the conservation of MN and V1 molecular organization between the frog, the most ancient tetrapod, and the mouse, a four-limbed mammal.

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Day 1

Distinct axonal mechanisms in lateral and medial entorhinal cortical inputs to hippocampus

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Lateral and medial entorhinal cortices (LEC and MEC) form morphologically similar axonal bundles in the dentate gyrus, but they carry distinct physiological information about objects and spatial context, respectively. Here we tested whether and how axonal signaling contributes to the different physiological functions of LEC and MEC. First, we used direct patch clamp recording to measure action potential (AP) characteristics of immunohistochemically and morphologically identified LEC and MEC axons in the dentate gyrus. These experiments revealed remarkably different AP shapes in the two axon types. While MEC axons had narrow APs -that is typical in most axons-; the APs of LEC axons were unusually wide. Furthermore, MEC axons showed activity-dependent broadening, while the shape of the LEC axon APs was stable. These findings suggest that MEC and LEC axons form substantially different output signals that fit their functional characteristics as the wider LEC APs can promote reliable and unconditional transmission of object information, while the plasticity of MEC axon APs can be important for the adaptation of spatial information transfer. We then applied outside-out patch measurements to study the active ionic mechanisms relevant to AP dynamics. Our data imply that lower amounts of potassium currents (IK) are responsible for the unusually wide APs in the LEC axons, while MEC axon APs are accelerated by additional IK. We also investigated the potassium channels that contribute to the different AP signaling. Patch-Seq data from retrogradely labeled LEC and MEC cells revealed differences in the expressed potassium channels. We are currently testing their contribution by measuring the effects of different IK blockers on calcium signals in axons originating from LEC and MEC. The AP dependent calcium signals of LEC and MEC axons show different sensitivity to broad-spectrum potassium blockers, TEA and 4-AP. This observation supports the hypothesis that specific potassium channel functions can underlie different axonal signaling in MEC and LEC axons that can be further tested with subunit-specific potassium channel inhibitors. Altogether, our results suggest that LEC and MEC axons have fundamentally different signaling mechanisms that can contribute to the functionally different information transfer from LEC and MEC regions to the hippocampus.

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Day 2

Gain modulation of spatial tuning by vasoactive intestinal peptide expressing inhibitory neurons in cortical circuits

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Inhibitory neurons control how principal neurons (PNs) integrate excitatory synaptic inputs into output firing rate. By controlling distinct subcellular domains, inhibition enables PNs to perform various input-output computations. Gain modulation is one among these fundamental cortical computations: PNs can adapt to different sensory input strengths while maintaining input tuning selectivity. However, in sensory cortices, inhibitory neurons that express vasoactive intestinal peptide (VIPs) has been shown to control the gain of auditory and visually tuned neurons by disinhibiting their dendrites (1, 2), the role of VIPs in modulating spatial tuning has not been explored. To address this, we explored the modulation of spatial selectivity of principal neurons by VIP cells in the retrosplenial cortex (RSC), a major hippocampal target. We studied spatially tuned neurons recently has been described in the RSC (3), and analyzed the change in their tuning properties during optogenetic manipulation of VIPs. We employed two-photon microscopy and Ca2+ indicators in head restrained mice that perform a goal-oriented spatial task. First, we recorded activity of VIPs by using VIP-Cre transgenic mice injected with Credependent GCamp6s virus. Our results showed that most VIPs are either activated or inhibited by locomotion, confirming previous work in other brain areas. Next, to test how VIPs affect the spatial tuning properties of PNs in RSC, we crossed VIP-Cre mice with Thy1-GCaMP6s mice and used optogenetics (Cre-dependent ChrimsonR and ArchT viruses) to either up- or downregulate VIP activity, while we imaged simultaneously the activity of PNs. The optogenetic experiments showed that activation of VIPs increases place cell responses, and accordingly, inhibition of VIPs decreases place cell responses without changing spatial selectivity. Changes in spatial tuning curves showed that VIPs exert a purely multiplicative/divisive modulation on PN activity. Moreover, using Bayesian decoding models we showed that spatial information significantly decreases when VIPs were inhibited, whereas it increases when VIPs cells were activated. Altogether, these data demonstrate the ubiquitous role of VIPs in controlling gain in cortical circuits and highlight a key contribution to spatial coding in the cortex. References: (1) Pi et al., Nature, 2013, 28;503(7477):521-4; (2) Zhang et al., Science, 2014, 8;345(6197):660-5; (1) Mao et al., Nature Communications, 2017, 15;8(1):243.

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Day 3

Investigation of astroglial heterogeneity in the human cortex and caudate nucleus

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Astroglia and neurons populate the human cerebral gray matter in a 1:1 ratio. While there is much information available on the diversity of neuronal populations, relatively little is known about that of the astroglia. We aimed to quantitatively investigate different astroglial populations present in the human cortex and caudate nucleus with morphometric and topographic analyses. We focused on the dorsolateral prefrontal cortex whose involvement in neuropsychiatric disorders is already demonstrated. Human brain tissue was provided by the Netherlands Brain Bank and Oxford Brain Bank. Our results showed that GFAP+ and ALDH1L1+ astroglial populations were distributed in a partially overlapping pattern in the dorsolateral prefrontal cortex. The GFAP+ population was preferentially located in L1 and L6, whereas the ALDH1L1+ population was predominantly found in L2-L5. Furthermore, two times more ALDH1L1+ than GFAP+ astroglia was found in both the cerebral cortex and caudate nucleus. Our study indicates diverse astroglial populations distributed in the human cerebral cortex and caudate nucleus in a complementary fashion. Furthermore, our results suggest that the use of GFAP in routine pathological investigations only informs about approximately one-third of the cortical astroglia. Regional distribution of diverse astroglial populations was mapped quantitatively in the human grey matter which will allow future investigations of potential astroglial alterations in conditions such as autism spectrum disorder and schizophrenia.

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Poster ID:121

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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Day 2

Cyclodextrins affect TRPV1 and TRPA1 channel activation via lipid raft disruption

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Transient Receptor Potential Ankyrin 1 (TRPA1) and Vanilloid 1 (TRPV1) are nociceptors involving in pain sensation and development of neurogenic inflammation. These non-selective cation channels are located in the lipid rafts, the cholesterol-rich membrane domains of the plasma membrane of primary sensory neurons and peripheral nerve terminals. Cyclodextrins (CDs) are able to form inclusion complexes with cholesterol, depleting it from lipid rafts. Our research group found that lipid raft disruption by Methyl- β -cyclodextrin (MCD) inhibits TRP ion channel function and has analgesic effect in animal models. Different CD derivatives (Randomly methylated β-cyclodextrin: RAMEB, (2-Hydroxypropyl)-γ-cyclodextrin: HPGCD, (2-Hydroxyproyil)- β -cyclodextrin: HPBCD, Sulfobutylated β -cyclodextrin sodium salt: SBECD and (2-Hydroxy-3-N,N,N-trimethylamino) propyl-β cyclodextrin: QABCD; CycloLab Ltd.) were tested in respect of their cytotoxicity (1, 3, 10, 50, 100 mM; 24 h) on chinese hamster ovary (CHO) cells with CellTiter-Glo® Luminescent Cell Viability Assay. To reveal the effect of 24-hour CD treatment on mitochondrial functioning of CHO cells MitoTracker™ Red CMXRos fluorescent dye was used in laser scanning confocal microscopic experiments. Radioactive 45Ca2+-uptake measurements were performed on TRPA1 and TRPV1 receptor-expressing CHO cells to detect alterations in receptor activation after CD treatment. In CellTiter-Glo® Luminescent Cell Viability Assay the methylated derivative RAMEB showed significant cytotoxic effect in 3.5 mM concentration, but none of the non-methylated derivatives decreased cell viability in 10 mM concentration. HPBCD treatment (1 mM and 10 mM) and QABCD treatment (10 mM) resulted in significantly increased fluorescence intensities of CHO cells' mitochondria labeled with MitoTracker™ Red CMXRos. All of the investigated CDs were able to inhibit the 45Ca2+-uptake in TRPA1 and TRPV1 receptorexpressing CHO cells in a concentration dependent manner. In conclusion, non-methylated derivatives have much lower cytotoxicity compared to RAMEB, HPBCD and QABCD affected significantly the mitochondrial function and all investigated CD derivatives were able to inhibit TRPA1 and TRPV1 channel activation, presumably via the disruption of lipid rafts. Targeting hydrophobic interactions of the protein-lipid interface seems promising to be a novel mechanism of action in analgesia.

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Poster ID:321

SATB2 organizes the 3D genome architecture of cognition in cortical neurons

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SATB2 is genetically associated with human intelligence (1). Since its protein structure predicts a function in DNA loop formation (2), we analyzed the impact of SATB2 on the three-dimensional (3D) genome architecture and chromatin accessibility in cortical neurons. Our data reveal strong effects of SATB2 on chromatin looping between enhancers and promoters of neuronal activityregulated genes. We also identify SATB2-dependent alterations in A/B compartments, Topologically Associated Domains (TADs) and Frequently Interacting Regions (FIREs), which closely correlate with gene expression. Gene sets with SATB2-dependent 3D genome changes are highly enriched in genes with specialized neuronal functions. Notably, different gene sets are affected by loss of SATB2 at each 3D genome architectural level and show little overlap between them. All level-specific gene sets combined, we find that SATB2 affects the spatial organization of almost half of all genes within neuron- and cognition-related GO categories. The affected genes contribute to the genetic mechanisms of cognitive ability, neuropsychiatric and neurodevelopmental disorders. The altered non-coding regions are enriched for common variants associated with educational attainment, intelligence and schizophrenia. Our data establish SATB2 as a 3D genome organizer that operates both independently and in cooperation with CTCF to set up the chromatin landscape of pyramidal neurons for cognitive processes.

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Poster ID:122

Nanobodies targeting $\alpha 2\delta$ proteins to study the molecular synaptic organization

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Background: Neuronal communication depends on signal conduction between neurons at synaptic sites via neurotransmitter release into the synaptic cleft. Neurotransmitter release is triggered by calcium influx through voltage-gated calcium channels (CaV). CaV complexes consist of a pore-forming $\alpha 1$ subunit, an intracellular β , and an extracellular membrane-anchored $\alpha 2\delta$ subunit. To date, four $\alpha 2\delta$ isoforms ($\alpha 2\delta$ -1 to -4) are known, with $\alpha 2\delta$ -1 to -3 being abundantly expressed in brain. $\alpha 2\delta$ subunits have crucial roles in regulating CaV channel trafficking and current kinetics as well as synapse formation. Consequently, mutations in $\alpha 2\delta$ subunits are linked to neurological disorders such as epilepsy, schizophrenia, and autism spectrum disorders. Up to now, the interacting proteins with $\alpha 2\delta$ within the synaptic cleft are still not well known. Even though the synaptic cleft is relatively wide, not all classical antibodies are capable to reach and bind to epitopes of the targeted proteins in this area. Within this project, we are aiming to use an epitope tag (ALFA) along with a comparable smaller variant of antibodies, known as nanobodies, to detect $\alpha 2\delta$ subunits at synaptic locations. Methods: The previously published cryo-EM structures of CaV1.1, CaV1.3 and CaV2.2 channel complexes made it possible to test and to identify alternative tag positions within the $\alpha 2\delta$ subunit. We successfully cloned a single ALFA-tag into a new location (compared to the one previously used for HA tags). To detect the ALFA-tag, we used a recombinantly expressed anti-ALFA nanobody fused to an mCherry fluorophore. Results: ALFA-tagged $\alpha 2\delta$ -2, expressed in tsA-201 cells along with CaV2.1 and β 4e subunits, shows similar calcium current modulation when compared to wild type $\alpha 2\delta$ -2. A specific interaction between ALFA-tagged proteins and the nanobody could be confirmed by an in vitro pulldown assay. Preliminary fluorescent microscopy experiments on hippocampal neurons, transfected with ALFA-tagged $\alpha 2\delta$ -2, show a specific staining of $\alpha 2\delta$ -2-ALFA proteins by mCherryfused anti-ALFA nanobodies. Perspectives: We will test modified positions of the ALFA-tag and the use of double ALFA-tags to improve detection sensitivity of $\alpha 2\delta$ -2 in the synaptic cleft. Ultimately, we are aiming to fuse an APEX2 enzyme to the nanobody in order to biotin label all proteins, which are in close proximity to $\alpha 2\delta$ -2.

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Day 2 Poster

ID:222

Role of pre- and postsynaptic PirB for hippocampal asymmetry formation

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Left-right asymmetry is a fundamental feature of higher-order brain structure and function. In the mouse hippocampus, properties of synapses between pyramidal cells depend on the hemispheric location of presynaptic CA3 neurons. In stratum radiatum, right-input synapses consist of larger postsynaptic density (PSD) with higher ratio of perforations and lower density NR2B subunits compared with left-input synapses. The major histocompatibility complex class I (MHCI) and immunoglobulin-like receptor B (PirB) are essential for the formation of this inputside dependent asymmetry, implying a potential trans-synaptic signalling via MHCI and PirB. We aimed to investigate if the PirB is necessary for signalling on the input or target side. To this end, we conducted electrophysiological and morphological analysis. NMDA EPSCs at the PirB-deficient mice (KO) pyramidal cell synapses showed no asymmetry in sensitivity to a NR2B-selective antagonist. Postsynaptic, but not presynaptic AAV-mediated PirB expression rescued this asymmetry. However, ultrastructural analysis revealed that conditional KO of PirB in either preor postsynaptic neurons abolished the asymmetry. Both left- and right-input synapses showed a low perforation ratio similar to that of wild-type left-input synapses. This suggests that PirB is necessary on both sides of the synapse for the asymmetry formation. Our results indicate that PirB expression in target side is critical for the asymmetry formation. The discrepant results of presynaptic PirB manipulation might be due to its indirect effects on postsynaptic PirB expression. Further work is needed to elucidate how the PirB in the pre and postsynaptic sites work in concert for the generation of hippocampal asymmetry.

Poster ID:322

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 (α 1E), which belongs to the Rtype 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 α 1 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 somatodendritic labelling pattern is similar to the previously characterized expression patterns of the Ltype 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.

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Galectin-1 as a marker for microglia activation in the aging brain

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Microglia are the brain's resident immune cells that express immune regulatory molecules that play a central role in age-related brain phenotypes. According to our hypothesis, an antiinflammatory member of the beta-galactoside-binding lectin family, galectin-1, regulates microglia related to neuroinflammation in the aging brain. Our in silico analysis revealed a microglia sub-cluster in the aged mouse brain with enriched galectin-1 mRNA expression. In our mixed rat primary cortical cell cultures, the OX42(CD11b/c)-labeled ameboid microglial cells changed to a ramified, branched phenotype during long cultivation; meanwhile, the expression of galectin-1 completely disappeared. In our Western blotting analyses, the galectin-1 protein content of our cultures decreased with cultivation time. Furthermore, the immune activator lipopolysaccharide significantly increased the expression of the galectin-1 protein in microglial cells. Flow cytometry indicated that some of the expressed galectin-1 was localized on the cell surface of the microglial cells. We found a link between chronological aging and galectin-1 expression based on transcriptomic analysis of galectin-1 in a distinct microglial subpopulation in an animal model of aging. Moreover, our in vitro study showed that the expression of galectin-1 is associated with the activated functional state of microglia cells with specific ameboid morphological characteristics. From our results, we identify galectin-1 as an aging coupled microglia activation marker.

Cellular neuroscience

Poster ID:223

NLRP2 inflammasome activation in spinal astrocytes is potentiated by glutamate

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Chronic neuroinflammation plays an increasingly accepted role in the induction and/or maintenance of persistent pain states. Activated glia are capable to produce pro-inflammatory cytokines which are (among other substances) mediators of neuroinflammation. The prototype of pro-inflammatory cytokines is IL-1beta. The maturation of IL-1beta is under the control of multiprotein complexes called inflammasomes. We reported earlier that when mechanical allodynia was highest in the CFA model of inflammatory (nociceptive) pain, spinal astrocytes (SA) are responsible for the production of IL-1beta and we identified NOD-like receptor protein 2 (NLRP2) inflammasome sensor on the GFAP+ SA of spinal dorsal horn. However, the receptor (IL-1R) of the cytokine is mostly expressed by neurons and is known to modulate NMDA and AMPA receptor activation. To date the literature on NLRP2 activation is relatively scarce. Thus our aim was to study NLRP2 expression/activation on primary SA cultures. Inflammasomes are activated upon danger or pathogen associated molecular patterns (DAMPs or PAMPs). Extracellular ATP acts as a DAMP and is a well-known activator of all inflammasome types. Glutamate is an excitatory neurotransmitter, but many of the glutamate receptors are expressed on astrocytes as well. Astrocytes are normally involved in glutamatergic neurotransmission by removing excess glutamate from the perisynaptic space. However, when glutamate concentration is increased for prolonged times, astrocytes cannot fulfill these functions anymore and become reactive. In our experiments, we found concentration dependent effect of glutamate on the SA cultures and when glutamate was used in combination with ATP treatment it lead to NLRP2 overexpression. Besides the inflammasome marker we detected the assembly and cellular re-distribution of apoptosis speck-like protein (ASC) monomers which serve as organizers of inflammasome complexes. In further experiments we utilized the glutamate receptor antagonist, kynurenic acid (KYNA). We measured intracellular calcium concentration changes evoked with 500 μ M KYNA in SA loaded with Fluo-4 AM calcium indicator dye. The average fluorescence intensity normalized to background was 1.78±0.07 F/F0 (average±SEM, 35 cells from 5 independent cultures). In conclusion, ATP and glutamate can provide sufficient signals for NLRP2 activation. How ATP and glutamate collaborates to induce NLRP2 upregulation in SA requires further experiments.

Cellular neuroscience

Poster ID:323

Day 3

AgRP neurons control structure and function of the medial prefrontal cortex

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Hypothalamic agouti-related peptide (AgRP) neurons have a critical role in both feeding and non-feeding behaviors of newborn, adolescent, and adult mice, suggesting their broad modulatory impact on brain functions. Here we show that constitutive impairment of AgRP neurons or their peripubertal chemogenetic inhibition resulted in both a numerical and functional reduction of neurons in the medial prefrontal cortex (mPFC) of mice. These changes were accompanied by alteration of oscillatory network activity in mPFC, impaired sensorimotor gating, and altered ambulatory behavior that could be reversed by the administration of clozapine, a non-selective dopamine receptor antagonist. The observed AgRP effects are transduced to mPFC in part via dopaminergic neurons in the ventral tegmental area and may also be conveyed by medial thalamic neurons. Our results unmasked a previously unsuspected role for hypothalamic AgRP neurons in control of neuronal pathways that regulate higher-order brain functions during development and in adulthood.

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Single-cell gene expression analysis of senescence cerebromicrovascular endothelial cells in mouse model of accelerated aging

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Cellular senescence is a DNA damage induced stress response, which is characterized by permanent cell cycle arrest, functional impairment and secretion of pro-inflammatory factors including cytokines and proteinase. Pre-clinical data strongly supports the hypothesis that ageassociated accumulation of senescence cells in the brain microvasculature, especially among the endothelial cells can significantly contributes to the development of vascular cognitive impairment and dementia in elderly. In our study, raw data from three single-cell experiments containing brain microvascular cells from aged, irradiated and chemotherapy treated mice were pooled and reanalyzed. Irradiation and chemotherapy can induce senescence transformation in the brain and this way can mimic aging phenotype. The single-cell sequencing was performed by the 10X Chromium platform and Illumina technology. Our analysis was conducted in R environment by the help of Seurat workflow. After the initial, stat-of-the art quality control and data integration endothelial cells were identified using canonical endothelial marker genes. Gene set enrichment analysis implemented in the AUCell package was used to detect and count senescence cells. Embedding and clustering analysis found multiple subclusters of senescence endothelial cells. Gene expression between treatment groups and senescence subclusters was compared using the MAST package. The results were interested by the help of Reactome Pathway and Gene Ontology databases. Our findings can help further understand the intracellular signaling pathways in senescence cells which can lead to the development of more efficient senescence cell removal treatments.

Poster ID:224

The phenomenon of compensatory brain activity in older adults as measured by EEG

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Compensatory brain activity in older adults is an important research area concerned with cognitive aging and the possibilities of cognitive enhancement in late adulthood. In the most comprehensive way these issues are addressed by the STAC model – Scaffolding Theory of Aging and Cognition, developed by D. C. Park and P. Reuter-Lorenz. Compensatory brain engagement is the overactivation observed in certain brain regions in older adults which is linked to a better performance on cognitive tasks. In this poster, we present part of the results of a wider research project. We focus here on the STAC model assumptions about the cognitive processes triggered during compensatory brain activity in older adults, such as cognitive control, top-down processing, and executive functions engagement. The study sample comprised both old (60-75 years old, n=54) and young adults (20-35 years old, n=63), without intellectual disability, cognitive impairment and mental disorder. The possibility to assess whether these effects are specific to late adulthood will be ensured by the comparison of the older group with the younger one. Study participants performed the following cognitive tasks during the electroencephalographic measurement: n-back task at three difficulty levels (1-back, 2-back and 3-back) as a measure of updating in working memory; Stroop task and go/no-go task as measures of executive attention and inhibition. The EEG signal was recorded with a 24-bit electroencephalograph using a set of 32 active electrodes (sampling rate: 2048 Hz) arranged according to the international 10/20 system. At the present point in the research, we are finalising the data collection. The analyses planned in the next step concern the neural brain activity accompanying cognitive engagement during particular tasks execution, namely eventrelated oscillations, including event-related synchronization and event-related desynchronization. To examine the event related dynamics of cognitive processing the power of the signal will be estimated in three frequency bands: theta (4-8 Hz), alpha (8-12 Hz) and gamma (30-80 Hz).

Data for this presentation were collected in the research project "Compensatory brain activity in older adults. The search for the electrophysiological indicators of cognitive processes involved in this activity, and its possible changes induced by working memory training", funded by the National Science Centre, Poland (2017/25/B/HS6/00360).

Poster ID:324

Day 3

Tracing statistical learning with frequency tagging in a visual linguistic paradigm

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A great way to track the cortical correlates of statistical learning is frequency tagging (FT), which helps us identify regions associated with segmenting a continuous information stream based on the transitional probabilities between information chunks. FT has been used in auditory linguistic, auditory non-linguistic, and in visual non-linguistic paradigms. So far, most FT studies reported the engagement of central electrodes at the midline. It has been established that statistical learning facilitates reading by acquiring the transitional probabilities between letters, syllables, and words. To our knowledge, neural entrainment with visual linguistic stimuli has not been reported yet. To fill this gap, we conducted an experiment, with written syllables as stimuli. Twenty-nine participants attended to a random and then to a structured stream of syllables at a 2.5Hz stimulation frequency. In the structured stream, triplets of syllables formed artificial words (e.g., tu-pi-ro), and the whole sequence would consist only of such words. If a brain region picks up the structure, then we expect the triplet frequency (one-third of the syllable frequency, 0.83Hz) to be detectable in the EEG signal with an elevated inter-trial phase coherence (ITPC) compared to the random stream. Average ITPCs were calculated on all channels along 4.8s pseudotrials and compared at the syllable and triplet frequencies with paired t-tests (Bonferroni-Holm correction). Scalp distribution was determined with permutation-based statistics with cluster-based correction. ITPC across all channels showed a significant peak difference at the triplet frequency (Δ ITPC0.83Hz = 0.024, t = 3.0788, p = 0.0064) which was absent at the syllable frequency (Δ ITPC2.5Hz = 0.007, t = 0.3452, p = 0.7312). Pursuing the difference in the word frequency, we found a significant cluster in the centroparietal region around the midline. Our results show that the learning of transitional probabilities between syllables is traceable based on the ITPC peak at the triplet frequency which is clear evidence for the acquisition of the artificial words. This visual linguistic finding fits nicely into the literature, as we found statistical learning to emerge in a central cluster of electrodes, which appears to be the same, regardless of modality. This result supports the theory that statistical learning has a domain-general center.

Poster ID:125

Day 1

Late gamma activity influences information recollection in visual statistical learning

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Statistical learning (SL) is assumed to be a fundamentally general sensory process across modalities, age, other cognitive functions, and even species. Although it is claimed to be essential for our perception, the behavioral results of SL studies vary greatly. In the present study, we examined the correlation between the neural activity during an implicit, visual SL paradigm and behavioral results in an offline familiarity task. Twenty-nine subjects (16 female, mean age: 26.38y) were shown an image sequence, where unbeknownst to them, certain pictures formed stimulus pairs that always followed each other. The second images of the pairs became predictable compared to the preceding ones and the unpaired control pictures. After acquiring 64-channel EEG data during the task, participants were divided into two groups based on their results of a familiarity test (above-chance (n=14) or chance (n=15)). We examined the timefrequency data between the groups and the conditions (predictable & unpredictable) and used permutation statistics with cluster-based correction. After visual inspection, a window of interest was selected in the time-frequency range of 45 to 70 Hz and 500 to 700 ms after stimulus onset. The mean power of the window showed positive, significant correlations with the behavioral results (r = 0.3705, n = 29, p = 0.0478). Subsequent analysis showed a significant cluster in the window of interest comparing the above-chance and chance performers. This cluster emerged in the left frontoparietal region on the scalp. Pursuing this activity, the gamma power was compared within the above-chance group between conditions, which resulted in a significant power elevation in the preceding condition against the control with remarkably similar scalp distribution. Based on its latency and location, this difference was identified as a late gamma activity, a correlate of model-based learning. Such learning is a summary of several topdown mechanisms that modulate the recollection of statistical relationships such as the capacity of working memory or attention. These results suggest that, during acquisition, individual behavioral variance is influenced by dominant learning processes which affect the recall of previously gained information.

Poster

ID:225

Fear memory recall via hippocampal somatostatin interneurons

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In the brain, spatial and episodic memories are encoded by a small sub-population of principal cells in the hippocampus, called engram cells. These are selected based on their higher excitability state during memory acquisition, which could therefore also be controlled by their disinhibition. Previously, our group has discovered that GABAergic neurons in the nucleus incertus (NI) can influence memory trace formation through inhibition of hippocampal somatostatin (SOM) positive interneurons. We now aimed to find out the specific mechanism underlying the precise selection process of these principal cells, and how this will affect the recall of memory traces. Our work used viral vectors, genetically modified mice and optogenetic behaviour experiments. For our evaluations, we used behavioural analysis, fluorescence immunohistochemistry and microscopic methods. We have discovered, that NI GABAergic neurons can inhibit granule cells through inhibition of hippocampal dentate gyrus SOM interneurons. If this occurs at the moment of a negative experience, the experience is associated with a sub-population of granule cells that are selected. Re-inhibition of the same SOM cells or re-activation of the NI GABAergic cells that inhibit them, has the ability to recall the negative experience. Our results have revealed a novel memory mechanism based on a key disinhibitory mechanism of hippocampal SOM cells and their brainstem inputs. Our results may also help to better understand the mechanisms of memory problems. Defects in hippocampal SOM cells are well known to play a role in the development of Alzheimer's disease and could therefore contribute to a better understanding of the disease associated memory problems. Furthermore, our results may help in understanding how damage to hippocampal SOM cells might contribute to the cognitive symptoms of schizophrenia.

Poster ID:325

Understanding the impact of individual annual, monthly and daily timing configuration on cognition

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Organisms possess multiple biological timers that help them in adjusting their behaviour and physiology in accordance with the environment that they thrive in. Several studies have shown that a broad range of activities vary across the 24-hour time period in human beings (corresponding to their inner circadian clock). There is also evidence that point to an impact of seasonal and even lunar cycles on human physiology and behaviour (Wehr & Helfrich-Förster, 2021, Andreatta & Tessmar-Raible, 2020, Häfker & Tessmar-Raible, 2020, Y.Bhattacharjee, 2007, Partonen & Lönnqvist, 1998). Chronotypes are the differences in the circadian clock between individuals that can be measured by the start and end of sleep on days without temporal restrictions like alarm clocks (Roenneberg et al, 2015). Our project aims to understand to what extent the combination of chronotype, seasonal and lunar rhythms is linked to a person's cognitive ability and psychological characteristics, and how individuals with likely disrupted biological clock features will respond to various psychological tasks. We are currently assessing the chronotypes of healthy individuals as well as patients diagnosed with primary adrenal insufficiency, which is a clinical condition defined by a failure of glucocorticoid synthesis and secretion. Glucocorticoids are a class of steroid hormones that contribute to the synchronization of cell autonomous clocks in the body (Dickmeis, 2008), and hence individuals diagnosed with the disease are likely to have a disrupted circadian clock. All participants assessed for their chronotypes were subjected to various psychological tasks and experiments performed at repeated intervals to allow for the analyses of possible relationships to annual/seasonal and/or monthly/lunar time.

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Poster ID:126

Day 1

Simple visual stimuli inhibit the memory processes connected to audiovisually guided associative learning

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Acquired equivalence learning is a specific kind of associative learning, where the subject learns that two or more stimuli belong to each other and are equivalent because they have the same consequences. The forming of associations is related primarily to frontostriatal circuits, and retrieval and generalization are related to the hippocampus. Our aim was to investigate how and to what extent could simple visual stimuli affect the acquired equivalence learning and the connected memory processes in visual and audiovisual paradigms. In the visual test the subjects had to make associations between four simple polygons (triangle, square, rhombus and concave deltoid) and four grayscale circles (Polygon test). These visual stimuli are simple, do not contain color information and have less emotional and semantic content than the stimuli in the original Rutgers Acquired Equivalence Test (FaceFish test). In the audiovisual test the subjects had to associate the same polygons used in the Polygon test to four different sounds (SoundPolygon test). The data from 127 healthy adult subjects were analyzed. There was no significant difference in performances and reaction times during the acquisition phase between the Polygon and the SoudPolygon tests. However, our subjects made significantly worse performance in the retrieval and generalization parts of the SoundPolygon test than in the unimodal visual one. Based on these results, we can conclude that simple visual stimuli had no significant influence on association forming in audiovisual learning, similar to our former results where complex visual stimuli were used. Thus the association building seems to be fairly independent of the stimulus modality. On the other hand, the simple visual stimuli reduced the performances during retrieval and generalization in the audiovisual test, in contrast to our former results with complex visual stimuli, which could slightly improve these memory processes.

Day 2 Cognitive neuroscience

Poster ID:226

The effect of visual stimulus complexity on the audiovisual associative learning and the connected memory processes

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The Rutgers Acquired Equivalence Test (RAET) is a learning paradigm, where the subjects make associations between visual stimuli (drawn faces and fishes). Based on the structure of this test, we developed two audiovisual equivalence learning tests, in which the antecedents were four different distinguishable 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 psychophysical performances of 54 healthy volunteers between the two audiovisual tests. We asked 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. In all of the compared parameters, i.e. the effectiveness in equivalence building, the retrieval of the associations and the application of the equivalence rule, were the performances significantly poorer in the SoundFish test. Similarly, the reaction times were longer here, too. Our results suggest that the complexity of the visual stimuli (we argue that the faces contain more information than the fishes) could influence the effectiveness in audiovisual associative learning. Additionally, the emotional contents of the faces could also facilitate audiovisual associative learning and the connected memory processes.

Poster

ID:326

Time-frequency correlates of personal face familiarization

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Recognizing previously seen faces is essential in a social environment. Previously, multivariate pattern analysis of EEG data showed that neural representations of personally familiar face processing emerge around 450 ms post-stimulus with a peak at 600 ms, with a right temporoparietal dominance (Ambrus et al, 2019). A long series of studies showed that enhanced neural synchronization reflects memory effects for faces in multiple frequency bands and suggested that gamma activity reflects the activation of pre-existing neural representations, necessary for recognizing a famous face as familiar (Zion-Golumbic et al, 2009). To test how brief personal familiarization affects neural synchronizations, we analyzed the data of Ambrus et al (2019) and tracked the oscillatory activity involved in face recognition. The EEG data of twenty people (7 females, mean age: 23.65) were analyzed before and after personal familiarization. During EEG recording ten images of four female persons were presented to the participants 22 times, while participants performed an unrelated orientation discrimination task. Afterward, participants were familiarized with two of the persons, whose pictures were presented previously. This familiarization period consisted of 1 hour-long free-discussion sessions for 3 consecutive days then EEG was recorded again. The data were preprocessed and analyzed in the time-frequency domain. Permutation-based statistics with cluster-based correction were applied to compare familiar and unfamiliar stimuli during pre- and post-familiarization, separately. Subsequently, to determine the power-based connections, the mean power of the clusters was correlated using Spearman correlation. We focused on the previously determined 450-850 ms window and we found two clusters where familiarization affected synchronization: a left temporoparietal cluster appeared in the gamma range (50-70 Hz, p = 0.049) while the other cluster (p = 0.046) spread over the right temporo-occipital cortex in the low beta range (13-15) Hz). Spearman correlation revealed a negative relationship between these clusters (r = -0.5564, p = 0.0121), suggesting a competitive relationship between high and low frequencies during memory tasks, in the sense that familiar stimuli elicit higher gamma power while attenuating lower frequencies. A possible source of this activity change might be the hippocampus, which has shown engagement during recollection and modulation of parietal cortical activities.

Poster ID:127

Automated eye-blink artefact removal from 64-channel human electroencephalogram (EEG) recordings

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Introduction: Electroencephalograph (EEG) measurements record cortical electrical activity. It can provide important information for a better understanding of many neurological and psychiatric conditions. Our work is focused on eye-blink artefact removal and automated filtering during the pre-processing work of EEG recordings, which were recorded on healthy adults and on neurological or psychiatric patients, too. Methods: First, independent component analysis (ICA) was used to visualize the source of the eye-blink artefact on topoplots. In the following, those artefact components from the topoplots had to be extracted, which source is primarily in the frontal lobe. This selection was performed using image processing methods such as Hough Line transformation and pixel count analysis, focusing not only on the location of the source but on the direction of the frontlines originating from the source. Results: Our approach enabled the objective filtering of eye-blink components and their automatic removal without arbitrary selection of subjective thresholds in the MNE-Python environment which is an open-source package capable of visualizing and analyzing neurophysiological data. The created software was tested with 60 EEG samples, of which in 44 (73.3%) cases the unwanted artefacts were completely removed. In the remaining recordings, the software was only able to partially filter out blinking in 11 cases (18.3%) and failed to select the appropriate noise component in 5 cases (8.3%). Discussion: Based on our first experiences, the principle of the method we developed seems to be good, the software can be functional, but it needs further refinement. We aim to achieve a minimum of 90% efficiency by improving the existing software. We believe that with our software we can significantly speed up the processing of EEG signals and reduce subjective errors due to the previously partly manual pre-processing.

Poster ID:227

In vivo examination of age-dependent changes in the activity of basal forebrain cholinergic neurons in ChAT-Cre and in Alzheimer-model animals

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By releasing acetylcholine (ACh), the basal forebrain cholinergic neurons (BFCNs) and their widespread projections to the cortical mantle play a key role in the control of cognitive functions, like sensory processing, attention, arousal and reinforcement expectation. During ageing and in Alzheimer's disease (AD) the BFCNs undergo several physiological and morphological changes, such as degeneration of dendrites, axons and synapsis; nonetheless, the connection between cholinergic activity during learning and the age-related neurodegeneration is still not completely clear. To address this, we examined the changes in the activity of BFCNs in different age groups of ChAT-Cre and AD-model animals. In our experiments, we used headfixed mice during an auditory cued Pavlovian conditioning task. First, we made electrophysiological recordings in the cholinergic cells of the horizontal band of Broca (HDB). Second, we optogenetically inhibited the cholinergic cells of the HDB during the presentation of conditioned stimuli (CS). Third, we simultaneously measured ACh release in two major outputs of the HDB, the basolateral nucleus of the amygdala (BLA) and in the medial Prefrontal Cortex (mPFC) by using dual fiber photometry and a newly developed ACh sensor. In the optogenetic manipulation experiments, we found that the animals, which received the inhibitory virus in their HDB, had difficulties learning the task compared to those animals, which received the control virus. Our electrophysiology and photometry results suggest that BFCNs respond to the reward-predicting CS and to the unconditioned stimuli (US) with an increase of activity and ACh release. It seems that ACh release in the BLA and in the PFC occurs only during the reward predicting but not the punishmentpredicting CS. In old mice and in AD-model animals ACh levels in the BLA and in the mPFC showed weaker to no response to the reward-predicting CS. According to our results, ACh release from BFCNs is required during the acquisition of the CS-US association during Pavlovian conditioning. We found that during ageing and in AD-model animals, both the activity patterns and the ACh release of the BFCNs changed.

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Day 3

Poster ID:327

A custom referencing method for high channel count EEG registrations

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EEG referencing is a mandatory step in the signal-processing chain. Without it, the commonmode rejection ratio could reduce up to 40 dB. With a high count of channels, the amplification and acquisition module will often have multiple identical modules, each with its wiring. Having so will change the electromagnetic balances leading the classical rereference methods to be insufficient. Furthermore, blink removal algorithms could have a different axis than the asymmetry of the instrument. In this case, the two algorithms may interfere. A possible solution for this interference in Biosemi 64-channel systems is an alternating reference-blink correction progress. The results of the implementation are presented in this poster.

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Day 1 Cognitive neuroscience

Poster ID:128

Stimulus modality or stimulus complexity influence primarily the performances in associative acquired equivalence learning in healthy humans?

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The associative learning is a basic cognitive function, which depends critically from the frontostriatal circuits of the human brain. Previous studies denoted, that in healthy adults were only slight differences in visually and multisensory (audiovisual) guided associative learning. On the other hand, in another study it was described if the visual stimulus complexity is decreased the learning effectiveness will be decreased, too. In the present study we have investigated whether the modality or the complexity of the visual stimuli affects primarily the associative acquired equivalence learning in the same large population of the involved healthy adult participants. In this study 119 healthy volunteers were involved. Visually and audio-visually guided acquired equivalence learning paradigms were applied with complex (FishFace and SoundFace) and with reduced complexity visual stimuli (Polygon and SoundPolygon). We found, that the reduced visual stimulus complexity had weak but significant effect on the performances in the acquisition phase (building of associations) of the audiovisual learning, however the performances were much worse in retrieval (where the earlier learnt associations were asked) and generalization (where hitherto not learnt but predictable associations were asked) in the multisensory test with simple visual stimuli. To assess exactly whether the modality or the stimulus complexity has a greater effect on the performances factorial ANOVA was applied in the multiple comparison in the four (two visual and two audiovisual) tests. This analysis revealed that both in the acquisition and the test phases (retrieval and generalization parts) the stimulus complexity has the stronger effect on the performances. Our results suggest that the visual stimulus complexity is the primary determiner of the effectiveness in associative learning and the modality of the applied stimuli (unimodal visual or multimodal audiovisual) has much weaker effect on the associative learning and the connected memory processes.

Poster ID:228

Day 2

Sex-dependent differences in noise-related impairment in number processing

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Acute and chronic exposure to noise affect cognitive performance in children and adults (Thompson et al., 2022). In the present study, we quantified the impact of acute noise exposure on number processing in young adults. In a number comparison paradigm, a pair of two-digit numbers is said to be unit-decade-compatible when the comparison between the tens and units leads to the same conclusion (for example: 67_43, where 6 > 4 and 7 > 3), and is said to be unitdecade- incompatible when the tens and units do not lead to the same conclusion (for example: 62 48, where 6 > 4, but 2 < 8). Interestingly, given the same absolute distance between unitdecade- compatible and unit-decade-incompatible number pairs, the response time (RT) to unitdecade- incompatible number pairs is slower (unit-decade compatibility effect) (Nürk, Willmes, 2005). In a previous study, we documented sex-dependent differences in RT when participants had to identify the larger two-digit number within a number pair (Pletzer et al., 2013). While men did not differ in RT significantly between unit-decade-compatible and unit-decade-incompatible number pairs, women showed slower RT to unit-decade-incompatible compared to unit-decadecompatible number pairs. In the present study, we exposed 41 young adults to environmental noise (rain, mover) and compared the RTs between unit-decade-compatible and unit-decadeincompatible number pairs between men and women. A two-way ANOVA (3 x 2) using the main factors GROUP (quietness, rain, mover) and SEX (women, men) revealed significant effects for both main factors (GROUP: F2, 178 = 4.29, p = 0.015; SEX: F2, 178 = 22.98, p < 0.001). Posthoc tests revealed a significant difference in the unit-decade compatibility effect (small decade distance) between quietness and rain or mover. Interestingly, we observed a significant difference only in women. In men, RT-difference did not differ significantly across the three conditions. In women, the RT- difference between unit-decade-compatible and unit-decadeincompatible number pairs was significantly larger in noise-exposed women compared to women in a quit environment. This finding indicate that women may not only use different mental strategies in number comparison (Pletzer et al., 2013) but may also be more sensitive to environmental noise.

Poster

ID:328

Encoding time and serial position in the Paired Associates Learning task

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In a free recall task of a list of 25-30 words, human participants can remember the first couple of words (primacy effect) and the last couple of words (recency effect) the best. Additionally, introducing a free-time interval after items – i.e., increasing the encoding time – is known to facilitate memory performance for all subsequent, but no preceding items, implying a proactive and global mechanism. However, the way current theories on interference and short-term consolidation could account for such encoding time effects is currently unresolved. Also, most previous studies have used tasks that are overtly verbal, which limits the translational generalizability of the paradigm and the results obtained. Thus, we used a short-term memory object-location binding paradigm: Paired Associated Learning (PAL) task, in which 5 or 6 putatively nonfigurative visual objects were presented sequentially at distinct locations, each one for either 0.75s, 1s or 1.5s. After a 1-sec delay, the testing occurred in which each object was presented in multiple locations on a touch screen and the correct location had to be chosen. Each session consisted of an introductory block of the PAL task and 9 blocks in a pseudo-random order with uniform presentation times within the block. 35 healthy, young subjects were included in the analysis (25 female, average age: 24.5 yrs). As expected, the shorter the presentation time was, the lower the overall performance proved to be. Similarly, in accordance with previous results, the primacy and the recency effects were present: the first and the last item showed the highest performance while the items in the middle had the lowest performance. Interestingly, an interaction between these two factors was found in the intermediate encoding time in which the primacy effect showed much higher performance, similar in nature to the one observed in long encoding time while the recency effect was much lower in performance approaching the performance observed with short encoding time. То conclude, the observed interaction between serial position effects and encoding time supports the difference in the underlying mechanisms for primacy and recency effects while shedding new light on the multiple components involved in short-term consolidation.

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Poster ID:129

Application of multiple AAV serotypes and experimental setups for inhibition of food intake by silencing LHA using DREADD technology

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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 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.

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Day 2 Cognitive neuroscience

Poster ID:229 Combinations of memantine and alpha7 nicotinic acetylcholine receptor ligands exert superior efficacy over monotreatments in the improvement of cognitive performance of aged rats

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Combination treatments based on pharmacological interaction on α7-nicotinic acetylcholine receptor (nAChRs) targets have been suggested as possible therapeutic approaches in the treatment of neurocognitive disorders (NCDs). Memantine, an already approved medication in NCDs, may not only act as an antagonist of the glutamatergic NMDA receptors (NMDAR) but also serve as an antagonist of the α 7-nAChRs. Here we set out to utilize a combination treatment regime using an α 7-nAChR selective agonist (PHA-543613) and a proprietary α 7-nAChR positive allosteric modulator (PAM) to test the efficacy of cognitive enhancer combination treatments in naturally aged rats, Our results showed that aged rats exhibited marked cognitive decline in the novel object recognition (NOR) memory test, and they displayed pathological changes at the molecular level indicated by the increased occurrence of various inflammatory markers. In addition, aged rats also exhibited remodelling of the brain cholinergic system indicated by α 7nAChR mRNA upregulation. Memantine and PHA-543613 or memantine and PAM combination treatments successfully alleviated age-related recognition memory decline of rats by exceeding the null-effects of the corresponding subtherapeutic levels of monotreatments. Results also indicate a positive interaction between the effects of memantine and α 7-nAChR agonists and PAMs, that may reflect on the prominent role of α 7-nAChRs in the cognitive enhancement of combination treatments. Moreover, the putative direct action of memantine on α 7-nAChRs may also contribute to the beneficial synergistic interaction between memantine and selective α7nAChRs compounds.

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Poster ID:329

Day 3

Application of the Self-ordered Spatial Search (SOSS) task for the investigation of the spatial working memory in non-human primates

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The Self-ordered Spatial Search (SOSS) task is a non-verbal paradigm probing visual spatial working memory (SWM) that is suitable for testing the performance of non-human primates in a translational experimental setting. In our study we inspected if introducing various length of delay periods may make the task useful for the assessment of SWM in adult male rhesus macaques. In addition, we used scopolamine, a muscarinic receptor antagonist amnestic agent to measure the performance of the animals with temporarily impaired cognitive functions. We trained 14 adult macaques to perform the task. We measured the animals' performance in 1hour sessions with 300-500 trials each. In every trial the animals were shown 4-8 identical blue squares on a touchscreen that they had to touch in an arbitrary order once, and only once. Each response was followed by a delay period (0,5-2s). Besides the proportion of correct trials, we analyzed the frequencies of two error types: continuous perseverative errors (CPE: a stimulus is touched two times in a row) and recurrent perseverative errors (RPE: a formerly touched stimulus is touched again, not directly after the previous touch). By increasing the number of stimuli, both the error types were selectively increased, however, RPE increased to a greater extent (10-15%) than CPE (1-2%). Also, RPE typically occurred in the later phase of the choice sequence. These results suggest that the task is suitable for the examination of SWM. Compared to the strong set size effects, varying the length of the delay between 1500 and 2000 ms only had a minor detrimental effect (4%). Though scopolamine treatment worsened the animals' performance dose-dependently, it was not selective to the error types, indicating the limitations of the model. However, an exploratory analysis revealed that scopolamine effects were similar regardless of set size, the effects on recursive errors were stronger for the longer delay. Based on the present results, our modification of the task enables the assessment of SWM during task completion. The specificity of the observed scopolamine effects on performance endpoints that are considered memory-related were found to be weak, but could be improved by introducing a longer delay. After validating the reversibility of the amnestic effects of scopolamine, the SOSS task may be suitable for preclinical determination of the efficacy of potential cognitive enhancer pharmaceutical candidates.

Poster ID:130

Day 1

Modeling the temporal dynamics of food intake of non-human primates in an operant feeding task

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We studied daily operant food intake (FI) in five young adult male rhesus macaques in two sessions (S1: from 9 to 11 am, and S2: from 12 to 1 pm) in four possible feeding schedules with two types of flavored food pellets (high-palatability very berry as 'v' and low-palatability banana as 'b'): S1 b / S2 b, S1 b / S2 v, S1 v / S2 b, S1 v / S2 v. Each schedule was offered for 5 consecutive experimental days, from Mondays to Fridays. While FI was only slightly higher for the more palatable pellet type ('v') when offered in S1, intriguingly, FI in S1 strongly depended on the food that was consequently offered that week in S2: animals ate significantly less in S1 when the S2 meal was highly palatable, compared to weeks with low-palatability S2 meals. Importantly, this modulation of S1 FI depending on S2 palatability was only present from Tuesdays to Fridays but not on Mondays, when the weekly feeding schedule was not yet known by the animals. To accommodate the observed variability, we modeled the temporal dynamics of banana pellet intake in S1 as a function of the palatability of the prospective pellet type in S2 using a mixture of a linear and a sigmoid model. From the mixture models, ceiling and floor consumption rate parameters and two corresponding temporal parameters were extracted and compared in second-level linear mixed models. Intriguingly, only one of the four parameters accounted for the future palatability effect described above: the time point when S1 food consumption reached the minimum was 44±13 minutes (effect mean ± SE) earlier under high (very berry in S2) compared to low (banana in S2) future palatability. The results of the present study imply that monkeys decrease their food intake when an option that is more valuable to them is known for them to be available in the near future (in a few hours time). To our knowledge, this is a demonstration of delaying gratification with a time horizon that was thought to be far beyond consideration for old-world monkeys and even debated for apes. Our novel modeling approach demonstrated that the restraint in food consumption arises gradually in time. A possible interpretation of this pattern is that the gradual dissipation of imminent hunger allows the animal to trade its current homeostatic needs for (subjectively more valuable) future hedonic needs. Developed further, this task and modeling approach may enable us to study humanrelevant dietary self control and decision making in non-human primates.

Poster ID:230

Investigation of interactions between response inhibition and temporal expectation in a flanker conflict task

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Temporal expectation based on explicit cues or implicitly learned temporal contingencies is known to facilitate stimulus detection and speeded responses. One hypothesized mechanism of temporal expectation is the adaptive release of motor inhibition of a partially initiated response, which raises the possibility of shared motor inhibitory processes with response inhibition. However, the way different forms of temporal expectation might influence inhibitory executive control functions is less clear. We addressed this question in 34 young adult university students using a combination task devised from of an Eriksen flanker and a variable foreperiod temporal preparation task. In this combination task, each trial started with a warning cue, and was followed by a foreperiod (800 ms, 1500 ms or 3200 ms). Then a target arrow appeared on the screen which was surrounded by congruent, incongruent or neutral flanker distractors. Using a constant 800 ms foreperiod we replicated the classical flanker conflict effects (congruency and incongruency) in the 'pure flanker' blocks of the combined task. Using the three different foreperiods randomized and a neutral target stimulus requiring a speeded response with the dominant hand ('pure foreperiod' block), we also replicated the foreperiod effect and the sequential effects, the classical correlates of implicit temporal expectation. We obtained the following novel results in the combined blocks involving all combinations of the three flanker and the three foreperiod conditions: While responses were substantially slower due to the temporal uncertainty introduced by the variable foreperiod, the flanker effect showed no interaction either with the block type (pure vs. combined) or with the foreperiod length. Interestingly, the classical foreperiod effect was completely absent in the presence of the flanker task, while the sequential effects prevailed. This is in accordance with models suggesting that temporal preparation entails two dissociable processes, an automatic implicit motor learning process that manifests in the observed sequential effects, and a controlled process resulting in the foreperiod effect that requires executive control resources that are captured by the concomitant flanker task.

Poster ID:330

The tachykinin hemokinin-1 is involved in learning and memory functions in mice

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The tachykinin hemokinin-1 (HK-1) is expressed in several brain regions such frontal cortex, hippocampus, amygdala both is mice and humans, their roles in pain and mood regulation are well established. In contrast, little is known about their involvement in learning and memory functions. Only one study demonstrated stimulatory action of HK-1 on cholinergic neurons, and data described that SP improved learning. Therefore, here we investigated the role of HK-1 in learning and memory functions under normal conditions and after inducing memory loss by the muscarinic antagonist scopolamine in 3-5-mont-old male and female Tac4 gene-deleted (Tac4-/-) mice compared to C57BI/6 wildtypes (WT). Different memory functions were assessed with Y and radial arm mazes (YM and RAM) as well as novel object recognition test (NOR). During the 5-minlong experimental periods spontaneous alternations and arm entries in YM, reference and working memory errors in RAM and discrimination as well as recognition indices in NOR were determined 24 hours after intraperitoneal injection of 1 mg/kg scopolamine compared to the vehicle saline. In the YM test male WT animals showed higher alternation index than females, and scopolamine induced significant reduction of this parameter in males, but not in females. In male Tac4-/- mice the number of alternations was lower than the number in WTs, but in females no genotype difference was detected. Tac4-/- animals of both sexes made more arm entries than WTs in YM test. In the RAM female WT mice made less working and reference memory errors than males. Female Tac4-/- mice (both saline and scopolamine-treated) showed worse memory with more errors, but this difference was not detected in males. Furthermore, scopolamine treatment did not significantly influence the parameters of the RAM in any groups. Scopolamine did not induced significant alterations in WT animals in the NOR test, but after scopolaminetreatment Tac4-/- animals of both sexes showed decreased recognition index compared to the WTs. We provide here the first data for the involvement of HK-1 in memory consolidation. Investigating its mechanisms of action the effect of scopolamine treatment in an earlier phase can help to understand the modulatory roles of HK-1 in cognitive functions.

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Poster ID:131

Sharp-wave ripple doublets induce complex dendritic spikes in parvalbumin interneurons *in vivo*

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Neuronal plasticity has been shown to be causally linked to coincidence detection through dendritic spikes (dSpikes). We demonstrate the existence of SPW-R-associated, branch-specific, local dSpikes and their computational role in basal dendrites of hippocampal PV+ interneurons in awake animals. To measure the entire dendritic arbor of long thin dendrites during SPW-Rs, we used fast 3D acousto-optical imaging through an eccentric deep-brain adapter and ipsilateral local field potential recording. The regenerative calcium spike started at variable, NMDA-AMPA-dependent, hot spots and propagated in both direction with a high amplitude beyond a critical distance threshold (~150 µm) involving voltage-gated calcium channels. A supralinear dendritic summation emerged during SPW-R doublets when two successive SPW-R events coincide within a short temporal window (~150ms), e.g., during more complex association tasks, and generated large dSpikes with an about 2.5-3-fold amplitude increase which propagated down to the soma. Our results suggest that these doublet-associated dSpikes can work as a dendritic-level temporal and spatial coincidence detector during SPW-R-related network computation in awake mice.

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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 or 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 young healthy 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 fatiguesensitive (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 analyse 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 TOTrelated 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.

Poster ID:231

Poster ID:331

Day 3

Entorhinal grid-like codes and time-locked network dynamics track others navigating through space

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Navigating through crowded, dynamically changing environments requires the ability to keep track of other individuals. Grid cells in the entorhinal cortex are a central component of self-related navigation but whether they also track others' movement is unclear. Here, we propose that entorhinal grid-like codes make an essential contribution to socio-spatial navigation. Sixty human participants underwent functional magnetic resonance imaging (fMRI) while observing and re-tracing different paths of a demonstrator that navigated a virtual reality environment. Results revealed that grid-like codes in the entorhinal cortex tracked the other individual navigating through space. The activity of grid-like codes was time-locked to increases in co-activation and entorhinal-cortical connectivity that included the striatum, the hippocampus, parahippocampal and right posterior parietal cortices. Surprisingly, the grid-related effects during observation were stronger the worse participants performed when subsequently re-tracing the demonstrator's paths. Our findings suggests that network dynamics time-locked to entorhinal grid-cell-related activity might serve to distribute information about the location of others throughout the brain.

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Day 1

An approach for structural MRI artefact characterization using matched motion-corrupted and clean structural MRI brain scans

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Magnetic Resonance Imaging (MRI) provides a unique opportunity to investigate neural changes in healthy and clinical conditions and there is a growing interest in developing approaches sensitive enough to capture subtle changes in the structural brain organization sometimes even before the onset of the clinical symptoms. Its large inherent susceptibility to motion, however, often confounds the measurement which is an issue in highly kinetic participants, especially in the developing and ageing populations. Approaches assessing, correcting, or preventing motion corruption of MRI measurements are under active development, and such efforts can greatly benefit from carefully controlled datasets. We present a unique dataset of structural brain MRI images collected from 148 healthy adults which includes both motion-free and motion-affected data acquired from the same participants. This matched dataset allows direct evaluation of motion artefacts, their impact on derived data, and testing approaches to correct for them. Our dataset further stands out by containing images with different levels of motion artefacts from the same participants, is enriched with expert scoring characterizing the image quality from a clinical point of view and is also complemented with standard image quality metrics obtained from MRIQC. The goal of the dataset is to raise awareness of the issue and provide a useful resource to assess and improve current motion correction approaches.

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Poster ID:232

I feel, therefore I control? Within-individual changes in cognitive control predicit emotional reactivity in daily life

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It's acknowledged that synchronized functioning of brain areas related to cognitive control and emotional processing is crucial in effective emotion regulation. Furthermore, the relationship between impaired cognitive control and maladaptive emotion regulation is well-established between individuals. Yet, it remains to be investigated if the association also holds at the withinindividual level. Our study aimed to demonstrate that within-person fluctuation in cognitive control performance (working memory updating and response inhibition) predicts emotional reactivity in daily life. We conducted an experience sampling study (8 two-hourly prompts daily for max. 28 days) where participants repeatedly performed short 2-back and Go-Nogo tasks using their own devices in the context of their daily life. We also assessed negative and positive affective states as well as the perceived pleasantness of a recent significant event. The statistical relationship between perceived event-pleasantness and affective states captures emotional reactivity, a suitable indicator of effective emotion regulation. We analyzed two partially overlapping samples: one for Go-Nogo data (NParticipants = 161, NObservations = 2494, MAge = 41.7, SDAge = 14.5) and another for 2-back data (NParticipants = 158, NObservations = 2641, MAge = 41.8, SDAge = 14.5). Our results indicated that higher 2-back performance predicted negative emotional reactivity positively within individuals. That is, when momentary working memory updating was better than an individual's average, they demonstrated higher negative emotional reactivity. However, independently from perceived stress, 2-back and Go-Nogo performance per se showed a negative relationship with negative affective states. Cognitive control performance did not significantly influence positive emotional reactivity. Our results imply that cognitive control training alone may not necessarily contribute to the effectiveness of emotion regulation since enhanced cognitive control performance can predict increased negative emotional reactivity within individuals. These findings even raise the provocative question of whether between-person results related to neurobiological mechanisms in emotion regulation can be generalized to within-person functioning.

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Day 3

Disorders, disease models

Poster ID:332

A Cav1.4 L-type calcium channel truncation mutation affects primarily the retinal rod pathway

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In the retina, Cav1.4 L-type calcium channels are expressed at the synaptic terminals of photoreceptors and bipolar cells to allow continuous calcium influx to support tonic neurotransmitter release. Therefore Cav1.4 channels lack calcium-dependent inactivation due to active suppression by an inhibitory domain in their C-terminus, referred to as C-terminal modulation (CTM). Mutations in the CACNA1F gene, which encodes Cav1.4 channels, can cause congenital stationary night blindness type 2 (CSNB2). In the truncation mutation R1827X (Cav1.4-RX) CTM is abolished. Heterologous expression studies showed calcium-dependent inactivation, as well as a left-shift in the voltage-dependence of activation in the Cav1.4-RX channel. To determine the impact of the missing CTM domain in Cav1.4 channels in vivo, we investigated a mouse model carrying the Cav1.4-RX mutation functionally (multielectrode array analyses (MEA), electroretinogram (ERG)), morphologically and biochemically. Western blot analyses showed a significant decrease of Cav1.4 channel protein in Cav1.4-RX mice explained by a similarly strong reduction of Cav1.4 mRNA expression observed in gRT-PCR experiments. Reduced channel expression destabilized the synaptic integrity obvious from the fact that synaptic ribbons were dislocated in the outer nuclear layer (ONL) and of punctate shape. We also found dislocated photoreceptor terminals in the ONL of Cav1.4-RX mice. These changes in the retinal presynapse affected also second-order neurons, as we observed neurite sprouting of horizontal and rod bipolar cells in Cav1.4-RX retinae, comparable with previously published mouse models. However, the cone bipolar cells seemed to be largely unaffected. This phenotype was also reflected in our functional analyses: both, ex-vivo (MEA) and in-vivo (ERG) recordings. Moreover, we could also observe higher glial fibrillary acidic protein expression in Cav1.4-RX compared to wildtype mice suggesting retinal stress. The unaltered cone pathway phenotype contrasts with previously published findings in other CSNB2 mouse lines and raises new questions about the differential role of the distal Cav1.4 C-terminus in the retinal pathways. Our observation might be explained by differences in the protein composition in rod and cone photoreceptor terminals. Further investigations will therefore also include a proteomic approach to better understand the molecular role of the distal Cav1.4 C-terminus in retinal synapses.

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Day 1 Disorders, disease models

Poster ID:133

Enhancement of cocaine-seeking behaviour in male rats following the maternal high-fructose diet.

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Cocaine use disorder (CUD) is the compulsive use of cocaine that cause medical, psychological, and behavioural consequences. CUD affects more and more people globally regardless of gender, and age leading to many disabling and costly public health problems. Many risk factors for CUD have been identified, including genetic, environmental, and individual mental health predisposition. Recent data have indicated that diet patterns, especially maternal high-sugar consumption, predispose to the development of mental illness and prone to substance use disorders, such as CUD. The aim of our preclinical research was to examine the impact of maternal fructose diet consumption on cocaine-seeking behaviour in offspring. Wistar male rats after maternal fructose diet during pregnancy and lactation were used in the intravenous cocaine self-administration (SA) model with a stable dose of cocaine (0.5 mg/kg/infusion) and an increased schedule of reinforcement (from FR1 to FR5 on the consecutive daily sessions over a week) procedure. Later on the progressive ratio test and extinction training, the reinstatement of cocaine-seeking was performed. During cocaine SA on the FR5 schedule, maternal fructose males had higher active lever presses than the control rats fed on the maternal standard diet, what means enhancement of reinforcement properties of cocaine. After cue-(tone+light) and cocaine-(10 mg/kg; i.p.) induced reinstatement maternal fructose male offspring rats increased active lever presses. Our results showed that perinatal offspring exposure to the maternal fructose diet can predispose to changes in the sensitivity to addictive drugs, and enhanced cocaine-seeking behaviour. We emphasize the inappropriate role of fructose in the maternal diet on the offspring's brain function development. Based on the data, it is strongly recommended limitation in fructose consumption in an individual's everyday diet.

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Day 2

Disorders, disease models

Poster ID:233

LIT-001 - first nonpeptide oxytocin receptor agonist improves animals' cognitive performance in the neurodevelopmental schizophrenia model

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Schizophrenia is a chronic, debilitating disease of uncertain etiology with strong neurodevelopmental component. Researchers distinguish three clusters of symptoms: positive (psychotic; hallucinations), negative (social withdrawal, lowered motivation) and cognitive (deficits in learning and memory). Methylazoxymethanol acetate (MAM) is a mitotoxin that disrupts brain development when administered to a pregnant rat dam. Behavioral and anatomical changes in the offspring resemble those present in schizophrenia patients. Oxytocin (OXT) is a neuropeptide involved in social functions, such as sociability and social memory. Deficits in oxytocin's production or secretion are present, among others, in depression, autism spectrum desorders and schizophrenia. Previous studies on exogenous OXT administration to schizophrenia patients have provided inconsistent results. First nonpeptide OXTR agonist, LIT-001 may bring a breakthrough in the oxytocin studies due to its better penetration of brain tissue and longer half-life of the compound. The schizophrenia model was obtained by intraperitoneal administration of the MAM toxin on GD 17 to pregnant rat dams. Offspring of such treated dams were tested in early adulthood in the Novel Object Recognition Task (NORT) to evaluate cognitive effects of LIT-001. Animals received intraperitoneal injection of LIT-001 (1mg/kg) or vehicle either 30 min prior to the first phase of the NORT (the acute paradigm) or for 9 days before test (the repeated paradigm). Animals prenatally treated with MAM toxin presented a deficit in the NORT test independently of gender. The discrimination index value was decreased in both males in females. The deficit is also visible in the exploration time: while it should be higher for the novel object, MAM animals didn't prefer any of the objects. The data suggests that 1mg/kg of LIT-001 given acutely or sub-chronically can reverse cognitive deficits present in the MAM model of schizophrenia, improving animals' performance in NORT. As oxytocin is mainly involved in social activities, the efficacy of the OXTR agonist against MAM-induced social dysfunctions warrants further studies.

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Day 3 Disorders, disease models

Poster ID:333

Glutamate transporter expression in the hippocampus, subiculum, entorhinal cortex and superior temporal gyrus in Alzheimer's disease

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Alzheimer's Disease (AD) is the most common form of dementia. The underlying causes of AD are not well understood, and no current treatments are preventing the onset or delay progression of the disease. Two classes of glutamate transporters, the vesicular glutamate transporters (VGluTs) and excitatory amino acid transporters (EAATs), play critical roles in regulating neurotransmission. Expressional alterations to these transporters in AD tissue likely disrupt synapse function and contribute to the disease pathophysiology. However, human studies examining the expression of these transporters are limited, especially in the medial temporal lobe, the most severely affected brain region in AD. Therefore, we aimed to investigate the regional and layer-specific expression of VGluT1/2 and EAAT1/2 in the medial temporal lobe. Fluorescent immunohistochemistry and confocal imaging were used to quantify and compare the density of VGluT1/2 and EAAT1/2 in the hippocampus, subiculum, entorhinal cortex and superior temporal gyrus (STG) between control and AD cases. In AD, VGluT1 density was significantly reduced in the stratum moleculare of the dentate gyrus (p = 0.0051). VGluT2 density was decreased in the subiculum (p = 0.015) and STG (p = 0.0023). Astrocytic EAAT1 staining was significantly higher in AD across most regions examined, while EAAT2 expression on astrocytic main branches appeared reduced. In summary, these results indicate that a better understanding of the drivers and consequences of localized glutamatergic transporter changes would help to identify potential therapeutic targets for the prevention of AD pathology and cognitive decline.

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Day 1 Disorders, disease models

Poster ID:134

Age-dependent changes in nmda-induced excitotoxicity and neuroprotective effect of kynurenic acid in mouse brain tissue

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Aims: Kynurenic acid (KYNA) is one of the main products of the tryptophan metabolism, formed along the kynurenine pathway. KYNA has a dose-dependent neuromodulatory effect, which means that it has a neuroprotective effect at low concentrations and a toxic effect at higher concentrations. Since this effect is realized through N-methyl-D-aspartate (NMDA) receptors, the NMDA-induced excitotoxicity model can be a suitable method to investigate the possible neuroprotective effect of kynurenic acid. Our aim was to study the neuroprotective effect of KYNA against NMDA-induced excitotoxicity using acute brain slices from C57BL/6J mice of different ages. Methods: Small-volume incubation system was used to investigate the effect of NMDA and KYNA in cerebral and cerebellar slices. After 4 hours of incubation, the supernatant was analyzed by lactate-dehydrogenase (LDH) assay, and the acute brain slice preparations were examined using NeuN immunolabeling. Results: The experiments were performed on mice of different ages (1, 4, 8 weeks, and 1 year) using 10 µM NMDA to induce excitotoxicity. The experiments showed that the NMDA-induced excitotoxicity resulted in age-dependent damage. Accordingly, young animals (1 and 4 weeks old) showed higher resistance to the damaging effect of the NMDA, while in the groups of young adults (8 weeks old) and elderly (1 year old), damage of higher level was detected. However, KYNA at 40 nM concentration almost halved the released LDH level in the supernatant in all age groups, thus it proved to be effective against NMDA treatment regardless of the age groups. In addition, higher degree of damage could be observed in the CA1 region of the hippocampus compared to the untreated groups during the histological examination, although this damage was significantly reduced by adding KYNA to the system. The results also showed that cerebellar acute brain slice preparations were more sensitive to the NMDA treatment than cerebral slices in experiments measuring LDH release. Conclusions: In summary, animals from different age groups responded differently to NMDA treatment, but KYNA proved to be neuroprotective in all groups.

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Poster ID:234

Cav1.3 channel gain of function results in altered channel gating, aberrant dendritic spine morphology and minor changes in dendritic branching

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Voltage-gated L-type Cav1.3 calcium channels regulate neuronal firing and play a crucial role in synapse maturation, neurogenesis and dendritic refinement. Typical gain-of-function gating changes permitting increased Ca2+ influx at subthreshold voltages were demonstrated for a range of de novo missense mutations in the Cav1.3 α 1-subunit detected in patients with a neurodevelopmental disorder. These mutations caused profound gating changes as, for example, variants S652L and A749G, which induced a dramatic shift of the voltage-dependence of activation and inactivation to more hyperpolarized potentials. In this study, we further investigated the effect of autism-linked mutation A749G on dendritic spine morphology and density, and dendritic branching in vitro and in vivo. We evaluated spine morphology parameters in cultured differentiated hippocampal neurons transfected with Cav1.3 wildtype (WT) and A749G channels. We observed a significant increase in dendritic spine length and decrease in spine density in neurons expressing A749G channels. Spine shape factor was decreased in A749G-transfected neurons which points to an overall spine elongation compared to WT. In line with these findings, we also found that the A749G mutation increased the percentage of filopodia and thin spines and significantly decreased the proportion of mushroom spines. Importantly, we did not find major changes in the surface expression of mutant channels expressing an external HA-tag, which indicates that overall spine elongation is likely caused by alterations in channel gating but not by changes in membrane expression. Next, we aimed to study whether mutation A749G induces profound changes in dendritic spine morphology and branching in Golgi-stained CA1 hippocampal pyramidal neurons from a A749G knock-in mouse model generated in our laboratory. In heterozygous Cav1.3A749G mice we observed a small but significant increase in dendritic arborization and a decrease in the cell body area compared to WT. Moreover, we observed a significant decrease in the percentage of thin spines and an increase in the percentage of stubby spines. Altogether, our data show that the neurodevelopmental phenotype of the A749G mutation may be not only caused by Cav1.3dependent alterations of neuronal excitability, but also by changes in neuronal morphology.

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Day 3 Disorders, disease models

Poster ID:334

Ultrastructural analysis of synapses in the hippocampus of patients suffering from major depressive disorder

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Major depressive disorder (MDD) is one of the most serious mental disorders causing social and economic burden world-wide. The manifestation of MDD is heterogenous, symptoms can be depressed mood, diminished interests, impaired cognitive function and vegetative symptoms, such as disturbed sleep or appetite. Although the exact pathophysiology of the disease is still not uncovered, there are numerous studies describing structural alterations in the hippocampus of depressed patients. In vivo observations prove reduced hippocampal volume and post-mortem histopathological studies report changes in cellular number and morphology affecting both neurons and glial cells in MDD. Synapses are one of the most important units of the central nervous system through which neurons affect each other. Synaptic excitation and inhibition organize activity from neurons to the whole brain network. Since loss of synapses in the prefrontal cortex of depressed patients has been reported before (Kang et al., 2012), therefore, we expect to see similar synaptic changes also in the hippocampus of depressed patients. Our aim was to investigate the number and morphology of synapses in post-mortem hippocampal samples originating from depressed patients. Hippocampal tissue blocks were received from the brain bank of the University of Mississippi Medical Center. Three subgroups were included in this collection: 1) tissue samples from patients with MDD (n = 11); 2) samples of alcoholic individuals (n = 8) and 3) control samples (n = 10), i.e. individuals who died in an accident and had no neuropsychiatric disorder. We performed routine transmission electron microscopic sample preparation and investigated the main sub-areas of the hippocampus, i.e. Dentate Gyrus, CA3 and CA1. Ultrathin sections were inspected and microphotographs were taken for the further quantitative analysis via a JEOL JEM 1400 FLASH transmission electron microscope. The systematic quantitative analysis was carried out with the Neurolucida system (MicroBrightField), using unbiased counting principles. The quantification of the samples is currently in progress. Preliminary data will be presented on the poster. Kang HJ et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nature Medicine 2012;18(9):1413-1417. doi:10.1038/nm.2886

Keywords: major depressive disorder, electron microscopy, hippocampus

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Poster ID:135

Activation of SIRT1 leads to an amelioration of DPR induced genomic instability in C9orf72-ALS

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Background SIRT1 is a key regulator of genomic stability and was reported to be involved in the pathophysiology of different neurodegenerative diseases including Alzheimer's dementia, Parkinson's disease and amyotrophic lateral sclerosis (ALS). As a NAD+-dependent deacetylase, SIRT1 is crucial for the maintenance of heterochromatin structure and nucleolar organization and promotes DNA damage repair, which were shown to be affected by the various dipeptide repeat proteins (DPRs) resulting from the translation of the GGGGCC-hexanucleotide C9orf72-repeat expansion as the most common monogenetic cause of ALS (C9-ALS). However, the role of SIRT1 has not yet been investigated in the context of C9orf72-associated disease. Objectives This project aims to unravel the possible therapeutic effect of SIRT1 activation in ALS with underlying C9orf72 mutation. Methods The mCherry-tagged poly-DPRs50 were transfected into N2a cells, and used together with human post-mortem brain tissue and induced pluripotent stem cells (iPSCs) of C9-ALS patients to assess the role of SIRT1 in DPR pathology. Phenotypic characterization was mainly performed by immunocytochemistry, western blot analyses, qPCR and ATAC-Seq. Resveratrol and other reagents were either added to N2a cells 4 hours after transfection or directly when seeding iPSCs. Results The transfection of N2a cells with individual DPRs resulted in i) disintegration of fibrillarin, a nucleolar marker, ii) reduced HP1 α expression, a core protein of heterochromatin, iii) increased DNA double strand breaks, as measured by yH2AX foci, and iiii) an increase of p53, a transcription factor driving apoptosis. SIRT1 levels were identified to be decreased when co-expressed with poly-GR50 or poly-GA50 in N2a cells. Activation of SIRT1 by resveratrol, by contrast, led to an amelioration of all genomic instabilities described above. Investigation of SIRT1 in C9-ALS iPSCs shows a significant decrease of SIRT1 in C9-iPSCs when compared to isogenic control. Furthermore, C9-iPSCs present a disintegration of fibrillarin, an increase of p53 and cleaved-PARP1, which can be rescued using Resveratrol. Discussion Our data provide evidence for a dysregulation of SIRT1 to underlie DPR pathology in C9orf72-associated disease. The activation of SIRT1 in our model cell line and in C9 patient derived iPSCs led to a significant alleviation of DPR pathology, highlighting SIRT1 as a potential novel therapeutic target in C9orf72-associated diseases.

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Poster

ID:235

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.

Poster ID:335

Day 3

Anxiolysis is associated with mciroglial modulations in a model of high trait anxiety

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Neuroinflammation is discussed to play a role in specific subgroups of different psychiatric disorders including anxiety disorders. We have previously shown that a mouse model of trait anxiety (HAB) displays enhanced density and phagocytic activity of microglia (the resident myeloid immune cells of the CNS) in key regions of the anxiety/stress circuitries as compared to their normal-anxiety controls (NAB). Positive environmental stimuli have been shown to modulate inflammation-related markers in humans and rodents. Here, we demonstrate that positive environmental stimuli in form of housing in an enriched environment (EE) when presented during adulthood reduces the innate hyperanxiety of HABs in different anxiety tests. The EE-induced anxiolysis coincided with an attenuation of enhanced microglial density and phagocytic activity in the DG and/or medial prefrontal cortex as indicated by a reduced number of microglia co-expressing Iba1+ and CD68+. The local infusion of the anti-inflammatory drug minocycline reduced microglial activation within the DG and attenuated enhanced anxiety in HABs providing a causal link between anxiety and microglia densities. Together with our previous findings, these results indicate that beneficial environmental changes have the capacity to alleviate hyper-anxiety in individuals predisposed to trait anxiety via dampening neuroinflammatory events representing potential biomarkers for specific anxiety disorder subgroups. Future studies aimed at understanding how EE exerts such anti-anxiety effects via the activated microglia system could also hold the key to developing more targeted pharmacological treatments for anxiety disorders.

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Disorders, disease models

Poster ID:136

Spectral analysis of after-discharges elicited by intracranial 50 Hz stimulation of epileptic patients

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Introduction. Rhythmic stimulation-induced discharges, known as after-discharges (AD) were described and related to epileptic processes almost a century ago and clinicians routinely use them to aid the localization of the epileptogenic zone (EZ). Nevertheless, ADs appear in both epileptogenic and non-epileptogenic areas and present high inter- and intrasubject variability. Hence, the latent neuronal processes, as well as its exact relationship with the EZ are still poorly understood. Objectives. Our goal was to delineate spectral characteristics of ADs derived from macro- and microelectrode recordings. Additionally, we aimed to differentiate measures predicting their appearance and correlation with the EZ. Methods. Our study examines the data of 12 patients undergoing presurgical evaluation with intracerebral depth or subdural grid electrodes, presenting prominent ADs in the course of a 50 Hz stimulation protocol. Simultaneously with diagnostic macroelectrodes, laminar multielectrode arrays (LME) were also implanted in the hypothesized epileptogenic zone. ADs were visually identified on the macroelectrode recordings of all patients. Following careful artifact rejection, the spectral characteristics of the detected events were calculated and AD containing epochs were compared with AD-free stimulation periods. Patients with LMEs placed near an AD-presenting electrode (at 0.5-1.5 cm distance), were selected for further analysis. Results. We have demonstrated that ADs contain prominent high delta, theta and beta frequency components. During stimulation, AD epochs were characterized by increased gamma oscillations, while pre-stimulation periods showed increased low delta power compared to epochs with no ADs. ADs detected on macroelectrode recordings proved to be very localized, mostly involving only one channel. Not even LMEs located at ~1 cm were able to register visible discharges, although changes in the spectral pattern were observed. Implications. We have described oscillatory components associated with the generation of ADs, and offered insights into its micro-scale level dynamics. These findings might contribute to the better understanding of this phenomenon and its relationship to the epileptic network.

Day 2 Disorders, disease models

Poster ID:236

Quantitative electron microscopic analysis of mitochondrial changes in the hippocampus of depressed patients

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Introduction Major depressive disorder (MDD) is a common, potentially life-threatening disease causing severe social and economic burden world-wide. This complex disorder is characterized by depressed mood, diminished interests, impaired cognitive function and vegetative symptoms, such as disturbed sleep or appetite. Despite decades of research the exact aetiology is still unknown. Numerous in vivo and post-mortem studies document structural changes in the hippocampus of depressed patients. Neuroimaging studies report on reduced hippocampal volume in depressed patients whereas, post-mortem histopathological studies document changes in cellular number and morphology affecting both neurons and glial cells. Mitochondria are intracellular powerhouses generating chemical energy for biochemical reactions of the cell. Recent findings suggest that individuals with inadequate mitochondrial function could be vulnerable to the stress-induced depletion of the brain's energy resources and, by that, to the development of psychopathologies.

The aim of the present study was to investigate the number and morphology of mitochondria in post-mortem hippocampal samples originating from depressed patients. Hippocampal tissue blocks were received from the brain bank of the University of Mississippi Medical Center. This collection included three subgroups: 1) tissue samples from patients with MDD (n = 11); 2) samples of alcoholic individuals (n = 8) and 3) control samples (n = 10), i.e. individuals who died in an accident and had no neuropsychiatric disorder. We performed routine transmission electron microscopic sample preparation and investigated the main sub-areas of the hippocampus, i.e. Dentate Gyrus, CA3 and CA1. Ultrathin sections were inspected and microphotographs were taken for the further quantitative analysis via a JEOL JEM 1400 FLASH transmission electron microscope. The systematic quantitative analysis was done with the Neurolucida system (MicroBrightField), using unbiased counting principles. The quantification of the samples is currently in progress. Preliminary data will be presented on the poster. Keywords: major depressive disorder, electron microscopy, hippocampus

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Disorders, disease models

Poster ID:336

Selective induction of Krebs cycle enzyme subunits in the parahippocampal cortex of suicide victims

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Altered functional connectivity in human cortical networks has been reported in psychiatric disorders. One of these networks, the default mode network (DMN) is critical in mood disorders. Abnormal activity in the parahippocampal cortex (PHC), a moderating hub of the ventral DMN, has been reported in depressed patients and suicide attempters. Alterations in neuronal mitochondrial function may contribute to depression and suicidal behavior, however, little is known about the underlying molecular level changes in relevant structures including the PHC. Therefore, we addressed the protein level alterations of tricarboxylic acid cycle (Krebs cycle) enzyme subunits in the PHC of suicide victims by reverse phase protein array (RPPA). Postmortem human brain samples were collected from 13 control and 11 suicide individuals. The entorhinal cortex (EC), adjacent to the PHC, was selected to serve as a control brain region. RPPA analysis revealed that the protein levels of DLD, OGDH, SDHB, SUCLA2 and SUCLG2 were significantly induced in the PHC but not in the EC. Subsequently, qRT-PCR was used to examine if mRNA level changes are behind altered protein levels associated with suicide. The identified expressional changes suggest the selective upregulation of major Krebs cycle enzyme subunits belonging to glutaminolysis in the PHC suggesting the potentiation and a prominent role of this process in the pathophysiology of suicidal behavior.

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Disorders, disease models

Poster ID:137

P2X7R modulates dendritic outgrowth during brain development in physiology and pathology

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ATP operates as a "danger" signalling under pathological conditions through purinergic receptors, including the ionotropic P2X7 receptor (P2X7R). Its endogenous activation is associated with neurodevelopmental disorders; however, its function during early embryonic stages remains largely unclear. Our objective was to determine the role of P2X7R in regulating neuronal outgrowth. For this, primary hippocampal cells were obtained from wild-type (WT) and knock-out (KO) embryos and compared with sholl analysis. This allows comparisons between different conditions determining the number of intersections per radio for each neuronal trace. As abnormal dendritic branching is a hallmark of certain neurodevelopmental disorders, such as schizophrenia, a model of maternal immune activation (MIA)-induced schizophrenia was also used. Intraperitoneal poly (I:C) was performed on pregnant mothers on E12.5, and further morphological investigations in primary hippocampal neurons were performed. Then, we studied schizophrenia-like behaviour in young adult mice, females and males. As a result, P2X7R deficient neurons showed reduced dendritic growth, indicating that P2X7R might have a role in the neuronal maturation process. We confirmed the consequences of the morphological deficits in hippocampal pyramidal neurons with cognitive tests in young WT and KO males and females, where KO exhibited deficits in working memory. In pathological conditions, MIA treatment produced deficits in the dendritic morphology of primary hippocampal neurons from WT mice but not those from KO mice. In addition, P2X7R drives PIC-induced schizophrenic-like behavioural symptoms in WT-treated mice. In conclusion, P2X7R has different roles in developing hippocampal dendritic growth under physiological and pathological conditions. Firstly, we found a novel role for the receptor in neuronal branching in the early stages of development under physiological conditions and that a posterior decrease in the expression of P2X7R during brain development causes the receptor to play pathological roles in adulthood. Secondly, in a neurodevelopmental model of schizophrenia, endogenous activation of P2X7R is necessary and sufficient for developing cognitive symptoms.

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Day 2 Disorders, disease models

Poster ID:237

Alteration of extracellular circulating miRNAs expression as a potential biomarker in neurological disorders: multiple sclerosis and epilepsy: a preliminary study

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In the last decades, due to the development of molecular genetic based laboratory investigation methods, numerous studies focused on the molecular background of neurological disorders, such as epilepsy and multiple sclerosis. One of the main objectives is to understand the function of micro RNAs (miRNAs) in the pathophysiology of these disorders and their potential application as peripheral biomarkers to predict disease progression and therapeutic response. Aims: The aim of our study was to investigate the expression levels of circulating miRNAs in peripheral blood and brain samples originating from humans and experimental mice. Methods: The present study demonstrates findings originating from patients with epilepsy (EP) and multiple sclerosis (MS). 52 serum samples from MS patients, 71 serum samples from EP patients and mouse brain samples were investigated. C57BL/6 male mice were used for induction of temporal lobe epilepsy (TLE). Following the intra-hippocampal kainic acid injection TLE mice were terminated after 1, 2, 3 and 4 weeks and brain tissue was removed from animals, and samples containing the prefrontal cortex, hippocampus and cerebellum were collected separately. According to sample type total RNA or miRNA were isolated and were described into cDNA. For downstream workflow droplet digital PCR reaction was prepared, using specific LNA-enhanced miRNA primers. Results: Our preliminary findings demonstrate an association between miRNA expression levels in human serum samples and clinical examination including MRI in MS patients. Conclusion: ddPCR is an extremely sensitive qPCR system, that allows rapid and simple absolute quantification of miRNAs in case of low yield samples, thereby it could provide a promising additional laboratory test method to improve making diagnosis or choosing the most efficiency therapy.

Keywords: neurological disorders, epilepsy, multiple sclerosis, miRNA, ddPCR

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Disorders, disease models

Poster ID:337

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 μ M) 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). Conslusion: 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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Poster ID:138

Acute systemic inflammation causes widespread proteomic changes in the synapses of the murine prefrontal cortex (PFC)

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It has long been observed that acute systemic inflammation induces various neuropsychiatric symptoms both in humans and other mammals. One of the intensively studied behavioral effects of peripheral immune activation is the manifestation of sickness behavior; however, in addition to this depression-like behavior, there are other cognitive effects of peripherally induced neuroinflammation that can be associated with functional disturbances in the central nervous system, especially in the prefrontal cortex (PFC). E.g., learning and memory impairments, abnormal motor coordination, and deficits of exploratory behavior have been observed in rodent models of neuroinflammatory conditions. Synaptic processes largely contribute to network-level functions underlying cognition and behavior, we thus assumed that peripherally induced neuroinflammation may cause molecular changes in the synapses of the PFC. To elucidate this question, we performed the proteomic analysis of synaptosome samples prepared from the PFC of control and lipopolysaccharide (LPS)-treated mice using two-dimensional differential gel electrophoresis (2-D DIGE) and identified the altered proteins by mass spectrometry. We detected 1,330 protein spots in the 2-D gels and could identify 48 proteins from 38 significantly altered spots with absolute fold changes above 1.4. Most of the altered spots showed an intensity increase and only some of them showed a decrease in response to LPS treatment. Functional annotation revealed that the majority of altered proteins are related to cellular signaling, cytoskeletal organization, carbohydrate metabolism, redox state regulation, and synaptic transmission. In addition, we found several connections between the altered proteins and the canonical interleukin-1 (IL-1) signaling pathway, which is a key proinflammatory pathway associated with inflammation-related brain disorders. In conclusion, the results of the present work suggest that peripherally evoked acute neuroinflammation contributes to PFC dysfunctions by various cellular and molecular mechanisms. The reported proteomic changes together with our earlier findings (i.e., the upregulated IL-1 signaling affects PFC excitatory/inhibitory balance via its different electrophysiological effects on glutamatergic and GABAergic neurons) imply that the altered intrinsic and/or synaptic activity of PFC neurons can be associated with the wellknown behavioral and cognitive symptoms of acute systemic immune challenge.

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Disorders, disease models

Poster ID:238

Peripherally induced acute neuroinflammation leads to electrophysiological changes in the visual system of the rat

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Neuroinflammation induced by peripheral immune activation (e.g., bacterial or viral infection) causes diverse neuropsychiatric symptoms in individuals with otherwise normal nervous system functions. The whole of these behavioral alterations associated with infectious diseases is called sickness behavior that is guite uniform across distant species and shows many similarities with clinical depression. However, in addition to the well-known deterioration of higher-order brain functions, clinical and experimental data also draw attention to the impairment of more basic nervous processes. E.g., visual dysfunctions including visual field deficits have been reported in survivors of severe sepsis, in acute encephalitis, and in encephalopathy due to COVID-19. Thus, we aimed to investigate functional changes in the visual system using the lipopolysaccharide (LPS) rat model of peripherally induced acute neuroinflammation. We applied single light flashes and higher frequency (10 and 20 Hz) flash series and recorded the electrophysiological response of the retina (electroretinogram, ERG) and primary visual cortex (visual evoked potential, VEP) in freely moving animals before and after LPS treatment. Our results indicate functional changes both in the retina and visual cortex related to systemic inflammation. In the case of single-flash stimulus, retinal response showed a significant decrease, while the major positive component of the cortical response showed a significant increase within 8 hours following LPS treatment. A similar decrease of the retinal response could be observed during 10 Hz light stimulation; however, no remarkable alterations were shown by the cortical response. Interestingly, the steady-state ERG and VEP responses (induced by 20 Hz light stimulation) were not affected by LPS treatment, suggesting different retinal and cortical mechanisms for the single-flash and steady-state responses. The observed changes seemed to be reversible, as shown by the recordings 24 hours after LPS treatment. In summary, the present data, together with our earlier findings (i.e., the LPS-induced changes in fronto-occipital synchrony) indicate remarkable functional changes in the mammalian visual system during acute systemic inflammation, which may partially underlie the visual dysfunctions related to neuroinflammatory conditions.

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Day 3 Disorders, disease models

Poster ID:338

Behavior and cortical activation following mild hypercapnia in high-anxiety subjects

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Patients with dysregulated anxiety processing often display aberrancies in sensing the internal state of the body. Interoceptive pathways can be activated by mild hypercapnia causing homeostatic disturbances of the body and eliciting anxiety or even panic-like behavior across species. Subjective and physiological responses to CO2 inhalation are elevated in subjects with high trait anxiety compared to those with normal anxiety. Yet, although altered interoception is increasingly recognized as an important component of anxiety-related disorders, its underlying neural mechanisms remain insufficiently understood. In the present study, we aimed to elucidate whether differences in trait anxiety levels determine the engagement of the anxiety network in response to CO2 challenge. Mice selectively bred for either high (HAB) or normal (NAB) anxietyrelated behavior were exposed to CO2-enriched (10%) air for a short time (10min) and neuronal activation patterns were assessed by mapping the expression of the immediate early genes c-Fos and Zif268 using immunohistochemistry. Relative to NAB mice, HABs moved less in the test arena under control air condition. CO2 exposure further reduced locomotor activity of HAB mice. On the contrary, CO2 exposure did not affect locomotor activity in NABs, it rather promoted active coping strategies including rearing and jumping. We found that the number of c-Fos-positive cells was generally increased in the agranular insula, a brain area known to mediate interoceptive stimuli, following CO2 exposure as compared with control air condition. Preliminary data indicates that this effect was more pronounced in NAB than in HAB mice. The quantification of c-Fos induction in other cortical brain areas of HAB and NAB mice in response to CO2 exposure is currently ongoing. Taken together, the present findings indicate increased CO2 sensitivity in individuals with high trait anxiety. The differential engagement of the insula cortex for the processing of interoceptive signals in high trait anxiety may represents a potential biomarker for stratifying patient subgroups to optimize individualized therapeutic interventions.

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Disorders, disease models

Poster ID:139

Transient receptor potential melastatin 4 (TRPM4) regulates hilar mossy cell loss in temporal lobe epilepsy

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Mossy cells comprise a large fraction of excitatory neurons in the hippocampal dentate gyrus and their loss is one of the major hallmarks of temporal lobe epilepsy (TLE). The vulnerability of mossy cells in TLE is well known in animal models as well as in patients, however the mechanisms leading to cellular death is unclear. One possible explanation for their sensitivity is linked to their specific ion channel composition. TRPM4 is a Ca2+-activated non-selective cation channel regulating diverse physiological function of excitable cells. Here, we identified that TRPM4 is present and functionally active in hilar mossy cells. Furthermore, we showed that TRPM4 contributes to mossy cells death following status epilepticus and therefore modulates seizure susceptibility and epilepsy-related memory deficits in the chronic phase of TLE.

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Day 2 Disorders, disease models

Poster ID:239

Quadruple-transgenic mice model of Alzheimer's disorder, with Aβ1-42 and 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 exact role 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 A β 1-42 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 (A_β1-42 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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Brivaracetam induced changes of the neuron-astrocyte-microglia triad in the rat kainic acid model of temporal lobe epilepsy

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Efficient treatment of temporal lobe epilepsy can be particularly challenging. On one hand because the cellular and network changes in epilepsy, especially in the hippocampus are not completely elucidated, and on the other hand due to the fact, that the mechanism of how new antiepileptic drugs interfere with these changes is up for debate. This study aimed to examine and to quantitatively determine the impact of brivaracetam treatment on the adaptive and maladaptive neuroinflammatory changes in the CA1 and CA3 regions of the hippocampus in the kainic acid model of temporal lobe epilepsy. Male Wistar rats (P56) were divided into three groups. Rats assigned to the epileptic and brivaracetam treated groups were injected with kainic acid in the right lateral ventricle, during stereotaxic operation and under isoflurane anaesthesia. Kainic acid induced status epilepticus and, weeks later, spontaneous seizures occurred. After a three-week long latency period the animals received treatment with p.o. brivaracetam (60 mg/kg body weight), which was administered twice daily for 3 weeks. The epileptic and sham operated groups received placebo pills. The animals were sacrificed after the treatment period, and fluorescent immunohistochemistry was performed on bilateral hippocampal slices to identify the changes in astrocyte (GFAP+), microglia (IBA1+) and neuronal (NeuN+) populations. Quantitative changes differed depending on the cell type, but a drastic increase in microglia and astrocyte density could be observed in the epileptic and treated groups. Interestingly in the brivaracetamtreated group a significant increase in microglia density could be detected compared to not only the sham operated group but the epileptic group as well in the right CA1, CA3 and left CA1 regions. A significantly higher density of astrocytes could be seen in the same hippocampal regions. A decrease in the number of neurons was expected in the kainic-acid injected groups, which was indeed significant in the right CA3 and in the left CA1 regions, and was not influenced by the brivaracetam treatment. Brivaracetam treatment increased the microglia activation under epileptic conditions which is consistent with recently published in vitro data. Further studies must be performed in order to elucidate how these alterations influence epileptogenesis and seizure frequency.

Day 1 Disorders, disease models

Poster ID:140

Medial prefrontal cortical interneuron activity underlying fear generalization and extinction deficit

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Experiencing traumatic stress results in psychiatric disorders including post-traumatic stress disorder (PTSD). Core symptoms are enhanced fear generalization and fear extinction deficits, which appear only in a subpopulation of exposed individuals (vulnerable subjects). The medial prefrontal cortex (mPFC) plays a key role in the regulation of fear expression and extinction with significant morphological and functional alterations in individuals with PTSD diagnoses. However, the underlying mechanisms of vulnerability in mPFC networks are not unclear. Our aim was to investigate mPFC characteristics (i.e. global and cell-type specific activity patterns) of vulnerable and resilient subjects in an animal model of PTSD. We exposed adult Long-Evans rats to unpredictable footshock as a traumatic stressor and investigated long-term (28 days) fear generalization and extinction in order to distinguish vulnerable and resilient subjects (i.e. low and high extinction in a safe context). We immunolabeled their mPFC neurons for activity marker c-Fos with interneuron markers parvalbumin (PV), calretinin (CR), somatostatin (SOM), and vasoactive intestinal polypeptide (VIP). We found that neuronal activity in the prelimbic area exhibited reduced activity, whereas the infralimbic cortex exhibited elevated activity in vulnerable subjects. Co-labeling revealed that VIP+ interneurons showed significantly reduced activity in the prelimbic cortex whereas other cell-types (PV, CR and SOM) showed no alterations in activity patterns between groups. Our results suggest that altered VIP interneuron function may contribute to altered fear expression extinction underlying PTSD-like states.

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Poster ID:240

Differential effects of repeated dose scopolamine on cognitive functions in experienced rats

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Scopolamine is an anticholinergic compound widely used as a pharmacological model of cognitive impairment. The drug is typically applied in single dose and in naïve or freshly taught animals. Our objective was to examine the effects of repeated scopolamine treatment on several cognitive functions in young, experienced Long-Evans rats and to see to what extent donepezil can block these actions. We used 35 male rats with 11 weeks learning experience in assays of five different cognitive domains: 5-choice serial reaction time task (5CSRTT, attention), Morris water maze (MWM, spatial learning), pot jumping test (PJ, motor learning), pairwise visual discrimination (PWD, visual learning) and cooperation test (social learning). After baseline measurements rats were randomly assigned into three treatment groups: saline, scopolamine (0.3 mg/kg ip.), and scopolamine+donepezil (3 mg/kg ip.), injected 30 min before the tests. Animals were treated for 20 days, donepezil was only given in the second 10 days. After the drug-period an 11-day wash-out phase followed. Cognitive performance was tested in the above assays 2 times during each phase of the study. Statistical significance (p<0.05) was determined by repeated measures ANOVA. Scopolamine treatment caused differential effects on the studied cognitive domains. The compound did not exert significant effects in the MWM and PWD. In the 5CSRTT and the cooperation test, the scopolamine-treated group yielded significantly lower number of successful trials than the control group. However, these impairments gradually decreased during the treatment period. In PJ, the control group could jumped significantly longer distances compared to the scopolamine-treated groups, and in this paradigm – in contrast to the former two tasks – the magnitude of the scopolamine-effect increased by repeated treatments. Donepezil treatment did not ameliorate the learning performance deficit in any of the tests. All groups showed similar performance to their baseline levels already two days after discontinuation of the treatments. Based on our results, repeated dose scopolamine could not induce lasting changes in the functioning of cognitive neural networks, therefore it may not be an appropriate model for testing potential antidementia drugs, especially in young animals.

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Day 2

Poster ID:340

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, FCDIB 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 CB1Rimmunopositive 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-, CB1Rexpressing 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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Day 1 Disorders, disease models

Poster ID:141

Investigation of the effect of dimethyl trisulfide mediated by TRPA1 ion channels on anxiety and depression-like behaviour

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Background Anxiety and depression can be treated with a variety of medications. Many patients, however, do not respond to drug treatment. Others experience side effects and discontinue treatment. Sulfide administration has been found to relieve depression-like behavior in experimental animals. The polysulfide dimethyl trisulfide (DMTS) is commonly found in garlic and is used as a food additive. According to our earlier results, DMTS inhibits the movements and breathing of mice, depressing the central nervous system. Based on these it can be an ideal candidate for further study as a dietary supplement or therapeutic medication for the complementary treatment of depression and anxiety. Aims We aimed to examine the effect of DMTS in a mouse acute stress model of anxiety and depression, as well as underlying mechanisms. Methods To elucidate the mechanism of the action we designed to use TRPA1 gene-knockout (KO) and wild-type (WT) mice. The appropriate dose of DMST was determined via open field test. Then the experimental animals were subjected to acute stress test, so called forced swim test to detect depression-like behaviour and anxiety. Results The dose of 50 mg/kg DMTS was the highest which did not diminish the natural activity of mice. DMTS treatment reduced inactive duration, increased highly active duration and activity frequency in TRPA1 WT animals compared to either the untreated or the vehicle treated group in the FST. DMTS did not alter parameters in TRPA1 KO animals relative to naïve mice or vehicle treatment. Conclusion Since the beneficial effects of DMTS were not presented in TRPA1 KO mice, but we experienced them in TRPA1 WT mice, we conclude that DMTS reduces depression-like behavior in the forced swim test mediated by TRPA1 ion channels. DMTS may be an alternative to complement the treatment of depression and anxiety.

Day 2 Disorders, disease models

Poster ID:241

Examination of the density of macro- and microglia coverage of the bloodbrain 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 human epileptic 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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Poster

ID:341

Gut-microbiome analysis in a 'three-hit' schizophrenia rat model (Wisket)

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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 disabilities, memory impairments, altered social behavior, and decreased pain sensitivity. Based on clinical and preclinical observations, there is growing evidence that suggests a bidirectional relationship between the gut microbiome and the central nervous system. Thus, imbalances within the gut microbiome may play a role in the development of various neuropsychiatric disorders, including schizophrenia. The present study aimed to examine the sex-dependent taxonomic diversity and the abundance of the gut microbiome in a 'three-hit' schizophrenia rat model (Wisket). Twelve-week-old male and female, 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 either by group or by sex. Microbiome analysis demonstrated significant differences in gut microbial abundance between the Wisket and control groups at the genus, family, and phylum levels, partially correlated with human and preclinical findings. These findings suggest that the 'three-hit' schizophrenia rats show complex abnormalities at the level of the microbiome, too. Thus, the Wisket model may be useful for investigating the role of the gut-brain axis in the etiology of schizophrenia. It may also support the importance of prebiotic add-on therapy in patients.

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Day 1 Disorders, disease models

Poster ID:142

The in vitro effects of beta-cyclodextrin complexed antiepileptic drugs on low-magnesium induced seizure-like events

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Temporal lobe epilepsy is the most common form of pharmacoresistant epilepsy. Previous studies indicate that this is partly caused by the poor pharmacokinetic properties of the available antiepileptic drugs (AEDs). Overcoming drug-resistance with new pharmacological treatments remains a challenge for both researchers and clinicians alike. The aim of this study was to assess the in vitro-efficacy of carbamazepine, lacosamide and rufinamide using beta-cyclodextrin (BCD) as an excipient to improve the solubility and bioavailability of AEDs. Transverse brain slices were obtained from P7-14 rats and a microelectrode was inserted in the CA3 region of the hippocampus. The slices were perfused with artificial cerebrospinal fluid (nACSF) in order to record the baseline neuronal activity. Seizure-like events (SLEs) were induced by magnesium-free ACSF (OMgACSF), followed by OMgACSF containing one of the AEDs complexed in 1% BCD. To assess the reversibility of the effect OMgACSF and nACSF washout were performed. We observed that BCD significantly reduced the duration of the ictal period to 76.39±5.24% (all data presented as mean±SEM) of control values. Furthermore it reduced the interictal length to 62.47± 4.24%, thus increasing seizure frequency. Each of the tested AEDs decreased the ictal period: carbamazepine in 100 μ M concentration to 55.07±3.9%, rufinamide in 100 μ M and 50 μ M to $58.05\pm4.78\%$ and $50.23\pm6.21\%$, respectively. The reduction of the ictal period in 25μ M and 50μ M lacosamide concentrations was similar (63.83±4.87% and 67.33±8.72%). We also observed an increase in seizure frequency, due to the reduction of interictal periods. Carbamazepine reduced it to 51.78 \pm 4.53%. In 50 μ M rufinamide it was 25.35 \pm 4.67%, but in 100 μ M it was decreased only to 68.62±6.51%. This resulted in a significantly lower seizure frequency. Lacosamide applied in 25μM concentration reduced the interictal period to 62.44±7.48%, in 50μM it was slightly longer (74±3.35%). Although this difference is not significant, the trend indicates that a higher lacosamide concentration is associated with lower SLE frequency. In conclusion, each of the tested AEDs complexed in 1% BCD preserved its well known anticonvulsant effects by shortening the duration of SLEs. Although 1% BCD's own effect on seizure-like activity is not at all negligible, since it increases the SLEs frequency and decreases its duration, it can be used as a solubilizing agent in in vitro epilepsy experiment.

Poster ID:242

Day 2

Effects of valproic acid treatment on vocal learning and social behaviour in zebra finches

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Previous animal studies have shown that valproic acid (VPA) administered during the embryonic development causes autism-like symptoms. We are currently working on adapting this treatment to zebra finches (Taeniopygia guttata), as these songbirds have been shown to be good models of language development, vocal learning and social behaviourtraits thet are affected by autism spectrum disorder in humans. After treatment of the embryos with VPA (or saline as a control), we monitored the development and survival of the offsprings, and, after matured, we examined their social behaviour and vocal learning. Our preliminary results showed that the effect of VPA did not significantly affect mortality and morphometric variables. VPA-treated individuals showed altered, but not reduced, sociability in the standard three chamber test adapted to finches. The vocalizations of males in the control group were significantly more similar to their father's vocalizations, whereas the vocalizations of VPA-treated males significantly differed from those of their father's. The less effective social vocal learning in the VPA individuals suggests, that the brain regions responsible for vocal communication, as well as for social preference or learning, might be affected by the VPA treatment. We conclude that VPA treatment in zebra finches can be a useful model of certain aspects of autism, however other behavioural tests than the adapted standard rodent sociability test are needed to properly assess the social capabilitities of songbirds.

Poster ID:342

Glucose transporter 2 expression in the medial prefrontal cortex of a mice model of posttraumatic stress disorder

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Glucose-responsive neurons have been discovered in a variety of brain regions, including the medial prefrontal cortex (mPFC). They are involved in glucose homeostasis, feeding, and energy expenditure. As a result, glucose transporters are critical in the brain, and changes in their expression are linked to a variety of diseases. In particular, glucose transporter 2 (GLUT2) is found in glucose sensing cells in the brain and plays a role in homeostatic regulation. A large body of research suggests that the mPFC is a critical region that regulates adequate threat processing by exerting top-down control over the amygdala. Dysregulation of the mPFC might impair mechanisms that control and reduce fear responses, leading to the development of severe psychiatric disorders such as post-traumatic stress disorder (PTSD). The purpose of this study was to confirm the presence of GLUT2 positive cells in the mPFC of both animal and human brains, as well as to investigate their role in fear response in connection with its possible role in PTSD. Immunhistochemical method detected GLUT2 positive cells in the mPFC of both mouse and human brains. The results of RNAscope in situ hybridisation revealed GLUT2 mRNA expression in VGluT1 positive neurons, as well as in neurons that were both VGluT1 and VGluT2 positive. However, neurons that were only VGluT2 positive did not express GLUT2 mRNA. In the infralimbic area of traumatized mice an increase in GLUT1 and glucokinase and a decrease in GLUT2 expression was found by rtPCR. Manipulation of mPFC GLUT2+ cells of GLUT2-Cre mice by chemogenetic tools (DREADD) during fear memory consolidation and recollection had no direct effect on animal freezing behavior during a fear conditioning test several weeks later. However, further manipulation at a different time window might shed new light on the regulatory role of mPFC GLUT2 positive cells in the development of PTSD. Our findings might contribute to a better understanding of the pathomechanisms of PTSD, which will aid in the development of new target treatments for this debilitating disorder.

Disorders, disease models

Poster ID:143

Analysis of thalamocortical cellular network activity in a genetic animal model of absence epilepsy

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Aims: The somatosensory ascending pathways are topologically aligned. In this system the barreloids of the ventral posteromedial nucleus of the thalamus are directly and reciprocally connected to the proper barrels of the primary somatosensory cortex. The tactile information originating from the whiskers transmitted to the somatosensory cortex via this well-organized pathway. This thalamocortical circuitry is involved in several oscillatory activities, like sleep spindles and spike-and-wave discharges, the major electrophysiological hallmark of absence seizures. In our project we aimed to investigate the thalamocortical cellular network activity in a genetic absence epilepsy model of mice. Methods: Experiments were carried out on young adult C57BL/6NTac and GABAAy2 R43Q mice. The detailed mapping analysis of somatosensory pathway was made under urethane anaesthesia using in vivo intrinsic imaging, combined with acute silicon probe recordings. Thalamic and cortical tetrode recordings were made in freely moving animals, using tungsten electrodes. Data were analysed semiautomatically to identify seizure and spindle events, while single cell activity was analysed with klusta, followed by a manual supervision. Results: We show that intrinsic imaging can be used for mapping a whisker related barrel organization. Acute single cell activity analysis revealed a huge number of direct excitatory and inhibitory synaptic connections between the recorded cell population both in wild type and GABAAy2 R43Q mice. Single-cell activity clustering revealed lots of cell-to-cell interaction, which could be used for determining the area of initialization of the seizure. It was also observed that transgenic animals have several SWD seizures, and the incidence of seizures increases with age. Conclusion: In the present study, a more accurate picture of seizure manifestation was obtained in a genetic animal model of absence epilepsy.

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Disorders, disease models

Poster ID:243

FRACTALKINE RECEPTOR (CX3CR1) INHIBITION IS A POTENTIAL NOVEL THERAPEUTIC APPROACH FOR COMPLEX REGIONAL PAIN SYNDROME

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Complex Regional Pain Syndrome (CRPS) is a severe chronic pain condition accompanied by edema and autonomic disorders, which develop after a small injury. The pathophysiological mechanisms are unknown, but immune response against sensory nerve-derived antigens, complex neuro-immune-vascular interactions and neuroinflammation are involved. Since the treatment is unsatisfactory, it is necessary to identify the key mediators and new therapeutic targets. The inflammatory chemokine (fractalkine) receptor 1 (CX3CR1) expressed on microglia cells and macrophages plays a crucial role in neuroinflammatory processes. Here we investigated its involvement in a passive transfer-trauma translational CRPS mouse model. Methods Female CX3CR1-gene deficient and wildtype mice were treated daily with plasma IgG purified from CRPS patients or healthy volunteers. Plantar skin-muscle incision was performed on day 0 to model the microinjury. The paw mechanonociceptive threshold was measured by dynamic plantar aesthesiometry, astrocyte and microglia in pain-related central nervous system regions by glial fibrillary acidic protein (GFAP) and Iba1 immunohistochemistry. The CX3CR1 antagonist AZD 8797 (80µg/kg i.p) was administered daily to wildtype mice. Results Daily i.p. injections of CRPS IgG significantly increased the mechanical hyperalgesia, as well as astrocyte and microglia markers in the spinal cord dorsal horn, periaqueductal gray and somatosensory cortex during the 7-day experimental period after plantar skin-muscle incision compared to healthy IgG treatment in wildtype animals. Both CX3CR1 deficiency and the antagonist treatment significantly diminished the CRPS IgG-induced increased pain behavior and glia cell activation. Conclusions CX3CR1 activation is likely to mediate CRPS-associated pain and neuroinflammatory mechanisms suggesting that CX3CR1 inhibition might provide novel analgesic perspectives.

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Poster ID:343 Transient receptor potential ankyrin 1 (TRPA1) ion channel in the centrally-projecting Edinger-Westphal nucleus is downregulated in a mouse model of posttraumatic stress disorder

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Introduction: Post-traumatic stress disorder (PTSD) is an anxiety disorder related to stress maladaptation. The centrally projecting Edinger-Westphal nucleus (EWcp) is implicated in stress adaptation response. TRPA1, a non-selective cation channel, is expressed both in mouse and human urocortin1 (UCN1) positive neurons of the EWcp. The EWcp Trpa1 mRNA is downregulated upon chronic stress in mice and in suicide victims. Our aim was to examine the TRPA1/UCN1/EWcp neurons in a mouse model of PTSD. We hypothesized the involvement of these neurons in the pathophysiology of PTSD. Methods: Male TRPA1 wild-type (WT) and genedeficient (KO) mice were exposed to repeated electrical foot-shocks combined with acoustic startle stimuli to induce PTSD. The freezing behavior was evaluated as an indicator of PTSD-like state. Trpa1 and Ucn1 mRNA expressions as well as UCN1 peptide contents were assessed in the urocortinergic neurons of the EWcp using RNAscope in situ hybridization combined with immunofluorescence. Results: The validity of the model was proven by increased freezing behavior in both genotypes upon foot-shock. The Trpa1 mRNA was downregulated, while higher Ucn1 mRNA expression was observed in WT animals upon foot-shock, compared to the controls. The latter change was not detectable in KO mice. Furthermore, upon foot-shock, the UCN1 peptide content was significantly higher in WT animals, compared to the KO counterparts. Conclusion: Decreased Trpa1 mRNA expression and increased neuronal Ucn1 mRNA content suggest that TRPA1/UCN1/EWcp might contribute to the stress (mal)adaptation in PTSD.

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Day 3

Poster ID:144

Alleviation of longterm cognitive impairment with memantine combined with alfa7 nicotic receptor ligand after repetitive mild traumatic brain injury in rats

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Single mild traumatic brain injury (mTBI) mostly results only in minor symptoms. However, after repetitive mild traumatic brain injury (rmTBI) long term defects occur and may lead to irreversible decline of cognitive functions. To this date no medical treatments known to selectively reverse or alleviate such medical conditions. In this study, we used a subchronic treatment regime to evaluate the combined effects of noncompetitive NMDA receptor antagonist memantine and the α 7 nicotic acethylcoline receptor agonist PHA-54613 in a rat model of rmTBI. We performed Marmarou weight drop model for 5 days, once in every 24 hours. The animals were divided into two groups. The TBI group was subjected to weight drop injury, the Sham group was only subjected to surgery but not weight drop injury. To assess the animals overall neurological status, we performed the modified neurological severity score (mNSS) test before and after TBI. Subchronic pharmacological treatments begin at 7 weeks after surgery and were performed for 14 days, in every 12 hours. Novel object recognition test (NOR) was used to measure the animals' cognitive performance. Animals did not show any signs of motor or sensory deficits in the mNSS. In the NOR test, rats treated with memantine 0.3 mg/kg showed improvement after the 3rd treatment day. However the lower dose of memantine (0.03 mg/kg) did not improve memory performance. Low dose of PHA (0.1 mg/kg) did not improve the animals performance, however, the high dose of PHA (2.0 mg/kg) increased the animals cognitive performance on the 3rd treatment day, however, this effect was gradually diminished during the subsequent days of the treatment. The lower dose of memantine (0.03 mg/kg) combined with PHA (0.1 mg/kg) resulted significant memory improving effect from the 3rd treatment day and this effect lasted until the end of the whole experiment. We used subchronic treatment to evaluate the combined effect of memantine and PHA-54613. The 0.3 mg/kg memantine monotreatment increased the animals cognitive performance. However low dose of memantine (0.03 mg/kg) combined with PHA 0.1 mg/kg resulted good memory performance in the NOR test. Our present results indicate that, as memantine combined with PHA successfully restored cognitive impairment in rats caused by rmTBI, the combination treatment using nicotinic receptor agonists with memantine may serve as a promising future option for alleviating longterm deficits of repetitive traumatic brain injury.

Disorders, disease models

Poster ID:244

Calretinin interneurons in human dorsolateral prefrontal cortex are involved in autism spectrum disorder

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Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder, which is characterized by social deficits and repetitive, stereotypic behavior. A widely accepted hypothesis states that an imbalance of excitatory and inhibitory activity may play an important role in ASD. Our research group previously found the density of calretinin-immunopositive (CR+) neurons was lower in the caudate nucleus in ASD. Thus, we aimed to investigate the distribution of CR+ interneurons across the layers of the dorsolateral prefrontal cortex (DLPFC), Brodmann area 9, an area already proven to be affected in ASD. Formalin-fixed, paraffin-embedded tissue was requested from 13 ASD and 10 control brain samples from the Oxford Brain Bank. After immunohistochemical staining, slides were digitalized with Aperio ScanScope AT Turbo whole slide scanner. Immunopositive cells were annotated in Aperio ImageScope software after delineating cortical layers based on cytoarchitecture. For the evaluation of the data, linear mixed model and contrasts were used. According to our results the density of CR + interneurons was reduced by 23% in the in layer 2 of DLPFC of the ASD group (p=0,00036), suggesting that these cells may be affected in ASD. Interestingly, Velmeshev et al. (2019) identified VIP (CR+) neurons as one of the clusters with most abundant differentially expressed genes in the same brain region, in a larger cohort of ASD and CTR samples. These results inspire us to explore the cellular background of ASD further, by involving additional cell types and brain areas in forthcoming investigations and applying a multiscale research approach.

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Poster ID:344

MicroRNA signatures and their predicted targets in peripheral blood mononuclear cells during ictal and interictal periods of migraineurs

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Background: Migraine is a primary headache with genetic susceptibility, but the pathophysiological mechanisms are poorly understood, and it remains an unmet medical need. We demonstrated earlier significant differences in the transcriptome of migraineurs' peripheral blood mononuclear cells (PBMCs) suggesting the role of neuroinflammation and mitochondrial dysfunctions. Post-transcriptional gene expression is regulated by microRNAs (miRNAs), which are emerging drug targets. However, little is known about the miRNA transcriptome in migraine. Methods: We determined miRNA expression of migraineurs' PBMC during (ictal) and between (interictal) headaches compared to age- and sex-matched healthy volunteers. Small RNA sequencing was performed from the PBMC, and mRNA targets of miRNAs were predicted using a network theoretical approach by miRNAtarget.com[™]. Predicted miRNA targets were investigated by Gene Ontology enrichment analysis and validated by comparing network metrics to differentially expressed mRNA data. Results: In the interictal PBMC samples 31 miRNAs were differentially expressed (DE) in comparison to healthy controls, including hsa-miR-5189-3p, hsamiR-96-5p, hsa-miR-3613-5p, hsa-miR-99a-3p, hsa-miR-542-3p. During headache attacks, the top DE miRNAs as compared to the self-control samples in the interictal phase were hsa-miR-3202, hsa-miR-7855-5p, hsa-miR-6770-3p, hsa-miR-1538, and hsa-miR-409-5p. MiRNA-mRNA target prediction and pathway analysis indicated several mRNAs related to immune and inflammatory responses (toll-like receptor and cytokine receptor signalling), neuroinflammation and oxidative stress, also confirmed by mRNA transcriptomics. Conclusions: We provide here the first evidence for disease- and headache-specific miRNA signatures in the PBMC of migraineurs, which might help to identify novel targets for both prophylaxis and attack therapy.

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Day 1 Disorders, disease models

Poster ID:145

Inhibiting the functions of complement classical pathway by single-chain C1q recognition module

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C1q is the recognition molecule of the classical complement pathway of innate immunity with well-characterized pathway-activating interaction partners. Moreover, C1q has been recently described in the central nervous system having a role in synapse elimination in both the healthy brain and neurodegenerative diseases. However, the molecular mechanism of C1q-associated synapse phagocytosis remains unclear. Exploration of synaptic interaction partners and phagocytosis-related functions of C1q can be facilitated by inhibitors. Here, we designed monomer and multimer protein constructs consisting of the globular recognition parts of mouse C1q (gC1q) as single-chain molecules (sc-gC1q proteins) without its effector collagen-like region, and expressed them in E. coli expression system. These molecules were able to competitively inhibit the function of C1q. Their structure and binding capabilities with known CP activators were validated by analytical size exclusion chromatography, analytical ultracentrifugation, circular dichroism spectroscopy and ELISA. We further characterized their interactions with immunoglobulins and neuronal pentraxins by surface plasmon resonance spectroscopy. We demonstrated that sc-gC1qs potently inhibit the function of C1q by hemolysis assay and C4 ELISA. In addition, they competed with C1q in binding to embryonal neuronal cell membrane. The application of sc-gC1qs can reveal neuronal localization and functions of C1q in assays in vivo and might serve as a basis for engineering inhibitors for therapeutic purposes.

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Poster ID:245

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

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Aims. Corticothalamic circuit mechanisms shape neuronal oscillatory activities like sleep spindles and slow wave rhythm. In addition, dysfunction in this network is also responsible for the epileptic activity, as its contribution to the development of spike-and-wave discharges - a hallmark of absence epilepsy – has been experimentally proved. The present project aims to validate a novel genetic model of absence seizures and to investigate the contribution of layer 6 corticothalamic feedback on the initiation, maintenance and termination of epileptic events. Methods. Experiments were carried out on C57BL/6NTac wild-type and GABAAy2 R43Q mutant adult mice. Electrophysiological recordings in non-anaesthetized freely moving conditions were acquired by tungsten electrodes which were implanted bilaterally into the following target areas: layer 6 of motor and somatosensory cortices, ventral posteromedial nucleus of the thalamus and into the right hippocampus. Automatic offline detection of spikeand-wave discharges and sleep spindle events was followed by manual verification and analyzed in detail for different parameters of oscillatory activity. The validation of the absence seizures as a phenotype of GABAAy2 R43Q animals was made by the administration of i.p. 200 mg/kg ethosuximide. Results. Epileptic events hallmarked by spike-and-wave discharges could be recorded from both cortical and thalamic regions, in a synchronized and generalized manner in the GABAAy2 R43Q animals. The synchrony of the oscillatory patterns as well as the length and incidence of spike-and-wave discharges increased over time showing an age-dependent characteristic. The intraperitoneal injection of the antiepileptic drug ethosuximide resulted in a significant reduction of spike-and-wave discharges, as was expected. In ongoing experiments, the contribution of the cortico-thalamic pathway on seizure activity is tested by chemogenetic inhibition via activating the hM4D receptors, expressed by layer 6 cortico-thalamic cells. Conclusion. In this study, we have successfully validated a novel genetic absence epilepsy model which can provide us with a deeper understanding of the efficacy of cortico-thalamic feedback on absence epilepsy.

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Day 2

Day 3 Disorders, disease models

Poster ID:345

Sex-biased and isoform-specific rescue of working memory deficits by developmental GSK3 inhibition in a mouse model of schizophrenia predisposition

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Working memory, a cognitive process involving short-term encoding and maintenance of information relies on prefrontal cortex functionality, is reliably modeled in preclinical animal models and is profoundly impaired in schizophrenia. The 22q11.2 Deletion Syndrome is a clinically relevant genetic cause of schizophrenia and non-selective Glycogen Synthase Kinase (GSK)3 (α and β isoform) inhibitors have been found to rescue cognitive deficits in preclinical models, but their non-selective profiles hamper their preclinical research utility. Recently developed selective inhibitors allow targeted inhibition of each isoform, but their impacts on prefrontal cortex cognition and disease-relevant cognitive dysfunction are unresolved. Here, we tested their potential to rescue prefrontal cortex dependent spatial working memory deficits in the Df(16)A+/- mouse model of the 22q11.2 deletion syndrome. The selective GSK3 β inhibitor BRD3731 administered during postnatal development rescued acquisition deficits in spatial working memory in male but not female Df(16)A+/- mice (n = 121, p=0.01, 3-way ANOVA). Developmental medial prefrontal cortex and ventral hippocampus bulk-seq transcriptomics data supports the findings by delineating earlier sex-biased RNA expression profiles in Df(16)A+/mice. GSK3β inhibition also rescued deficits in theta-frequency (4-12 Hz) coherence between ventral hippocampus and medial prefrontal cortex, a neurophysiological correlate of spatial working memory performance, in Df(16)A+/- mice (n=98, p=0.02, 3-way ANOVA). Ongoing analysis of medial prefrontal single-unit recordings aims to further verify behavioral and neurophysiological findings. Conversely, selective postnatal GSK3a inhibition by BRD0705 failed to rescue task acquisition deficits, but did reverse deficits in task performance under conditions of increased working memory demand in both male and female Df(16)A+/- mice (n=109, p=0.003, 3-way ANOVA). Overall, the combined set of experiments indicates differential roles of GSK3 α and β isoforms in the development of the prefrontal-hippocampal circuitry supporting spatial working memory, its disease-relevant dysfunction in mice and highlights the import of sex-specific analysis in pre-clinical research.

Day 1 Disorders, disease models

Poster ID:146

Regulating epilepsy by manipulation of hippocampal VIP-expressing interneurons

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Introduction: In the ventral hippocampus, two groups of VIP-expressing interneurons, containing CCK-expressing basket cells and/or interneuron-selective interneurons (ISIs) control pyramidal cell activity and GABAergic transmission. The aim of the current study is to assess the possible role of VIP-expressing interneurons in the pathophysiology of epilepsy. Methods: We permanently inhibited GABA release selectively from VIP interneurons of the ventral subiculum by injecting a viral vector expressing tetanus toxin light chain (AAV-TeLC) in epileptic as well as non-epileptic VIP-Cre mice. Mice were then subjected to telemetric EEG recording for 4 weeks. Spontaneous alternation Y-maze and novel location recognition tests were conducted to evaluate spatial memory and learning, respectively. Furthermore, by injecting a vector expressing GqDREADD, we explored the possibility of manipulating seizures via stimulation of VIP-expressing interneurons. Results: In non-epileptic mice, injection of AAV-TeLC and AAV-GFP did not cause development of seizures in both groups. In addition, behavioral tests addressing anxiety, memory, and navigation showed no differences between groups. In epileptic animals, the average number of spontaneous seizures per day as well as the average time spent in seizure per day showed a significant reduction in AAV-TeLC-injected mice in comparison to AAV-GFP-injected controls. Interestingly, stimulation of VIP-expressing interneurons led to a proconvulsive tendency. Discussion: ISIs mainly target other interneurons; therefore, silencing them would increase inhibition in pyramidal cells. However, the outcome of the silencing of VIP-interneurons in epileptic mice is highly dependent on the status of the network before silencing. To prove, we need further assessment by triple immunohistochemistry labeling for GFP, CCK, and VIP, which is currently ongoing in our lab.

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Poster ID:246

Regional redistribution of CB1 cannabinoid receptors in human fetal brains with Down's syndrome, and their functional modifications in Ts65Dn +/+ mice

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Aims The endocannabinoid system with its type 1 cannabinoid receptor (CB1R) expressed in postmitotic neuroblasts is a critical chemotropic guidance module with its actions cascading across neurogenic commitment, neuronal polarization and synaptogenesis in vertebrates. Here, we present the systematic analysis of regional CB1R expression in the developing human brain from gestational week 14 until birth. In parallel, we diagrammed differences in CB1R development in Down syndrome foeti and identified altered CB1R signalling. Methods Fetal brains with normal development or with Down's syndrome were analysed using standard immunohistochemistry, digitalized light microscopy and image analysis (NanoZoomer). CB1R function was investigated by in vitro neuropharmacology from infant Ts65Dn transgenic mice brains carrying an additional copy of ~90 conserved protein-coding gene orthologues of the human chromosome 21. Results We detected a meshwork of fine-caliber, often varicose processes between the subventricular and intermediate zones of the cortical plate in the late first trimester, when telencephalic fiber tracts develop. The density of CB1Rs gradually decreased during the second and third trimesters in the neocortex. In contrast, CB1R density was maintained, or even increased, in the hippocampus. We found the onset of CB1R expression being delayed by ≥ 1 month in age-matched fetal brains with Down's syndrome. In vitro, CB1R excitation induced excess microtubule stabilization and, consequently, reduced neurite outgrowth. Conclusions We suggest that neuroarchitectural impairments in Down's syndrome brains involves the delayed development and errant functions of the endocannabinoid system, with a particular impact on endocannabinoids modulating axonal wiring.

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Poster ID:346

Optimization of Valproic acid treatment to induce autistic behaviours in zebra finches: dosage, time of administration and development

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Autism spectrum disorder (ASD) is a human neurodevelopmental disorder associated with impaired communication and social behaviors. ASD is associated with delayed or absent spoken language, sometimes with cognitive delay, and repetitive patterns of behaviour. Valproic acid (VPA) is an antiepileptic and mood-stabilizing drug that, when administered during certain stages of pregnancy, might result in ASD-like symptoms of the newborn. VPA has been applied successfully in previous animal models of autism: domestic chicks and mice. We argue, however, that zebra finches (Taeniopygia guttata) provide a new and more adequate animal model to study ASD as those currently used. Zebra finches are highly social, gregarious animals, with ample social interactions and acoustic communication. Here we apply VPA in zebra finch embryos for the first time, and aim at optimizing dosage and time of administration to maximize hatching success while inducing ASD-like symptoms. As a reference, we used data available for domestic chicks, and extrapolated from these to establish the approximate dose (0.6µmol) and timing (day 9 of incubation). Pairs were allowed to breed, and their eggs (n=332) were injected using 0.3µmol or 0.6µmol of VPA (experimental group) or 3.3µl of a normal Saline solution (control group) on day 8, 9 or 10 of incubation. Hatching success and post-hacthing mortality were monitored. Our results suggest that incubation day 8 corresponds to a relatively sensitive embryonic developmental stage, hence it might be too early for administration; even with saline control, mortality is high in these time groups. On the other hand, in the day 10 group, even the higher dosage failed to induce an observable effect on hatching rate, suggesting that the embryonic development at day 10 is too close to hatching, hence VPA-treatment at this stage might have no more an adequate effect on neuronal development. The most appropriate incubation day which resulted in the expected effect is day 9. We have concluded that incubation day 9 with 0.45μ mol of the same volume (3.3μ) per egg should be considered as the optimal day and VPA concentration that results in high hatching success and low post-hatching mortality rate. The subjects of this study are currently tested for their sociability in various behavioural tests. The optimal parameters found and described based on mortality rates will then be confirmed (or slightly modified if needed) considering the behavioural effects.
Day 1 Disorders, disease models

Poster ID:147

Investigation of the neuronal activity of calretinin expressing cells in the thalamic paraventricular nucleus in an acute stress disorder model of mice

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Acute stress disorder, or ASD could maintain in persons following a trauma, in most common cases verbal or physical violation, serious injury, threat of or actual death. ASD presents with similar symptoms to PTSD, but immediately after the trauma and research of ASD became extremely relevant, as the current evidences show that treating ASD can lead to a reduction in the severity of PTSD. Here we modeled ASD in mice after a single severe stressor. We found that this stressor induced a sustained change in calretinin expressing neurons of the paraventricular thalamic nucleus (PVT/CR+), which may form a stress centre between several subcortical regions and the cortex through their unique connections. This neuronal change proved necessary for the emergence of ASD-like phenotype because ASD-like symptoms are rescued by reducing PVT/CR+ activity increase using 1 hour long photoinhibition protocol following the stress. In conclusion, our data suggest that PVT/CR+ neurons play a critical role in mediating the acute forms of stress-related affective disfunctions.

Poster The value of very

ID:247

The role of monoamines for the physiological modulation of microglia

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Microglia are the resident immune cells of the central nervous system (CNS). They sense and respond to inflammation, but they also mediate physiological functions such as the refinement of synaptic plasticity and the support of adult neurogenesis. Microglia are readily alerted of injury and cell damage by molecules such as ATP or lipopolysaccharides (LPS). The latter leads to a proinflammatory state, triggering not only the release of cytokines, but also a switch in pattern of receptor expression, which can result in different microglial sensitivity to several neuromodulatory molecules, including monoamines. Therefore, we questioned modulatory impacts of monoamines on resting and activated microglia. We used murine immortalized microglia (BV-2) and human microglia-like cells (iMG) to perform calcium imaging, motility/migration assays, phagocytosis assays, immunohistochemistry, flow cytometry, and gene expression analysis (RT-PCR). Microglia activation was readily achieved by acute or chronic stimulation with LPS and acute stimulation with ATP. Our preliminary analysis focused on the impact of monoaminergic modulation by serotonin (5-HT) and noradrenaline (NE) of microglia. Preliminary data suggest significant differences in the sensitivity of microglia to monoaminergic modulation between physiological and pathological conditions. For instance, NE triggered an acute intracellular calcium response in resting BV-2 microglia in a dose-dependent manner. However, responses to NE were potentiated when microglia were pre-activated by LPS. Conversely, no calcium responses were elicited following 5-HT stimulations of either resting or activated microglia. Moreover, chronic exposure to NE (but not 5-HT) desensitized both resting and activated microglia to further acute noradrenergic stimulation. In all conditions, calcium responses were readily elicited in microglia upon acute ATP application. With these data and further preliminary work, we shed new light on the complex and subtle balance between levels of monoamines and microglia responsiveness under pro-inflammatory states. In the course of some pathologies, as well as in aging, the monoaminergic neuromodulation of the CNS changes in synchrony with altered microglial pro-inflammatory states. Thus, direct (neuron mediated) and indirect (microglia-mediated) consequences of altered monoaminergic neurotransmission on neuronal function, connectivity, and plasticity will need to be further scrutinized.

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Day 3 Disorders, disease models

Poster ID:347

Spreading of P301S aggregated tau investigated in organotypic mouse brain slice cultures

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Background: Neurofibrillary tangles composed of hyperphosphorylated tau protein aggregates are a key neuropathological feature of Alzheimer's disease (AD). Tau pathology extends throughout the brain in a prion-like fashion through connected brain regions. However, the details of the underlying mechanisms are incompletely understood. The present study aims to examine the spreading of P301S aggregated tau, a mutation that is implicated in tauopathies, using organotypic slice cultures. Methods: Coronal hippocampal organotypic brain slices (170 μm) were prepared from postnatal (day 8–10) C57BL6 wild-type mice. Collagen hydrogels loaded with P301S aggregated tau were applied to slices and the spread of tau was assessed by immunohistochemistry after 8 weeks in culture. Results: Collagen hydrogels prove to be an effective protein delivery system subject to natural degradation in 14 days and they release tau proteins up to 8 weeks. Slices with un- and hyperphosphorylated P301S aggregated tau demonstrate significant spreading to the ventral parts of the hippocampal slices compared to empty collagen hydrogels after 8 weeks. Moreover, the spread of P301S aggregated tau occurs in a time-dependent manner, which is interrupted when the neuroanatomical pathways are lesioned. Conclusions: We illustrate that the spreading of tau can be investigated in organotypic slice cultures using collagen hydrogels to achieve a localized application and slow release of tau proteins. P301S aggregated tau significantly spreads to the ventral areas of the slices, suggesting that the disease-relevant aggregated tau form possesses spreading potential. Thus, the results offer a novel experimental approach to investigate tau pathology.

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Day 1 Disorders, disease models

Poster ID:148

Early structural changes of the dopaminergic pathway in a valproate-based mouse model of autism spectrum disorder

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An established experimental model of autism spectrum disorder (ASD), valproate (VPA) treatment of mice in utero is known to impair the social behavior of offspring. Yet the neuroanatomical and developmental alterations evoked by VPA are less well-known. In previous studies, we reported defasciculation and fiber reduction of the dopaminergic (DAergic) mesotelencephalic (MT) pathway in 7-day-old (P7) pups of mothers treated with VPA. DAergic neurons were selectively reduced in the ventral tegmental area (VTA) but increased in substantia nigra (SN). In addition, tissue DA concentration was diminished in the nucleus accumbens (NAc) while unchanged in the caudoputamen (CPu). We hypothesized that reduced DA level and fiber input at a critical stage of brain development might lead to suboptimal neuronal and synaptic patterning of DAergic target regions. Here, we monitored apoptotic changes in forebrain DAergic target areas, using caspase-3 immunohistochemistry in P7 mice born to VPA-treated mothers. Increased apoptosis was observed in the anterior cingulate (ACC) and retrosplenial (RSC) cortices, as well as in the CPu, septum and bed nucleus of stria terminalis (BNST). Yet the NAc, primary target of the mesolimbic DAergic pathway, showed no significant change. Thus, the previously reported deficit in the MT DA afferents, observed in VPA exposed P7 mice, is not associated with a specific surge of apoptosis in NAc. Concerning neuroprotective mechanisms, we analyzed the distribution and density of neurons containing calcium-binding proteins (CBP) in pallial and subpallial regions. CR was reduced by VPA in the ACC and RSC, while subpallial areas were unaffected. CB showed a significant reduction in CPu of VPA-treated P7 mice, disappearing in P60 animals. PV at P60 was unchanged by VPA. Notably, Casp3+ neurons did not colocalize with any of the CBPs. Proteomic analysis (WB) showed a significant decrease of TH protein relative to synaptophysin in the NAc of VPA-treated animals, compared to controls, with no change in CPu, indicating that the reduction in TH is not accompanied by an overall decrease of synapses. The data are consistent with our previous findings showing reduction of DAergic neurons in the VTA (not SN), and reduction in tissue DA in NAc (not CPu). This suggests that the VPA-evoked defasciculation of dopaminergic fibers selectively affects the mesolimbic, rather than the nigrostriatal, pathway.

Poster ID:248

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 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 patientspecific 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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Disorders, disease models

Poster ID:348

Microglial morphology shows alteration in focal cortical dysplasia type II epilepsy samples

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Focal cortical dysplasia (FCD) is one of the leading causes of intractable epilepsies. Patients have seizures from early age and can be cured only by surgical removal of the epileptic tissue. FCD type II (FCDII) is a neurodevelopmental disorder, with dyslamination of the cortical tissue and pathological cell types, like dysmorphic neurons and balloon cells. The role of microglia in FCDII is unclear yet, the aim of our study was to investigate that. We used six post mortem control and six FCDII samples. The control brains were perfused with Zamboni fixative in a relatively short time (3h±30') after death. Therefore, these remained comparable to the epileptic tissues, which were immediately immersed in the same type of fixative after surgical removal. The cortical tissue blocks were sliced to 60 µm thick slices and fluorescent immunohistochemistry procedures were made on them. We used anti-P2Y12-receptor- (P2Y12R), anti-NeuN and in another experiment also anti-Kv2.1 primary antibodies to label microglia, neuronal somata and membranes respectively. The slides were investigated with Nikon C2 confocal laser scanning microscope. We measured the density of different morphologies of microglia in layers 3 and 5 and in the white matter and the somatic junctions between microglia and neurons in layer 3. The overall density of P2Y12R-immunopositive microglia did not differ significantly between control and FCDII samples in the gray matter, but it was increased in the white matter. Significantly more cells showed dystrophic morphology in all invsetigated regions. We did not find significant difference in the microglial coverage of neuronal somata between the two groups, however FCDII samples show higher heterogeneity. Our results suggest that P2Y12R-immunopositive microglia show dystrophy, the morphological sign of dysfunction in FCDII. This is interesting, because epilepsy is usually linked to gliosis, and so to microglial hypertrophy and proliferation. One possible explanation might be that P2Y12R-immunopositive cells are a subgroup of microglia and other subpopulations show the typical signs of gliosis. The greater heterogeneity of microglia-neuron somatic junctions suggests, that pathological cells, like dysmorphic neurons and balloon cells, might have different relationships with microglia compared to healthy neurons. According to our preliminary results, microglia play a role, but further studies are needed to determine their importance in FCDII pathology.

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Day 1

Disorders, disease models

Poster ID:149

Ucp2-deficient microglia contribute to the progression of neurophysiological abnormalities in Alzheimer's disease

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The cellular underpinnings linking amyloid-beta deposition and neural network disruption that precede and parallel cognitive decline are not well understood, limiting the rational design of new therapeutic interventions for Alzheimer's disease (AD). Given the ambiguous role of microglia and its metabolic profile in this process, a new mouse model 5xFAD-MgUCP2-/- was generated by genetic modification of amyloid-beta overproducing 5xFAD mice through targeted deletion of mitochondrial uncoupling-protein 2 (Ucp2) from their microglia. We utilized these mice between their 4-5 months of age for extensive neurophysiological screening both in acute and chronic paradigms. Hippocampal slice recordings showed significantly disrupted LTP in 5xFAD-MgUCP2-/- mice compared to 5xFAD counterparts. Spontaneous and brainstem nucleus pontis oralis stimulation-induced hippocampal theta oscillations were also reduced in 5xFAD-MgUCP2-/- compared to age-matched 5xFAD mice and their common wild-type controls under urethane anesthesia. We also found markedly diminished elicited theta oscillation in 5xFAD mice compared to controls suggesting hippocampal network integrity impairment reminiscent of the altered neuronal synchrony observed in AD patients. Chronic EEG recording in freely behaving mice over four months revealed disrupted sleep patterns in 5xFAD-MgUCP2-/- which have longer and more frequent waking episodes than 5xFAD during the light phase. These results imply the importance of Ucp2-related mitochondrial adaptations in microglial functionality in the progression and severity of AD-related neural abnormalities.

Day 2

Disorders, disease models

Poster ID:249

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-pituitarythyroid (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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Poster ID:349

Day 3

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 opensource 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.

Poster ID:150

Investigating the role of dendritic spines 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 HippoUnit's Oblique Integration and Pathway Interaction tests. In the original optimized models, we accounted for spines using the F-factor and placed synapses on the shaft. Next, we explicitly modelled those spines that receive excitatory synapse, and 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 exist in 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 in 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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Poster

ID:250

Modeling hippocampal CA3 oscillatory mode transitions

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The hippocampus displays three major patterns of population activity, namely theta, gamma and sharp wave-ripple (SWR) oscillations. These are closely linked to behavior, as animals performing exploratory behavior will exhibit gamma and theta oscillations, while the hippocampus of an animal at rest will show sharp wave-ripples, during which the network replays spatially linked activity reminiscent of earlier exploration. It is unclear however, how cellular and network properties influence which oscillatory pattern will be exhibited. In vitro experiments conducted in thick hippocampal slices indicate that the change in synaptic conductance values and cellular parameters of pyramidal and basket cell populations of the CA3 area, brought upon by cholinergic neuromodulation, could explain the transition from a SWR-presenting to a gammapresenting state. During this research project, a network model of the CA3 area was used to characterize these oscillatory mode transitions. The model has been shown to autonomously generate sharp wave ripples and the associated replay events, following a simulated exploration phase during which the synaptic weights of the recurrent pyramidal cell connections were adjusted according to an STDP learning rule. Using grid search analysis over the parameter space defined by the synaptic conductance values, combined with optimization of synaptic and cellular parameters using evolutionary methods, we show that the network is capable of producing gamma oscillations of various levels of synchrony. Furthermore, we show that it is possible to adjust the synaptic parameters of a previously SWR-presenting state of the model to a gammapresenting state, such that the direction and magnitude of change is comparable to the experimentally determined values.

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Poster ID:350

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 enables the 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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Poster ID:151

Day 1

From chaos to clock in recurrent neural network. Case study

Alexander Vidybida, Olha Shchur

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What is the reason for complex dynamical patterns registered from real biological neuronal networks? Noise and dynamical reconfiguring of a network (functional/dynamic connectome) were proposed as possible answers. In this case study, we report a complex dynamical pattern observed in a simple deterministic network of 25 excitatory neurons with fixed connectome. After a short initial stimulation, the network is engaged into a complex dynamics, which lasts for a long time. Eventually, with no external intervention, the dynamics comes to a periodic one with a short period. The long transient is positively checked for being chaotic. We conclude that the complex dynamics observed is the output of neural computation performed in the process of neuronal firings and spikes propagation.

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Poster ID:251

Gap junction formation from hemichannels is controlled by redoxsensitive cysteines

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Gap junction channels (GJC) are formed by two connexon hemichannels (HCs) embedded in two opposite cell membranes each comprising six identical connexin proteins (Cx). HCs are connected by three disulfide bonds per chain, altogether by eighteen disulfide bonds in each HC, connecting the extracellular loops. These disulfide bonds have been shown to be capable of opening depending on the redox environment. In addition, two opposing HCs or connexons are bound by H-bonds farther from the membrane to form GJCs. GJCs are abundant throughout the body allowing essential molecule and ion flux between cells. Astrocytes are also rich in GJCs playing a vital role in various synchronized neuronal activities, such as slow wave sleep and epilepsy. Understanding of the effect of gap junctions in these processes is currently severely limited by the lack of GJC-specific inhibitors. Since GJCs have no endogenous ligands, the first step to develop efficient inhibitors is to understand the molecular steps of GJC formation. To understand how GJC are formed from two HCs, we performed molecular dynamics (MD) of paired HCs of the astrocytic subtype Cx43. To understand the coupling process, sole HCs were positioned 5 angstroms away from their physiological GJC gap distance and a series of MD simulations were performed at decreasing distances. MD runs were also performed with open disulfide bonds at 3 angstroms and at the physiological gap distance, to reveal the role of Cys residues in coupling. Furthermore, the full GJC structure was subjected to MD with open and closed disulfide bonds to simulate alternative redox conditions and to reveal whether it effects trans-junctional H-bonding. We found that 1) we could simulate the coupling process demonstrated by the appearance of trans-junctional H-bonds at decreasing distances. 2) the disulfide bonding system orients extracellular residues to adapt their H-bonding pose and 3) structural reorganization is achieved through hubs of interactions named stabilization centers. We propose that disulfide bonds – although located farther from the gap – have an important effect on GJC formation. Since these redox-sensitive Cys sequences align well in human Cx GJCs, it seems likely that all isoforms are engaged similarly. These findings may lead to the understanding of the inhibition of HC coupling to GJCs, which can advance to a rational design of GJC inhibitors in the future.

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Poster ID:351

Digital processing of István Apáthy's scientific histological collection

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István Apáthy (1863-1922), professor of zoology at the Franz Joseph University of Kolozsvár was an outstanding neuroscientist of his time, who became world-famous for his innovations in microtechnology and neuroscience. He developed several innovations in histological microtechnology which were far ahead of his time. His modification of the sectioning apparatus (microtome) and his special staining techniques led to the discovery of "neurofibrils" (the precipitated form of the much later described neurofilaments and neurotubules) and the visualisation of neuronal structures with an unprecedented clarity. To mark the 100th anniversary of the move of the Franz Joseph University from Kolozsvár to Szeged and the death of István Apáthy, we started a collaboration between the University of Szeged and the Babes-Bolyai University in Kolozsvár to explore István Apáthy's scientific legacy. The Department of Anatomy, Histology and Embryology of the University of Szeged, in cooperation with the Zoological Museum of the Babeş-Bolyai University, is determined to explore and create a digital archive of István Apáthy's scientific histological collection. Our aim is to make the future digital archive available for those scientists, who would like to get an insight into István Apáthy's nearly forgotten scientific heritage. In Kolozsvár, the slides are being cleaned, catalogued and macroscopically photographed under the supervision of Gergely Osváth, at the Museum of Zoology. The most important specimens in the collection will be digitised by the members of the Szeged team using a high-resolution slide scanner or a special digital camera mounted on a research microscope, depending on the characteristics of the slides. According to the primary survey of the collection in Kolozsvár, more than 10,000 sections can be linked to the 30 years scientific activity of István Apáthy's laboratory. Categorization of these specimens identified by the year of preparation is already in progress. Our preliminary experience has shown that approximately half of the sections can be digitised with a slide scanner, while the rest have to be photographed individually by using a research microscope. The scientific evaluation and archiving of the already digitised samples are under progress.

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Poster ID:152

Day 1

Modelling of UTP Activated Ca2+ Signaling in the Deiters' cells in the Organ of Corti in Different Postnatal Developmental Stages from Prehearing to Matured

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The supporting cells of the organ of Corti are studied extensively in cochlear explants of newborn mice (1-2 days old) and the fundamental role of the purinergic signaling controlled spontaneous activity in cochlear development has been shown. However, information on purinergic Ca2+ signaling during cochlear development and in mature stage are much sparse. In addition, mice are born deaf and only the end of the second postnatal week reach the matured structure and function of the organ. We have investigated the UTP- and ATP-evoked Ca2+ signals in Deiters' cells in the hemicochlea preparation in different postnatal development stages (P5 – P18). Single-cell electroporation of Deiters' cells with Ca2+ sensitive dyes and their fluorescent imaging showed that the UTP- and ATP-induced Ca2+ transients have different characteristics. For mathematical modeling the intracellular Ca2+ dynamics of the Deiters' cells, we set up a closed cell model to investigate the UTP induced Ca2+ responses, and an open cell model to simulate the ATP induced ones. Our results showed that both extracellular Ca2+ dependent P2X and intracellular Ca2+ store dependent P2Y receptors were involved in the ATP and UTP-evoked Ca2+ transients in each developmental stages, and our models are replicate the Ca2+ transients with good fidelity. In case of UTP induced responses SERCA parameters also show developmental changes, which were never predicted before.

Poster ID:252

Modelling transcription dynamics of neuronal cells based on single-cell RNA-sequencing data

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The current mRNA pool in cells is not constant, it follows a natural dynamics. In addition, the composition of the transcriptome is strongly influenced by the rate of expression and degradation of gene products, as well as transcriptional responses to external and internal factors. These responses regulate the switch between the "on" and "off" state of genes. A singlecell RNA-sequencing data set containing normalized copy numbers of several mRNAs can be interpreted that each cell in the dataset is a time point (snapshot) in the dynamically fluctuating transcriptional process in an as many dimensional space as the number of mRNAs revealed. The single-cell sequencing data are usually sparse matrices with several zero values. The common belief is that zero values are result of the gene transcription "off state". To test this hypothesis we used our Patchseq dataset sequenced to 22 million reads and recovered more than 19.000 transcripts from 127 cells of the frontal cortex in rats. Such an ultra-deep sequencing allows to investigate the complete transcriptome of the neurons. Neurons were divided to two sets, one was the Pyramidal cell group, and the other was the fast spiking interneurons group. By examining the presence and level of gene expression, we searched for groups of genes that help us understand the dynamics of the neuronal transcriptome, the pattern of "on"-state - "off"state alteration of individual genes. Our results may lead to a better understanding of the phenotype of neurons at the transcriptome level and how changes in transcriptome dynamics lead to neurodegenerative symptoms.

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Poster ID:352

Day 3

What is the snow in a neural avalanche?

Chaitanya Chintaluri, Tim P. Vogels

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Neurons spike spontaneously in many experimental settings. Such firing patterns are often characterized by prolonged periods of silence followed by an unknown trigger of spontaneous activity that propagates throughout the slice. These were dubbed `neural avalanches' as they resemble avalanches in which accumulated snow rapidly flows down a mountain slope. Expanding this analogy -- if the network connectivity is equivalent to the mountain slope, what is the 'snow' that accumulates prior to a neural avalanche? Here, we propose that it is the accumulation of ATP in neuronal mitochondria, and that avalanches provide a respite from toxic conditions that arise during lower-than-baseline ATP consumption. Neurons, presumably in anticipation of synaptic inputs, keep their ATP levels at a maximum. As metabolic recovery from synaptic inputs requires substantial energy resources, neurons are ATP-surplus/ADP-scarce during synaptic quiescence. With ADP availability as the rate-limiting step, ATP production stalls in the mitochondria when energy consumption is low, leading to the formation of toxic Reactive Oxygen Species (ROS) which disrupt many cellular processes. We hypothesize that neurons actively sense their metabolic state and trigger `metabolic spikes' to restore ATP production, to avoid ROS. To test this, we built a recurrent network in which neurons sense their metabolic state (based on recent inputs and outputs) and modulate an intrinsic metabolic current to control spiking when necessary. When the network goes silent, neurons initiate metabolic spikes to increase their own energy expenditure and avoid ROS poisoning. These first spikes trigger a domino effect of activity that ripples through the network and ceases when neurons have increased their ATP expenditure either through synaptic inputs or by spiking. This mitochondrially mediated homeostatic mechanism can account for many intrinsic firing patterns observed in neurons, as well as the avalanche-like activity, and it explains how networks maintain criticality without loss of stability.

Poster ID:153

Mechanisms of plasticity for pup call sounds in the maternal auditory cortex

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Distress calls of mice pups outside their nest elicit pup retrieval in maternal female mice but not in their virgin ('naive') conspecifics. However, when co-housed with maternal mice, naive mice become 'experienced' and learn to perform pup retrieval. This process correlates with neuronal changes in the primary auditory cortex: While excitatory (E) neuron responses are sharply tuned to a certain inter-pup-call interval and inhibitory (I) neuron responses are broadly tuned in naive mice, the two neuron types are co-tuned in experienced mice. This change in behavior and tuning is mediated by oxytocin (Schiavo et al., 2020). Here, we aim to dissect the underlying mechanisms behind the behaviorally-relevant changes in tuning from naive to experienced mice by combining computational modeling and in-vitro experiments. Using optogenetic targeting of somatostatin-positive (SST) or parvalbumin-positive (PV) inhibitory neurons, we quantified shortterm plasticity at SST-to-E and PV-to-E connections. Furthermore, pairing experiments reveal sufficient long-term plasticity at SST-to-E but not PV-to-E connections. Using a model, we study the interaction of three neuron populations with synapses experiencing short- and long-term plasticity. We show that 1) short-term plasticity leads to the tuning of excitatory and inhibitory neurons to inter-stimulus intervals; 2) oxytocin-gated long-term plasticity of E-to-E and SST-to-E connections lead to changes in tuning from naive to experienced mice. Furthermore, 3) shortterm plasticity can control the signal amplitude without changing the tuning properties. Our results reveal that short- and long-term plasticity cooperate to generate tuning of excitatory and inhibitory neurons in microcircuits with important implications for maternal behavior.

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Austria)

Poster ID:253

Neuromodulation in cortical networks enables simultaneous motor-null and motor-potent dynamics for the generation of complex movements

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Juan Sebastian Calderon Garcia, Tim Vogels

Cortical networks can rapidly generate flexible sequences of neuronal and motor activity. These sequences - or chunks - are composed of consistent units of activity, called syllables. The process of syllable concatenation can be driven by a sequence of instructions signaling every syllable in a chunk. Indeed, experiments can confirm independent preparation and execution of each syllable. Such serial activation requires accurate coordination between motor cortex (M1) and upstream regions that signal the timing and identity of each syllable, but the neural mechanisms for this coordination remain unclear. Current thalamo-cortical models string syllables together, alternating between rapid preparatory activity and movement execution. However, experiments show that M1 performs motor preparation and execution simultaneously during motor chunks. In contrast with the proposed modelling solution, here we show that modulation of neuronal input/output gains to adjust neural activity and thus muscle outputs, allows the incorporation of coexisting preparatory and execution activity during movement orchestration. To train the modulation patterns, we include in the dynamics a control input that drives neural activity towards the initial condition of the subsequent syllable while the current movement is underway. Coordination between motor preparation and execution allows gain patterns to be flexibly arranged to generate compound movements. Towards that goal, we divide chunks into segments corresponding to single syllables under variable conditions of preparatory activity during movement execution. A sequential ordering and linear interpolation of the neuromodulatory patterns representing these syllables generate chunks in which motor preparation and execution occur simultaneously. Furthermore, we evaluate the population dynamics of our model during a compound movement. By generating a motor sequence with speed transitions, our model exhibits a well-behaved dynamics consistent with M1 population activity at different speeds. Our results offer a plausible biological description for neuromodulator-assisted motor control of compound movements.

Poster ID:353

Layer 1 interneurons modulate cortical responses depending on arousal

Laura Bella Naumann, Tim Vogels

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Nestled between the apical tufts of excitatory pyramidal cells (PC) of lower layers, interneurons in cortical layer 1 (L1) are strategically positioned to shape cortical processing (Larkum 2013). They receive a range of top-down inputs and their firing rates are strongly modulated by arousal (Abs et al. 2018, Cohen-Kashi Malina et al. 2021), but it is largely unknown how they affect their downstream targets. Recent work showed that both activation and inhibition of a newly classified type of L1 interneurons, i.e., neurons expressing neuron-derived neurotrophic factor (NDNF), can decrease PC firing (Cohen-Kashi Malina et al. 2021). Additionally, PC responses were shown to depend on arousal, indicating a more complex scenario than direct NDNF-mediated modulation. Indeed, NDNF interneurons influence PC activity through two parallel pathways: they directly inhibit PC dendrites, but also indirectly disinhibit the PC soma by targeting parvalbumin-expressing (PV) interneurons (Abs et al. 2018, Cohen-Kashi Malina et al. 2021). Yet, the relative contribution of these two pathways and their dependence on arousal are unresolved. We build a cortical circuit model with multiple cell types to study the downstream effects of NDNF interneurons and explore how both increases and decreases in PC firing can be explained by intricate arousal-dependent dendro-somatic innervation patterns. We find that reproducing the effect of NDNF interneurons on PCs requires nonlinear neural interactions shaped by arousal. Moreover, PC responses during high arousal can only be explained if the dendro-somatic innervation pattern is modulated to favour NDNF-mediated disinhibition. We show that this is achieved if arousal decreases the somato-dendritic coupling, increases the NDNF-to-PV interneuron inhibition, or modifies the dendritic nonlinearity. While each of these potential mechanisms reproduces the observed PC responses, they predict distinct responses within the rest of the circuit. These neural signatures could be leveraged to experimentally delineate the proposed arousal-dependent mechanisms. Our work demonstrates that the downstream effects of manipulating L1 NDNF interneurons depend on an intricate balance of (dis-)inhibitory pathways and dendritic nonlinearities. We propose a range of mechanisms for arousal-dependent modulation of dendro-somatic innervation patterns that can be probed in future experiments.

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Poster ID:154

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 higherlevel 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.

Day 1 Poste

Poster ID:254

Day 2

Functional and evolutionary characterization of molluscan neuroendocrine system using a widely used invertebrate model species, the great pond snail (*Lymnaea stagnalis*)

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There is a continuing debate about the functionality of sex steroids in molluscan reproductive processes and their neuroendocrine systems. Evidence has been accumulating that mollusks can absorb vertebrate sex steroids from the environment and store them and/or their metabolites for a long time. This calls into doubt how much of the vertebrate sex steroids are of endogenous origin in mollusks. Moreover, key genes involved in sex steroid synthesis and receptor-mediation in vertebrates seem to be missing in molluscan genomes. This is at odds, however, with the immunohistochemical evidence in the literature - which shows that tissues in a range of mollusks can be stained with antibodies to human enzymes and steroid nuclear receptors. We sequenced the neuronal transcriptome of the widely used model species of invertebrate neuroscience and neuroendocrinology, the great pond snail (Lymnaea stagnalis), and confirmed the lack of several of the key protein sequences that would be required to accomplish full sex steroid biosynthesis and sex steroid receptor-mediation as found in vertebrates. Although we found homolog sequences to vertebrate membrane sex steroid receptors, the steroid-binding ability of these proteins is unknown. We exposed L. stagnalis specimens to radiolabelled sex steroids and confirmed that snails can absorb and accumulate them for a long time. Despite the lack of homologous genes, we demonstrated that commercially-available antisera generated against mammalian CYP19A and nuclear progesterone receptor yielded positive signals in the central nervous system (CNS). Western blotting of CNS extracts showed that the three antibodies stained two or more proteins. Subsequent mass spectrometry analysis demonstrated the lack of homologous sequences to the vertebrate proteins recognized by the antibodies. Our molecular results support that the classical vertebrate sex steroid biosynthetic pathway, as well as functional sex steroid receptors, are not present in mollusks. Further studies should aim at the deorphanization of the homolog sequences to vertebrate membrane sex steroid receptors. Also, our findings highlight that immunostaining with antibodies generated against vertebrate proteins is a highly unreliable procedure for identifying or localizing specific proteins in invertebrate tissues. In summary, our results support that molluscan (neuro)endocrinology differs from the well-characterized vertebrate (neuro)endocrine system.

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Poster

ID:354

Role of NUCB2 in osmotic challenge evoked neuronal plasticity

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NUCB2 is the prohormone of nesfatin-1, an anorexigenic neuropeptide that also inhibits water intake. It is coexpressed with oxytocin (OT) and vasopressin (AVP) in the hypothalamic supraoptic nucleus (SON). Chronic osmotic challenge induces plastic morphological changes in the SON, which are triggered by intranuclear cellular signaling mechanisms in response to the increased AVP and OT demand. Since NUCB2 is not transported to the neurohypophysis and acts locally via dendritic release of nesfatin-1, we assumed it is an important molecule in the high osmolarity induced changes in the SON. For chronic osmotic challenge rats received 2% NaCl instead of tap water, ad libitum. In experiment 1, pair-fed rats were also used as controls. Rats were killed after 4 days and NUCB2 mRNA in the SON was measured by RT-PCR. In experiment 2, we silenced the expression of NUCB2 bilaterally in the SON by AAV-delivered shRNA in rats 3 weeks before salt loading. A scrambled shRNA (scr)-AAV was injected into control rats. The bodyweight as well as the daily water and food intakes of rats were measured. The animals were perfusion-fixed on day 7 of the osmotic challenge. Serial coronal sections containing the SON were immunostained for nesfatin-1, GFAP, IBA, OT and AVP. Alkaline-phosphatase reaction was used to visualize the vessels. The immunostainings were analyzed in microphotographs using the ImageJ software. We found that NUCB2 mRNA levels were increased in the SON after 4 days of 2% NaCl intake compared to the controls. Salt loading increased the vascularization and activated the microglial cells in the SON, while it decreased the thickness of the ventral glial limitans. The AVP and OT cells were enlarged in the salt-loaded group. AVP immunoreactivity was reduced in the cellular somata and was elevated in the ventral dendritic zone, while the OT immunoreactivity was increased within the perikarya. Silencing of NUCB2 expression by shRNA triggered similar changes to salt-loading and enhanced the effect of salt-loading for most of the measured parameters. Based on our results, we suggest that NUCB2 plays a regulatory role in the development of adaptive responses to salt-loading.

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Day 1 Neuroendocrinology

Poster ID:155

Involvement of nesfatin-1/NUCB2 in glucose homeostasis in the arcuate nucleus

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Nesfatin-1, the secreted fragment of nucleobindin'2 (NUCB2) protein was identified as an anorexigenic neurotransmitter. It is widely expressed in the brain including the hypothalamic arcuate nucleus (ARC). Both nesfatin-1 and the ARC have recently been linked to the central regulation of glucose homeostasis, however the exact physiological role of nesfatin-1/NUCB2 in the ARC is not known. In the present study, we manipulated the expression of nesfatin-1/NUCB2 within the ARC in different groups of rats using synapsin promoter-driven NUCB2 overexpressing, or Sh-RNA expressing AAV9 vectors respectively, with appropriate controls. After recovery, the bodyweights of rats were monitored. To assess the regulation of the blood glucose, intraperitoneal glucose (ipGTT) and insulin tolerance tests (ipITT) were performed following the onset of virus expression. To assess the insulin signaling mechanism in the ARC, we injected icv insulin to rats, and analysed the expression of phAkt protein in immunostained sections. The gluconeogenetic capacity of the liver was investigated by measuring the expression of glucose-6phosphatase (G6Pase) mRNA expression in fasted and postprandial animals by RT-PCR. Additionally, a retrograde transsynaptic virus was injected to the liver of control animals to show the involvement of nesfatin-1-expressing Arc cells in the autonomic innervation of the liver. Downregulation of nesfatin-1/NUCB2 in the ARC resulted in a slight, significant increase of the bodyweight-gain, while overexpression of the peptide failed to cause any changes in the bodyweight-gain compared to controls. Up- and downregulation of nesfatin-1/NUCB2 level in the ARC improved and worsened the glucose tolerance of the animals, respectively. The insulin sensitivity of rats was in harmony with this. Silencing of nesfatin-1/NUCB2 in the ARC dampened the phosphorylation of Akt protein in response to local insulin injection. It also lead to the elevation of G6Pase mRNA levels in the liver in postprandial state, but caused depression of G6Pase mRNA levels in fasted state. Several of the liver innervating ARC neurons were immunopositive for nesfatin-1. Our results suggest that the ARC NUCB2/nesfatin-1 system profoundly affects the glucose homeostasis through influencing the liver function both in postprandial and fasted conditions.

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Poster ID:255

Day 2

Emerging role of A20 as a potential negative regulator of pro- and antiinflammatory factors in the genetically modified knock-in mice APPNL-F/NL-F - model of Alzheimer's disease

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Alzheimer's disease (AD) is the major cause of cognitive impairment and dementia. Despite many years of intensive research, AD pathogenesis has not been unambiguously discovered. Microglia, the long-lived primary immune effector cells of the brain, are crucial in shaping and fine-tuning brain circuits. Moreover, they control homeostasis and development via scavenging cellular debris, secretion of trophic factors, and monitoring synaptic development and activity. During perinatal and early postnatal development microglia regulate neurogenesis, control synaptic pruning as well as maintain the balance of pro- and anti-inflammatory mediators expression. The non-resolution of inflammation due to the deregulation of NF-kB signaling has been recently linked to AD. A20 (also known as TNFAIP3) is an important negative feedback regulator of NF-kB, acting by restricting the duration and intensity of microglial activity. Therefore, the aim of the present study was to determine the expression of A20 and some pro- and anti-inflammatory factors in the hippocampus and frontal cortex of the late-onset AD (LOAD) animal model. The research was carried out using, 7-days, and 1-months old APPNL-F/NL-F knock-in mice and wildtype (WT) mice as a control group. Animals were decapitated and the hippocampus and frontal cortices were dissected. Subsequently, the mRNA expression of A20, pro-inflammatory (II-1 β , iNos, Cd40, Cd68) and anti-inflammatory (Arg-1, Igf-1, Cd200, Cd200r) genes was measured using qRT-PCR method. Biochemical research revealed long-lasting diminished expression of A20 in the hippocampus and frontal cortex of 7-days and 1-month-old APPNL-F/NL-F animals. Furthermore, we found age- and structure-dependent dysregulation of pro- and anti-inflammatory genes expression in knock-in mice in comparison to control animals. In frontal cortex up-regulation of II-1b and Cd68, as well as Cd200 down-regulation was the most striking observation. Moreover, our results indicated decreased expression of Arg-1, lgf-1, and Cd200-Cd200r genes in the hippocampus, and a simultaneous increase of Cd40, II-1b, and iNos expression. Our study demonstrated strongly marked deficits in the A20 gene expression as well as an age-dependent imbalance of pro- and anti-inflammatory factors. Although our observations require further research, it can be suggested that deregulation observed at an early stage of development may be of crucial importance for deficits manifested as LOAD in adulthood.

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Poster ID:355

Investigating the function of an AVP/OXT-like neuropeptide homolog in the marine bristle worm

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Background: Vasotocin-neurophysin (vtn) encodes a preproneuropeptide in the marine bristle worm Platynereis dumerilii that is homologous to mammalian oxytocin and vasopressinneurophysin preprohormones. Mammalian oxytocin is known to be involved in uterine smooth muscle contractions during parturition and milk ejection from mammary glands, while vasopressin is involved in the regulation of blood pressure and the peripheral fluid balance. There is also growing evidence that oxytocin has a metabolic effect. In rodents it has been shown to be involved in glucose homeostasis, food choice and stimulation of lipogenesis. In annelids, such as the earthworm Eisenia foetida, an oxytocin-related peptide is involved in cocoon formation and egg-laying behaviors. Platynereis dumerilii displays a complex regulation of its reproduction including temporal (diel and moonlight controlled monthly), as well as metabolic cues. Due to the implication of vtn orthologs from other animals in both reproductive and metabolic regulation, as well as recent work suggesting that the naturalistic interpreter L-Cry impacts on Vasotocin levels depending on lunar phase or light, we got interested in its function in the marine bristle worm. Methods: Two vtn knock-out alleles were generated. Combining quantitative RNA sequencing, immunohistochemistry, in situ hybridization chain reaction, qPCR and tracking of behavior and spawning, I am currently characterizing the function of vtn in the marine bristle worm. Additionally, I am using I-cry+/-; vtn+/- combined mutant crosses to analyze possible genetic interactions and the survival performance of different genetic combinations in a competitive environment. Current Results: Quantitative RNAseq data comparing homozygous vtn mutants vs. wildtype worm heads show a differential expression of transcripts from neurotransmitter systems, metabolic and muscle markers. F2 generations obtained from I-cry+/-; vtn+/- double mutant incrosses show an underrepresentation of vtn homozygous mutants and wt, while I-cry-/- mutants are overrepresented under competitive conditions. L-cry-/-, vtn-/double mutants at expected ratios, suggesting genetic compensation between the two genes. Besides their prominent expression in few cells in the worm brain, vtn and vtnR also exhibit sex specific expression differences in the trunk. At present we further focus on the molecular analyses, including sex specific difference and peripheral versus central tissues.

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Poster ID:156

Day 1

Distribution of insulin-like growth factor-binding protein-3 in the human infundibular region

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The primary source of IGF1 circulating in the blood is the liver, which is formed under the influence of growth hormone. IGF-1 has a significant effect on different components of the neuroendocrine system. IGF-1 binds to various binding proteins, the most important of which is insulin-like growth factor binding protein 3 (IGFBP-3). In previous studies, we have already explored the expression of IGFBP-3 in the rat hypothalamus, in which we were able to establish the increased expression of IGFBP-3 in the maternal arcuate nucleus, which also suggests its role in maternal adaptation. In the present study, we addressed the distribution of IGFBP-3 in the human tuberoinfundibular region. Cell bodies were located in the infundibular nucleus (corresponding to the arcuate nucleus in human) and also in the paraventricular hypothalamic but not the supraoptic nucleus. In addition, a high density of IGFBP-3 fibers were present in the median eminence. Comparison of adjacent immunolabelled sections suggested that IGFBP-3 is not present in oxytocin, vasopressin and NPY neurons. Since the distribution of IGFBP-3 cells overlapped with that of dopaminergic and growth hormone releasing hormone (GHRH) neurons, double labeling was performed with these markers, which suggested that IGFBP-3 and the dopaminerg marker tyrosine hydroxylase are co-expressed only in a small percentage of neurons while no co-localization was present at all with GHRH. In conclusion, we suggest that a new population of tuberoinfundibular neurons was discovered. Since the distribution pattern of IGFBP-3 in humans is similar to that of rats where IGFBP-3 level is induced in mothers, we propose that the IGF-1 system in humans may also be involved in the control of prolactin secretion.

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Poster ID:256

Day 2

Localization of galanin and galanin receptors in the human anterior pituitary

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Introduction Galanin (GAL) is a 29 (30 human) amino acid peptide that is widely distributed in the endocrine system, the central and peripheral nervous system, but is also expressed in nonneuronal tissues. GAL exerts its biological effects by signaling via G protein-coupled receptors. To date three endogenous GAL receptors (GAL1-3R) have been identified. There is ample evidence that GAL plays a role in the modulation of the hypothalamus-pituitary (HP)-axis response to stress, energy metabolism and reproduction. However, the majority of these studies have been carried out in rodents, and their results need to be confirmed in humans since GALR expression has not been determined in the human HP-axis up to now. Methods To elucidate subtypes of secretory cells (somatotrophs, lactotrophs corticotrophs, tyrotrophs, gonadotrophs) expressing GAL and GALRs immunofluorescence (IF) co-staining of human pituitary tissue with anti-GAL and anti-GALR antibodies in combination with antibodies against adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) and thyroidstimulating hormone (TSH) on post mortem human pituitary glands of individuals (n=7) without clinical signs of neuropsychiatric disease were performed. Results GAL-immunoreactivity (IR) was detected in 9% of pituitary cells, whereas GAL1R and GAL3R IR were found in 3% and 4%, respectively. The number of hormone-expressing cells also revealing IR of the galanin system strongly varied among cases. Most consistently, 71% of ACTH+ pituitary cells also showed GAL-IR, 13% GAL1R-IR and 18% of GAL3R-IR staining. 10% of LH+ pituitary cells revealed GAL-IR. Co-Expression of FSH with GAL (15% of FSH+ cells) and GH with GAL (4% of GH+ cells) was observed in 4 of 7 samples. Co-expression of GAL1R and GAL3R were found in only 3 or less samples and only in less than 5% of FSH, LH, TSH, GH and PRL expressing cells. GAL2R was not detectable at all in the pituitary. Conclusion GAL is mainly produced by ACTH+ pituitary cells, whereas only small subpopulations of different secretory cell types are also expressing GAL1R and GAL3R. GAL2R seems to be absent in the pituitary.

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Poster ID:356

Functional-morphological analysis of corticotropin-releasing hormonecontaining neurons in the rotenone model of Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder with motor (tremor, rigor, hypokinesia) and non-motor (e.g. depression, anxiety) symptoms. Our group investigates the background of mood disorders as a non-motor symptom of PD. We have previously found a correlation between damage to urocortin-1 (UCN1)-containing cells of the centrally projecting Edinger-Westphal nucleus (cpEW) and mood disorders in the rotenone model of PD, in the rat. An inverse correlation between corticotropin-releasing hormone (CRH) and UCN1 expression levels has been previously found, raising the question of what changes occur in the major CRH-containing systems in the PD rotenone model. Therefore, we aimed to investigate functional morphological changes in the CRH neurons of the hypothalamic paraventricular nucleus (PVN), central amygdala (CeA) and the bed nucleus of stria terminalis (BNST). Six weeks of subcutaneous rotenone treatment was applied to induce a PD-like state. Control rats received vehicle injections. Half of the treated rats also received levodopa/benserazide anti-PD therapy. The animals' locomotion was analyzed by rotarod test, the anhedonia by sucrose preference, and anxiety level by open field test. Morphological changes were assessed by a combination of RNAscope in situ hybridization and immunofluorescence. The rotenone-induced motor deficits improved on levodopa/benserazide treatment, in contrast to non-motor symptoms. Rotenone treatment did not induce remarkable CRH neuron death in any of the regions studied. In rotenone-treated animals, Crh mRNA levels were reduced in the PVN and CeA, which were not reversed by levodopa/benserazide treatment. The FOSB neuronal activity of CRH neurons was reduced by rotenone treatment in the CeA and BNST, but not in PVN. No CRH neuron death occurs in the rotenone model of PD. The change in CRH neuronal function may be interpreted as a compensatory mechanism due to cpEW/UCN1 neuronal death, which may be the result of an inverse relationship between the two systems.

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Poster ID:157

Elevated glucagon-like peptide-1 receptor level in the paraventricular hypothalamic nucleus of type 2 diabetes mellitus patients

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Glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonists have been approved for the treatment of type 2 diabetes mellitus (T2DM), however, the brain actions of these drugs are not properly established. We used post mortem microdissected human hypothalamic samples for RTqPCR and Western blotting. For in situ hybridization histochemistry and immunolabelling, parallel cryosections were prepared from the hypothalamus. We developed in situ hybridization probes for human GLP-1R and oxytocin. In addition, GLP-1 and oxytocin were visualized by immunohistochemistry. Radioactive in situ hybridization histochemistry revealed abundant GLP-1R labelling in the human paraventricular hypothalamic nucleus (PVN), particularly in its magnocellular subdivision (PVNmc). Quantitative analysis of the mRNA signal demonstrated increased GLP-1R expression in the PVNmc in post mortem hypothalamic samples from T2DM subjects as compared to controls, while there was no difference in the expression level of GLP-1R in the other subdivisions of the PVN, the hypothalamic dorsomedial and infundibular nuclei. Our results in the PVN were confirmed by RT-qPCR. Furthermore, we demonstrated by Western blot technique that the GLP-1R protein level was also elevated in the PVN of T2DM patients. GLP-1 fibre terminals were also observed in the PVNmc closely apposing oxytocin neurons using immunohistochemistry. The data suggest that GLP-1 activates GLP-1Rs in the PVNmc and that GLP-1R is elevated in T2DM patients, which may be related to the dysregulation of feeding behaviour and glucose homeostasis in T2DM.

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Poster ID:257

Altered neuronal serotonin and tryptophan-hydroxylase content in the dorsal raphe nucleus in stress-evoked depression models in rats

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Genetic background, early-life stress and late life experience (e.g.: environmental stress) might result in manifestation of major depressive disorder (MDD). The altered expression of neuropeptides such as corticotrophin-releasing hormone (CRH) could associated with MDD. The involvement of serotonin (5-HT) synthesis in MDD is well known. However, due to the limited data, the proper neurobiological background of MDD pathoetiology is still poorly understood. We aimed to combine genetic, early life experience and late life stressors in male rat model in order to detect the possible differences (changes) of the dorsal raphe nucleus (DR) serotoninergic systems. Wistar rats offspring were selected to low-responder (LR), middleresponder (MR), high-responder (HR) groups based on their parents' corticosterone responses upon acute stress. Half of the litters were exposed to maternal deprivation (MD) vs. normal controls (NC). In each half of the subgroups (MD, NC) rats were exposed to chronic variable mild stress (CVMS) vs. controls (C). Behavioural assessment was performed by sucrose preference (SPT) and forced swim tests (FST). CRH and 5-HT/ tryptophan hydroxylase (TPH) systems were studied by multiple immunofluorescence labelling. Body, adrenal gland and thymus weights were measured to CVMS verification. The adrenal glands increased in the MD animals. Highest anhedonia was observed in the LR-MD-CVMS rats, while these animals have the highest 5-HT content in their DR. The TPH was low in LR and MR animals, but the HR rats have greater amount of TPH in the DR. The 5HT cell count decreased in NC-CVMS animals, but not in the MD-CVMS rats. In the CRH systems we did not detect drastic changes. These findings pointed out that the DR 5-HT system may show greater changes in changed mood status than CRH systems. Our 5-HT/TPH data showed that the 5/HT synthesis/release may change depending on early life experiences that can indicate the (mal)adaptation.

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Poster ID:357

Day 3

Regulation of adult thyroid hormone homeostasis by early postnatal hyperthyroidism in male mice

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The thyroid hormone (TH) negative feedback regulation enables the hypothalamic-pituitarythyroid (HPT) axis to maintain the relatively steady circulating TH levels. Internal and external factors influence the development of this feedback regulation and consequently evoke life-long changes of the HPT axis activity. The aim of our study was to reveal how perinatal alteration of TH status influences TH homeostasis of adult mice. Mice were treated with 1µg/bwg thyroxine (T4) or vehicle subcutaneously every day between postnatal day (P) 2-6 and sacrificed at adulthood. Early postnatal hyperthyroidism resulted in central hypothyroidism in adults, characterized by decreased thyrotropin releasing hormone (TRH) mRNA expression in the hypothalamic paraventricular nucleus (PVN) and lower serum free T4 level, accompanied by unchanged thyrotropin stimulating hormone β (TSH β) mRNA expression in the pituitary and serum free triiodothyronine level. The two main regulators of the HPT axis are the hypophysiotropic TRH neurons and tanycytes. Tanycytes affect the feedback regulation of TRH neurons by type 2 deiodinase (D2) mediated TH activation. To understand how postnatal T4 treatment results in central hypothyroidism in adult mice, tanycytes and TRH neurons of the PVN were isolated by laser capture microdissection from control and postnatally T4 treated adult mice. Postnatal T4 treatment did not change D2 expression in the tanycytes. Furthermore, using Thyroid Hormone Action Indicator (THAI) mice, we showed that the treatment did not influence TH action in the mediobasal hypothalamus of adult mice. These data together indicate that tanycytes are not involved in mediation of the postnatal T4 treatment induced effects. In contrast, the early postnatal T4 treatment markedly changed the transcriptome of TRH neurons in the PVN of adult mice. The expression of TH receptors, most TH receptor-related coregulators, TH transporters and genes involved in the synthesis of TRH were decreased. Despite of the central hypothyroidism, the energy expenditure of these mice were not decreased and TH action also remained unchanged in most tissues indicating that the peripheral tissues are able to compensate the effect of the generated mild hypothyroidism. These results indicate that alteration of TH levels during the early postnatal period can cause life-long effects on the activity of the HPT-axis likely via epigenetic regulation of TRH neurons.

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ID:158

Functionally active transient receptor potential ankyrin 1 ion channel is downregulated in the centrally projecting Edinger-Westphal nucleus upon acute alcohol exposure

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Introduction: The centrally projecting Edinger-Westphal nucleus (EWcp) contributes to control of alcohol consumption by its urocortin 1 (UCN1) and cocaine- and amphetamine-regulated transcript (CART) co-expressing peptidergic neurons. We recently showed that the urocortinergic EWcp is the primary seat of central transient receptor potential ankyrin 1 (TRPA1) cation channel mRNA expression. We aimed to examine the functional activity of TRPA1 in the EWcp and its possible role in a mouse model of acute alcohol exposure. We hypothesized that alcohol influences the UCN1/EWcp via TRPA1. Methods: Electrophysiological examination was performed on acute EWcp slices of C57BL/6J male mice to prove the functional activity of TRPA1 using a selective and potent agonist, JT010. Male Trpa1 knockout (KO) and wild-type (WT) mice were compared upon acute alcohol treatment. In both genotypes, half of animals was treated intraperitoneally with 1g/kg 6% ethanol vs. physiological saline controls. Transcardial perfusion was performed 2 hours after the treatment. EWcp neuronal activity was assessed by FOS immunohistochemistry. Trpa1, Cart and Ucn1 mRNA expression as well as UCN1 and CART peptide content was semi-quantified by RNAscope in situ hybridization combined with immunofluorescence. Results: JT010 activated TRPA1 channels of urocortinergic cells in acute slices. Alcohol treatment significantly activated FOS in both genotypes and decreased the Trpa1 mRNA expression in WTs. Lower UCN1 peptide immunoreactivity was observed in saline-injected KO mice compared to WTs. Alcohol affected the UCN1 peptide content genotype-dependently with decrease in WTs and increase in KO mice. Alcohol exposure influenced neither Cart and Ucn1 mRNA expression nor the EWcp/CART peptide content. Conclusion: We proved the presence of functional TRPA1 receptors in EWcp/UCN1 neurons. Reduced Trpa1 mRNA expression and UCN1 peptide content suggest the regulatory role of TRPA1 in UCN1 release upon acute alcohol treatment. The role of EWcp/TRPA1/UCN1 in chronic alcohol consumption and addiction models is under investigation.

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Poster

Novel techniques

Poster ID:258

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 proofof-concept system useable but further validation is required to prove its real-world feasibility.

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Day 3 Novel techniques

Poster ID:358 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 multishank 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 $20 \times 70 \,\mu\text{m}^2$ (thickness × width), a length in the range of 700 to 1200 μ m and were located at a fixed distance of 150 to 200 μ m from each other. The rectangular iridium oxide electrodes $(20 \times 30 \ \mu m^2)$ spread along the width and length of each shank, creating a grid with distances varying from 15 μ m to several 100 μ m. 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 μ m × 550 μ m. 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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Poster ID:159

Transparent, thiol-ene/acrylate-based electrode array for long-term multimodal neuroimaging

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Thiol-ene/acrylate, a shape memory polymer (SMP) is an excellent substrate material for intracortical probes. As a soft polymer, it can mitigate foreign body response and its transparent nature allows us to use it during multimodal neuroimaging. The combination of two-photon microscopy and electrophysiological signal recording enables to map the brain functionalities with high spatial and temporal resolution. The stability and biocompatibility of intracortical SMP probes have been shown and the tunable elastic characteristics are beneficial to achieve longterm stability. Our work demonstrates a multimodal neuroimaging scheme using a thiolene/acrylate-based cortical implant. The micro-electrocorticography (μ ECoG) device's feasibility of measuring intracranial EEG and fluorescent GCamP6 signals using two-photon excitation through the device is presented in mice. The stability of electrode yield was presented with in vivo impedance measurement over 75 days. During this period no sign of delamination or material degradation appeared. The high signal-to-noise ratio (1.04 to 5.74) and the easily identifiable theta oscillations indicated the recording quality throughout the course of the experiment. The chronic immune response was characterized by Glial Fibrillary Acidic Protein (GFAP) staining of astrocytes and fluorescent Nissl (NeuroTrace) staining of neurons. The histological analysis revealed only a modest foreign body response after 80 days of implantation. The result of cortical thickness measurement confirms the advantage of thiol-ene/acrylate as a substrate as no significant difference was shown between implanted and control cortices. To determine the effect of the device on optical distortion and resolution, the sizes of fluorescent beads and dendrites were determined without and under the transparent device placed in the light path of the two-photon microscope. The captured sizes of the detected objects showed a non-significant difference between the presence and the absence of the device. In addition, the change in the relative intensity of fluorescent signals was determined on in vivo images under the long-term implanted device. During the 22 weeks in vivo measurements, the fluorescent activity remained and Ca2+ signals were captured. Based on the results we showed that our device is suitable for multimodal imaging

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Day 1

Poster ID:259

Day 2

Concurrent imaging of Calcium signals and recording of electrophysiology in the hippocampus of awake mouse

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The hippocampus has crucial role in the formation, consolidation and recall of memories as well as in navigation related processes and behaviour. These functions are in the focus of neuroscience and different disciplines contributed to this research field for decades. Two-photon imaging of awake animals provide a valuable new aspect for these observations, especially when it is supported by electrophysiology. In this preliminary study, we coupled high speed twophoton hippocampal imaging with large scale ipsilateral hippocampal LFP recordings with a transparent electrode grid in awake mice. We recorded the impedance of the recording sites over the course of the experiments to observe long-term changes in recording quality. Implantation did not reduce the number of working contact sites markedly. We measured LFP across the dorsal hippocampus and imaged calcium activity from the pyramidal layer of CA1 immediately under a novel, transparent microelectrode array in thy1/gcamp6s transgenic mice. We investigated the immune response with GFAP staining after the end of chronic experiments. This dedicated transparent electrode device proved to be suitable for simultaneous two-photon imaging and large scale electrophysiology measurements in chronic experiments in mice. Our device is also compatible with head-fixed behaviour experiments due to its compact arrangement.

Poster ID:359

Day 3

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-µmthick 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 k Ω 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 goodquality 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 μ V 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.

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Poster ID:160

Day 1

Measuring GABA levels in the neocortex of humans using in vivo magnetic resonance spectroscopy: A methodical study

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Aims: The most widely used sequence for measuring GABA concentrations with magnetic resonance (MR) spectroscopy in the central nervous system is the so-called MEGA-PRESS (Mescher-Garwood Point Resolved Spectroscopy). However, this method is still technically challenging compared to conventional MR spectroscopy measurements. Our aim was to test this MEGA-PRESS sequence in a control sample and to make recommendations for its future application. Materials and methods: We carried out in total 60 MEGA-PRESS measurements involving 10 healthy subjects. We also performed repeated measurements after 1 week to evaluate test-retest reliability of the method. The regions of interests were the anterior cingulate cortex, occipital cortex and precuneus cortex. Results were evaluated using Gannet 3.1 software. Results: Our data shows that the measurement, including the specific cortical area, movement and individual neuroanatomical variations. Conclusion: Based on our experience, the application of the MEGA-PRESS sequence is a useful tool for the detection of altered GABA levels in the neocortex of patients with neuropsychiatric disorders, as well as for the follow-up studies of drug treatment, due to its high reproducibility.

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Poster ID:260

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 brainwide 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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Day 2

Day 3 Novel techniques

Poster

ID:360

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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Poster ID:161

On the way to layer-by-layer infrared neural stimulation: presentation of a new intracortical optrode

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The application of infrared (IR) light irradiation as a neuromodulation technique has been proven as safe and applicable in numerous studies. Either the continuous or the pulsed mode of IR stimulation (INS) showed promising neural responses under various conditions in vitro and in vivo as well. One of the advantages of INS compared to the classical electrical stimulation is that INS does not induce photoelectric artefacts in electrophysiological recordings. Another advantageous property of INS is that the propagation of light can be shaped easier than in case of electrical signals. Therefore, the stimulus can be more directional, the neuromodulation impact can be – more – localized. In this work we present a novel intracortical IR optrode, that can be implanted into the brain tissue and performs optical stimulation and electrophysiological recording simultaneously. This single crystalline silicon (Si) based microimplant has two modalities integrated into a single device: extracellular electrophysiological sensing and IR waveguiding. The needle-like Si shaft (0.19×0.17 mm) of the optrode holds 16 platinum (Pt) recording sites (900 μ m2) which can be implanted up to more than 4 mm tissue depth. IR waveguiding property is embedded into the Si substrate material of the same shaft. The optrode's shaft ends in a parabolic micromirror. This tip shape aims to direct the outcoupled IR light towards the side of the shaft, so more IR light beams will irradiate those parts of the neural tissue what surrounds the implant, therefore more photons get absorbed closer to the electrodes causing the positioning of the maximum of heating effect in the vicinity of Pt sites. Characteristics of its functional properties are demonstrated through optical investigations and thermal tests of optically induced heating. Furthermore, the in vivo performance of this novel design optrode, this new shape of IR stimulation is also validated via acute testing in anaesthetized rats.

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Poste

Day 1

Poster ID:261

Day 2

Electrochemistry meets Neuroscience – glucose biosensor development 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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Poster

ID:361

Chronic cranial window for long term multimodal imaging in rats

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Stable chronic cranial windows are essential for longitudinal access to brain function. Optical (one- and two-photon imaging, fiber photometry) and other imaging modalities (functional magnetic resonance imaging, functional ultrasound) have their own specific advantages and limitations. Combining multiple imaging modalities in an experiment can provide new insights into connectivity and plasticity of neuronal networks, in healthy and disrupted conditions from the scale of single cells to large-scale network level. Here, we describe a surgical technique used to sequentially or simultaneously deploy different brain activity access modalities in the same animal. The new surgical technique increases experimental success and provides repeatable imaging sessions across long periods of time.

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Day 1

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 trainingvalidation-testing datasets took place. Neural network architectures relied on 1D- and 2Dconvolutional, 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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Day 2

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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Day 3

Diffusion tensor imaging reveals microstructural changes in the white matter of depressed patients with and without negative childhood experiences

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Major depressive disorder (MDD) is a common and heterogeneous mental disorder with complex and not fully understood pathophysiology. Emotional abuse and neglect have the strongest association with the prevalence of MDD, although the different types of maltreatments typically co-occur. Numerous modern neuroimaging methods have been used to investigate the underlying neurobiology of MDD. The aim of this study was to examine minor, but structurally important white matter changes in MDD patients with childhood maltreatment (MDD+CM) and compare them to MDD and healthy control groups. Sixteen patients with major depression, 20 subjects with MDD+CM and 21 healthy controls participated. Childhood maltreatment was assessed with personal interviews and filling the short form of Childhood Trauma Questionnaire. Depression severity was evaluated by the Beck Depression and Anxiety Questionnaires. Diffusion tensor imaging was performed using a 3T Magnetom TIM Trio MRI scanner and for data postprocessing, FMRIB Software Library Tract-Based Spatial Statistics Toolbox was used. After comparing diffusion parameters, there was no statistically significant difference between the three groups. Mean diffusivity in the MDD+CM group showed weaker correlation with gender compared to MDD patients in the posterior thalamic radiation and the splenium of corpus callosum as well as with the severity of childhood emotional abuse in the superior corona radiata. In sum, our preliminary findings indicate that negative childhood experiences have a gender specific effect on diffusion parameters in MDD patients.

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Day 1

Spatial gene expression analysis of risperidone-induced changes in the mouse forebrain

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Psychotropic drugs affect neuronal activity, which triggers cellular signalling cascades, and leads to discrete changes in gene expression. These effects depend on neuronal connectivity and thus, the patterns of transcriptional alterations in the brain are drug-specific to a variable extent. We hypothesized that the patterns of changes in gene expression correlate with neuronal plasticity and behavioural effects of psychotropic drugs. Visium spatial gene expression (10X Genomics) methodology was applied to comprehensively map changes in brain transcriptome induced by a single administration of risperidone (0.5 mg/kg, i.p.). Forebrain sections, containing prefrontal cortex and basal ganglia from adult male C57BL/6 mice after treatment with risperidone were used to obtain cDNA libraries. Using the Visium system we performed RNA sequencing on whole brain sections. Alignment of reads to the reference mouse genome mm10 (GRCm38; "2020-A") was done using a custom analysis method that assessed read distribution and assigned reads to genes based on sequence proximity. We show that unsupervised clustering of the spatial transcriptomics data, mapped on section microphotography, correctly recapitulates the neuroanatomical structure of the brain coronal section. While genes with region-specific mRNA distribution had similar transcription profiles in control and risperidone-treated animals (e.g. Penk, Snap25, Cck), the activity-dependent transcripts showed specific patterns of risperidoneinduced expression. Immediate early genes (e.g. Egr1, Homer1) showed profiles of risperidoneinduced transcriptional changes in the cortex and the striatum. Studying gene expression changes of a set of immediate early marker genes identifies drug-induced transcriptional signatures. Therefore describing drug-induced transcription of commonly prescribed compounds could help to examine gene expression patterns that correlate with drug efficacy and adverse effects. We hope that gene expression profiling of registered antipsychotics can be used as a molecular predictor of the properties of novel drug candidates.

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Day 2

Resting-state functional connectivity changes in depressed patients with and without early life stress

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Major depressive disorder (MDD) is a common, complex, and severe mental disorder imposing major social and economic burden world-wide. It is well documented that childhood adversities represent a major risk factor for the development of MDD. A large number of in vivo neuroimaging studies investigated the neurobiological changes in depressed patients and the long-term consequence of negative childhood experiences. The aim of the present study was to examine resting-state functional connectivity network changes in depressed patients with or without the history of childhood maltreatment (CM) and compare the results to healthy controls. We examined 37 MDD patients (18 with CM and 19 without CM), and 20 healthy control subjects. We performed a resting-state MRI examination with a 3T Magnetom TIM Trio MRI device. The data processing, evaluation and the statistical analysis was made by MELODIC, FSL and CONN Toolboxes. The history of CM was assessed with the use of the Childhood Trauma Questionnaire and personal interviews were made to reveal the childhood abuse and neglect. Beck Depression and Anxiety Questionnaire were applied for further diagnostic examinations. We found significantly differences in network connectivity between the two sub-groups of MDD patients, as well as between control and depressed subjects. Detailed results will be presented on the poster. In conclusion, our findings suggest that differences in the strength of functional connectivity in occipital lobe structures, certain cerebellar areas and limbic structures may distinguish between depressed patients with or without childhood maltreatment.

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Three dimensional high density electrode arrays allow identification of synaptically coupled human neurons *in vivo*

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We pioneered functional assessment of human synaptic function in acute brain slices with multiple patch clamp recordings combined with correlated light and electron microscopy and identified distinctive features of human feed-forward synaptic networks. A landmark result of our human slice experiments was that individual neurons triggered sequences of events in the network lasting an order of magnitude longer than detected previously in other species. These event series were composed by specifically alternating glutamatergic and GABAergic postsynaptic potentials and required selective spike-to-spike coupling from pyramidal cells to GABAergic interneurons. Individual neuron activated groups of cells resembled the so-called functional assemblies which were proposed by D. Hebb as building blocks of higher order cognitive representations. In order to validate human slice results in behaving humans, we developed three dimensional, high-density electrode arrays for human in vivo recordings. The minimal vertical distance of recording sites (50 µm), and the minimal lateral spacing of shanks in the array is 1 mm. Our electrode arrays contain a scalable number of recording sites, can span all layers of the cortex, and allow quick manual surgical placement and incorporation into standard intracranial EEG grids. We successfully implanted several in-house built prototypes of the novel electrode arrays in combination with standard intracranial EEG grids for 7 to 11 days in human patients. Following the surgical removal of the arrays, we performed in vitro targeted patch clamp experiments in the neighborhood of in vivo electrode tracks with full anatomical recovery of the patched cells and having only a slight (17±8%) drop in the number of connected pairs relative to slices made from the tissue without in vivo electrode penetration. Preliminary analysis of human in vivo recordings using in-house developed microelectrode arrays allowed us to identify monosynaptically coupled human neurons in vivo. Moreover, we confirmed the existence of powerful human pyramidal cell to interneuron spike to spike coupling and relatively weaker pyramid to pyramid interactions in vivo. We conclude that the novel three dimensional high density electrode array is successful in identifying Hebbian sequences of firing in groups of relatively closely spaced pyramidal cells and interneurons with time scales corresponding to high frequency cortical motifs in the human cortex.

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Day 3

Day 1 Novel techniques

Poster

ID:164

Comparative definition of transcriptomic cell types in primary visual cortex

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The multitude of brain areas in mammals implement computations via distributed neuronal networks. Within brain areas, specific anatomical, connectivity and gene expression properties underlie the physiological, morphological and functional identities of computing units. In contrast to the apparent simplicity of Brodmann's original descriptions on functions of brain areas, the availability of multidimensional datasets defining the identity and boundaries of functional brain units dissolve the meaning of classical areal categorizations. Here we performed RNA sequencing of the primate and cat primary visual cortex. The sequenced reads were processed and aligned to the appropriate reference genomes. Differentially expressed genes were determined based on hypothesis testing. Known visual cortex marker gene subset was used to determine the cell types present in the samples. The differentially expressed visual cortex marker genes could highlight the difference in sample composition between species.

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Day 2 Poster

ID:264

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 at least 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 stimulationevoked signals in the cortex.

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Day 3

Phosphoproteomic analysis reveals post-transcriptional dysregulation in Huntington's disease patient derived induced neurons

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Huntington disease (HD) is a heritable fatal neurodegenerative disorder with rising prevalence characterized by severe symptoms but no successful treatment available. HD is caused by CAG expansions in the huntingtin (HTT) gene, leading to protein aggregation. It is challenging to study HD due to the lack of appropriate model systems that can capture human ageing. Our group studies HD using a novel induced neuronal (iN) model which serves as a unique patient-derived cellular system for age-related neuronal disease modeling. iNs uniquely maintain the aging, epigenetic and genetic features of the donor. Impairments in autophagy - an ubiquitinal lysosomal protein degradation pathway indispensable for protein homeostasis and cellular function – seems to play a critical role in the neuronal death in HD. However, understanding of how alterations in autophagy causes cellular dysfunction and death is lacking. In this study, we established an iN model to study impairments in HD at the proteome level with special interest in autophagy-related pathways. We performed mass spectrometry (MS) and phospho-MS measurements of iNs generated from HD-iNs and healthy donors (Ctr-iNs). We gained information about protein abundance and activity from MS and phospho-MS data, respectively. Following quality check and normalization of the raw data we performed bioinformatical analysis. We found 139 proteins with significantly altered abundance and activity, 68 of which has lower and 71 higher activity in HD-iNs. Most interestingly we identified 26 "ON/OFF" proteins with no detectable activity in HD-iNs. These proteins showed no significant differences in the RNA level or in the protein abundance, ensuring that HD specific alteration happened posttranslationally. This is a highly valuable finding, as the radical difference in these "ON/OFF" proteins suggest they play critical role in HD pathomechanism. To confirm this, we will validate the significance of 2-3 selected targets which showed such robust alteration in HD iNs. We will perform CRISPR modification experiments to silence (CRISPRi) or enhance (CRISPRa) the selected targets to gain new information about their role in neural function. Our main purpose in this project is to identify novel key protein targets dysregulated in HD which can serve for future therapeutic strategies.

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Poster ID:165

Day 1

Effects of ischemia on the migratory capacity of microglia along collagen microcontact prints on organotypic mouse cortex brain slices

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Ischemic stroke is a severe insult in the brain causing cell death, inflammation, and activation of microglia. Microglia are the immune cells of the brain and play a role in any inflammatory process during neurodegeneration. Microglia are round ameboid and migrate to the lesion site, where they differentiate into ramified forms and activated phagocytic microglia. On the other hand, microglia can also release growth factors to repair degeneration. The aim of the present study is to explore the migratory capacity of microglia after ischemic insults. Organotypic brain slices of the mouse cortex (300 μ m) were prepared. In order to study migration, the slices were connected to collagen-loaded microcontact prints (with or without monocyte chemoattractant protein-1, MCP-1) on the membranes. Slices were stimulated with lipopolysaccharide (LPS) for maximal microglial activation. Ischemic insults were simulated with oxygen-glucose deprivation (OGD) and acidosis (pH 6.5) for 3 days. After 3 weeks in culture, slices were fixed and immunohistochemically stained for the microglial markers Iba1, CD11b and macrophage-like antigen. Our data show that Iba1+ microglia migrated along the microcontact prints, differentiate and phagocyte 1.0 µm fluorescent microbeads. LPS significantly enhanced the number of round ameboid migrating microglia, while OGD and acidosis enhanced the number of ramified activated microglia. The effect was not visible on slices without any μ CP and was most potent in μ CP with MCP-1. We conclude that OGD and acidosis activate ramification and exhibit a similar mechanism, while LPS only activates round ameboid microglia. Collagen-loaded microcontact prints connected to mouse brain slices are a potent method to study activation and migration of microglia ex vivo.

This study was supported by the Austrian Science Funds (FWF grant P32558-B).

Poster ID:265

Seeing beyond the spikes: reconstructing the complete spatiotemporal membrane potential distribution from paired intra- and extracellular recordings

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Even though electrophysiologists have been routinely recording intracellular neural activity ever since the groundbreaking work of Hodgkin and Huxley and extracellular multi-channel electrodes have also been frequently and extensively used, a practical experimental method to track membrane potential changes along a complete single neuron is still lacking. Instead of obtaining multiple intracellular measurements on the same neuron, we propose an alternative method by combining single-channel somatic patch-clamp and multi-channel extracellular potential recordings. In this work, we show that it is possible to reconstruct the complete spatiotemporal distribution of the membrane potential of a single neuron with the spatial resolution of an extracellular probe during action potential generation. Moreover, the reconstruction of the membrane potential allows for distinguishing between the two major but previously hidden components of the current source density (CSD) distribution: the resistive and the capacitive currents. This distinction provides a clue to the clear interpretation of the CSD analysis, as the resistive component corresponds to transmembrane ionic currents: all the synaptic, voltagesensitive, and passive currents; while capacitive currents are considered the main contributors of counter-currents. We validate our model-based reconstruction approach on simulations and demonstrate its application to experimental data obtained in vitro via paired extracellular and intracellular recordings from a single pyramidal cell of the rat hippocampus. In perspective, the estimation of the spatial distribution of resistive membrane currents makes the distinction possible between active and passive sinks and sources of the CSD map and the localization of the synaptic input currents, which make the neuron fire.

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Day 2

Poster ID:365

Fast and sensitive GCaMP calcium indicators for imaging neural populations

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Calcium imaging with protein-based indicators is widely used to follow neural activity in intact nervous systems, but current protein sensors report neural activity at timescales much slower than electrical signaling and are limited by trade-offs between sensitivity and kinetics. We used large-scale screening and structure-guided mutagenesis to develop and optimize several fast and sensitive GCaMP-type indicators. The resulting 'jGCaMP8' sensors, based on the calcium-binding protein calmodulin and a fragment of endothelial nitric oxide synthase, have ultra-fast kinetics (half-rise times, 2 ms) and the highest sensitivity for neural activity reported for a protein-based calcium sensor. Furthermore, we have created and characterized several transgenic mice using jGCaMP8m and 8s to enable stable, long-term expression for in vivo imaging applications. A tetOjGCaMP8s x CaMKIIa-tetTA mouse had similarly fast kinetics and sensitivity compared to AAVinfected brain regions. The tetO-jGCaMP8s mouse shows ~5x increased SNR compared to tetO-GCaMP6s in a fast visual stimulus presentation protocol. In parallel, we generated several knockin strains at the TIGRE locus that co-express jGCaMP8s (or 8m) and tetTA in a Cre-dependent manner. These 3rd generation TIGRE lines enable targeting of genetically and anatomicallydefined neuronal subpopulations and transcriptional amplification of the GCaMP indicator. Both jGCaMP8s and jGCaMP8m mice displayed fast kinetic responses. Finally, by attenuating tetTA translation, we were able to avoid previously reported issues associated with tetTA overexpression; offspring from pan-excitatory and pan-inhibitory crosses displayed no signs of perinatal lethality or neurodegeneration. These mouse lines will be deposited at the Jackson Laboratory. jGCaMP8 sensors will allow tracking of large populations of neurons on timescales relevant to neural computation.

Day 3

Day 1 Repair and regeneration

Poster ID:166

Exploring the Structural, Morphological, and Chemical Properties of Spider Silk Crucial for its Success in Nerve Regeneration

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Introduction: Spider silk (SPSI) as one of nature's most fascinating materials has attracted vivid attention due to its remarkable performance in tissue regeneration. Particularly for facilitating the regeneration of large nerve defects, the biomaterial has proven to be incomparably successful. The material's variability and the difficulty to harvest it in large quantities constitute major limitations in translating the fiber into clinical practice. For this reason, the search for possible analogues for applicability in medicine is of tremendous scientific and clinical interest. Aim: So far, very little is known about the interactions between Schwann cells (SCs) and SPSI, rendering the targeted improvements of the natural silk and replacement with customised artificial fibers challenging. Therefore, this study investigates the structural, morphological, and chemical properties of diverse SPSI and compares those with the silks' nerve regenerative potential. Methodology: SCs were isolated from rats' sciatic nerves according to established protocols. The SCs were seeded on various SPSI and their migratory potential was evaluated by live cell imaging. By establishing multicolor immunofluorescence panels, the extent of the SC culture's purity and proliferation was examined. To elucidate the possible reasons behind the varying performances, a detailed analysis of the material characteristics of SPSI was conducted via Atomic Force Microscopy and nanoindentation. Results: SC adhere and migrate along various SPSI. Multicolor confocal micrographs of SCs indicated an overall rSC culture purity of over 95%. The proliferation of SCs showed no difference. A significant difference in the mean velocity of SCs on silk was observed between two species. This deviating velocity could not be related to the silks' morphology, but a potential correlation with the hardness of the SPSI can be observed. Conclusion: Our findings underline that the velocity of SC on various fibers varies. As the migration of SCs is an important feature to precede the guiding of the axons across the nerve defect in peripheral nerve injuries, the hardness of the fibrous luminar fillings should be taken into consideration for the production of SPSI analogous materials.

Repair and regeneration

Poster ID:266

Sculpting adulthood in the brain networks: a novel map of dormant precursor maturation in cortical and subcortical areas

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Dormant neuronal precursors are peculiar cells of the adult mammalian brain, including humans. Their latent post-mitotic immaturity from birth to adulthood precedes a progressive awakening, following largely unresolved mechanisms. Our past work explored the dormant precursor awakening in the murine paleocortex (piriform cortex) identifying the transition from the precursor to the neuron state during the early adulthood. Strikingly, several records hint towards the existence of this precursor cell type in many more brain areas outside the piriform cortex. Therefore, we generated a map describing the location, density and phenotypes of awakened and matured dormant precursors in the adult and aged brain. As of yet, we studied the brains of transgenic mice (DCX-CreERT2/fl-EGFP), in which immature dormant precursors were permanently labelled in vivo at different ages, and analyzed their maturation up to age 15 months. In this animal model, we pinpointed numerous hotspots that involve adult-neuron maturation based on immunohistochemistry and confocal microscopy. Those hotspots involve several nuclei of the hypothalamic area, the supraoptic nucleus, amygdala, bed nucleus of the stria terminalis, nucleus accumbens and associative cortices. Strikingly, adult matured neurons belonged to heterogeneous phenotypes, each expressing different patterns of proteins, for instance Tbr1 or oxytocin, vasopressin, tyrosine hydroxylase, GABA or parvalbumin. Our findings suggest that novel networks of adult matured neurons refine or reshape existing adult brain networks. Considering the age and the regions in which the process occurs, we speculate that the dormant precursors might be crucial for brain maturation and plasticity, shaping cognitive aspects relevant for adult life.

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Repair and regeneration

Poster ID:366

"Old prince meets young sleeping beauty": the slow awakening of dormant neuronal precursors in the adult and aged brain

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Dormant neuronal precursors are peculiar cells of the adult mammalian brain. Their latent postmitotic immaturity from birth to adulthood is followed by staggered awakening based on mechanisms that are still largely unresolved. Past works explored the dormant precursor awakening pinpointing the transition from the state of precursor to neuron during the early adulthood. However, since individual awakening events are staggered over months or years or even decades, according to species, the awakening process as a whole may be rather slow and even result in some cells retaining immaturity until the brain becomes old. We therefore questioned whether the maturation endures through advanced age and how does aging affect the maturation in case of extremely delayed awakening events. To this end, we studied the brain of transgenic mice (DCX-CreERT2/fl-EGFP) in which immature dormant precursors were labelled permanently in vivo at different ages, and analysed their maturation up to age > 24 months. Our data revealed that dormant precursors can indeed awaken and mature in the adult and in the old brain. Moreover, after becoming adult-matured neurons (AM), they undergo a subtle progressive process refinement throughout aging, involving shrinkage of the soma, shortening of the axon initial segment (AIS), reduction of dendritic branching, and increase of synaptophysin puncta juxtaposed to dendritic spines. On one hand, protracted immaturity did not prevent late awakening and maturation. On the other, the late age of awakening resulted in subtle morphological differences in AM awakening after nine postnatal months (late AM) as compared to AM awakening after three postnatal months. A functional comparison between AM, late AM and neonatal-matured neurons (NM) revealed small differences between AM and NM, and more significant differences between late AM and NM. Such differences were chiefly represented by the greater intrinsic excitability of late AM and by their extremely sparse spontaneous synaptic input. Thus, dormant precursors retain the ability to awaken and undergo neuronal maturation in the aged brain. However, the process is remarkably slow and late maturation onset might leads to different outcomes than early maturation. Thus the function of adult-matured neurons differs according to the age of awakening.

This project was possible thanks to the generous support of the Paracelsus Medical University of Salzburg (PMU), in the frame of the PMU Research and Innovation Fund (PMU-RIF) Seed Money for Novel Innovative Ideas and Preparatory Projects (SEED); project number: 2021-SEED-003-Benedetti.

Day 1 Repair and regeneration

Poster ID:167

Neuroectodermal stem cells improve the functional and morphological outcome after chronic spinal cord contusion injury via multiple mechanisms

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Spinal cord contusion injury leads to severe tissue loss and subsequent deficit of motor, sensory and vegetative functions below the lesion. In this study we investigated whether transplantation of neuroectodermal stem cells into the injured rat spinal cord is able to induce morphological and functional improvement in a chronic spinal cord injury model. Mouse embryonic clonal neuroectodermal stem cells (NE-TR-4C) were grafted intraspinally five weeks after a thoracic spinal cord contusion injury performed in SD rats. Control animals underwent contusion injury without stem cell transplantation. Functional tests (BBB test, video-based locomotor pattern analysis) and detailed morphological analysis were performed to evaluate the effects of grafted cells in different time points. Grafted animals showed significantly better functional recovery compared with control animals. Morphologically, the contusion cavity was significantly smaller, and the amount of spared tissue was significantly higher in grafted animals than in controls. Retrograde tracing studies showed a statistically significant increase in the number of FB-labelled neurons rostral (spinal cord segments, raphe nuclei, somatomotor cortex) to the injury. The extent of functional improvement was related to the amount of inhibitory factors (GFAP, CS-56) around the cavity and microglial reactions in the injured segment. Five days after transplantation the majority of grafted cells appeared to survive, formed clusters and a small proportion of the cells differentiated into neurons and astrocytes. Ten days after grafting the majority of the grafted cells appeared as nonviable fragments in microglia/macrophage cells. These data suggest that grafted neuroectodermal stem cells are able to induce morphological and functional recovery after chronic spinal cord contusion injury despite the limited survival of transplanted cells.

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Day 2

Repair and regeneration

Poster ID:267

Exploring the potential of human iNSCs to restore connectivity in the injured spinal cord in a rat model

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To this day, spinal cord injury (SCI) is causing irreversible loss of function affecting all parts of the body. The current treatment approaches mainly focus on preventing progression of the injury due to secondary damages. However, a replacement of lost neuronal cells upon injury is needed to regain function. Induced neural stem cells (iNSCs), which can be directly converted from patient-specific fibroblasts, are an ideal source for cell replacement therapy and would allow autologous transplantation. Here, we investigated the potential of iNSCs transplantation in the subchronic phase of SCI in a rat contusion model. Female Fischer-344 rats received a contusion at T8 causing moderate to severe SCI. At 30 days after contusion, fGFP-labeled human iNSCs or vehicle were injected caudal and rostral of the lesion epicenter. Due to the human origin of iNSCs immunosuppression was needed to avoid rejection of the graft. Immunosuppressive treatment was started one day before transplantation to allow natural pathophysiology within the first month of injury. Motor function was assessed at multiple time points by the BBB locomotor scale as well as the Catwalk XT system and sensory function by the Hargreave's test. Finally, after 1 month or 3 months, the cell fate of transplanted iNSCs was analyzed by immunohistochemistry. Transplantation of iNSCs at the lesion site neither improved nor deteriorated the functional outcome after SCI, compared to rats only receiving vehicle solution. Transplanted iNSCs can survive in the injured spinal cord for at least three months after transplantation according to immunohistochemistry. One month after transplantation, iNSCs mainly expressed immature NSC markers, e.g. Nestin, and early markers of neuronal differentiation, e.g. DCX and TUJ1, while glial markers were absent. In contrast, after 3 months, transplanted iNSCs exclusively expressed GFAP and neuronal as well as immature markers were absent. The lesioned spinal cord constitutes an inhospitable milieu which is pro-inflammatory, full of cysts and scarred tissue and lacks proper blood supply. The survival of iNSC-derived neurons may be compromised by the environment, whereas iNSCs differentiating into astrocytes may be more robust and even contribute to the scar. Future attempts to use iNSCs to restore the neuronal network in the lesioned spinal cord should therefore address the microenvironment to improve the support, the survival and integration of iNSC-derived neurons.

This project was supported by the Wings for Life foundation.

Day 3 Repair and regeneration

Poster ID:367

A potential therapeutic treatment with lipid nanoparticle-encapsulated nucleoside-modified mRNA after spinal cord injury

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Spinal cord injury results in irreversible tissue damage followed by limited recovery of function. Interleukin-10 (IL-10) attenuates the effect of pro-inflammatory cytokines and reduce apoptosis. In this study lipid nanoparticle (LNP)-encapsulated human (h) IL-10-encoding nucleosidemodified mRNA (hIL-10 mRNA-LNP) and recombinant hIL-10 loaded via osmotic pump were used to induce neuroprotection and functional recovery following spinal cord contusion injury (at the level of thoracic 10 vertebra) in a rat model. The hIL-10 mRNA-LNP or recombinant hIL-10 were administrated 7 days after injury directly into the lesion cavity. The functional analysis showed that hIL-10 in both treatment groups enhanced the coordinated movement relative to controls. Similarly, administration of hIL-10 in both treatment strategies resulted in significantly smaller lesion area at the epicentre of the injury and significantly greater amount of tissue. Analysis of supra- and propriospinal connections with the retrograde tracer Fast Blue indicated that hIL-10 treatment enhanced the number of connections between the segments caudal to the lesion and various cranial parts of the CNS. Astrocytes, microglial cells and neurons also expressed hIL-10 protein after hIL-10 mRNA-LNP injection up to 5 days in the injured spinal cord. The mRNA treatment induced time-delayed expression of TIMP-1 and CNTF in injured spinal segment. These results demonstrate that the delayed hIL-10 treatment is able to induce morphological and functional improvement after spinal cord contusion. The hIL-10 mRNA LNP provides a simple and well controllable new therapeutic approach that is less-invasive than other treatments and does not able to integrate into the genome.

Repair and regeneration

Poster ID:168

Day 1

Single-cell analyses of axolotl telencephalon organization, neurogenesis, and regeneration

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The axolotl (Ambystoma mexicanum), as an amphibian, represents one of the closest living relatives to amniotes and is therefore suited for comparative studies of brain cell types, neuronal connectivity and function among tetrapods. Cell type diversity in the axolotl brain and the evolutionary relation to other vertebrate brains had until now been studied mainly histologically. In addition, axolotls are exceptional at brain regeneration after injury. The cellular and molecular programs and the potential reestablishment of neuronal diversity and connections are however largely unexplored. To understand the organizational features of the axolotl telencephalon, we employed single nuclei genomic methods and spatial profiling. We analyzed cell types present in different telencephalon regions and defined their similarities to reptilian and mouse telencephalic cell types. We identified glutamatergic neurons with transcriptional similarities to amniote neurons of hippocampus, dorsal and olfactory cortex, and conserved GABAergic neuron classes. Projection tracing revealed that axolotl olfactory cortical-like neurons receive input projections from the olfactory bulb, indicating a conserved role in olfactory processing. Using trajectory analysis and multiomic profiling we inferred the transcriptional dynamics and gene regulatory relationships of postembryonic, region-specific neurogenesis, and unravel conserved differentiation signatures. To understand the molecular events during brain regeneration we used single nucleus RNA-sequencing of EdU-labelled cells. We find that after targeted brain injury, removing olfactory cortex-like neurons, stem cells activate an injury-specific molecular state before efficiently regenerating lost neurons through transcriptional programs highly similar to homeostatic neurogenesis. Finally, we performed projection tracing and determined that regenerated olfactory cortex-like neurons receive input projections from the olfactory bulb, suggesting circuit re-establishment. We are currently establishing tools to investigate neuronal connectivity and function to address the precise restoration of functional neuronal circuits after regeneration.

Repair and regeneration

Poster ID:268

Untangling neuronal circuits in the axolotl using an all-optical experimental setup

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The salamander species Ambystoma mexicanum (axolotl) shows a tremendous capacity to regenerate various tissues, such as limbs, tail, spinal cord and even the brain. In contrast to mammals, this ability is not lost as the animal grows but can still be observed in sexually mature axolotl. While studies have been performed to investigate this phenomenon in most tissues, the brain has so far been widely disregarded both in an intact and in a regenerative setting. To facilitate the investigation of neuronal circuits in the axolotl, tools established in other model organisms need to be implemented in the axolotl. A promising approach for this is an all-optical setting, where functional calcium imaging of neuronal activity is combined with the possibility of optogenetic manipulation using light-activated ion channels or pumps. We approached this aim from the biological side by testing the fluorescent calcium indicator GCaMP8s and red lightactivatable opsins in the axolotl system and from the physical side by setting up a state-of-the-art 2-photon microscope to achieve the best possible imaging results. Promising results have been obtained when expressing GCaMP8s in the midbrain of axolotl, where calcium spikes could be reliably recorded in an awake animal without external stimulation. Of the red-shifted opsins available, we are currently assessing ChRmine, ChrimsonR and C1V1 for in-vivo studies in spinal cord explant cultures under co-expression of the established GCaMP8s. Successfully utilization of the calcium sensing would enable the visualization of neuronal networks involved in a certain natural behavior while a follow-up using optical induction of neuronal activity would allow for the precise localization of brain areas crucial for the generation of patterns of neuronal activity as well as generating a certain behavior. The all-optical setup will be implemented to study the intact axolotl visuomotor circuitry in the brain as described above which will then open the possibility to investigate this circuit during a regenerative process. This will give insight into remodeling and adaptation of the system after injury.

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Day 2

Day 3 Repair and regeneration

Poster

ID:368

The role of motorneurons in neuroinflammatory processes

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Neuroinflammation plays a central role in both acute and chronic neurodegenerative diseases. Among the pro-inflammatory processes, the inflammasome signaling pathway is particularly important, as its activation results in the release of interleukin-1 β (IL-1 β). Here, we aimed to understand the role of inflammasome activation in inflammatory processes in the spinal cord after acute peripheral nerve injury. After sciatic nerve axotomy, the expression of NLRP3 inflammasome elements were significantly increased in the L4-L5 segments of the injured spinal cord in the first 3 days. Although glial cells are traditionally considered to be the main initiators of neuroinflammation, in this early phase of inflammation, inflammasome activation was exclusively observed in damaged motoneurons of the ventral horn in our model. The MCC950 as a specific inhibitor of NLRP3 inflammasome activation and 5-BDBD as a P2X4 receptor channel inhibitor significantly reduced the gene expression changes and also markedly decreased the IL-1ß release in the injured spinal cord. Although NLRP3 was also observed in glial cells 7 days after the injury, but we could not confirm inflammasome activation in this case. Inhibition of the inflammasome signaling pathway significantly reduced microgliosis, where IL-1β inhibition may have played a major role. Moreover, inflammasome inhibition in the acute phase significantly enhanced nerve regeneration on both morphological and functional levels. Based on our results, motorneurons play a prominent role in the development of neuroinflammation processes after peripheral nerve injury. Inhibition of neuronal inflammasome activation not only leads to significant reduction of microgliosis, but has a beneficial effect on the recovery as well.

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Poster ID:169

Inhibition of selectin by fucoidan promotes survival and regeneration of injured motoneurons after ventral root avulsion and reimplantation

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Avulsion injuries result in death of vast majority of motoneurons. Fucoidan, a sulfated polysaccharide enriched in brown algae, is widely used due to its anti-inflammatory and selectin modulator effect. Some studies have shown that selectins play an important role in the pathology of central nervous system. The aim of our studies is to reveal whether blocking of selectins with fucoidan promotes the survival and regeneration of damaged motoneurons following ventral root avulsion and reimplantation. In our experimental model, the left lumbar 4 (L4) ventral root was avulsed, and then the avulsed ventral root was reimplanted laterally. After the injury, fucoidan was administered intraperitoneally once a day at a dose of 50 or 100 mg/kg body weight for 1 week. In control animals, only the L4 ventral root was avulsed and reimplanted. One week after the injury, we mapped the microglia/macrophage reaction in the L4 segment using Iba-1 and CD68 immunohistochemistry. In the case of long-term survival groups (three-month survival), the ventral ramus of the L4 spinal nerve was transected and the proximal stump was covered with a fluorescent marker (Fast Blue) to label the reinnervating motoneurons. Functional reinnervation was investigated using movement pattern analysis. Fucoidan dramatically enhanced the survival and reinnervating capacity of injured motoneurons and resulted in functional reinnervation of denervated hind limb muscles. Fucoidan treatment decreased the expression of CD68 in the affected ventral horn. These data suggest that targeting the selectins with fucoidan could be a novel therapeutic strategy to arrest neuroinflammation and promote motoneuronal survival and functional recovery after avulsion injury.

Poster

ID:269

Prefrontal cortex shapes neuroblast migration in rodents

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The rostral migratory stream provides the olfactory bulb with newly born neuroblasts in rodents throughout life. This continuous renewing cellular supply enables the olfactory system to maintain its plasticity by including further neurons into its local functional circuitries. We have previously shown that a group of differentiated neurons reside along the margin as well as within the rostral migratory stream. These "shell cells" produce and externalize matrix metalloprotease-2 (MMP2) to demolish the extracellular matrix, thereby promoting the migration of neuroblasts. Here, we show that these secretagogin-containing cells receive input from the prefrontal cortex, but not from the amygdala, in adult rodents. By using VGAT-Cre mice, we show that local inhibition or excitation of the prefrontal cortex – achieved by administering AAV particles carrying Cre-dependent DREADD expression systems for neuronal activation or activation, respectively, - affects neuronal migration rate in the rostral migratory stream. We argue that neuroblast migration is responsive to select cortical signals which is transmitted and shaped by local differentiated neurons.

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Day 3 Stem cells and development

Poster ID:369

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

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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 RCresponses 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 Calcium-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.

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ID:170

Hyaluronan is required for mouse hippocampal development

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Hyaluronan a peculiar component of the brain the extracellular matrix (ECM) appears around neurons at very early stages of development of the central nervous system. This highly hydrated hyaluronan based ECM represents the most important microenvironmental factor for the whole life cycle of the neurons starting from their birth throughout their migration, differentiation, and circuit formation. We found abnormal laminarization of the spinal cord with altered dendritic morphology in developing neurons after the use of hyaluronidase in embryonic spinal cord organotypic slice cultures. We aimed to confirm these findings in-vivo as well, therefore we designed an electroporable inducible expression vector system for expressing streptomyces hyaluronidase (pHyase) that we injected into the lateral ventricle of embryonic mouse brain (E14.5) which was followed by in utero electroporation. At postnatal day 7 (P7) we sacrificed the young animals, and we observed that the hippocampus was failed to develop unilaterally in those of pups that were electroporated successfully with the pHyase vector and lacked hyaluronan during their hippocampal development. We also found abnormal distribution of layers in neurons labelled initially in the lateral ganglionic eminence and migrated into different cortical areas. Spatial and temporal memory of young adults was tested by IntelliCage system, that did not show any significant differences compared with the control group. Our results reflect on the essential function of the hyaluronan in neuronal migration or survival for populating the hippocampus.

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Day 2 Stem cells and development

Poster ID:270

Exploring the intersection between the light/dark cycle, circadian timing and neural stem cell regulation

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Most neural stem cells (NSCs) in the adult mouse brain remain in a reversible state of cell cycle exit, known as guiescence. The pool of NSCs and the long-term maintenance of adult neurogenesis is regulated through a controlled rate of NSCs activation – cell cycle entry. In this context, cell population heterogeneity within the NCS pool emerges as a key component, characterised by distinct activation and differentiation potentials and different responses to signalling cues. Growing evidence suggests the light/dark cycle and circadian rhythms as possible signals that may influence NSCs population heterogeneity. However, previous reports have not been able to disentangle the role of these two factors. Hence, it becomes imperative to investigate if NSCs have a functioning circadian clock, how this clock relates to the master pacemaker of the brain - the suprachiasmatic nucleus (SCN) - and explore a possible link between phase of the circadian oscillation, light/dark cycle and NSCs fate. In vitro live imaging of active NSCs isolated from both Per2::Venus and Per2:LUC animals revealed circadian-like rhythms of Per2. Furthermore, ongoing experiments aim to analyse Per2 levels in quiescent NSCs and on differentiating cells. However, to assess if the same is observed in vivo, C57BI/6 animals were sampled every four hours in a 14:10 light/dark cycle. Although a trend in Per2 levels was observed in NSCs, the signal amplitude was lower than in other brain regions - SCN and CA1. Therefore the same experiment is being performed with Per2::Venus animals to improve detection capability. Moreover, we are investigating if NSCs proliferation is related to the light/dark cycle and Per2 levels through EdU and Ki67 detection.

Day 3 Stem cells and development

Poster ID:370

Story of friendly mice: how serotonin influences adrenal gland development

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The adrenal gland is responsible for mediating stress response and behavior through the release of adrenalin and noradrenalin. Chromaffin cells - the main cell type, which produces these hormones, originate from nerve-associated Schwann Cell Precursors (SCPs) through a special intermediate "bridge" cell state. The key marker of this intermediate developmental state is the gene coding for the serotonin (5HT) receptor subunit HTR3A. Therefore, 5HT may play a role in chromaffin cell development and consequently be involved in the genesis of adrenal gland pathologies, like childhood cancer neuroblastoma. In this study, we have investigated the 5HT role for the adrenal gland development by a combination of single-cell transcriptomics, pharmacological treatments of animals, immunohistochemistry, RNA in situ hybridization, behavioral assays, and the evaluation of neuroblastoma cell lines. In rodents (mice and rats) chromaffin cells are serotonin positive at the early stages of development and "bridge" cells are serotonin-sensitive at the same developmental stage, defining the components of the probable paracrine connection within the developing adrenal gland. The increase of serotonin during the "bridge" stage results in decreased chromaffin cells. This is caused by a slowdown of "bridge" cells' cell-cycle progression. This paracrine feedback loop is proposed to be involved in the control of the generation of the proper number of chromaffin cells in the adrenal gland medulla and preventing overgrows of the tissue. Artificial excess of serotonin causes premature termination of chromaffin cell generation, which manifests in an altered level of catecholamines during adult life and behavioral patterns rendering animals more cooperative and explorative. Notably, some neuroblastoma cell lines express high levels of HTR3A. Such neuroblastoma cells are tumorigenic and respond to HTR3A stimulation with specific agonists by a decrease in proliferation. Altogether, increased levels of 5HT during a specific period of chromaffin cell differentiation results in a smaller chromaffin cell population. This mechanism is important for the control of excessive organ growth, and neoplasia, and plays an important role in animal behavior.

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Day 1 Stem cells and development

Poster ID:171

Effects of depolarization patterns on neuronal development and maturation

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The phenotype of a terminally differentiated neuron is determined partly by its own genetic history and partly by the environmental influences. Recent investigations have convincingly demonstrated that the intrinsic biophysical and physiological properties of neurons are strongly influenced by the tonic or synaptic inputs that they receive. This suggests that depolarization "training" by optogenetics using similar environmental stimulation patterns that occur in the developing nervous system may be useful to direct and/or activate cell differentiation and maturation. In this work, we have systematically analyzed the progress of neuronal development of immature neurons differentiated from the NE-4C mouse neuroectodermal stem cell line and how it is influenced by prolonged (48 h) application of different depolarization patterns. To achieve this, all-trans retinoic acid-induced NE-4C cells were transfected with channelrhodopsin 2 ChR2-H134R-YFP plasmid construct on the 6th day of induction, and 24 h later cultures were illuminated for 48 h in the tissue culture incubator with different illumination patterns. As controls, parallel cultures were kept in the dark for 48 hours. For training, we used both an oscillatory (which mimics the patterns that neurons are receiving in the embryonic brain) and a random-distributed light flash sequence (as illumination control). Depolarization training with oscillatory pattern increased the percentage of neurons exhibiting strong action potential output and altered the cells' intrinsic membrane properties. Action potential amplitudes increased, and the active membrane properties of the cells proved a more mature neuronal phenotype compared to cells kept in dark. The presence of the inward rectifying K-current (KIR) also increased in response to training. When random distribution pattern was used, values were similar to the dark control. Analyses of KIR2.x channel-subtypes expression by qRT-PCR also showed increased KIR channel expression but only following oscillatory training and not randomillumination. In conclusion, the applied theta oscillation proved to be effective in controlling the differentiation of neurons derived from mouse neural stem cells, promoting the formation of cells with more mature electrophysiological properties and selectively increasing the occurrence of a specific voltage-activated K-current.

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Day 2 Stem cells and development

Poster ID:271

Postnatal development of the hippocampal formation in the TRPV1 knockout mice

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Transient receptor potential vanilloid 1 (TRPV1) is a non-selective cation channel with a polymodal sensory function. In the hippocampal formation, functional TRPV1 channels are expressed by Cajal-Retzius cells, which have a role in guidance of migrating neurons during cortical migration phase of development. In addition, the contribution of TRPV1 channel in the apoptotic cell death of Cajal-Retzius cells was suggested. TRPV1 links to fever, and in previous studies on TRPV1 knock-out (KO) mice, the role of the channel in the generation of febrile seizure was reported, although, influence of the TRPV1 is debated. Despite the developmental aspects of febrile seizure as well as of Cajal-Retzius cells, no information is available about the hippocampal development in the TRPV1 KO mouse. Therefore, in the present study development of the hippocampal formation was studied in postnatal TRPV1 KO mice. Several morphological characteristics including neuronal positioning and maturation, synaptogenesis and myelination were studied following immunohistochemical detection of protein markers of various neurons, synapses and myelination. Regarding the cytoarchitectonics, neuronal migration, morphological and neurochemical maturation, no substantial difference was found between TRPV1 KO and wild-type control mice. Our data indicate that synapse formation and myelination occur similarly in TRPV1 KO and in control animals. We have found slightly, but not significantly larger numbers of persisting Cajal-Retzius cells in the KO mice than in controls. Our result strengthens previous suggestion concerning the role of TRPV1 channel in the postnatal apoptotic cell death of Cajal-Retzius cells. However, the fact that the hippocampal formation of KO mice lacks major developmental malformations supports the use of TRPV1 KO in various animal models of diseases and pathological conditions.

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Day 3 Stem cells and development

Poster ID:371

The effect of antipsychotic haloperidol, olanzapine, and risperidone on human iPSC-derived neural progenitors

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In the light of our current knowledge there are three neurogenic area in the mammalian brain remaining active throughout our live: the subventricular zone of the forebrain and hypothalamus, and the subgranular zone of the hippocampal dentate gyrus (DG) respectively. The neural progenitor cells (NPCs) located in these areas may play a role in learning, spatial memory, emotional and sexual functions, and regeneration as well. Therefore, NPCs are potential targets of numerous biomedical and therapeutic approaches. Several studies point to that, the mainly dopamine receptor agonist first- and second-generation antipsychotics can modulate the behaviour (i.e., proliferation, differentiation, viability) of NPCs, as a non-canonical side effect. However, these results are mostly emerged from animal models or post-mortem human samples, so either the human translatability is questionable or there are only limited possibilities for functional studies. Therefore, we applied a human induced pluripotent stem cell (iPSC) based NPC model, using directed in vitro differentiation protocol (published by Diana Yu et al.), to examine the effect of these psychopharmaceutical compounds on neural progenitors. Here below is a summary of our findings on the growing and differentiating properties of NPCs, treated by different concentration of haloperidol, olanzapine, and risperidone. Subtle drug induced morphological and gene expression changes were detected, suggesting that, these antipsychotic agents may have effect on the process of neural differentiation.

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Days

Day 1 Stem cells and development

Poster ID:172

Human cortical cultures and artificial models: understanding individuals with epilepsy

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Artificial neural networks simplify complex biological circuits into tractable computational models to distil their essence and test our understanding. It is often said that the simplicity of artificial models undermines their applicability to real brain dynamics. Typical efforts to address this mismatch add complexity to increasingly unwieldy models. We instead use simplified cortical cultures with two cortical neuron types derived from human induced pluripotent stem cells (hiPSCs) to compare model and reality. Over 6 weeks of development, we simultaneously record thousands of neurons using high-density microelectrode arrays (HD-MEAs). Recording at highdensity and large-scale allows an in-depth look at dynamics at both the neuron and systems levels. We build unique profiles of dynamics from a library of metrics measured from the 39 cultures. Our approach of deriving neural networks from hiPSCs also allows us, for the first time, to directly compare neural dynamics of epilepsy patients and close family "control" members. We uncovered surprisingly variable network activity across cultures from families with a common genetic variant. That is, no single measure or metric was sufficient to classify a culture according to the genetic background of its donor, even if differences within a family were evident. We address this using two complementary methods. First, a multi-metric approach that clusters individuals using dimensionality reduction of their dynamics within the dataset. Second, by building data-driven models - "digital twins", or artificial reproductions of each network - that allow rapid and reproducible probing of individuals' dynamics. Furthermore, the digital twins suggest ex vivo perturbation experiments for further understanding of the individuals' cultures and models. Our research showcases a promising personalised medicine approach for the understanding and treatment of people with epilepsy. It does so by using data-driven modelling that starts to bridge an important theoretical-experimental neuroscience gap for advancing our understanding of human neuron dynamics.

NOMIS Fellowship Program at ISTA; NVIDIA Grant program

Day 2 Stem cells and development

Poster ID:272

Effects of metformin on proliferation and neurite outgrowth in neuronal progenitor cells derived from diabetic patients and healthy controls

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Background: Sedentary lifestyle can lead to obesity and type 2 diabetes. Long-term consequences of the disease include atherosclerosis, retinopathy and neuropathy. However, recently, it has been shown that there may be increased comorbidity between diabetes and certain neuropsychiatric disorders. The link is particularly observed in Alzheimer's and Parkinson's disorder and OCD. The aim of our work is to investigate the effects of metformin on neuronal progenitors and neurons generated from induced pluripotent stem cells. We generated IPSCs from PBMCs obtained from a healthy participant and diabetic patients. Our model system may help to investigate DM2 related cellular phenotypes and possible neuronal comorbidities for a better understanding of disease pathomechanisms. Methods: IPS cells were generated via Sendai virus transduction of the four Yamanaka factors (Oct3/4, Sox2, klf4, cMyc). The stabilized lines were validated for pluripotency by immunocytochemical staining (Oct4, Nanog), qPCR and spontaneous differentiation. Neuronal progenitor cells were generated from the resulting lines. Progenitors show elevated Sox2 and Nestin expression compared to ipsc lines. The presence of these markers was also validated by immunocytochemical staining. The stabilized cells were seeded in 2500 cell / cm2 density and on the next day the lines were treated with metformin at different concentrations (100-1000 uM). After 24 and 48 hours the cell number was counted by using High Content Screening (HCS) microscope. For neurite outgrowth we seeded the cells in 2-3000 cell / cm2 depending on the given cell proliferation profile, then treated them with metformin. The neurites were stained with calcein, the records were also taken by using HCS. For image analysis, MetaExpress was used.Results: We successfully established iPSC lines and NPCs from diabetic patients and healthy control. The NPC shows concentration and cell line dependent response for drug treatment after 24 hours treatment. Based on our current result, there are no significant differences in neurite outgrowth in diabetic and control cell lines after metformin treatment.

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Poster

ID:372

Organization of a layered structure in the dorsal telencephalon of gobies

Ruth Gutjahr, Maximilian S. Bothe, Boris P. Chagnaud

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In a variety of vertebrates, layered neuronal structures are known to facilitate complex information processing. This is particularly true for the six-layered cortex of the mammalian forebrain, but other layered structures have also been found in the pallium of birds, lizards and tortoises. Interestingly, the telencephalon of teleosts is not organized in layers, with the exception of gobiid fishes. Within a region of the gobiid dorsal telencephalon, neurons are neatly stacked into four distinct layers. To investigate the connectivity of these layers with other nuclei in the goby brain, we performed in-vitro tract tracing experiments of the layered structure (Dl4-DI7), the medial (Dm), lateral (Dl) and central (Dc) parts of the dorsal telencephalon. These experiments revealed a high level of intratelencephalic connectivity and a tight link between the telencephalon and the preglomerular complex (PG). The PG is a major diencephalic sensory relay station among teleosts, considered as a functional equivalent to the thalamus of other vertebrates. Using highly localized Dil-labeling to label single and small groups of adjacent cells within the different layers, we in addition examined the individual neuronal morphology, as well as the microcircuitry within the layers. Labelling of individual neurons revealed a morphological diversity, with most neurons having dendrites projecting to adjacent layers, that are densely packed with dendritic spines. Immunohistochemical experiments revealed the presence of tyrosin hydroxylase, substance P, parvalbumin, and calretinin within the layers. Interestingly layers were not uniformly labeled but showed distinct patterns depending on the antigen investigated. Our results indicate that this layered structure likely belongs to the dorsolateral telencephalon (DI). This area is considered homologous to the medial pallium of higher vertebrates, which includes the hippocampus in mammals.

A role of limbic system in behavioral effects of psilocybin

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Introduction: Mood and anxiety disorders are one of the most common threats to mental health, while expressing high levels of comorbidity. Both ketamine and psilocybin are recently considered as a treatment for major depressive disorder. They seem to exhibit rapid antidepressant effect, in comparison to currently used drugs, which require prolonged treatment to alleviate the symptoms. The aim of this study was to characterise the effect of psilocybin exerted on hippocampus and nucleus accumbens, and compare it with ketamine. The impact on neurotransmission was measured with in vivo microdialysis, while anxiety and locomotor behavior was assessed with light/dark box and open field tests. Methods: Microdialysis was performed in freely moving rats. Animals were implanted with microdialysis probes into the hippocampus and nucleus accumbens. Seven days later, probes were connected to a syringe pump delivering artificial cerebrospinal fluid. After establishing baseline animals were injected with ketamine (10 mg/kg, ip.) or psilocybin (2 or 10 mg/kg, ip.) and fraction collection continued for 240 minutes. Dialyzates were analyzed using HPLC with electrochemical detection. The open field test was conducted on a round black arena (1 m in diameter), virtually divided into eight sections. Rats were placed in the middle of the arena 1 hour after drugs injection and their behavior was recorded for 10 min. The effect both drugs exerted on anxiety was assessed by the light/dark box test 1 hour after drugs' administration and their behavior was monitored for 10 minutes. Results: Psilocybin and ketamine significantly increased dopamine and serotonin release in the nucleus accumbens, while having opposing effects on extracellular glutamate and GABA levels. Both substances elevated extracellular glutamate (excluding lower dose of psilocybin, which drastically reduced it), GABA and acetylcholine levels in hippocampus. Both substances significantly affected the rats' behaviour, reducing the locomotor activity and increasing anxiogenic-like behaviour. Conclusion: The data shows that psilocybin and ketamine significantly affected the release of dopamine, serotonin, acetylcholine, glutamate, and GABA in the limbic system. As this neurocircuit regulates behaviour connected to fight-orflight response, the observed changes may result in inducing anxiety in animals, leading to "freezing" behaviour resulting in reduction of locomotor activity.

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Day 1 Poster

ID:173

Day 2 Systems neuroscience

Poster ID:273

A midbrain-extended amygdala pathway controls contextual fear memory and predator odor avoidance

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Neuronal circuits located in the midbrain play a critical role in controlling defensive behavior. However, it is still elusive how different neuron types contribute to distinct behavioral outcomes during the presence of threat. In this study, we investigated a group of neurons in the ventral periaqueductal gray and dorsal raphe nucleus that express vasoactive intestinal polypeptide (VIP). Using viral tracing conducted in Vip-Cre mice, we observed that these VIP neurons innervated exclusively the bed nucleus of stria terminalis (BNST) and central amygdala (CeA), the two main regions of the extended amygdala. Interestingly, neurons in these two brain regions contributed to the innervation of midbrain VIP neurons to a large extent revealed by monosynaptic rabies tracing. In vitro electrophysiological recordings combined with optogenetics revealed that light stimulation of VIP afferents activated ionotropic glutamate receptors on their postsynaptic partners in the extended amygdala. Electron microscopy determined that spines were the major targets of VIP immunoreactive boutons both in the BNST and CeA. To clarify the role of the midbrain VIP neurons in defensive behavior, we inhibited their activity using chemogenetics and observed that inhibition of these midbrain neurons during fear conditioning impaired the contextual, but not cued fear memory tested on subsequent days. In addition, inhibiting the VIP neuronal activity reduced avoidance behavior in a predator odor avoidance test. These results collectively show that the excitatory midbrain-extended amygdala pathway expressing VIP plays a critical role in the regulation of a set of defensive behaviors.

Day 3 Systems neuroscience

Poster ID:373

Evolution of spatial and context selective tuning of hippocampal CA1 pyramidal cells during behavioral adaptation in a virtual contextual go/no-go task

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The hippocampal CA1 region is crucial for contextual memory formation by generating abstract relational maps by pyramidal cells (PCs) selectively tuned to locations or events. While the hippocampal map is thought to support behavioral adaptation, the organization and refinement of representations during this process is poorly understood. Here we aimed to elucidate the dynamic changes in tuning of CA1PCs during the evolution of task-relevant behavioral responses. We trained water-restricted, head-fixed Thy1-GCaMP6s mice to run on a cue-less treadmill in virtual reality environments, and distinguish two visually distinct corridors by selectively licking in a hidden reward zone (RZ) in one of them. We monitored CA1PC activity by two-photon Ca2+ imaging during improvement of task performance, as assessed by measuring running speed and lick rate. We observed enrichment of spatially tuned CA1PC activity at task-relevant locations of the virtual corridors, i.e. at the start and near the RZ. In low performance sessions, a substantial fraction of tuned cells showed similar spatial tuning in the rewarded and the unrewarded corridor and the representations of the two corridors were highly correlated. However, in expert animals, the fraction of spatially tuned CA1PCs increased preferentially in the rewarded corridor and decorrelated representations of the two corridors emerged. Additionally, the fraction of corridor-selective CA1PCs increased with better performance in both corridors, most profoundly before the RZ. These changes in single neuron tuning during learning were also reflected by increased accuracy with performance in decoding corridor identity from the cell activities at positions close to the RZ. Our results suggest that hippocampal CA1PCs may initially generalize between environments but dynamically reorganize their activity according to behavioral relevance of corridor identity.

Anxiety-related dynamics of ventral hippocampal neurons

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Over the last 30 years, the ventral hippocampus (vH) has been shown to be a critical player in the processing of emotionally related information. Lesion studies demonstrated that vH is fundamental in avoidance behaviour, and optogenetic approaches highlighted the vH for anxietyrelated behaviour connected also with the amygdala and the medial prefrontal cortex. The synaptic connectivity of the vH has been extensively studied. However, the neuronal activity dynamics associated with anxiety-like behaviour within the vH circuitry still need to be understood. In order to determine the firing patterns in vH during avoidance behaviour, we recorded the activity of multiple single units in the vCA1 while animals shuttled along an elevated linear maze (ELM) with protective walls. We modified the maze appearance at different instances during the same recording day, allowing us to record the activity during two main configurations: the ELM with protective walls (CC) and the ELM with only half of the maze covered with protective walls and the other part completely open (CO). Neuronal activity in the vH remapped towards the anxiogenic locations (open area of the CO configuration), generating an overrepresentation of the opened arm. In addition, the remapped neurons' firing properties (coherence, spatial information and sparsity) significantly changed (from the CC to the CO configuration). Furthermore, directional-dependent activity was homogenised during the anxiogenic experience. Interestingly, the population activity of the vH neurons in the closed area of the CO configuration allowed us to predict the extent of exploration of the open area of the same configuration. Overall, our data suggest an active modulation of ventral hippocampal activity driven by anxiogenic stimulus not only dependent on exploring the open environment but already before exploring anxiogenic areas.

Day 2

Contributions of a distinct subtype of orbitofrontal cortex neurons to choice abandonment in a decision confidence task

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Effective decision-making requires not just resolving difficult choices but also knowing when to abandon a failing strategy. The orbitofrontal cortex (OFC) plays a key role in decision-making and has been shown to represent metacognitive computations such as post-decision confidence, i.e. the probability of being correct given the subjective evidence for a decision. How neural representations of decision confidence contribute to the determination to abandon or persevere with a choice is as yet unclear. Here we examined the activity of neurons in the OFC of rats, while they were performing an auditory choice task with a post-decision time investment option [1]. After making their perceptual decision, animals had to wait for a randomly delayed reward. The time animals were willing to invest into waiting for an uncertain reward before abandoning their choice served as a post-decision measure of confidence We used a function-first cell-type identification strategy to search for neurons that were specifically active when abandoning a choice commitment. We discovered a functional sub-type of OFC neuron defined by a unique activity profile that is indicative of the time animals were willing to invest into waiting for rewards on a per-trial basis and specifically signalled the imminent abandonment of waiting. Utilising juxta-cellular recordings in freely-moving animals [2] we searched for this specific activity pattern during behaviour and labelled identified neurons with neurobiotin for post-hoc cell-type characterization. Identified neurons were situated in deep layers of the OFC with specific axonal projection patterns and dendritic arborisation profiles. Our results reveal a group of subcortically projecting OFC neurons that predict choice abandonment. References 1. Masset, Ott, Lak et al., 2020, Cell 182(1):112-126 2. Lagler, Ozdemir, Lagoun et al., 2016, Neuron 91(6):1390-1401, 10.1016/j.neuron.2016.08.010

All-optical long-term functional access to large-animal brains

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Clinical acceptance of a gene therapy vector depends on the degree of invasivity of the delivery route, specificity to the target cell population as well as efficient and long-term stable expression of the therapeutic sequence. We seek to optimize long-term stable functional access to the brain of preclinical large-animal models using new adeno-associated virus constructs. We designed and injected new constructs locally into the brain cortex, intravenously and intrathecally into rodent and large-animal models and compared the applicability of each construct via functional assessment using optical activity access routes as well as via immunohistochemistry. The results indicate that brain-wide long-term stable functional gene delivery is now within reach supporting the applicability of gene therapy methods for neurological conditions.

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Poster ID:175

IL-6 signal transducer dependent processes in Nav1.8 expressing neurons associated with cognitive performance, gut motility and microbiome composition

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Primary afferent nociceptive neurons regulate immune cells and inflammatory reactions in the gut and increasing evidence links gut function and alterations of the gut microbiota with cognitive disorders. Interleukin 6 (IL-6), its receptor (IL-6R), and the ubiquitously expressed IL-6 signal transducer gp130 (IL-6ST) are well known regulators of innate immunity but also affect neuron morphology and function. Therefore, we aimed to identify the alterations in cognitive performance, gut motility, and feces composition in a transgenic mouse model with a conditional depletion of gp130 in neurons expressing the nociceptor specific ion channel Nav1.8 (SNS-gp130-/-) and littermate controls. Behavioral tests included the behavioral box test, marble burying test, forced swim test, open field test, and novel object recognition test. Feces were collected under sterile conditions and subject to 16S sequencing to identify differentially prevalent microbiota strains. CGRP release was stimulated by exposing colon preparations to a depolarizing 40 mM KCl stimulus for 5 min and quantified using a specific ELISA assay. Our preliminary results suggest that mice lacking the gp130 signal transducer in neurons expressing the nociceptor specific ion channel Nav1.8 exhibit lower stress levels, less anxiety-like behavior, and increased locomotion. Preliminary fecal analysis revealed diverse prevalent microbiota strains including Lachnospiraceae, Muribaculaceae, and Rikenellaceae with no genotype-related differences, but with evidence of sex-specific changes in fecal microbiome composition. Sex-specific differences in CGRP release were observed and colonic CGRP release was significantly decreased in SNSgp130-/- mice. CGRP release increases mucus production in the gastrointestinal tract. Therefore reduced CGRP release may not only affect the amount of feces but also microbiome and metabolite composition and this may possibly account for the behavioral differences of SNSgp130-/- mice.

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Poster ID:275

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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Poster ID:375

Differential distribution of calcium binding proteins (CBPs) in central pattern generators underlying social communication

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Calcium binding proteins are unique markers of neuronal identity and can be directly related to internal processing of neurons such as high frequency firing. The contribution of CBPs to locomotor behavior is well established, but their presence in other motor behaviors such as social communication remains mostly elusive. We investigated the distribution of four CBPs (calretinin, calmodulin, calbindin, parvalbumin) in the CPG underlying social communication in synodontid catfish. The constituents of this CPG have been previously identified (based on anatomical landmarks via transneuronal tract tracing), and consist of motor neurons, as well as three premotoneuronal populations (PN1-PN3). Depending on the synodontid species, the output of this evolutionarily conserved CPG produces either vocalizations (S. grandiops) or weakly electric discharges (S. nigriventris) as communication signals. Therefore, synodontids in addition offer a unique opportunity to study the contribution of CBPs to generate different social motor behaviors. All CBPs investigated were found in the CPG of both species: While calmodulin was present in both motor and some premotor neurons, parvalbumin was present almost exclusively in premotor neurons. We also found differences in the expression of some CBPs between the two species: lower densities of calbindin-ir and calretinin-ir cells were found in S. nigriventris. These two CBPs are present almost exclusively in some premotor neurons in S. nigriventris while in S. grandiops motor neurons and some premotor neurons express calbindin. In S. grandiops calretinin was present almost exclusively in motor neurons. The extensive presence of CBPs at all levels of the social CPG in synodontid catfish suggest an important role for calcium buffering in the generation of social signals, that are generally characterized by precise neuronal activation. How the CBPs affect pattern generation physiologically remains yet to be investigated.

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 in this process 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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Brainstem-hippocampal interactions support spatial memory formation

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Sleep has various physiological functions, including the consolidation of memories. Current theories establish that memories are transiently stored in the hippocampus and transferred to the neocortex for long-term storage during sleep. These processes involve brain-wide plastic changes, heralded by different types of macroscopic electrical activities that occur upon changes in the neuromodulatory activity of the brainstem. The brainstem prompts periods of both enduring and transient changes of neuronal excitability that affect the activity of other substructures in a precise manner. Thus, brainstem activity seems critical for the long-range coordination of several brain structures underlying memory formation. However, the specific neural mechanisms that allow these subcortical regions to participate in memory formation remain poorly understood. Here, 4 wild-type Long Evans rats were chronically implanted with recording micro-drives incorporating three bundles of movable recording electrodes targeting the dorsal hippocampus, the dorsal lateral geniculate nucleus (dLG) of the thalamus, and the parabrachial nucleus (PBn) of the brainstem. Each animal was recorded during the acquisition of a spatial memory task and subsequent sleep. We show that, across vigilance states, global changes in neuronal activity were accompanied by the occurrence of transient, coordinated highsynchrony neural events in the PBn-dLG electrical activity. These episodes displayed electrical characteristics consistent with pontogeniculooccipital (PGO) waves. Brainstem activity transiently modulates hippocampal high-synchrony events through PGO waves, selectively coupling with hippocampal sharp wave-ripple episodes and REM-associated phasic theta waves. Crucially, spatial learning resulted in an increase in the coupling between PGO waves and hippocampal events, where the emergence of post-sleep-, but not learning-PGO waves correlated with memory performance. The preliminary results of this investigation indicate that the control of hippocampal ensembles by PGO waves might be a phylogenetically-conserved neural mechanism. These episodes may correspond to windows for promoting hippocampal-cortical communication and plasticity during NREM and REM sleep, likely having opposite plasticity roles, and promoting memory consolidation and synaptic homeostasis.

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Day 3

Systems neuroscience

Poster ID:376

Studying visual system plasticity with mesoscopic brain imaging in developing and adult cats

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Understanding the mechanisms of neural circuit plasticity in the adult brain may play a key role in the treatment of neurological disorders. Short-term monocular deprivation represents a tractable plasticity model in adult subjects. However, the neural mechanisms underlying this phenomenon are not yet fully understood. To investigate the mechanisms of adult plasticity in a short-term deprivation context, we developed a functional ultrasound imaging framework. We record from anesthetized, head-fixed and from awake cats without head fixation to investigate the mapping of visual features onto cortical visual areas during behavior. Our preliminary data demonstrate that fast functional ultrasound imaging provides the right experimental tool for studying adult plasticity.

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Day 1 Systems neuroscience

Poster ID:177

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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Poster ID:277

Disruption of mGlu5 receptors in somatostatin-expressing neurons alters fear memory retrieval and brain oscillatory activity in prefrontal cortex and ventral hippocampus

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Metabotropic glutamate receptors 5 (mGlu5) are co-expressed in somatostatin-containing interneurons in different brain areas including: primary somatosensory and anterior cingulate cortex, basolateral amygdala and hippocampus. It is thought, that these receptors might play an important role in the regulation of social and anxiety-like behaviors. The present study describes the effect of the selective mGlu5 receptor disruption in somatostatin-positive (SOM+) neurons on the neuronal oscillatory activity in the prefrontal cortex (mPFC) and the ventral hippocampus (vHPC) of fear conditioned animals. Experiments were performed on male and female mice at the age of 8-12 weeks, from the mutant line SOM-Cre+/-::mGlu5 flox/flox and their littermates SOM-Cre-/-::mGlu5 flox/flox used as controls. We assessed the performance of these animals in the cued fear conditioning paradigm. Animal's neuronal oscillatory activity (local field potentials -LFP) in the mPFC and the vHPC was simultaneously recorded during fear memory retrieval. Our results revealed that the conditional knockout (cKO) of mGlu5 receptors in SOM+ interneurons decreased the level of freezing behavior, during fear memory recall in male mice. Moreover, it produced a pronounced reduction of spectral content (peak power) in the theta frequency band (4-12 Hz) both in the mPFC and vHPC, and disrupted theta synchronization between these two brain areas. Interestingly, we also observed that in female mGlu5 cKO mice, the expression of freezing behavior was strongly affected by the estrous cycle whereas the mPFC/vHPC neuronal oscillatory activity during fear memory retrieval was not significantly affected. In conclusion, our findings suggest that the lack of mGlu5 in SOM+ neurons impairs theta oscillatory activity in the mPFC and vHPC during aversive state processing. Moreover, the selective loss of these receptors from SOM+ neurons apparently leads to an impaired synchronization of neuronal oscillatory activities between the mPFC and vHPC during fear memory retrieval.

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Burst coding in hippocampal CA3 pyramidal neurons in vivo

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The hippocampal CA3 region plays an important role in episodic memory retrieval. Synapses between CA3 pyramidal neurons (PNs) are hypothesized to be endowed with Hebbian synaptic plasticity to support pattern completion (Guzman et al., 2016, Science 353, 1117–1123). Recent evidence suggests heterogeneity within CA3. First, the CA3 cell population exhibits an anatomical gradient in terms of functional properties and connectivity along the proximo-distal axis (Kowalski et al., 2016, Hippocampus 26, 668–682). Moreover, a novel type of CA3 PNs was described, which lacks DG granule cell input and was implicated in sharp-wave generation (Hunt et al., 2018, Nat. Neurosci. 21, 985–995). However, behavioral implication of the described CA3 PN heterogeneity remain enigmatic. To shed light on cellular mechanisms and intrinsic parameters involved in CA3-PN activity, we combine intracellular patch-clamp and multisite extracellular recordings in head-fixed mice navigating on a linear treadmill. While animals run for a water reward, a series of somatosensory cues are presented to record place-field activity. To correlate anatomical position and morphological properties of CA3 PNs with their activity pattern, recorded neurons are filled with biocytin for post-hoc morphological analysis. In total, we recorded from 40 morphologically identified CA3 PNs (ntotal=54). To characterize information output we analyzed the suprathreshold activity during running and immobile periods. CA3 PNs are very active (mean firing rate: 2.7±0.4 Hz) and their inter-spike-interval distribution can be described by 4 Gaussian log-normal components. Both single action potentials (APs) and bursts of APs can be observed, but burst firing is more frequent (mean burst index: 0.92). During theta modulation, spiking is phase-locked to the ascending theta phase. To elucidate intracellular subthreshold mechanisms underlying such heterogeneous firing, we investigated membrane potential dynamics during quiet-run transitions, showing that CA3 PNs hyperpolarise (3.6%) and depolarise (3.2%) during running periods. As previously shown in CA1, CA3 PNs display intracellular theta modulation during running periods with single APs being phase-locked to peak and descending theta cycle. Analysis of spatial tuning revealed that place cell firing in CA3 PNs was substantially less prominent than previously described in CA1, suggesting that the activity of CA3 PNs is primarily governed by internal synaptic computations.

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Poster ID:178

Day 1

Rapid retinotopy mapping using functional ultrasound imaging of deep visual cortex in cats

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Functional ultrasound imaging (fUSI) has recently emerged as a new way to access brain activity. In contrast to optical imaging methods, fUSI can report changes in neuronal activity in deep layers of the cortex and beyond without the need for invasive elements like GRIN lenses. To demonstrate the unique value of fUSI in animal models with large brains, we have reconstructed retinotopy maps in Brodmann areas 17 and 18 in anaesthetised, head-fixed cats. We could achieve a high-enough signal-to-noise ratio to reliably detect single-trial responses. Utilising our novel motorised imaging chamber design, we can record functional maps across large distances and reconstruct a large volume 3D functional map. We implemented a short acquisition protocol and on-line data analysis that offers significant experimental advantage by offering rapid feedback to the experimenter. Our rapid, large field-of-view functional mapping pipeline may become an indispensable method for understanding brain function in large-animal models.

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Poster ID:278

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 groups 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.

Poster ID:378

Day 3

Spontaneous traveling activity waves of retinal ganglion cells encode surface uniformity and object contiguity

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Frog dark detectors do not respond to changes of illumination or movement, but they are rather active when there is a lack of temporal and/or spatial contrast of the image (Maturana et al. 1960). Whether a similar image constancy encoding exists in the mammalian retina remains unclear. In this work we describe a spontaneous laterally spreading activity wave of ganglion cells in both the adult mouse retina and also in our reductionist virtual retina model. In both cases the waves sweep across a retinal surface that is exposed to extended homogeneous illumination. We also show that the generation of the traveling waves highly depends on gap junction contacts, whereas chemical signaling via GABA-, glycine or cholinergic transmission only modulates their spatial-temporal parameters. We find that gap junctional signaling between polyaxonal amacrine cells and retinal ganglion cells are key to generate traveling waves in the artificial retina suggesting that corresponding circuit elements are responsible for wave-like activity in the live mammalian retina as well. These converging data from both the mouse retina and the model strongly suggest that traveling waves encode image constancy. Finally, the virtual retina model predicts that the observed traveling waves demarcate homogeneously lit retinal areas thereby encoding object contiguity.

Poster ID:179

Multidirectional propagation of SPW-R complexes in the rat hippocampus, *in vitro*

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Substantial efforts have been made to understand memory coding and consolidation mechanisms. The hippocampus is presumed to have a crucial physiological role in the creation and short-term storage of memory traces. To this day, the unidirectional propagation model is the most widely accepted theory regarding the nature of information transfer in the hippocampus. Previous studies showed that the hippocampal connections are anatomically suitable for a reciprocal relationship between the regions. The in vitro model of the sharp wave ripple complexes (SPW-Rs) gives an excellent tool to investigate the possibility of multidirectional information flow in the hippocampus. These population events typically emerge in the CA3 and spread to other regions. There have been only a handful of studies emphasising that synchronous events might be able to propagate reciprocally in the hippocampus. However, these articles did not systematically investigate the relationship between the dentate gyrus (DG) and CA3 regions. In accordance with them, our preliminary data suggests that SPW-Rs can propagate multidirectionally between the two areas. Furthermore, the characterisation of underlying mechanisms, e.g. which cell populations are activated or independent of synchronous events, might lead to a better understanding of the SPW-R function. The oscillatory packaging of hippocampal assemblies might contribute to the alteration of synaptic circuits in the cortex and by that assists memory coding, storage and transmission. The insertion of an extra circle to the trisynaptic circuit might amplify the information packages mediated by the SPW-R complexes throughout the hippocampus. That could lead to more efficient memory consolidation. Based on this, we can state that this phenomenon is a useful model of learning, providing a possible explanation for how memory traces are transmitted from the hippocampus into the cerebral cortex and how long-term memory is formed.

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Transient galanin expression shapes peripheral-to-central connectivity in the somatosensory thalamus during whisker development

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Galanin, a 29-amino acid-long neuropeptide, increases neuronal survival during fetal development, stimulates neurite outgrowth, and acts as a directional chemotropic guidance cue, at least in vitro. Nevertheless, it is unknown if galanin affects the specification and wiring design of any neurocircuit, including those processing sensory information. This gap of knowledge is surprising given that transient sits of galanin expression exist in the neonatal mouse brain, with peak expression during postnatal days (P)6-9 coinciding with neurocircuit determination. By using intact tissue imaging (iDISCO+) in (BAC)Gal-Cre::A14 reporter mice, we place galanin expression in the thalamus as early as P1. Next, we used single molecule in situ hybridization and (BAC)Gal-Cre::A14 reporters to show that preprogalanin mRNA expression in the VB is transient: peaked during the first postnatal week and tailed off by P21. These expressional dynamics coincided with the wiring of the whisker pathway. Indeed, galanin+ neurons transduced with AAVs to express GFP became polarized by P3, and projected to the barrel cortex. A combination of subcellular fractionation, neuroanatomy and subcellular imaging revealed that galanin was enriched in both the somatodendritic compartment of VB neurons, and in a subset of glutamatergic (Vglut2+) afferents targeting the thalamus. Given that the VB is the central relay of the whisker-to-barrel cortex pathway, galanin+ VB neurons receive Vglut2+ afferentation from the principal sensory trigeminal nucleus (pr5). Paired-looped single-nucleus RNA-seq at P7 identified the expression of many chemotropic factors and galanin itself in VB neurons. This expression pattern was complemented by a repertoire of cognate receptors (including GaIR1) in pr5 neurons, identifying galanin as a molecular participant in establishing peripheral-to-central connectivity. Indeed, Vglut2+ synaptogenesis and maturation in the VB concluded by P10, was delayed in Galr1 null mice, and sensitive to siRNA-mediated galanin knock-down in situ. Taken together, we suggest that neonatal galanin expression in the somatosensory thalamus modulates axonal elongation, target recognition, and synapse selection, to scale whisker inputs.

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The question of homology – comparing the human and rat frontal cortices

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Laboratory animals are widely used models in scientific research and pharmacology. These models are based on the principle of comparative medicine that animals share physiological, pathological, behavioral, or many other characteristics with humans. Our knowledge about the structure, connection and function of the human brain is mainly based on the work with these animals. Besides their usefulness in general, these models also have their limitations, especially regarding the central nervous system. The question has emerged whether a model animal which is so different and evolutionally so far from the human species could be used for brain studies. The answer mainly depends on which part of the brain is in focus. Here we compare systematically the human and the rat frontal cortex based on up-to-date literature data, pointing out the possible homologues/analogues areas within it. We paid particular attention on nomenclature as inconsistency is frequently occurred due to several seasons (e.g., synonyms, difference between atlases). In the human frontal cortex numerous regions can be delineated: frontal pole, prefrontal, motor, and insular cortex, while in the rat's prefrontal, frontal association, insular and primary motor cortex can be distinguished. The primary motor cortex is functionally conserved across mammals so the human and rat primary motor cortices can be regarded as homologue areas of each other. The highest size difference could be found between the two species in the prefrontal cortex: more than 20% of the brain in human and less than 5% in rat. The ventral part of the human prefrontal i.e., orbitofrontal cortex can be equated partly, as its posterior, agranular cortical regions can be considered as homologue of the rat orbitofrontal areas. In spite of the huge anatomical differences, there are functional similarities in the insular cortices between the two species. Moreover, there are some brain areas which are evolutionally new and can be found exclusively in Primata, e.g., the frontopolar cortex which is also known as Brodmann area 10. The identification of homologous cortical areas in different mammalian groups, like human and rat, is an important step to establish a solid basement for comparative neuroanatomy.

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Poster ID:180

Day 1

Locomotion induced by medial septal glutamatergic neurons is linked to intrinsically generated persistent firing

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Medial septal glutamatergic neurons are active during theta oscillation and locomotor activity. Prolonged optogenetic activation of medial septal glutamatergic neurons drives theta oscillation and locomotion for extended periods of time outlasting the stimulus duration. However, the cellular and circuit mechanisms supporting the maintenance of both theta oscillation and locomotion remain elusive. Specifically, it remains unclear whether theta-modulated stimulus of glutamatergic neurons is a necessary prerequisite for locomotion, and whether neuronal activity within the medial septum underlies its persistence. In the present study, we show that persistent theta oscillation can be induced in the hippocampus by a brief transient optogenetic activation of medial septal glutamatergic neurons. By blocking synaptic transmission pharmacologically in the medial septum, we observed persistent locomotion upon photoactivation of the glutamatergic neurons while theta oscillation was abolished in the hippocampus. We discovered persistent spiking of medial septal neurons that outlasts the stimulus for several seconds and correlates with the length of the induced locomotion. We further tested the effect of the synaptic receptor antagonists and extracellular Ca2+ concentration on persistent firing in medial septal slice preparation using multi-electrode array system recordings. These results led to the conclusion that persistent activity is driven by the intrinsic excitability of medial septal glutamatergic neurons.

The role of neuromodulatory systems in implicit learning

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Neuromodulators are central to normal cognitive functions. Lesions to the cholinergic, dopaminergic and serotonergic systems all impair memory and learning processes. Additionally, disorders of the neuromodulatory systems underlie certain degenerative neurological conditions such as Alzheimer's and Parkinson's diseases; therefore, a more precise understanding of these systems might lead to significant steps towards better treatments. While the role of neuromodulators is increasingly in the focus of the research of explicit learning, their participation in implicit learning (non-conscious learning) is poorly understood. To address this issue, we have developed a mouse model of implicit learning and examined the release of neuromodulators in brain areas heavily involved learning. We trained adult, male mice (n = 9) in a custom-built automated training system on a sequential learning task. Animals were required to respond by nose pokes to light signals appearing at different locations in a defined sequence to receive water rewards. When the animals were able to follow the sequence stably, we introduced blocks of trials in which the light signals follow each other in a random order. Meanwhile, we used fiber photometry to measure acetylcholine, dopamine and serotonin release in the basolateral amygdala, the ventral striatum and the medial prefrontal cortex. Comparing the animals' behaviour between sequential and randomized blocks, we found that the reaction time was lower, and the accuracy was higher in the sequential blocks. We observed robust and strongly correlated cholinergic and dopaminergic activation during learning and the execution of the task. However, while cholinergic activation was more pronounced during task execution, the dopaminergic response had a more robust reinforcement evoked component. In contrast to the positive cholinergic-dopaminergic correlation, serotonin levels were negatively correlated with both other neuromodulators. Furthermore, we found that neuromodulatory levels precisely represent the current stage of the animal in the sequence, i.e., how many more steps are required to receive reward. Surprisingly, we found characteristic differences between cortical and subcortical neuromodulatory signals. Our results suggest that neuromodulators play a crucial role in implicit learning, but they act in a heterogeneous manner across brain areas.

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Day 3

Feedback inhibition in the entorhinal cortex mediated by the neurogliaform cells

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The role of local GABAergic inhibitory neurons in generating the entorhinal specific cell activities is still not entirely known. Several studies focused on the function of parvalbumin+ fast spiker interneurons, and only limited data has been published on the connectivity-matrix of other GABAergic cell types. Several interneurons are localized in the layer I, where apical dendrites of layer II-V pyramidal and stellate cells are located. The majority of these critically positioned interneurons are neurogliaform cells. Neurogliaform cells have been shown to elicit prolonged GABAA and GABAB receptor mediated inhibition in the neocortex and hippocampus in virtually all cell types which are located within the range of the rich axonal clouds of the neurogliaform cells. They are generally supposed to perform feed-forward inhibition: in the somatosensory cortex thalamic input; in the dentate gyrus entorhinal input; in the CA1 entorhinal and CA3 inputs give excitatory synapses on neurogliaform cells. The feedback inhibition, however, has not been linked with neurogliaform cells. In the present work, we aimed to shed light on the involvement of layer I GABAergic interneurons in the local microcircuits. We used in vitro acute brain slice electrophysiology combined with optogenetics and different specific transgenic mouse lines. Specifically, we investigated whether these neurogliaform cells receive excitatory inputs from the layer II pyramidal and stellate cells. Our results showed strong, monosynaptic excitatory connection from layer II principal cells to neurogliaform cells. Moreover, we found that the properties of the EPSPs in neurogliaform cells elicited by layer II stellate cells are different from the EPSPs generated by layer II pyramidal cells. We hypothesize that these cells are involved in effective feedback inhibition of the entorhinal cortex microcircuits. Furthermore, we found that the neurgliaform cells are evenly distributed in layer I, therefore, they can convey inhibition in all cell types sending dendrites to layer I.

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Day 1

Multisensory signal association by glutamatergic and GABAergic tectothalamic cells

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In an ever-changing multisensory environment, the brain plays an important role in recognizing and integrating the behavioural relevant 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 LAprojecting 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 somatosensorypain) and complex signals with optogenetic and electrophysiological approaches. We found that multisensory signals rather than the unimodal ones 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.

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State-specific activity of pyramidal cells and interneurons in supragranular neocortical layers during natural sleep and wakefulness

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Rhythmic population activity of neocortical neurons is linked to behavioral states. We applied a drug-free technique of juxtacellular recording/labeling to determine the contributions of neocortical pyramidal cells (PYR) regular spiking interneurons (RSIs) and fast-spiking interneurons (FSIs) in neural oscillations in freely behaving rats during natural sleep and awake states. In general, layer 2 and 3 PYRs (n=48) showed sporadic activity in non-REM sleep with moderate spindle phase coupled firing detected in layer 3 PYRs. Sporadic and phase unrelated firing was characteristic of layer 2 PYRs during theta oscillations in REM sleep with a moderate increase in firing in theta oscillations of quiet wakefulness. Layer 3 PYRs showed phase related packets of sporadic firing in REM theta with decreased activity in quiet wakefulness. The rhythmic activity was observed in all FSIs (n=32) and most RSIs (n=27 out of 34) during spindles with FSI and RSI firing locked to different phases of spindle cycles, respectively. RSIs (n=14) showed elevated firing during REM sleep theta relative to nonREM episodes, and the theta phase relatedness in REM was preserved during awake theta in n=4 cells. Most interneurons (both FSI, n=18 and RSI, n=20) showed a shift in phase preference in spindle vs theta oscillations, but a minority of individual FSIs (n=3) and RSIs (n=5) fired at the same phase of spindle and theta oscillation. In conclusion, the sporadic firing of layer 2 and 3 PYRs is accompanied by heterogeneous involvement of FSIs and RSIs during nonREM, REM sleep and revealed a prominent contribution of RSIs to theta periods relative to FSIs.

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Poster

ID:381

Silent juxtacellular field potentials correspond to neuronal cell types

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Extracellular recording techniques characterize single neurons based on firing characteristics of monitored cells in relation to field potentials generated by population activity. Thus, silent network states or subthreshold periods of individual cells make cell identification difficult if not impossible with extracellular approaches. Juxtacelluar recordings provide means to record the suprathreshold activity of individual neurons together with local field potentials while allowing anatomical labeling of the recorded cells. In freely behaving rats, we juxtacellularly recorded pyramidal cells (PYRs), fast spiking interneurons (FSIs) and regular spiking interneurons (RSIs). The three cell types were distinguished based on morphology and firing characteristics during nonREM sleep packets, sleep spindles and down to up (DU) state transitions. We observed that down states (DSs) preceding DU transitions were different in FSIs than those in RSI and PYR cells and hypothesized that silent periods of local field potentials might express complex cell type specific characteristics. Indeed, simultaneous triple juxtacellular recordings confirmed heterogeneous DSs in neighboring cells. We developed a workflow for clustering individually recorded silent DSs (n>23000) based on principal component analysis, unsupervised learning algorithms and self-organizing maps (SOMs). Cell groups of PYRs, FSIs and RSIs showed significant difference in SOM profiles constructed from silent DSs. We conclude that local field potentials recorded juxtacellular to nonspiking individual cells are cell type specific. This suggests that field potentials in the network are highly compartmentalized and retain identities of cellular units in space and time even if neuronal populations are in a silent state.

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Day 1 Systems neuroscience

Poster ID:182

Prefronto-striatal representation of perceived reward probability difference in a two alternative choice dynamic foraging paradigm

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Prefrontal cortex (PFC) and basal ganglia (BG) are both important brain systems in establishing and switching between flexible-goal-directed-strategies, and repetitive behaviours. The direct anatomical connection between PFC and striatum (STR; the input nucleus of BG) is strong and almost exclusively unidirectional, with described topology (Gabbott, Warner, et al, 2005; Mailly, Aliane, et al, 2013). But how behavioural variables are represented and transmitted along this pathway in flexible goal-directed behaviour is not known. Here we report in double silicon probe recordings, that both prefrontal and striatal units represent the perceived-reward-probabilitydifference (PRPD) between the two alternative response options, in a head-fixed mouse dynamic foraging paradigm; but only PFC represents the reward history information, measured by the overall reward proportion in previous trials. Pairwise-cross-correlation analysis suggests that on average, the activity change of PFC units in response of PRPD change precedes activity change of STR units. Correlation strength increases for many PFC-STR pairs when overall reward proportion decreases; indicating potentially stronger PFC influence on STR in time periods when there is more need for change towards optimal behaviour. Moreover we found putative monosynaptic PFC-STR pairs, in a sizable subset of which both pair members encoded the PRPD. These results are consistent with a model in which PFC tracks outcome history faster and sends this information to STR to enable faster behavioural adaptation in response of reward-probability changes, when there is enough knowledge about the environment, in a flexible-goal-directed framework. As cognitive flexibility deficit is an important symptom in many psychiatric conditions, these basic research findings in turn can provide a foundation for better understanding existing, and or developing new treatments.

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The role of mPFC spatial coding in supporting a contextual association task

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The medial prefrontal cortex (mPFC) has a broad role in decision making and executive functions, as well as consolidation of long-term memories. These distinct functions are reconciled by the mPFC's role in context-dependent decision making, which requires the evaluation and selection of representations that are relevant for a particular task or goal. Moreover, the mPFC has recently been shown to encode spatial information in well-trained animals during tasks that rely on spatial information for correct decisions. Importantly, this spatial encoding may not be present during purely exploratory behavior. Instead, it may arise as a result of coordination between the hippocampus and mPFC while animals engage in specific spatial tasks. Our work aims to identify at what point in the learning process these spatial representations appear in the mPFC. We use 32-tetrode microdrives to record from the hippocampus and mPFC while rats learn to associate a particular food cue with a specific reward location in an 8-arm maze. Two paired cue-location associations are learned in parallel. To find the reward, the rats must flexibly adapt their behavior based on which cue is presented, i.e. which "context" they find themselves in. During the acquisition of the behavioral data, we observed a sudden jump in performance after 6-7 days of training. This shift may coincide with the appearance of spatial representations in the mPFC. Determining when mPFC spatial representations first appear during contextdependent decision making will provide insight into how behavioral demands may drive the appearance of task-relevant information in the mPFC.

Poster ID:382

Day 3

Spontaneous and reversible switch of hippocampal place representations in stable environments

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The dorsal hippocampal CA1 area is involved in the spatial and contextual representation of different environments. Global remapping is a sudden change in the activity of hippocampal neurons so that the representation becomes orthogonal, which can be observed for example when the animal enters a new environment or at re-entry to the same environment. In the entorhinal cortex, which is the main input of the hippocampal formation, similar spontaneous and reversible remapping can occur without any change in the environment. Is the hippocampus capable of similar spontaneous representational switches in non-changing environments? To address this question, we used in vivo two-photon calcium imaging in transgenic animals expressing GCaMP6s in the principal cells of the dorsal hippocampal CA1 area. Head-restrained mice repeatedly ran through an 8-meter-long virtual linear track for water rewards. A stable representation of the virtual environment was observed in most of the animals, however, in some mice, multiple orthogonal representations of the same environment coexisted for multiple days. In a minority of the mice, spontaneous and reversible switches between representations occurred during single sessions without any observable change in the animal's behavior. Uncovering the mechanism of these switches needs further experiments.
Day 1 Systems neuroscience

Poster ID:183

An alternative cortico-subcortical loop for motor coordination via the thalamus

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The cortico-basal ganglia-thalamocortical loop has been known to be involved in movement control. Disturbance of the basal ganglia activity results in characteristic, unilateral rotation. Similar to basal ganglia the pontine reticular formation (PRF) also sends inhibitory terminals to the intralaminar thalamic nuclei (IL) and parafascicular nucleus (Pf). The photoactivation of PRF inhibitory fibers in IL/Pf induced a strong motor-related phenotype, a complete behavioral arrest. Here we asked whether similar to basal ganglia PRF may also participate in a motor-related cortico-subcortico-thalamocortical loop by examining the effect of unilateral optogenetic activation of PRF inhibitory cells (PRF/GlyT2+) on locomotor behavior and investigating the impact of cortical inputs on the PRF/GlyT2+ neuronal activity. Using anterograde viral tracing, AAV-ChR2 injections into the frontal cortex (M2 and Cingulate) of RBP4-Cre/Glyt2-eGFP transgenic mice revealed that mid-caliber dendrites and spines of the PRF/GlyT2+ cells receive L5 inputs. In vivo juxtacellular recording showed that photoactivation of the cortical L5 cells evoked short-latency APs with high probability in the PRF/GlyT2+ cells. Spontaneous rhythmic activity of PRF/Glyt2+ neurons was strongly linked to slow cortical oscillation. Photoactivation of PRF/Glyt2+ neurons leads to a significantly decreased firing rate of the IL/Pf cells. Furthermore, the PRF/Glyt2+ cell activation promoted the movement, resulting in unilateral rotation and movement initiation. We assume that synchronous frontal cortical activity conveys behavioral signals to PRF. PRF/GlyT2+ cells transfer cortical input as inhibitory signals to the IL/Pf before they return to the cortex via the thalamocortical pathway. Both the concept of network organization and the evoked behavioral response are reminiscent of the cortico-basal ganglia loop.

Day 2

Complexity-based causal discovery in epileptic EEG recordings

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Non-interventional causal discovery is a challenging task. This is particularly true for causal relations of dynamic systems with chaotic attractors. The known solutions are data-intensive and cannot detect a hidden common driver (common cause or confounder). We propose a new method which eliminates both deficiencies. The method is based on Takens' embedding theorem and complexity of the rank order patterns of the embedded series measured by the compressibility using non-sequential recursive pair substitution. The method works on short samples and is capable of detecting all kinds of causal connection (including hidden common cause). The new method is validated on synthetic data sets and applied to two types of human electrophysiological data from epileptic patients. First, we analyzed electrophysiological data recorded from semi-invasive foramen ovale electrodes. To estimate the more independent sources of the measured potentials, the Current Source Density has been calculated as the discrete second spatial derivative of the signals. There are some time points where a circular connection can be observed, and the role of driver and driven changes. Those points may indicate the change of the system status. In the intermediate periods, typically a hidden common driver is indicated. Second, another patient was implanted with a subdural grid and two strip electrodes. We analyzed the phases of a seizure and found that the causal structure between the areas changes. The causal relations inferred by our method and the observation of medical experts meet at several points. In both cases, the method revealed self-consistent, contradictionfree and biologically relevant causal connections between the investigated areas. Thus the method may provide additional indication for the location of intervention for the decision making medical panel. Given the method advantages and simplicity it might be applied in many other scientific and practical areas with success.

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Poster

ID:383

Septal-preoptic connectivity involved in maternal adaptation

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The lateral septum (LS) is a forebrain area involved in the regulation of social behaviors including maternal care. However, the mechanisms how LS neurons control maternal behaviors are not well understood. Therefore, we addressed to characterize maternally activated LS neurons neurochemically and map their distribution pattern in mice. We established that LS neurons activated after pup exposure are GABAergic suggesting the importance of limbic inhibitory system in maternal care. As GABAergic calbindin (Cb) and calretinin cell groups localize in the LS, we determined their relation to pup induction. We showed that many c-Fos-activated neurons are positive for the marker Cb in the ventral part of LS (LSv). The ratio of Cb neurons in c-Fos activated neuron population was significantly higher in the presence of the pups compared with control mothers. We previously showed that LS contains a maternally induced neuropeptide, parathyroid hormone 2 (PTH2) positive fibers in high density. PTH2+ fibers closely apposed activated neurons suggesting synapses that was confirmed by electron microscopy in GABAergic neurons. Moreover, Cb neurons in the LS are also closely surrounded by PTH2+ terminals. As PTH2+ fibers arise from the posterior intralaminar nucleus of the thalamus (PIL), we examined the activation level of this region in the presence and absence of pups. We found that c-Fos expression was induced exclusively in PTH2+ neurons and all these PTH2+ cells were activated in response to pup exposure. PIL neurons are known to send PTH2+ projection to the medial preoptic area (MPOA), too. This phenomenon might be important in the aspect of maternal behavior as MPOA is the central regulatory area of parenting. We showed that the same neurons of PIL project to both LS and MPOA neurons which raises the possibility of simultaneous regulation of neurons in these 2 brain regions by PTH2+ PIL neurons. Based on our results of retrogradely transported tracer technique, we showed that a high number of MPOA-projecting LS neurons are Cb+ suggesting that these neurons may have an impact on maternal adaptation. We confirmed Cb+ projection by performing anterograde tract tracing in Cb-Cre mice too. Moreover, some LS-projecting neurons in the MPOA show synaptic-like vicinity to PTH2 terminals on dendritic process. In conclusion, the data suggest that PIL neurons convey stimulatory signal of pups to both LS and MPOA and the neurons of these areas may interact with each other.

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Day 1

Unique organization of layer 5 projections from the frontal cortex to the thalamus

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Recent data indicate that communication between cortex and thalamus is far more complex than it was thought before. Research in the last 20 years highlighted the importance of fine wiring in the corticothalamic pathways and the central role the thalamus plays in cognitive processes and sensory-motor functions. Giant corticothalamic terminals arising from the collaterals of layer 5 pyramidal cells are critical components of the corticothalamic pathways. These afferents allow faithful top-down control of selected thalamic nuclei. In this project we asked whether cortical L5 terminals in the thalamus display any region specific heterogeneity. We found that giant L5 terminals were completely absent in the fronto-thalamic L5 pathway innervating the ventromedial (VM), intralaminar, parafascicular, reuninens and parts of the mediodorsal nuclei. Instead, L5 terminals, investigated in detail in VM, were small but still could reliably activate VM neurons. They also differed in size, targets and ultrastructure from the L6 corticothalamic terminals and. At a single cell level, the small boutons of fronto-thalamic L5 pathway displayed less short-term depression in VM than the large boutons of S1/L5 pathway to nucleus posterior, both in in vitro preparations and in anesthetized animals. Surprisingly, the main targets of small frontal L5 to VM axons were dendritic spines of various size and form. Two-photon glutamate uncaging revealed that large thalamic spines in VM could function as calcium compartments similarly to cortical spines. We conclude that the presence of functional spines on thalamic dendrites with a specialized cortical input can potentially endow thalamocortical cells with the ability of scaling and plastic regulation of incoming cortical inputs.

Day 2 Systems neuroscience

Poster ID:284

Ultrastructural characteristics of dendrites and local axon collaterals of spinal lamina I projection neurons

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Morphological studies confirmed the presence of local ipsilateral axon collaterals of lamina I projection neurons (PNs) in the spinal dorsal horn. These PN collaterals segregate into different classes based on their distribution in grey matter laminae and in the white matter and these differences suggest their distinct roles in sensory information processing. Nevertheless, their exact targets and function are still not known. It is also well established that lamina I PNs are integrating local, descending and primary afferent axon terminals. Serial block face scanning electron microscopy (SBF-SEM) technology allows previously unprecedented quantitative ultrastructural analyses of the dendrites and axons of PNs. To target lamina I PNs, we injected AAV vectors into the lateral parabrachial complex of mice, to retrogradely transfect lamina I PNs and induce TdTomato expression in them. TdTomato was transformed into a visible diaminobenzidine precipitate by an immunocytochemical reaction against the red fluorescent protein (anti-RFP). 25 dendritic and 15 axonal pieces were serially scanned and reconstructed using the AMIRA 3D (2021.2) software package. Approximately 500 micrometers of neuronal processes have been analyzed and the number of synaptic contacts (established or received) counted. Our preliminary results suggest that dendrites in the dorsolateral funniculus integrate more synaptic inputs than their counterparts in the grey matter. Axon varicosities that belonged to local collaterals rarely formed classical synaptic contacts on dendritic spines, shafts or neuronal somata. Another important conclusion is that, besides its advantages, the identification of synapses formed by HRP-DAB revealed axons with the SBF-SEM technology is more challenging than with conventional transmission EM.

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Poster ID:384

Day 3

Hierarchical generative model of natural images reproduces key features of the early visual cortex

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Phrasing visual perception as unconscious inference in a generative model of former visual experience is an appealing theoretical concept and has yielded deep insights into the principles underlying vision in mammals. Progress along this avenue has been hampered by a lack of understanding how computations in a non-linear hierarchical generative model can be performed. Despite the introduction of the Variational Autoencoder (VAE) modeling framework, learning such a model is still challenging. We explored hierarchical Variational Autoencoders (hVAEs) to understand the contribution of constraints on computational complexity, priors, and other inductive biases to learning hierarchical representations. We use both natural images and natural textures to show that hVAEs are capable of reproducing key features of the representation found in the ventral stream of mammals. Using a linear generative model at lowlevel processing and a highly nonlinear generative model for high-level computations, we found Gabor-like representations at low level vision (corresponding to V1) and texture-like representations at high-level vision when learning natural image statistics. Further, we reproduce classical electrophysiological findings on higher selectivity for stimulus identity at the level of V1, while high-level selectivity for texture-like statistics at the level of V2, along with reduced selectivity for stimulus identity, a hallmark of progressive compression of data. A key feature of our hVAE architecture is that it introduces top-down connections in a manner that is well motivated by the principles of probability theory. We show that such top-down connections affect how high-level features can be decoded from low-level cortices: statistics that cannot be represented in a non-hierarchical generative model will become linearly decodable when topdown influences are present. We show that top-down influences introduce noise correlations, whose structure is specific to the high-level structure of stimuli. Finally, we demonstrate that top-down computations help reproduce experimental findings on illusory contour perception in V1. Taken together, our work provides critical insight into the way hierarchical representations can be learned in an unsupervised manner and provides an alternative to deep discriminative and predictive coding models to study the computations taking place in the ventral stream.

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Detecting causality with Cross-Mapping Coherence

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We present Cross-Mapping Coherence (CMC), a novel method for detecting causality in the frequency domain. Our approach extends Convergent Cross-Mapping by incorporating Coherence, enabling us to identify nonlinear, frequency-dependent causal relationships in a model-free manner. We tested CMC on various systems, including coupled logistic maps, Lorenz systems, and Kuramoto oscillators, and found that it can accurately identify the direction of links in coupled logistic and Lorenz systems, as well as frequency-specific couplings in a network of Kuramoto oscillators. We also applied CMC to a Wilson-Cowan population model of the cerebral cortex, revealing frequency-specific causal coupling between V1 and V4 as bottom-up and top-down information flows in the gamma and alpha bands, respectively. In neuroscience, CMC can be used in combination with other frequency-domain methods, such as Granger causality, phase-amplitude coupling, and wavelet coherence, to provide a more comprehensive view of the mechanisms underlying brain activity. Overall, our results demonstrate the effectiveness of CMC for analyzing complex systems.

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Day 2 Systems neuroscience

Poster ID:285

Cortex-wide mechanism of reinforcement signaling via a cholinergic pathway

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Reward and punishment powerfully inform ongoing behaviors and drive learning throughout the brain, including the neocortex. Yet it remains elusive how these global signals reach the cortex, how are they represented there and how they impact local cortical computations. To address these questions, we used 3D random-access two-photon microscopy to monitor neural activity in dozens of cortical areas while mice performed simple auditory decision tasks. We found that VIP and SOM interneurons were recruited differently by reinforcers during the initial learning procedure. The amplitude of the reward response and the responses to predictive cues were modulated by reward expectation. The rapid, cortex-wide activation of most VIP interneurons upon reinforcement decreased when mice learned the task. This change was mirrored in the acetylcholine release recorded at the vicinity of the VIP cells, implying that this neuromodulator may be responsible for the transmission of reinforcement signals. We suggest that this acetylcholine-dependent global response mode of VIP cortical inhibitory neurons provides a cell-type-specific circuit mechanism by which organism-level information about reinforcers regulates local circuit processing and plasticity.

Poster ID:385

Day 3

Optical brain computer interface for measuring circuit plasticity during learning

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Learning a new task or skill is thought to depend in part on synaptic plasticity in cortex. Previous work has revealed that the responses of cortical neurons change during learning of novel tasks and it is thought that these changes in neuronal firing arise due to synaptic plasticity. However, establishing a causal link between changes in connectivity and neural activity has been challenging largely due to the complexity of neural circuitry, and difficulties measuring synaptic connections. To overcome these challenges, we have developed an optical brain computer interface (BCI) task and combined it with all-optical circuit mapping. In the BCI a mouse controls the position of a motorized lickport using the activity of a single conditioned neuron (CN) in layer 2/3 of primary motor cortex, recorded using two-photon imaging. We chose CNs that did not show task-locked activity before learning. At the start of a trial, the lickport is positioned out-ofreach of the mouse's tongue, each time the CN is activated, the lickport moves closer to the mouse. Rewards are received if the mouse can reach the lickport before the end of the 10 s trial. On average mice improve the rate of rewarded trials from 50% to 75% within 25 trials (5 minutes), caused by an increase in task-locked activity of the CN. The learning is also sparse: on average 3% of the imaged neurons increase their activity as much as the CN. Since the responses of the surrounding population were stable across days, with 10-20% of neurons showing triallocked activity, learning-related changes in activity of the CN is orthogonal to this stable behavioral manifold. These results demonstrate the ability of a neural circuit to rapidly learn offmanifold patterns of activity. To probe network connectivity, we use holographic photostimulation to activate ensembles of neurons and observe their effective connections onto the surrounding network. We found that activation of groups of 10 neurons caused significant changes in the activity of 25 non-stimulated neurons on average. Most of these connections were inhibitory (66%) and were strongest between nearby neurons with similar task-related activity. Furthermore, photostimulation based circuit mapping revealed the preferential strengthening of connections between neurons whose task-modulated activity is enhanced during learning. These results suggest that local circuit plasticity contributes to the learningrelated reshaping of cortical dynamics.

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Novel techniques

Poster ID 186

Cytoarchitectonic and excitatory afferent based mapping of the anterior part of the human thalamus

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The connectivity between the anterior part of the human thalamus (ATh) and the frontal cortex is crucial for complex cognitive processes. The ATh is also a major target for deep brain neurosurgery in various neurological disorders such as epilepsy, Parkinson's disease, or essential tremor. Functionally relevant nuclear segmentation is essential for understanding both healthy and pathological processes of the brain, however, a comprehensive division of the human ATh, based on morphological and biological properties, is still lacking. We aimed to create a reliable nuclear segmentation of the ATh based on thalamic cell types and afferentation. In this project, we performed a quantitative analysis of vesicular glutamate transporter type 1 and 2 (vGluT1, vGluT2) afferents as well as calbindin, calretinin, and parvalbumin immunostainings in consecutive sections of post-mortem human thalami to label cortical and subcortical excitatory inputs and compare their localization to well-established cellular markers. Our high throughput automated data collection method enabled reliable and large-scale quantification and morphological analysis of the afferent boutons. We used this information for the parcellation of thalamic nuclei and to compare this functional information with the previously existing thalamic maps.

Although we found important inter-individual differences regarding the size and proportions of thalamic nuclei, the bouton distribution and density of corresponding nuclei were remarkably similar among different patients. The highest vGluT2 bouton density was observed in midline nuclei (5.5*104 1/mm2) followed by intralaminar (3.8*104 1/mm2), anteroventral (2.7*104 1/mm2) nuclei. The bouton density of other nuclei in the anterior thalamus, e.g. ventrolateral, reticular, mediodorsal, or reuniens was below 1*104 1/mm2. We found a notable discrepancy in spatial orientation and size relative to traditional atlases (PVT, MD, VA-VL). Furthermore, analyses of excitatory inputs allowed us to draw functional predictions to the human thalamus. Our data form the basis of a rational segmentation of the human thalamus, which is necessary for invasive brain surgeries. Furthermore, it allows quantitative characterization of excitatory afferents and their alteration in pathological cases.

Day 1

Day 2 Neuroendocrinology

Poster ID:286

Vgf-derived neuropeptide TLQP-21 acting on arcuate and RP3V kisspeptin neurons is a critical regulator of mouse fertility both in males and females

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Vgf is a neurotrophin-inducible neuropeptide gene highly expressed in endocrine organs and in the brain, including the hypothalamus. Genetic ablation of the Vgf gene causes infertility in mice. Males show delayed puberty and exhibit lower testicular weight and motile sperm number than those of wild-type littermates. Although Vgf is synthesized in the gonads, the ovaries of Vgf-KO mice become fully functional when transplanted into wild-type recipients indicating that infertility of the Vgf-KO mice is caused by hypothalamic/hypophysial dysfunctions. Vgf-derived fragment peptides, such as TLQP-21, are also critical regulators of puberty and reproduction. When administered to adults, Vgf-derived peptides either stimulate or inhibit gonadotropin secretion, depending on estrous cycle stage. In the present work, whole-cell patch-clamp slice electrophysiology was carried out in ZsGreen-tagged kisspeptin (KP) neurons to investigate effect of TLQP-21. We show that TLQP-21 modulates firing of KP neurons mediating negative estrogen feedback from the arcuate nucleus (ARC) and positive estrogen feedback from the rostral periventricular area (RP3V) to gonadotropin-releasing hormone (GnRH) neurons in an 17β estradiol(E2)-, sex- and location-dependent manner. TLQP-21 robustly activates ARC KP neuron population in orchidectomized/ovariectomized (OChX)/OVX) male/female mice. Weaker action is observed in testosterone- or E2-treated male mice, whereas no significant change is revealed in E2-treated female mice. In contrast to the ARC KP neurons, TLQP-21 administration to RP3V KP neurons of OVX female mice resulted in a significantly reduced firing rate, which effect was even more robust in E2-treated female mice. Furthermore, our measurements reveal that effect of this peptide is independent of G-protein-coupled receptors expressed in the measured KP neuron. Collectively, these data suggest that Vgf-derived TLQP-21 neuropeptide acts in negative and positive sex steroid feedback via currently unknown receptors in KP cells.

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Elucidating the role of $\alpha 2\delta$ proteins in synapse organization

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Neurons communicate via synapses to allow normal brain functions such as cognition, memory formation, and learning. In these processes, synapses show plasticity and can be remodeled. Synapse formation is driven by synapse-organizing proteins that span across the synaptic cleft to orchestrate the alignment of pre-and postsynaptic molecules. Recently, presynaptic $\alpha 2\delta$ proteins have been identified as crucial organizers of synapses by regulating axonal wiring, presynaptic differentiation, and postsynaptic receptor clustering. So far, $\alpha 2\delta$ proteins have been extensively studied as subunits of the voltage-gated calcium channels (CaV) complex, where they regulate channel trafficking and current kinetics. As presynaptic calcium influx is the critical trigger of neurotransmitter release, it is not surprising that mutations in $\alpha 2\delta$ proteins are found in patients with epilepsy, autism spectrum disorder, and schizophrenia. Considering its role as a synaptic organizer and based on previous experiments, we hypothesize that mutations in $\alpha 2\delta$ proteins may also mediate pathophysiological mechanisms independent of the channel complex. To test this, we performed immunocytochemistry experiments in neurons expressing a mutated $\alpha 2\delta$ -2 incapable of binding CaV and analyzed its ability to recruit postsynaptic GABAA-receptors. Strikingly, channel-independent $\alpha 2\delta$ -2 recruits more postsynaptic GABAA-receptors than the CaV associated forms, revealing the synaptic organizing function of $\alpha 2\delta$ being independent of the channel. This leads us to hypothesize that interfering with the trans-synaptic function of $\alpha 2\delta$ proteins will allow us to modulate trans-synaptic signaling and synapse formation while leaving the presynaptic CaV signaling unaltered. Results from this ongoing project could open a new path toward novel treatment options for neurological and neuropsychiatric disorders.

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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 towards 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.

Neuroendocrinology

Poster ID:287

17β-estradiol does not have a direct effect on the function of striatal cholinergic interneurons in adult mice *in vitro*

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The striatum is an essential component of the basal ganglia that is involved in motor control, action selection and motor learning. The pathophysiological changes of the striatum are present in several neurological and psychiatric disorder including Parkinson's and Huntington's diseases. The striatal cholinergic neurons are the main regulators of striatal microcircuitry. It has been demonstrated that estrogen exerts various effects on neuronal functions in dopaminergic and medium spiny neurons (MSN), however little is known about how the activity of cholinergic interneurons are influenced by estrogens. In this study we examined the acute effect of 17β -estradiol on the function of striatal cholinergic neurons in adult mice in vitro. We also tested the effect of estrus cycle and sex on the spontaneous activity of cholinergic interneurons in the striatum.

Our RNAscope experiments showed that ER α , ER β , and GPER1 receptor mRNAs are expressed in some striatal cholinergic neurons at a very low level. In cell-attached patch clamp experiments, we found that a high dose of 17 β -estradiol (100 nM) affected the spontaneous firing rate of these neurons only in old males.

Our findings did not demonstrate any acute effect of a low concentration of 17β -estradiol (100 pM) or show any association of estrus cycle or sex with the activity of striatal cholinergic neurons.

Although estrogen did not induce changes in the intrinsic properties of neurons, indirect effects via modulation of the synaptic inputs of striatal cholinergic interneurons cannot be excluded.

Day 2

A septal-VTA circuit drives exploratory behavior

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To survive, animals need to balance their exploratory drive with their need for safety. Subcortical circuits play an important role in initiating and modulating movement based on external demands and the internal state of the animal; but how motivation and onset of locomotion are regulated remains largely unresolved. Here, we show that a glutamatergic pathway from the medial septum and diagonal band of Broca (MSDB) to the ventral tegmental area (VTA) controls exploratory locomotor behavior in mice. Using a self-supervised machine learning approach, we found an overrepresentation of exploratory actions, such as sniffing, whisking, and rearing when this projection is optogenetically activated. Mechanistically, this role relies on glutamatergic MSDB projections that monosynaptically target a subset of both glutamatergic and dopaminergic VTA neurons. Taken together, we identified a novel glutamatergic basal forebrain to midbrain circuit that initiates locomotor activity and contributes to the expression of exploration-associated behavior.

Day 1

Poster ID:188

Behavioral effect of GABA release from forebrain cholinergic neurons

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The basal forebrain cholinergic system comprises several nuclei that provide innervation to cortical areas. It contributes to arousal, attention and memory, including fear and extinction learning, and it is implicated in anxiety and post-traumatic stress disorder. We have recently shown that cholinergic terminals synaptically release not only acetylcholine, but GABA as well, the release of which can be modulated independently. Although previous studies demonstrated that the alteration of GABAergic cotransmission is possible and has functional consequences in other non-cholinergic brain regions, the role of GABA release from forebrain cholinergic cells is unknow. We created a conditional knockout mouse strain (ChAT-vGAT-cKO) to decrease GABA release from cholinergic neurons. Our preliminary behavioral tests showed that these mice had increased hippocampal theta activity during sleep and performed significantly better in a cognitive task, likely due to a relatively more efficient cholinergic effect. However, ChAT-vGAT-cKO mice showed significant deficits in fear extinction learning after cued fear conditioning. These results may provide a formerly unrecognized mechanism for certain pathological conditions.