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(alphabetically)

GLS Campus

October 10/11, 2024

BNM 2024
BERLIN NEUROSCIENCE MEETING

no. 4 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Basal forebrain cholinergic innervation of the visual cortex during postnatal development in ChAT-cre transgenic mice

Jude Abeje

Charité – Universitätsmedizin Berlin

Cortical development and formation of synaptic connections occur within a critical developmental window. Both activity-dependent synapse development and cortical organization are subject to modulation by neuromodulators such as acetylcholine synthesized in the basal forebrain. Although basal forebrain cholinergic neurons are present at birth, the development of cholinergic projections to the visual cortex before the first visual stimuli (eye-opening) has not been well-characterized. This study investigated the distribution and density of cholinergic axons originating from the basal forebrain to the visual cortex (specifically layers 1 and 2/3) in transgenic (choline acetyltransferase) ChAT-Cre mice before eye-opening. Our results showed a dense population of ChAT+ cholinergic neurons in the basal forebrain, consistent throughout the second postnatal week. We found that axons projecting from the basal forebrain cholinergic neurons arrived in the visual cortex at the beginning of the 2nd postnatal week. Although cholinergic innervation continues throughout the second postnatal week in L1 and L2/3 of the visual cortex, we did not observe clear differences in the density of cholinergic axons between age groups or layers. Our results reveal that basal forebrain cholinergic axons are already present in the developing visual cortex before eye-opening. This outcome is particularly important for investigating how basal forebrain cholinergic neurons modulate spontaneous network activity in the visual cortex within this critical developmental window.

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Functional characterization of the disease-associated scaffold protein CNKSR2

Poornima Anantha Subramanian

Charité – Universitätsmedizin Berlin

Connector Enhancer of Kinase Suppressor of Ras-2 (CNKSR2), also known as CNK2 or membrane-associated guanylate kinase-interacting protein-1 (MAGUIN), is a multidomain scaffold protein that is predominantly expressed in the brain, specifically localized at the postsynaptic density (PSD) of excitatory synapses. Our overarching aim is to understand the functional role of the CNK2 scaffold molecule at the synapses. We validated novel interaction partners of CNK2 through co-immunoprecipitation and discovered an interaction between CNK2 and other synaptic scaffold molecules localized at the postsynaptic density.

Further, based on our preliminary unpublished data, we know that the disease-associated truncation mutation, CNKR712*, which is truncated at the C-terminal region, is associated with altered spine morphology. We utilized this mutant in a comparative mass spectrometry (MS)-based approach to map disease-mediated changes in protein-protein interactions to study the potential of the C-terminal region to regulate the scaffolding function of the protein, possibly through the modulation of specific interactions with other proteins. We identified a differential interaction between six different isoforms of the 14-3-3 family with the disease-associated mutant. In the future, we will explore this differential interaction in depth to contribute to the understanding of how the alterations in CNK2 might cause developmental defects.

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session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Integrating FAIR Principles into RDM and Bioimage Analysis at AMBIO

Niclas Gimber André Lampe

Charité – Universitätsmedizin Berlin

The Advanced Medical BIOimaging Core Facility of the Charité-Universitätsmedizin (AMBIO) annually enables over 200 research projects that require advanced fluorescence-based imaging modalities, including high-resolution, 3-dimensional, live-cell and super-resolution modes. One major challenge is the management and analysis of the growing amount of multi-modal imaging data. Within the INF project of CRC-TRR384 (IN-CODE) AMBIO is building a state-of-the-art research data management (RDM) infrastructure to enable collaborative data processing according to the FAIR principles.

Here, we describe the data-workflow currently used in AMBIO to store, transfer and analyze large, complex data sets, using examples from 3D, live-cell, time-lapse imaging (lattice light sheet) and super-resolution single molecule (DNA-PAINT) imaging projects. We show examples of custom-written data analysis pipelines to investigate nanoscale structures, dynamics and protein distributions in neuronal samples. Future work will focus on a framework of tools and services that ensures the FAIR RDM of the imaging data throughout its life cycle. This will facilitate collaborative and comparative data analysis and modeling.

no. 19 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

The Word and the Brain: Premodern Neuroscience of Speech

Maria Avxentevskaya

Max Planck Institute for the History of Science

The production of speech in the human body and the brain has long been the focus of religious, philosophical, and scientific disputes as part of the questions about the mind-body relationship. Modern-day neuropsychology continues to explore these issues through a different set of methods. My poster will present an overview of premodern anatomical representations of how the human nervous system and the brain were supposed to work in producing speech. I will display preliminary findings of my current research in the early history of science and medicine, supported, among others, by the Max Planck Institute for the History of Science (Berlin) and the Warburg Institute (London), including the interpretation of imagery from the earliest printed anatomies (Peyligk 1499, Hundt 1501, Dryander 1537, Vesalius 1543, Willis 1681). My work examines a broad spectrum of premodern views on the psychophysiology of speech as part of the soul-and-body interrelation, which seeks to contribute a historical perspective on the modern-day issues of conceptualizing the mind-and-body relationship. Participation in the Berlin Neuroscience Conference will allow me to deepen my understanding of the cutting-edge issues in the neuroscience of speech, affective, and cognitive neuroscience; my contribution will offer a longue durée historical perspective on these issues.

no. 46 session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

PLPPR3 facilitates cytoskeleton-membrane interactions by condensate formation in vitro and in vivo

Shannon Bareesel

Charité – Universitätsmedizin Berlin

Neuronal branching is a developmental program, by which neurons acquire their complex morphologies. This highly dynamic process relies on various signaling molecules, cues and proteins such as the phospholipid-phosphatase related protein (PLPPR) family. PLPPR3, a family member of PLPPRs, is a transmembrane protein with a long intracellular domain (ICD) that primarily localizes to the axonal plasma membrane. Previous work demonstrated that PLPPR3 is highly expressed during neuronal development and can induce axonal filopodia. Here, we describe a conclusive model of PLPPR3 ICD-facilitated filopodia formation by the process of liquid-liquid-phase separation (LLPS). LLPS is an interaction-driven process that orchestrates intrinsically disordered regions to form condensates, which serve as membrane less reaction compartments. PLPPR3 ICD condensates, follow liquid-like properties of phase separating proteins such as coalescence, fusion and circularity. With help of a blue-light inducible optogenetic PLPPR3 ICD CRY2 fusion construct, we were able to validate these properties in cells. In vitro work demonstrates that PLPPR3 ICD condensates can deform giant unilamellar vesicles (GUVs), co-partion actin monomers and serve as actin nucleating compartments. Hence, we exhibit ring-shaped F-actin structures that polymerize out of PLPPR3 ICD condensates. We propose that PLPPR3 ICD condensates serve as actin nucleating compartments that facilitate filopodia formation at the axonal membrane.

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Establishing Sustainable and Functional Research Data Management (RDM) in Neuroscience: The RETAIN Fellowship Program

René Bernard

Charité – Universitätsmedizin Berlin

Establishing effective research data management (RDM) in diverse, collaborative research environments is challenging, especially in neuroscience. Despite initiatives like the creation of German nation consortia to enhance discipline-specific RDM, creating reusable, well-annotated, FAIR-compliant data remains difficult due to complex research methodologies and incompatible datasets often arising from the same research environment. Researchers often lack the resources and time to address these obstacles. While external expertise can help, it may lead to unsustainable dependencies.

The best solutions for overcoming RDM challenges come from within research teams. Recognizing this, the NeuroCure Cluster of Excellence launched the Research Data Management Implementation in the Neurosciences (RETAIN) Fellowships, offering 24-month, 50% FTE positions to PhD-level Neuroscience researchers interested in RDM. Fellows develop personalized RDM strategies by assessing current practices, identifying obstacles, and setting goals. They receive guidance from NeuroCure's Coordinator for Value and Open Science and report progress regularly. Training on RDM fundamentals is also provided.

A crucial aspect of RETAIN is the integration of RDM solutions into the research environment. Fellows create workflows, educational materials, onboarding processes, and templates tailored to their team's needs, ensuring a sustainable RDM system. The program aims to produce model laboratories that can serve as RDM model environments for others, both within and outside the NeuroCure cluster.

Successful completion of the RETAIN fellowship equips researchers with practical RDM skills, making them competitive for data stewardship roles. All tools, code, and materials developed produced from the fellowship are published openly, contributing to broader RDM efforts. Ultimately, programs like RETAIN are vital for building a FAIR data landscape in the neuroscience and beyond, by developing both the infrastructure and expertise needed for discipline-specific, sustainable RDM.

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Molecular Mechanisms Underlying UNC13A Loss

Moritz Boll

Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP)

Munc13-1 is a highly conserved and essential protein for synaptic transmission, acting as a regulator of synaptic strength and plasticity. A pivotal role for Munc13-1 in human neurological disorders is emerging. Patients carrying variants in the protein-coding sequence of the UNC13A gene show a neurodevelopmental disorder characterized by profound developmental delay, intellectual disability, and dyskinesia/intention tremor. In addition, deep intronic single nucleotide polymorphisms in non-coding regions of the UNC13A gene have been repeatedly identified as strong risk factors for amyotrophic lateral sclerosis and frontotemporal dementia (ALS and FTD). Recent findings highlight a mechanism whereby, in neurons with ALS/FTD pathology, Munc13-1 levels are gradually reduced due to mis-splicing events. Here we study the consequences of gradual Munc13-1 removal from hippocampal mouse neurons for neurotransmission after and before the formation of synapses using a novel conditional knockout mouse line, in combination with whole-cell electrophysiological recordings. We show that as UNC13A levels decline, augmentation after a 40 Hz action potential train is increased in magnitude and is the earliest-detected event. Other electrophysiological parameters are affected at a much later time point which exceeds the expected lifetime of Munc13-1 protein in culture. This raises the possibility of upregulation of Munc13 isoforms that compensate for the loss of Munc13-1 or changes in proteomic composition of the active zone optimizing synaptic transmission. Identifying these mechanisms will aid in determining how Munc13-1 levels control different properties of synaptic transmission, and, importantly, the minimal levels of Munc13-1 that are necessary for proper synaptic transmission. Together, this essential information is needed for the development of approaches to stabilize UNC13A mRNA expression levels, which are currently sought for as a therapeutic approach for ALS/FTD.

no. 15 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Exploring Amyloid-β propagation and related metabolic alterations in early-stages of Alzheimer's disease

Maria Calvo Noriega

Berlin Institute for Medical Systems Biology (BIMSB)

Alzheimer's disease (AD) is the most common neurodegenerative disorder and represents the major cause of dementia, contributing up to 70% of the 55 million cases worldwide. Toxic amyloid plaques, formed by aggregated amyloid β (Aβ) peptides, constitute a major AD hallmark and are present in all AD brains. Aβ originates from the processing of Amyloid Precursor Protein (APP), highly expressed in neurons and glial cells, and propagates throughout the cortex as AD progresses.

However, what exactly defines the vulnerability to the spread of toxic Aβ peptides across different brain cell types and how neuron-astrocyte communication influences Aβ production and spreading dynamics remains unknown. Currently, the earliest biomarkers used for diagnosis include elevated levels of Aβ in the cerebral spinal fluid (CSF) and PET scans, together with Aβ-related cerebral glucose hypometabolism. Altogether, these emphasizes the importance of understanding Aβ dynamics as well as its impact on metabolism in early stages of disease.

To address these questions, we have developed a powerful system in human induced pluripotent stem cells (hiPSC) that allows us to control and monitor APP expression, cleavage, secretion and propagation with high spatiotemporal resolution. This is accomplished by a light-inducible dual-tagged APP system containing a C-terminal HaloTag and an ALFA-tag that allows the detection of Aβ using anti-ALFA nanobodies. Using this tool, we trace Aβ propagation trajectories in hiPSC-derived neurons and organoids. By harnessing advanced imaging techniques, we identify changes in neuronal and astrocytic metabolic cell-states upon propagation and investigate how these metabolic alterations reflect changes at the transcriptome and proteome levels. These insights will improve our understanding of neuronal and glial metabolic rewiring upon Aβ spreading, paving the way for the discovery of early-stage biomarkers and new approaches to halt disease progression.

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Non cell-autonomous regulation of synaptic upscaling by neuronal autophagy in mice

Giovanna Cazzolla

Charité – Universitätsmedizin Berlin, Freie Universität Berlin

Autophagy is a major degradation system that delivers cytoplasmic constituents to the lysosome, known to be a critical and conserved intracellular quality control pathway essential to maintain proper neuronal proteostasis. Neuronal autophagy has been described to decline with aging. Additionally, accumulating evidence suggests a role for Neuropeptide Y (NPY), the most widely expressed neuropeptide in the brain, in autophagy induction, as well as aging and lifespan determination. Studies in Drosophila demonstrated a causal connection between neuronal autophagy and the NPY-family member sNPF in presynaptic upscaling (“Prescale”), e.g. structural and functional modifications at the presynaptic active zone (AZ) associated with age-dependent cognitive decline, in a non-cell autonomous manner.

In mice, NPY was found to mediate beneficial effects exerted by caloric restriction and nutrient-sensing pathways via autophagy induction in hypothalamic neurons. Understanding the mechanisms underlying this bidirectional cross talk could be an attractive strategy to develop therapies maintaining health span and cognition in aged individuals.

Combining proteomic screenings, immunohistochemistry and super-resolution light microscopy with genetics, we here test the hypothesis that NPY and autophagic signaling might interact in a bidirectional manner within NPY secreting neurons of mice.

In global NPY KO mice, we find that loss of NPY regulates RIM-BP2 cluster density at hippocampal synapses, suggesting NPY as negative regulator of RIM-BP2 recruitment or stabilization at these synapses. Knocking out autophagy regulator ATG5 under the hypothalamic AgRP-Cre driver control (ATG5 cKO) we investigate the interplay between autophagy and NPY on Prescale via non-cell autonomous mechanisms. Our first proteomic data suggest a down-regulation of the mitochondrial electron transfer chain (ETC) complex I proteins in the hypothalamus as well as a non-cell autonomous up-regulation of hippocampal synaptic signaling upon ATG5 cKO.

Our results suggest that hypothalamic NPY neurons might send signals such as NPY and potentially others to age-protect aspects of metabolic state and synaptic function in the remainder of the brain.

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session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Fasting changes the circadian activity of melanocortin-3 receptor (MC3R) neurons in the paraventricular thalamus (PVT)

Robert Chesters

Charité – Universitätsmedizin Berlin, Deutsches Institut für Ernährungsforschung

The brain exerts control over energy homeostasis by regulating signaling within the melanocortin system. Whilst we understand the role of the hypothalamus within this system, how extra-hypothalamic brain regions are involved in the control of energy balance is still under investigation. The melanocortin-3 receptor (MC3R) is implicated in modulating feeding behavior and body weight changes under different nutritional challenges, and MC3R deficient animals show a defective fasting response, highlighted by decreased refeeding upon food presentation. MC3R is highly expressed in the paraventricular nucleus of the thalamus (PVT): a brain region that integrates information about internal energy state with environmental stimuli to determine feeding and reward behaviors. This region also receives innervation from the hypothalamic POMC and AgRP neurons, and stimulation of AgRP neurons to this region can drive food intake. Thus, the presence of MC3R in this region suggests a role for the melanocortin system in modulating the complex behavioral networks orchestrated by the PVT. In this study we show that, in ad-libitum fed mice, MC3R-PVT neuronal activity follows a circadian pattern of activity. Moreover, this fluctuation of activity is dependent on food availability, as during a 16-hour overnight fast, this pattern of neuronal activity changes and MC3R neurons maintain a reduced level of activity in to the light period. Upon refeeding, however, this activity significantly increases to that seen under fed conditions.

In conclusion, we have identified circadian fluctuations in PVT-MC3R neuronal activity. These fluctuations are significantly impacted by energy state, as fasting results in changes to the activity pattern. Furthermore, we show feeding related changes to GCaMP signals that are time-locked to interactions with food. Thus, the PVT MC3R neurons are modulated by feeding and energy state and further in-depth analysis of this neuronal population may yield advanced understanding of feeding-related behaviors.

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session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Investigating the effects of theta-burst magnetic stimulation on cellular mechanisms of memory in ex vivo and in vitro mouse and human models

Maria Economou

Charité – Universitätsmedizin Berlin, Berlin Institute of Health (BIH)

Attrition bias, resulting from systematic differences in the number and way animals are lost from an experiment, is a well-recognized issue in preclinical research. Despite existing research suggesting that even small numbers of missing animals could lead to large effects, reporting standards for missing data remain poor and imputation methods to account for lost animals are seldom used. Hence, the extent and impact of attrition often remains unclear in preclinical systematic reviews.

The current project aims to assess attrition reporting in systematic reviews of preclinical stroke studies, and investigate the impact of attrition, including methods to account for it, on effect estimates. Here, we present a comprehensive characterization of attrition in a large dataset from the Stroke Preclinical Assessment Network (SPAN), a large-scale multi-lab preclinical study in stroke, by calculating attrition rates per group (treatment vs control), type (procedural or technical) and reason of exclusion. We achieve this by using revised definitions for data missingness in preclinical research.

Second, our plans to conduct systematic literature reviews and meta-analysis on the six interventions tested in SPAN will be presented. These will be further used to simulate the effect of the attrition rates seen in SPAN on the meta-analysis effect estimates and to evaluate how different imputation methods used in preclinical research impact the effect estimates.

Results from this analysis will provide novel insights on the impact of attrition on the results of preclinical meta-research. The findings will be essential in providing guidance on appropriate statistical methods to overcome potentially biased estimations in systematic reviews and deal with missingness in single laboratory studies in stroke and other research areas.

no. 31 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Mapping the functional diversity of Cerebrospinal fluid-contacting neurons

Nadezhda Evtushenko

Max Delbrück Center for Molecular Medicine

Cerebrospinal fluid-contacting neurons (CSF-cNs) are inhibitory sensory neurons nestled along the central canal of the spinal cord. Identification of Pkd2l1 as a selective CSF-cNs marker prompted studies of their chemo- and mechanosensory functions and helped revealing an important role in motor control. Differential expression of neurotransmitters and neuromodulators has been described in lamprey and zebrafish CSF-cNs, however molecularly distinct subtypes of CSF-cNs in mammals have not been identified yet. Thus, we started a systematic anatomical and molecular study of mouse CSF-cNs. We first analyzed a scRNA-seq dataset from mouse embryonic spinal neurons and found expression of several neuromodulators and their receptors in Pkd2l1+ neurons. In particular, we observed differential expression of Sst, Sstr2 and Ddc, an enzyme involved in the synthesis of serotonin and dopamine. To validate these data in vivo we performed immunostaining for TH and TPH2, but did not detect their presence in CSF-cNs. In addition, analysis of a mouse line expressing YFP under the control of the TPH2 promoter did not reveal reporter expression in CSF-cNs, but we found YFP-positive puncta juxtaposed to CSF-cNs cell bodies. Finally, we used an intersectional strategy to target neurons expressing both Pkd2l1 and Sst and found labeling in a subset of CSF-cNs. Overall, these data suggest the existence of distinct CSF-cNs subtypes in the mouse spinal cord and points to the importance of neuromodulatory signaling for their function.

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

SHEDDING LIGHT ON PRESYNAPTIC PLASTICITY: SYNAPTIC PLASTICITY AT COMMISSURAL PROJECTION SYNAPSES IN HIPPOCAMPUS CA1

Lukas Faiss

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Hippocampal CA1 pyramidal neurons receive excitatory inputs from both ipsi- and contralateral CA3 and CA2 regions. While synaptic plasticity at the intrahippocampal Schaffer collateral synapses has been extensively described, synaptic plasticity mechanisms at interhippocampal commissural fiber synapses are less well understood. In this project, we investigate cyclic adenosine monophosphate (cAMP)-dependent plasticity at commissural synapses in the CA1 region. We achieve selective stimulation of transmitter release at these synapses by unilateral stereotactic injections of AAVs in vivo to express ChrimsonR in CA3/CA2 glutamatergic neurons of one hippocampus. ChrimsonR, a red-light sensitive Channelrhodopsin, allows us to trigger transmitter release with short orange light flashes both at ipsi- and contralateral synapses in acute slices. We then induce presynaptic cAMP production either pharmacologically with forskolin, or optically by blue light-stimulation of coexpressed bPAC, a light-activated adenylyl cyclase. Both the pharmacological stimulation of endogenous adenylyl cyclases with Forskolin and the activation of bPAC enhanced synaptic transmission. Therefore, we propose that commissural synapses in CA1 express a presynaptic, cyclic adenosine monophosphate (cAMP)-dependent form of plasticity. It remains to be investigated from which specific cell population or network these cAMP-sensitive synapses originate, and further research is needed to uncover the intricate mechanisms and functions underlying this phenomenon.

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Subpopulations of hippocampal inhibitory interneurons contribute differently to engram formation in APP/PS1 mice

William Fernandes Paes de Barros

Charité – Universitätsmedizin Berlin

Understanding the neural mechanisms underlying memory formation and retrieval is fundamental to unraveling the pathophysiology of Alzheimer's disease (AD). Inhibitory interneurons have fundamental roles in shaping neural circuits and synaptic plasticity within the hippocampus, a brain region critical for memory encoding and consolidation. However, the specific contribution of inhibitory interneurons to the formation and maintenance of engrams, the neural representations of memories, remains poorly understood, particularly in the context of AD. To determine neurons participating in the engram formation in regions CA1, CA3, and DG of the hippocampus, we targeted the immediate early gene FOS as a marker following exposure to environmental enrichment in comparison to standard housing conditions. This was done in combination with markers targeting specific interneuron subpopulations (SOM, PV, VIP, CCK) to assess their participation in engram formation both in the APP/PS1 mouse model of Alzheimer's disease and matched controls.

Our preliminary results obtained from immunohistochemistry stainings imaged through high-resolution confocal microscopy indicate that the number and ratio of each inhibitory interneuron subpopulation analyzed here vary according to the housing conditions and genotypes. These findings have significant implications for understanding the pathophysiology of memory impairments in AD and may provide insights into novel therapeutic strategies for alleviating cognitive decline in affected individuals. Furthermore, by elucidating the role of inhibitory interneurons in engram formation and function, this research contributes to advancing our understanding of memory processes and may ultimately lead to the development of targeted treatments for memory-related disorders.

no. 22

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Human stem cell-derived neurospheres to explore the consequences of Listeria infection on brain development

Annika Fischer

Freie Universität Berlin, Tierärztliche Hochschule Hannover

Zoonotic infections during pregnancy can lead to central nervous system (CNS) infections in surviving offspring, often resulting in neurodevelopmental disorders as long-term consequences of pre- and perinatal CNS infections. Despite these known associations, the underlying mechanisms remain poorly understood.

To investigate these mechanisms we employ human induced pluripotent stem cell (iPSC)-derived neurospheres as a model to mimic the developing human brain. The neurospheres contain neural stem cells (NSCs) that differentiate into various neural and glial subtypes, including mature neuronal cell populations. Our objective is to assess the suitability of these neurospheres for studying the consequences of fetal CNS infections.

Our initial studies focus on infection with Listeria monocytogenes, a bacterial pathogen known to cause enduring neurological impairments in affected offspring. Pregnant women typically transmit the bacteria to the fetus via bloodstream following the ingestion of contaminated food. We hypothesize that infection induces primary NSC depletion and accelerates the maturation of surviving NSCs, which in turn impairs differentiation, alters migratory behavior, and disrupts network activity.

In the initial phase of the project, we successfully generated NSCs from a human iPSC line (IMR90, WiCell®) that can be stably cryopreserved to produce neurospheres from the same batch for reproducible follow-up infection experiments. Neurosphere differentiation protocols were established and the resulting spheres are currently being characterized via RT-qPCR and immunocytochemistry. Furthermore, we implemented cryopreservation protocols using two distinct media enabling the direct transfer of neurospheres to biosafety level facilities for subsequent infection experiments. The two media differ from one another in their use of either fetal calf serum (FCS) or Knockout Serum Replacement (KSR) in order to achieve greater standardization of the freezing medium. Preliminary results show no significant difference in recovery post-cryopreservation between the two media; however, long-term cell survival rates did not meet our requirements for further experiments, necessitating optimization of the cryopreservation protocol. Our next steps include conducting initial infection experiments to establish an appropriate infection dose. The results from previously conducted growth curve

analyses suggest that the optimal time for infection is 9 hours after the initiation of Listeria cultivation. Additionally, based on the results of performed dilution series, an optical density (OD) measurement of 0.5 corresponds to a bacterial concentration of 108 colony-forming units (CFU).

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session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

MAM-localised alpha-Synuclein alters transmitophagy by regulating mitochondrial dynamics

Elisabeth Fritsch

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The misfolding, aggregation, and sequestration of alpha-Synuclein (αS) in intracellular inclusion bodies called Lewy Bodies (LBs), have long been considered pivotal in Parkinson's Disease (PD) pathology. Recent findings reveal that membranous structures and fragmented intracellular organelles, particularly distorted mitochondria, also make up a large portion of LBs. Further, increasing evidence shows that αS is linked to abnormalities in mitochondrial function and membrane dynamics that are regulated at the contact sites between ER and mitochondria, known as mitochondria-associated membranes (MAMs).

Although αS-dependent mitochondrial dysfunction has been shown to alter intracellular homeostasis, it remains unclear whether mitochondrial defects also disturb intercellular homeostasis and communication, which underly the progressive nature of PD pathology. Moreover, the use of pre-formed αS aggregates or fibrils in many PD studies has often overlooked the potential importance of monomeric αS species in the emergence of pathological and propagating αS populations.

In this study, we model the propagation of monomeric αS species and demonstrate that propagating monomeric αS impairs intercellular mitochondrial redistribution by localising to MAMs and disrupting mitochondrial dynamics. Using confocal and single-molecule microscopy techniques, we show that propagating αS affects mitochondrial morphology and network connectivity at tri-organelle contact sites between MAMs and endosomes. These effects are specific to propagating αS and are exacerbated by αS disease variants. We find that αS-induced impairments in mitochondrial dynamics affect the ability of dopaminergic neurons to transfer mitochondria to neighbouring astrocytes in response to cellular stress, a process known as transmitophagy.

Overall, we reveal a regulatory role for propagating αS species in mitochondrial dynamics and redistribution, emphasising the relevance of monomeric αS propagation in the early stages of PD pathology.

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Molecular mechanisms of membrane remodeling by BAR-domain proteins

Clara Grosse

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The Bin/Amphiphysin/Rvs (BAR) superfamily proteins are crucial in regulating membrane shape by integrating signals from the membrane, cytoskeleton, and local interactors. Despite nearly 40 of these proteins are found in synapses, few are well-studied, and none are fully understood at the molecular level. Moreover, mutations in BAR proteins are linked to neurological diseases.

FBP17, known for roles in neurite outgrowth and dendritic spine density, was recently found enriched at synaptic vesicle endocytosis sites. Its homolog, TOCA1, involved in membrane remodeling and cytoskeletal signaling, is also present in synapses and identified as an Alzheimer's disease risk factor, though its synapse maintenance role is unexplored.

Oligophrenin-1 and GRAF1, with additional lipid-binding PH domains, are involved in cytoskeletal signaling and linked to intellectual disability and mental retardation, but their synaptic functions remain unclear.

Our preliminary data show these BAR proteins localize to presynapses. Knockdown of TOCA1 impairs synaptic vesicle endocytosis in mouse hippocampal neurons, suggesting redundancy with other BAR proteins like FBP17 and GRAF1.

My goal is to study the localization, interactomes, and functions of these four proteins in structural plasticity and membrane remodeling.

no. 11

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Electrical signaling at the endothelial cell pericyte syncytium during recurrent seizures

Mirja Grote Lambers

Charité – Universitätsmedizin Berlin, Humboldt-Universität zu Berlin

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

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

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

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

no. 7 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Causal inference in postdictive multisensory illusions

Gökberk Günaydın

Charité – Universitätsmedizin Berlin

Information from different sensory modalities is integrated in a temporal window of multisensory processing that can last several hundred milliseconds. Within this window, the processing of a stimulus is influenced not only by preceding and concurrent input, but also by input following a stimulus. A previous study using audiovisual (AV) beep-flash pairs showed that auditory or visual stimuli presented shortly after a stimulus can retrospectively influence perception of this first stimulus, resulting in an illusory flash or an invisible flash, respectively. In this behavioral study (N = 32), we applied a Bayesian causal inference (BCI) framework to investigate the mechanisms underlying the audiovisual illusory and invisible rabbit illusions. We replicated both illusions and found that causal inference framework can largely account for crossmodal postdiction and is superior compared to other models (forced segregation and forced integration).

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

SHANK3 as an Organizer of the Microtubule Cytoskeleton in Parvalbumin Neurons?

Daniela Hacker

Humboldt-Universität zu Berlin

The microtubule cytoskeleton mediates the stability of neurons as well as their ability to adapt to changes. Microtubules are polarised structures with a dynamic plus end and a more stable minus end. This polarity controls intracellular trafficking and plays a fundamental role in establishing and maintaining the compartmental integrity of neurites. In developing neurons, microtubules are generated at the centrosome localised within the soma. In mature neurons, this complex is lost and exclusively non-centrosomal microtubules are found throughout dendrites. This raises the question how constantly growing and shrinking microtubules can be maintained in mature neurons while maintaining their cellular compartmentalisation. Non-centrosomal microtubules are stabilised by the microtubule minus end-binding protein CAMSAP2 that we show can be anchored at the postsynaptic density while bound to microtubules. This process might enable CAMSAP2-mediated stabilisation of synapse-bound microtubules at shaft synapses of Parvalbumin neurons that display the vast majority of their excitatory postsynapses on the dendritic shaft in direct contact with the microtubule network. This association is increased to 5-fold in synapses carrying the SHANK3 L68P mutation relevant in Autism Spectrum Disorder. This point mutation causes an increase in CAMSAP2 levels at the synapse level and intramolecularly alters the folding of the domains responsible for SHANK3 binding to CAMSAP2. Consistently, we show that CAMSAP2-SHANK3 L68P protein interaction is increased 4 to 5-fold.

Here, we propose a mechanism by which synaptic microtubules and dendritic polarity are maintained through association with the postsynaptic density of shaft synapses in Parvalbumin neurons. The increase in synapse-microtubule association in the context of the disorder-associated SHANK3 L68P mutation might alter stability of non-centrosomal, synapse-associated microtubules.

no. 38

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Myosin VI controls localization of Golgi satellites at active presynaptic boutons

Nathalie Hertrich

Humboldt-Universität zu Berlin

Local protein biosynthesis and the removal of aged proteins are critical for synaptic plasticity. Besides in the soma, secretory organelles are found in dendrites and axons, where they serve as supply stations for local proteins and lipids as well as mediate recycling and degradation of membrane components. The somatic trans-Golgi network modifies and sorts many plasma membrane proteins. Previously, we have shown that Golgi-satellites (GS), are present in primary hippocampal dendrites, and several synaptic proteins can locally pass through them on the way to the synapse. However, the roles of GS in dendrites and axons remain mostly uncharacterized. Here, we describe axonal GS and how GS transport and localization is regulated in axon and dendrites, focusing on neuronal activity and the actin cytoskeleton. Further, we show that myosin VI is involved in the active stalling of GS in the Axon. This investigation will further our understanding of GS transport and recruitment to synapses, and what role they play in synaptic plasticity.

no. 9

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Characterization of mGluR1 function and dysfunction using human organotypic brain slice cultures

Johanna Hintze

Charité – Universitätsmedizin BerlinHumboldt-Universität zu Berlin

In neuroscience, animal models are widely used for understanding brain physiology and pathophysiology, but are limited when translating experimental findings to humans. To address these limitations and to study human brain physiology in a species-specific approach, we established ex vivo human brain slice cultures, which enable the functional investigation of neuronal activity within a 3D structure with preserved local connectivity.

Beyond physiological assessment, our approach allows to investigate pathological conditions such as the autoimmune encephalitis spectrum caused by autoantibodies against cerebral antigens. To this end, we aim to perform a functional, electrophysiological investigation of metabotropic Glutamate Receptor 1 autoantibody (α-mGluR1) effects in acute slices and brain slice cultures. mGluR1 belongs to G-protein-coupled receptors and is involved in synaptic signaling and plasticity. Upon binding of α-mGluR1, mGluR1 is likely internalized, leading to loss of function and motor impairments in patients.

Exposing living human brain tissue to mGluR1 agonist and antagonists as well as mGluR1 autoantibodies, we aim to understand the role of human mGluR1 in signaling and plasticity and to identify targets for treatment of α-mGluR1-autoimmune encephalitis.

no. 39

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Neural traces of working memory representations in patients with schizophrenia

Wiebke Hofmann

Charité – Universitätsmedizin Berlin

Patients with schizophrenia (PSZ) show alterations in working memory (WM) that are already present at early stages of the illness. To date, it is not well understood how these alterations manifest at the neural level. The hyperfocusing hypothesis (Luck et al., 2019) suggests that patients have an abnormally narrow focusing of processing resources, which reduces the number of items that they can hold in WM. Accordingly, alterations of WM processing in patients should primarily occur under high memory load. In this electroencephalography (EEG) study, we will investigate the neural signatures of WM representations in different memory load conditions in PSZ and healthy control participants. Participants will be instructed to remember one (load 1) or two (load 2) images of either faces or houses. After a delay, participants will be presented with a probe, which matches the remembered image(s) or not. We will perform multivariate pattern analysis to distinguish between load conditions as well as between faces and houses in both study groups. We expect an overall lower decoding accuracy of category (faces vs. houses) in PSZ. Furthermore, we anticipate a bigger difference in category decoding accuracy for PSZ between the two load conditions, as it is assumed that WM deficits in PSZ are mainly present in high load conditions. Pilot data of this project will be presented and discussed.

no. 40

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Neurogenesis in action: probed with multiphoton microscopy

Yusaku Hontani

University of Zurich

Neural stem cells generate new neurons throughout life in the mammalian dentate gyrus, a part of the hippocampus, which is critically involved in certain forms of learning and memory. For a deeper understanding of neurogenesis in the hippocampus, direct observation of cellular dynamics is essential. To capture the cellular process of generating neurons in real time in the living mouse brain, we employ two-photon and three-photon excitation microscopy using femtosecond lasers. In the presentation, I will demonstrate the strengths and current limitations of two-photon and three-photon excitation imaging, together with “cellular movies” of neural stem cells in the living mouse hippocampus.

no. 59

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

The Role Of Drebrin In Blood Brain Barrier Functioning

Robert Hülse

Charité – Universitätsmedizin Berlin

Brain functionality relies substantially on extensive communication between the neuronal cells and the vascular system. The blood-brain barrier (BBB) is a remarkable example of the closely regulated interaction between cells of the central nervous system (CNS) and endothelial cells (ECs). It represents a selective physiological barrier between circulating blood and the brain parenchyma. While many BBB components have already been extensively studied, the role of the BBB cytoskeleton and its association with the extracellular environment remains rather unexplored. For this study, we aim to investigate the role of the actin cytoskeleton in BBB integrity and functioning. The actin- binding protein Drebrin (DBN) is highly abundant in neurons. Previous research by our group demonstrates that DBN is not only expressed in neurons but also in astrocytes after brain injury, whereas deletion of DBN in astrocytes leads to defective scar formation and escalating neurodegeneration (Kreis et al., 2019; Schiweck et al., 2021). Mechanistically, we show that DBN loss affects the trafficking of adhesion molecules that are involved in astrogliosis, such as the surface receptor β1-Integrin. Moreover, excessive amounts of membrane material accumulate as multilamellar bodies and whorls in the processes and endfeet of DBN-deficient astrocytes. Based on these findings, we hypothesized that deletion of DBN in astrocytes might also affect BBB integrity since β1-integrin is reported to link the astrocytic endfeet to the extracellular matrix (ECM) in mouse brains. Indeed, permeability assays demonstrate BBB leakage in non-injured DBN-deficient animals, accompanied by altered inflammatory responses and increased GFAP- and Iba1 reactivity in the mouse cortex. Surprisingly, immunohistochemical staining revealed DBN expression in the brain vasculature for the first time. We now aim to understand if the observed defects are age-dependent and to what extent DBN deletion in the brain vasculature is responsible for malfunctional BBB properties by inducing cell type specific DBN deletion in mice. Finally, we address the question of how cytoskeletal defects at the BBB contribute to its malfunction mechanistically.

no. 33

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Model of spiral ganglion neurons as a module for sound-to-neuron information transmission framework

Lukasz Jablonski

University Medical Center Göttingen

Spiral ganglion neurons (SGNs) are primary afferent neurons of the auditory pathway. They are ordered according to their characteristic frequency along the tonotopic axis of the cochlea and project auditory action potential from hair cells directly to the auditory brainstem. In deafness, when functional sensory hair cells are lost, SGNs became a target for direct electrical stimulation with cochlear implants providing a sense of hearing to around 1 million of patients worldwide. Although this makes cochlear implants the most successful neuroprostheses, reported experience is far from natural hearing. This is due to the wide spread of the electrical current within cochlea leading to activation of vast number of SGNs. Alternative approach using optogenetic cochlear implants in animals showed already promising results offering increased spectral selectivity of optical stimulation of SGNs together with significantly higher number of cochlear implant channels (even hundred in optogenetic CI vs maximum 24 in state-of-the-art electrical CI). Nevertheless, before the medical device would reach the marked, number of tests and optimisations has to be performed. Also, sound coding strategy, an algorithms to convert sound into optical stimulation, has to be developed. Here, modular computational framework that takes sound as an input, perform coding strategy, simulate cochlear spread of light, perform SGN stimulation responding with spikes that can be further analysed to compare the performance against input is an essential tool. This includes a module consisting of an SGN synaptic transmission model with voltage-gated sodium (Na), low-voltage activated potassium (LVAK), high-voltage activated potassium (HVAK), and hyperpolarization-activated cyclic nucleotide–gated (HCN) channels as well as light-sensitive chanelrhodopsins.

no. 24

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Investigating the 3D genome structure of pyramidal glutamatergic neurons in neurodevelopmental disorders

Berta Jiménez-Alfaro Hacha

Max Delbrück Center for Molecular Medicine

Chromatin regulators have broad functions in most cell types, but are often mutated in association with complex developmental disorders that are accompanied by a spectrum of neurological impairments. Loss of ATRX (Alpha thalassemia/mental retardation syndrome X-linked) in post-mitotic glutamatergic neurons, using conditional knockout (cKO) mouse models, results in strongly impaired hippocampal-related learning and long-term memory in fear-based experiments. To examine the genomic targets and mechanisms of altered gene expression upon conditional ATRX knockout in adult pyramidal neurons of the hippocampal CA1, we currently apply Genome Architecture Mapping (GAM) and single-cell analysis of gene expression and chromatin accessibility, using 10x Genomics Multiome snRNA/snATAC-seq. By integrating these datasets, we seek to delineate the molecular mechanisms underlying ATRX-mediated genomic regulation and its implications for learning processes

no. 32 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Mechanical stress exposure controls phase separation of

Enrico Klotzsch

Humboldt-Universität zu Berlin

Protein aggregates are crucial in neurodegenerative diseases like amyotrophic lateral sclerosis (ALS). This study investigates how mechanical stress affects Fused in Sarcoma (FUS) protein aggregation, using oxidative stress from sodium arsenite (SA) as a reference. Wild type (WT) FUS and mutant FUS (R514S, R521C) cells were exposed to mechanical and oxidative stress, with aggregation studied via spinning disc confocal microscopy (SDC). Results showed SA as a strong aggregate inducer. Mechanical stress had a biphasic response: low doses reduced FUS aggregate area and compaction, while high doses increased both, triggering a cell stress response. Mechanical stress effects on pre-existing SA-induced aggregates were mutant-dependent. Additionally, peptides were identified as potential inhibitors of FUS aggregation, with showing significant promise for therapeutic application.

no. 35

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Molecular Determinants and Functional Consequences of UFMylation in the Developing Neocortex

Janina Koch

Charité – Universitätsmedizin Berlin

The cerebral cortex harbours a vast diversity of heavily interconnected cells, forming elaborate circuits, setting the biological substrate for our higher cognitive abilities. In recent years, major advances to the mechanisms orchestrating the development of the cerebral cortex have been made, majorly relying on transcriptomic analyses. We foster the notion that the ultimate gene expression products, the proteins, are the key players in the developing brain. A complex crosstalk of post-translational modifications regulates protein function, among them protein UFMylation. Genetic defects in UFMylation lead to severe intellectual disability and microcephaly in human patients, signifying its indispensability for brain function and development. While the biochemical mechanisms of the UFMylation cascade are relatively well characterized, its molecular targets and functional consequences, particularly in the brain, remain underwhelming.

We propose that UFMylation plays a role in progression of progenitor-to-neuron lineage in the developing cortex, via modulation of specific protein targets in cortical progenitors. Our objective is to thoroughly delineate the underlying causes of the patient phenotype using Ufm1-deficient murine brains, and induced knock-out by in utero electroporation. We employ cell sorting approaches to idenitfy progenitor-specific targets of UFMylation in the developing murine brain. Further, we have developed workflows to detect changes in protein translation upon Ufm1 knock-down. Our results reveal translational regulation of gene expression downstream of Ufm1, with Ufm1 deficiency leading to decreased global translation.

no. 63

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Using an endogenous Snap-Tag to monitor UNC13A (Munc13-1) expression levels and synapse nanoarchitectures

Maria Kowald

Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP)

The mammalian UNC13A gene encodes a large presynaptic multidomain protein called Munc13-1 which is essential for synaptic transmission. To monitor its protein expression and synapse nanoarchitecture, an Unc13A-Snap Knock-in mouse line was generated. Hippocampal neuronal cultures, derived from littermate wild-type and Unc13a-Snap mouse brains, were studied using immunocytochemical analysis. The cultures were labeled with antibodies against Munc13-1, the active zone marker Bassoon and neurofilament marker Map2. Different Snap-tag dyes were applied to label the Munc13-1 protein via the Snap-tag in the knock-in mouse line. Our analysis showed no significant differences in the expression levels of Munc13-1 between WT and Unc13a-Snap synapses, as measured by Munc13-1 antibody signal intensity. Similarly, Bassoons signal intensity remained unchanged, indicating that the Munc13-1-Snap fusion protein does not affect the expression of this active zone marker. Colocalization analysis between Bassoon and Munc13-1 signals revealed a high degree of overlap, with only a minor but statistically significant reduction in colocalization in Unc13a-Snap samples. Overall, these findings demonstrate that Munc13-1-Snap is well-expressed and correctly localized within the active zone, validating the use of the Unc13A-Snap knock-in mouse line as a reliable tool for investigating synaptic nanoarchitecture.

no. 10 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

DEVELOPING A HUMANIZED ASTROCYTIC CALCIUM IMAGING PIPELINE FOR COMPOUND SCREENING

Jeremy Krohn

Charité – Universitätsmedizin Berlin, German Center for Neurodegenerative Diseases Berlin

Astrocytes are crucial mediators of diverse aspects of brain function such as energy metabolism and synapse formation and maturation. They form a vast network in the brain and signal both with each other and with neurons. Calcium is the primary information carrier in astrocytes and can be measured using fluorescent indicators.

Therapeutic approaches for cognitive diseases are commonly designed to influence neurons, but neglect astrocytes, despite them accounting for half the mass of the brain. Furthermore, screenings in murine cells result in low confidence of potential drugs that translate to humans. Here we use astrocytic calcium signals and recent advances in analysis to develop an astrocytic compound screening pipeline in a humanized model.

Astrocytic calcium signals were measured using virally expressed calcium sensors based on GCaMP. Benchmarking was performed with a set of compounds of known effect in mouse hippocampal neuron-glia cultures.

We then established an induced pluripotent stem cell-derived human astrocyte culture system and again measured calcium signals. Human induced astrocytes showed wave-like events similar to those seen in mouse cells, and stimulation with ATP caused an increase of calcium events as expected. These preliminary data demonstrate that our humanized astrocyte cultures could replace murine cells in screens of compounds that affect astrocytic function.

In the future, we will validate the pipeline with compounds of unknown effect. Calcium imaging data from this humanized model can be used to investigate potential drug effects on neuronal and astrocytic function and predict efficacy in treating cognitive diseases with greater confidence.

no. 16

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Exploring parallels in Humans and AI prospective memory task performance embedded in a virtual week game

Sushma Kumari

Berlin School of Business and Innovation

This study aimed to explore the execution of prospective memory tasks within the context of a virtual week game. The task was carried out by both human participants and artificial intelligence. Prospective remembering or prospective memory (PM) is a relatively newer area of research in cognitive psychology, that takes on added significance when considering its implications on artificial intelligence.

This research paper presents an investigation into the recreation of the game "Virtual Week" within the Unity3D game engine, along with an analysis of the performance disparity between human players and AI agents. "Virtual Week" serves as a platform for evaluating player performance by presenting tasks that players must remember to execute in the future, thereby testing prospective memory. The recreation of "Virtual Week" in Unity3D facilitated the replication of its mechanics and provided a controlled environment for conducting comparative studies between human and AI players. The primary focus of this research lies in comparing the cognitive abilities of human players against those of AI agents when faced with tasks embedded within the game's narrative.

A total of 26 volunteers were recruited from the general student population of Berlin School of Business and Innovation to participate in this experiment. The game used in this experiment is in the form of a board game like LUDO converted to a program that runs on a computer. The participant interacts with the game through a monitor and a mouse. This study was conducted to simulate three virtual days. The participants had to roll die, take a move, and make decisions on certain activities on a Virtual Week board game. Upon the occurrence of a certain event, or at a certain point of time, an associated prospective memory task was required to be performed, among other distracter tasks. Each round of the game simulates one virtual day in the life of the participant. Each day starts at 7 am and ends at 10 pm. Every 2 box represents 15 minutes of the day. The game begins at the START box. Based on the number rolled through the dice by clicking it, which is at the center of the board, the blue coin, representing the participant, moves. There are certain tasks in the game which has emotional valence. The prospective memory tasks are performed by identifying the time or event when they are to be performed and then clicking the ‘Perform Task’ button on the event card or ‘Perform Task’ card. This results in the appearance of

a list of tasks and the participant is supposed to click on the right task that is supposed to be performed.

Findings indicate that human players exhibit a nuanced approach towards task prioritization, often influenced by emotional cues present within the game environment. Conversely, AI agents demonstrated a uniform treatment of tasks, irrespective of their affective valence, resulting in a performance gap between human and AI players.

Through this study, we aim to shed light on the complexities of human cognition in virtual environments and the challenges associated with replicating human-like decision-making processes in AI agents. By understanding the differences in how humans and AI approach tasks within "Virtual Week," this research contributes to the ongoing discourse surrounding human-AI interaction and the development of more human-like AI systems.

no. 48

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

RIM-Binding Protein regulates Ca2+-channel function at central synapses.

Malgorzata Lubas

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In synaptic transmission, the fast, precise, and synchronous release of neurotransmitters relies on a tight coupling between the synaptic release machinery, the synaptic vesicles, and the voltage-gated calcium channels (P/Q-type). Scaffolding molecules, including Rab-Interacting molecules (RIM), RIM-Binding Protein (RBP), ELKS, Munc13, Bassoon/Piccolo and Liprin-α are the main known regulators of this coupling. Specifically, RIM and RBP have been shown to uniquely regulate synaptic vesicle docking and fusion, since no synaptic activity remains in RIM/RBP-deficient neurons (Acuna et al, 2016). The purpose of our study is to investigate the involvement of the scaffold protein RBP in voltage-gated Ca2+-channel function using an autaptic model of mouse hippocampal glutamatergic neurons with conditional genetic deletions of RIM1α, RIM1β, RBP1 and RBP2. Synaptic vesicles can be artificially brought in the vicinity of Ca2+-channels by expressing the fusion protein Zn-β4 composed of the RIM1α Zinc-finger domain and the β4 subunit of Ca2+-channels (Tan et al, 2020). When expressed in RIM/RBP-deficient neurons, Zn-β4 is not sufficient to restore Ca2+-dependent neurotransmitter release, as measured electrophysiologically. Using calcium imaging of GCAMP6f signal, we show that the influx of Ca2+ occurring during cell depolarisation is also significantly impaired. Immunocytochemistry reveals that both Munc13 and P/Q-Ca2+-channel expression is reduced in RIM/RBP-deficient neurons, whereas the levels are restored upon the Zn-β4 expression. Most recently, we found that co-expressing the Zn-β4 fusion protein with RBP in RIM/RBP-deficient neurons rescues Ca2+-evoked response to wild-type levels, strongly suggesting a critical function of RBP in presynaptic Ca2+-channel gating.

no. 8

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

CHARACTERISATION OF MURINE LAYER-6B AND ITS ROLE IN MODULATION OF PERINATAL CORTICAL DEVELOPMENT.

Aasha Meenakshisundaram

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Layer 6b (L6b) is the deepest layer of cortex, which arises during development from the cortical subplate. The subplate consists of specific subpopulations of neurons, which contribute to the establishment of thalamocortical and corticocortical networks early in neocortical development. A large portion of neurons in the embryonic subplate undergo programmed cell death during perinatal cortical development. Aberrant development of L6b may alter the cortical circuitry and activity, resulting in manifestation of Autism Spectrum Disorder (ASD) associated behavioural phenotypes. Autistic individuals have been observed to possess a higher number of persistent L6b neurons. These neurons also show increased dendritic arborization and spine density, a morphological feature observed on the modulation of PTEN. PTEN is a tumor suppressor gene, which regulates neuronal survival and morphology by modulation of growth factor/ PI3K signalling. Here, we studied a mouse line carrying the conditional deletion of PTEN in L6b specific Drd1 neurons. Immunohistochemical analysis of early postnatal brains is used to analyse the pattern of apoptotic Drd1-cre neurons in L6b. Further, confocal microscopy of coronal sections of these mouse brains indicate a distinct increase in the number of Drd1 neurons persisting into adulthood in the PTEN deficient condition. There is also a PTEN dependent variation in the cell size and dendritic arborisation of pyramidal Drd1 neurons. Whole-cell patch clamp recording shows a dose-dependent difference in the excitability of these neurons. The behavioural characterisation of the adult mice with conditional PTEN deficiency in L6b further indicate modulation of ASD associated behavioural phenotypes. This includes an enhanced retention of spatial memory and variation in sociability associated behaviour. We speculate that the PTEN deficient Drd1 neurons may play a role in an untested behavioural phenotype such as attention.

no. 53

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Stability of synaptic connections and intrinsic cellular properties of cortical human L2/3 neurons

Verjinia Metodieva

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The brain undergoes constant activity fluctuations related to processes like learning, development, and sleep. Neuronal plasticity enables information storage relevant to those changes but also serves to regulate stable neuronal firing. Homeostatic plasticity mechanisms protect neurons from activity extremes that are associated with pathological conditions such as mood disorders, epilepsy, and dementia. Our aim is to assess how targeted human brain neurons and the synaptic connections between them adapt to prolonged elevation of activity. To assess plasticity, we perform whole-cell patch-clamp recordings of pyramidal neurons in layers 2/3 of acute human brain slices prepared from surgically resected tissue. Following recording, slices are incubated in aCSF supplemented with 8 mM potassium for over 18 hours before subsequently targeting the same set of neurons for repatching. We observe an increase of the action potential (AP) threshold after prolonged whole network depolarization. Passive cellular properties are not affected by the treatment once the elevated potassium is washed out. We aim to assess the amplitude and frequency of spontaneous and miniature synaptic events given analogous experimental conditions. In conclusion, in line with previous research conducted in non-human, model organisms, prolonged network depolarization appears to decrease the intrinsic excitability of pyramidal neurons in layer 2/3 of the human temporopolar cortex.

no. 27

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

K-BiPOLES: The next generation of bidirectional optogenetic actuator

Niklas Meyer

Charité – Universitätsmedizin Berlin

The spatio-temporal precision of Optogenetics is one of the main reasons for its versatile utilization within Neurosciences. Recently developed tools like BiPOLES allow bidirectional optogenetic control regarding activation and inhibition. But while the current mode of inhibition, using anion-selective channelrhodopsins proved effective when targeted to the soma of the neuron, it is yet insufficient in terminals and smaller compartments. Building upon the recent discovery of light gated potassium channels, K-BIPOLES could constitute a promising alternative with the light controlled outflow of potassium ions as a more physiological form of inhibition. WiChR, a Channelrhodopsin from Wobblia lunata, features so far unmatched K+-selective, large currents. In combination with a selection of kinetic mutations it proves to be a game changer regarding bidirectional constructs and opens up the next geneation of BiPOLES.

no. 44

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

PHOSPHORYLATION OF PLPPR3 MEMBRANE PROTEINS AS SIGNALLING INTEGRATOR AT NEURONAL SYNAPSES

Domonkos Nagy-Herczeg

Charité – Universitätsmedizin Berlin

The growth of neuronal processes, the branching of axons and filopodia formation all play essential role in establishing neuronal circuits. Phospholipid-phosphatase related protein 3 (PLPPR3, previously known as Plasticity Related Gene 2 or PRG2) belongs to a family of transmembrane proteins, highly expressed in neuronal development, which regulate critical growth processes in neurons. Prior work established crucial functions of PLPPR3 in axon guidance, filopodia formation and axon branching. Through the inhibition of PTEN PLPPR3 directs neuronal growth to branches and accelerates actin based filopodia formation even in the absence well known nucleators such as ARP2/3 or ENA/VASP.

However, little is known regarding the signaling events regulating PLPPR3 function. We identify here 26 high-confidence phosphorylation sites in the intracellular domain of PLPPR3 using mass spectrometry. Biochemical characterization established one of these – S351 – as a bona fide phosphorylation site of PKA. Experiments in neuronal cell lines suggest that phosphorylation of S351 does not regulate filopodia formation. Instead, it regulates binding to BASP1, a signaling molecule previously implicated in axonal growth and regeneration. Interestingly, both PLPPR3 intracellular domain and BASP1 enrich in presynapses in primary neurons. We propose that the presynaptic PLPPR3-BASP1 complex may function as novel signaling integrator at neuronal synapses.

no. 20

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Functional consequences of Satb2 ubiquitination in the developing neocortex

Julius Nowaczyk

Charité – Universitätsmedizin Berlin

Establishment of brain connectivity requires a concerted sequence of cellular and molecular transitions. The development of upper cortical layers and their projections is determined by a transcription factor Special AT-Rich Sequence Binding 2, SATB2. Efferent projections of upper layer neurons form the corpus callosum. In Satb2 knock-out mice, deep layer markers are expressed in upper layers and the corpus callosum fails to form. In humans, loss of function of SATB2 leads to SATB2-associated syndrome, associated with inability to speak and intellectual disability. In this work, we demonstrate that Satb2 function is modulated by ubiquitination. We hypothesize that ubiquitination regulates subcellular localization of Satb2 and hence its transcription factor function. Using bioID proximity assay, we aim to characterize the interactome of Satb2, particularly, the E3 ligases and deubiquitinating enzymes. Using state-of-the-art proteomics, we will map ubiquitination sites on Satb2 to uncover amino acids critical for such regulation. Finally, we will study the functional consequences of loss of ubiquitination on Satb2 using gene replacement strategies in Satb2 conditional knock-out mice and in utero electroporation. This work further expands the role of ubiquitination in the brain and the functional repertoire of ubiquitin in the developing neuron.

no. 28

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Local Field Potentials from Motor Cortex, Striatum and Motor Thalamus of the Mouse Brain Show Movement-Related Oscillatory Changes in the Beta and Gamma Bands

Öykü Okur

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Neural activity recorded from the cortico-basal ganglia network in humans, non-human primates, and rats exhibit movement-modulated oscillations. These primarily manifest as event-related desynchronization (ERD) of beta band (13-30 Hz) and synchronization (ERS) of gamma band oscillations (60-80 Hz) before and during movement. However, it remains unclear whether these movement-related oscillatory changes (e.g., beta ERD, gamma ERS) generalize to the mouse model. To address this, we analyzed the local field potential from Neuropixels recordings of awake head-fixed mice brain during movement. We compared the oscillations from cortical (motor cortex, premotor cortex, orbitofrontal cortex, medial prefrontal cortex), subcortical regions (hippocampus, hypothalamus, olfactory area, striatum), and thalamic nuclei (pulvinar, inter, motor, and sensory) during bar hold (rest) and forelimb reaching (movement) periods. Power analysis revealed oscillations in the low-beta, high-beta, and low-gamma bands in a subset of these brain regions. During movement, we found a decrease of low beta (10-15 Hz) in the motor cortical regions, striatum, and motor thalamus, and an increase of gamma power in the motor cortex and striatum although in a lower gamma frequency range (25-65 Hz) than of humans. Our results provide novel evidence for the presence and modulation of beta and gamma band activity in the motor regions of the mouse brain. Our findings establish a foundation for understanding movement-related neural oscillations in the mouse brain which is crucial for future studies on mouse models of movement disorders.

no. 55

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Tau coalesce with intracellular neutral lipids to regulate brain lipid metabolism

Anna Oliveras

Berlin Institute for Medical Systems Biology (BIMSB)

The pathological aggregation of tau protein is a hallmark of a set of neurodegenerative diseases collectively referred to as tauopathies. Accumulating evidences support strong correlation between dysregulations of lipid metabolism and tau pathology. However, little is known about tau interactions with intracellular lipids in physiological conditions and its potential role in regulating brain lipid metabolism. Here, we employ a multiscale approach to elucidate the molecular and functional complexity of tau-lipid interactions by combining advanced imaging techniques with lipidomics on human 2D and 3D models. We find that tau propagates in brain organoids as highly dynamic intracellular droplet-like structures. Using electron microscopy and fluorescence lifetime imaging (FLIM), we demonstrate that tau transitions into a spectrum of structural states. Importantly we find that the propagation of tau alters the lipid landscape of brain organoids. Lipidomics on FACS-sorted single-cell dissociated brain organoids reveals that propagating tau induces early dysregulation of neutral lipids in a cell-type specific manner. FLIM in 2D iPSCs-derived cultures supports that tau adopts distinct structural conformations in neurons and astrocytes. While tau-lipid assemblies are absent in astrocytes, in neurons tau colocalize with neutral lipids preventing them to undergo lipid peroxidation even under excitotoxic conditions. On co-cultures, we find that tau promotes lipid transfer from neurons to astrocytes. The disruption of this process is likely to result in early phenotypes of tau-mediated pathologies. Our results bring together novel molecular and cellular insights on the interplay between inter-neuronal tau and intracellular neutral lipid, shining light on the molecular mechanism connecting early stages of tau pathology and lipid metabolism dysregulations. Targeting tau-lipid interactions in neurons promise exciting new avenues on developing novel therapeutic strategies for tauopathies.

no. 56

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

The actin binding protein Drebrin is acutely modulated upon chemically induced long-term depression

Rafaela Pedro Silva

Charité – Universitätsmedizin Berlin

The actin binding protein (ABP) Drebrin (Dbn) regulates cytoskeletal functions during neuronal development and is thought to contribute to structural and functional synaptic changes associated with aging and AD. Interestingly, decreased protein levels of Dbn have to been reported to be associated with mild cognitive impairment and AD. We previously identified Dbn phosphorylation at S647 to increase protein stability and stress resilience at the spines. Long-term depression (LTD) defined as a long-lasting weakening of a synapse has been suggested to be altered in age-related memory deficits.

Our ongoing work shows that induced chemical LTD (cLTD) in cortical neurons rapidly decreases full-length Dbn protein levels and alters phosphorylation of a number of amino acid residues. Further studies suggest Dbn is being cleaved by calpain. Using Dbn as an entry point, we aim to characterize the posttranslational modifications observed during cLTD targeting the actin cytoskeleton. This work will provide mechanistic and physiological insights into the functional role of the actin cytoskeleton to provide neuronal protection upon stress in neurodegeneration and with the progression of aging.

no. 2

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

AMPA receptor diversity

Andrew Plested

Humboldt-Universität zu Berlin

AMPA receptors are partnered in the brain by a menagerie of auxiliary proteins. These partnerships produce glutamate-activated channel complexes with elaborated properties that diverge from the canonical characteristics of simple, non-complexed receptors. In this work we show that auxiliary proteins introduce polyamine block to Calcium impermeable receptors, and can slow AMPA receptor responses by a factor of about 100.

no. 3

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Axonal proteostasis: Focus on re-routing of degradative cargo for secretion

Yannes Popp

Humboldt-Universität zu Berlin

The autophagy-lysosomal system plays a central role in synaptic remodeling. In addition to rather well-investigated functions of lysosomes and autophagosomes in degradation of proteins and other cellular components, new, unconventional roles have emerged. In this project we focus on axonal autophagosome and lysosome exocytosis as a mechanism responsible for a rapid clearance of 'aged' synaptic components as well as a way of intercellular communication. As a model system, we use adult dissociated primary hippocampal mouse neurons cultured in microfluidic devices, in which axons are separated from somas and dendrites so that neurons can be treated and studied in a compartment-specific manner. Proteomic analysis of somato-dendritic and axonal compartments indicated a cell-compartment-specific differential regulation of the secretome under autophagy-inducing conditions. In a next step, it would be interesting to investigate whether there is a link between the re-routing of autophagosomes/lysosomes to exocytosis and synaptic activity to maintain cellular homeostasis and enable synaptic remodelling.

no. 47

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Quantifying social behaviors in juvenile Shank3 mice using animal pose estimation tools

Rosalba Olga Proce

Max Delbrück Center for Molecular Medicine

Social interaction is a core aspect of mammalian behavior, and alterations in social behaviors are found across many neurodevelopmental and psychiatric conditions. Mice display a range of socioemotional behaviors and are commonly used as models to investigate the neuronal circuits and molecular mechanisms underlying differences in social behaviors. Analyzing social interactions in mice is often done by manual quantification of videos. Although multiple methods for automated tracking have been developed, reliable tracking and automated behavioral classification of multiple freely-moving unmarked animals have remained challenging. The use of an unbiased classification system in a more naturalistic environment could help obtain a translatable way to study social behaviors, in particular in mouse models for neuropsychiatric conditions.

Here, we use open-source toolkits: DeepLabCut, and DeepOF to track and quantify reciprocal self-selected social interactions in pairs of freely moving sex-and age-matched animals. We use the LiveMouseTracker (LMT) to investigate home cage phenotyping and how this compares with classical behavioral phenotyping. To achieve this, we use juvenile female and male mice that lack the autism-associated gene Shank3. We show that DeepLabCut can track the movement of two size-matched juvenile mice freely interacting, and behavioral classification using supervised methods can detect differences in social interaction between Shank3 knockout and control mice. Quantifying behavior in an unbiased way remains a challenge in animal research. We confirm that freely-available open-source toolkits can be used to track and classify social interactions in a home cage, thereby providing a simple, low-cost solution to analyze social behaviors in age- and sex-matched mice.

no. 14

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Evaluation of CA3 place cell remapping in the APP/PS1 model mouse of Alzheimer's Disease

Eva Maria Robles Hernandez

German Center for Neurodegenerative Diseases (DZNE) Berlin

Spatial navigation impairments are among the earliest clinical manifestations of Alzheimer's Disease (AD). Pyramidal cells of the hippocampus fire selectively when the animal is in a specific location in the environment, leading to the theory that the hippocampus plays a crucial role in forming a cognitive map of the environment. The phenomenon of "remapping", where specific cells exhibit selective firing in distinct environments, is thought to support the formation of different memories. By performing in-vivo electrophysiological recordings in freely moving mice while they navigate through different environments, we characterized 1) if the remapping of different hippocampal place cells (CA1, CA3, DG) is altered in the APP/PS1 mouse model of AD, a model known for spatial navigation deficits; 2) the potential involvement of CA3 interneurons in the early hyperexcitability of the CA3 network, a feature shared by both AD patients and the APP/PS1 mouse model. While interneuron firing rates and place cell remapping are mostly maintained in the CA1 cells during the early phases of plaque deposition, we found several alterations that are present in the CA3 cells. By investigating the interplay between CA3 place cell remapping and the role of interneurons, our research contributes to a deeper understanding of the neurophysiological changes associated with spatial navigation impairments in AD. This knowledge may pave the way for novel therapeutic approaches targeting specific alterations in the hippocampal network.

no. 18 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

FBP17 and its intrinsically disordered region in membrane remodeling

Leonie Rommel

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To maintain neurotransmission, synaptic vesicle (SV) pool is replenished by SV recycling. SV endocytosis takes place immidiately after calcium-triggered exocytosis. One proposed mechanism coupling exo- and endocytosis is membrane tension. Exocytosis causes plasma membrane expansion, which in turn reduces tension and induces membrane ruffling creating patches of high membrane curvature. Changes in membrane tension and curvature can possibly be detected by tension or curvature sensing proteins that subsequently trigger endocytosis. FBP17, a F-BAR protein, has been described as curvature or tension sensor in non-neuronal cells. As it is found in the presynaptic compartment, it is likely that it exhibits similar functions in SV endocytosis.

Aim: In this project we particularly aim to understand the role of the intrinsically disordered region of FBP17 in tension/curvature sensing and SH3 interaction during membrane remodeling.

no. 5 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Basal Ganglia Pathways Associated With Clinical Improvement Following Deep Brain Stimulation for Tourette Syndrome

Ilkem Aysu Sahin

Charité – Universitätsmedizin Berlin

Tourette Syndrome (TS) is a cortico-basal-ganglia-thalamo-cortical network disorder presenting with motor and phonic tics and deep brain stimulation (DBS) is a treatment option. In this study, we investigate the networks associated with clinical improvement following DBS in thalamus, pallidum and subthalamic nucleus (STN). We have included 80 patients who had undergone bilateral DBS in thalamus (n=33), pallidum (n=33) and STN (n=14). We have modeled the thalamostriatal, striatopallidofugal and pallidothalamic pathways using CurveToBundle module in 3D Slicer. We combined these with the pathways available in Human Basal Ganglia Pathway atlas. Then, in a group level analysis, we have correlated the clinical outcomes of each patient with their e-field magnitude on each streamline. The fiber scores derived from respective connectivity models correlated with empirical clinical outcomes in the thalamus ($R=0.44$, $p = 0.009$), pallidum ($R = 0.64$, $p = 0.001$), and STN ($R = 0.40$, $p = 0.152$) TS-DBS cohorts. Our results might shed light to optimal connectivity targets for TS-DBS for the common surgical targets.

no. 12 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Establishing otpoGPCRs for controlling dendritic signal integration

Aikaterini Salivara

Charité – Universitätsmedizin Berlin, German Center for Neurodegenerative Diseases Berlin

Layer 5 pyramidal neurons (L5PN) play a crucial role in cortical processing. L5PNs integrate information across all cortical layers, as their dendritic tree spans the entire cortical column. These cells receive fundamentally different input to their basal and apical compartment. The basal compartment receives feedforward sensory information, while the apical compartment receives feedback information from higher cortical areas. Key active properties of L5PNs arise from two main spiking zones: Na+ spikes initiated at the perisomatic region and Ca2+ plateau potentials in the apical dendrites. Ca2+ signals travel from apical dendrites to the soma and shape the neuronal output, but are critically modulated by dendritic G protein-coupled receptor (GPCR) signals. Here, we aim to investigate the interplay of GPCR signals and Ca2+ on signal integration in L5PNs of mice somatosensory cortex using optoGPCRs. To this end, we perform patch clamp recordings on L5PNs expressing different optoGPCRs and examine the effect of photocontrolled GPCR signals on the neuronal output.

no. 64

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Vesicle Redistribution at Potentiated Hippocampal Mossy Fiber Boutons

Andrea Sannio

Charité – Universitätsmedizin Berlin

Dentate gyrus granule cells form giant presynaptic boutons known as mossy fiber boutons, which are targeting the proximal dendrites of CA3 pyramidal neurons, among others (Acsády et al., 1998). These connections constitute the second relay of the tri-synaptic hippocampal circuit. Mossy fiber boutons have very low release probability at rest and are able to strongly potentiate their release (Nicoll & Schmitz, 2005). Mossy fiber long-term potentiation (LTP) occurs presynaptically, through a "non-Hebbian" mechanism.

Mossy fiber LTP expression is independent from N-methyl-D-aspartate receptors and postsynaptic terminal depolarization (Harris and Cotman 1986, Zalutsky & Nicoll 1990). In particular, the increase in the terminal's calcium concentration promotes the activity of the adenyl cyclases, which, following a buildup of cyclic adenosine monophosphate (cAMP), activate the cAMP-dependent protein kinase A (PKA) (Weisskopf & Nicoll, 1995). Activation of PKA has been shown to be necessary and sufficient to increase neurotransmitter release at the mossy fiber bouton and cause LTP (Nicoll & Schmitz, 2005).

However, the exact mechanism downstream of PKA is still under investigation but suggested to correlate with structural modifications and increase in the number of docked vesicles (Orlando et al., 2021; Kim et al., 2023).

In the following thesis project, we investigated whether the rapid structural remodeling occurring 15 minutes after initial forskolin application (Orlando et al., 2021), was also present after 1 hour incubation in forskolin. We performed chemical fixation and high-pressure freezing/ freeze-substitution of mice acute brain slices, to address ultrastructural changes in mossy fiber boutons and synaptic vesicles. We found that vesicle rearrangement is sustained even after 1 hour of forskolin-induced potentiation, suggesting that these mechanisms might underly long-term increase in neurotransmission.

no. 42

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Neuron-astrocyte coupled lipid clearance dysfunction in Parkinson's Disease

Paula Santos Otte

Berlin Institute for Medical Systems Biology (BIMSB)

Given that lipids comprise 60% of the brain's dry weight, it is not surprising that one of the first onsets of Parkinson's disease (PD) and other neurodegenerative disorders are alterations in lipid metabolism. In fact, abnormal accumulation of lipids is found intracellularly in dopaminergic neurons, as well as extracellularly in the cerebrospinal fluid (CSF) of PD patients. Neuropathologically, PD is characterized by the formation of intracellular inclusions enriched with the protein α-synuclein (α-syn) and a core of lipid species and membrane fragments, highlighting the importance of understanding α-syn-lipid interactions in cells and its potential role in lipid homeostasis. In the brain, the homeostasis of lipids is accomplished by their bi-directional transport between neurons and astrocytes. One of the main lipid transporters between these cell types in the brain is Apolipoprotein E (ApoE). Among its three allelic variants in humans (ApoE2, 3 and 4), the latter has been strongly associated with multiple neurodegenerative disorders and is found to contribute to lipid dyshomeostasis in the brain. In particular, it was found to impair fatty acid (FA) and cholesterol metabolism between neurons and astrocytes. Interestingly and a potential point of crosstalk, α-syn and ApoE have been found to co-localize in neuronal intracellular inclusions as well as in the CSF of PD patients. While many in vitro studies have highlighted α-syn and lipid interactions, this remains to be delineated in the intra- and inter-cellular context. Hence, we are interested in understanding whether the lipid-binding character of α-syn has a regulatory role on the neuron-astrocyte lipid homeostasis mediated by ApoE. My work demonstrates that propagating monomeric α-syn impairs the efficient ApoE3-mediated clearance of excess cholesterol esters and fatty acids from iPSC-derived dopaminergic neurons in co-culture with immortalized astrocytes. These findings motivate us to bring mechanistic insights on whether α-syn (i) impairs ApoE transfer from neurons to astrocytes and/or (ii) disrupts efficient lipid packing of ApoEs in neurons via competitive lipid interactions.

no. 60

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

The role of proprioceptive feedback in motor control

Alessandro Santuz

Max Delbrück Center for Molecular Medicine

In the wild, animals move through complex environments. To generate meaningful, robust movement, all vertebrates use several sensory systems, such as those for vision and balance (Grillner and El Manira, 2020). However, there are other less known sensory contributions to motor activity. Proprioception, for example, is the sense that allows continuous monitoring of the position of body segments in space and relative to the body itself. In mammals, proprioceptive information is conveyed to the central nervous system by mechanosensory neurons that carry signals mainly from muscle spindles and Golgi tendon organs. Recent advances in mouse genetics have provided the opportunity to dissect the function of the neural circuits that detect, transmit, and encode proprioceptive information (Santuz and Zampieri, 2024). Here, we assess the temporal dynamics of proprioceptive loss of function as a proxy to better understand the role of proprioceptive feedback in motor control.

We crossed PV::cre, Rx3::flpo and MaptdsDTR;Ai65D mice to allow for the expression of the human diphtheria toxin receptor (DTR) and the tdTomato reporter in cells expressing both parvalbumin (PV) and Runx3 (Rx3), corresponding to all proprioceptors and a negligible amount of Merkel cell afferents and Ruffini endings in the nail bed (Buch et al., 2005; Hippenmeyer et al., 2005; de Nooij et al., 2013; Oliver et al., 2021). We recorded high-speed sagittal videos of these mice (n = 5, two females, age 54 ± 3 days) locomoting on a treadmill at five different speeds, from 0.1 to 0.9 m/s. Locomotion at 0.3 m/s was perturbed using a custom-built perturbation treadmill (University of Cologne, Germany), which is capable of applying sudden mediolateral displacements or accelerations of the belt at random time intervals. For markerless body part tracking we processed the videos in DeepLabCut v2.3.10 (Mathis et al., 2018). Video recordings were made before (day one, or DT0) and after systemic injection of 100 µg/kg of diphtheria toxin (day DT1, or 24 hours after injection, until day DT7).

Modulation of kinematic (e.g. range of motion and Poincaré maps of joint angles, paw drag, etc.) and spatiotemporal parameters (e.g. number of steps per minute or cadence, stance and swing duration, etc.) in response to perturbations was clearly present at DT0 as previously reported (Santuz et al., 2022), but was already lost between DT2 and DT4, indicating a loss of modulation capability as a result of cell ablation. Similarly, 4 out of 5 mice were able to reach the maximum speed of 0.9 m/s at DT0, DT1 and DT2, but only 1 out of 5 mice maintained this ability at DT4 throughout DT7. At the same time, body mass loss was observed in 4 out of 5 animals, with a

negative peak at DT4 (-6.8 ± 4.8%). Histological analysis of dorsal root ganglia revealed an ablation efficiency of 72.1 ± 0.1% at DT7. Taken together, our results show that the temporal dynamics of proprioceptor ablation in a DTR model are irreversible as early as three days after injection. High resolution kinematic analysis revealed a generalised deterioration of locomotor function after ablation, particularly in parameters quantifying the timing, variability and quality of stepping. Further insight into the time course of sensory loss may shed new light not only on the role of proprioceptive feedback in motor control, but also on how sensory degeneration affects pathology and healthy ageing.

no. 49

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Integrating FAIR Principles into RDM and Bioimage Analysis at AMBIO

Jan Schmoranzer

Charité – Universitätsmedizin Berlin

The Advanced Medical BIOimaging Core Facility of the Charité-Universitätsmedizin (AMBIO) annually enables over 200 research projects that require advanced fluorescence-based imaging modalities, including high-resolution, 3-dimensional, live-cell and super-resolution modes. One major challenge is the management and analysis of the growing amount of multi-modal imaging data. Within the INF project of CRC-TRR384 (IN-CODE) AMBIO is building a state-of-the-art research data management (RDM) infrastructure to enable collaborative data processing according to the FAIR principles.

Here, we describe the data-workflow currently used in AMBIO to store, transfer and analyze large, complex data sets, using examples from 3D, live-cell, time-lapse imaging (lattice light sheet) and super-resolution single molecule (DNA-PAINT) imaging projects. We show examples of custom-written data analysis pipelines to investigate nanoscale structures, dynamics and protein distributions in neuronal samples. Future work will focus on a framework of tools and services that ensures the FAIR RDM of the imaging data throughout its life cycle. This will facilitate collaborative and comparative data analysis and modeling.

no. 25 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Investigating the effects of theta-burst magnetic stimulation on molecular and cellular mechanisms of memory in acute mouse hippocampal slices and hiPSC-derived systems

Hana Sheldon

Berlin Institute of Health (BIH), German Center for Neurodegenerative Diseases (DZNE) Berlin

Memory disorders such as Alzheimer's disease pose significant challenges to society due to their adverse impact on cognitive function. While many studies have provided insights into the pathological effects of memory disorders, an effective treatment strategy is lacking.

Non-invasive brain stimulation is used to treat neurological disorders, especially in treatment-resistant individuals or disorders without a standard treatment. Repetitive transcranial magnetic stimulation (rTMS), for example, is used to treat depression and obsessive-compulsive disorder.

rTMS can also attenuate fear memory if applied during recall, and enhance visual working memory in elderly individuals with subjective cognitive decline. Theta-burst magnetic stimulation (TBS) is a newer rTMS protocol that delivers patterned magnetic pulses, and is becoming favored in the clinic due to its shorter stimulation times and ability to enhance excitation (intermittent TBS) or inhibition (continuous TBS) of targeted neural populations. This could modulate neural oscillation patterns and synaptic plasticity, which are altered in patients with memory disorders. Non-invasive brain stimulation therefore has the potential to treat memory disorders. However, the underlying molecular and cellular mechanisms are not understood.

We aimed to investigate the effects of TBS at the cellular level in primary mouse cultures, acute mouse hippocampal slices and human induced pluripotent stem cell (hiPSC)-derived neural organoids. We first tested this in a well-studied mouse memory circuit to obtain a baseline measure, then applied our findings to human networks for translatability. We used a standard iTBS protocol of 1200 pulses to test whether this would induce long-term potentiation and excite neural networks. After stimulation, samples were immunostained with cell-type specific markers as well as Fos and Arc - immediate early genes that are expressed directly after cell activation and therefore specifically label active cell populations. Pilot results showed that iTBS (1200 pulses) selectively stimulated a small subset of cells in the subgranular zone of the dentate gyrus, which may correspond to progenitor or pyramidal basket cells. We plan to confirm this data and test additional stimulation protocols to identify activated cell populations in mouse brain slices and hiPSC-derived neurons and neural networks. We further plan to use spatial

sequencing to identify the transcriptomic profile of activated cells. This information may aid the development of new and more effective targeted stimulation protocols to treat memory disorders.

no. 34

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

GABAA RECEPTORS MODULATE ANXIETY-LIKE BEHAVIOR THROUGH THE CENTRAL AMYGDALA AREA IN RATS WITH HIGHER PHYSICAL ACTIVITY

Zahra Sudani

Charité – Universitätsmedizin Berlin

In this study, our objective was to explore the role of $GABA_A$ receptors within the amygdala region in modulating anxiety-like behavior in response to voluntary physical activity. We employed a stereotaxic instrument to implant two cannulae in the amygdala area, through which we administered the $GABA_A$ receptor antagonist, bicuculline. Subsequently, we exposed the animals to a running wheel for a duration of three hours over four weeks. Following this exercise regimen, we conducted behavioral tests, including the open field and elevated plus maze tests, to assess anxiety-like behavior. The findings revealed that the blockade of $GABA_A$ receptors led to reduced physical activity, subsequently resulting in increased anxiety-like behavior in rats.

no. 65

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

VOLUNTARY PHYSICAL ACTIVITY DECREASES DEPRESSION-LIKE SYMPTOMS VIA INTERLEUKINE-1β RECEPTORS IN STRESSED MICE

Zahra Sudani

Charité – Universitätsmedizin Berlin

Introduction: Inflammatory cytokines, such as interleukin-1 (IL-1) β, have been associated with major depressive disorder. Recent clinical and animal studies have demonstrated that blocking IL-1β receptors can alleviate depression-related symptoms, indicating its potential as a therapeutic target. Conversely, increased physical activity has been shown to enhance quality of life by reducing stress-related symptoms and fortifying the immune system. Furthermore, exercise has been found to mitigate stress-related disorders, encompassing anxiety, depression, and inflammatory responses. However, the interplay between physical activity and IL-1β in depression has remained unexplored. This study aimed to ascertain whether heightened physical activity could alleviate depression-related symptoms by influencing IL-1β receptors in stressed mice.

Methods: To investigate this, animals were subjected to a chronic stress protocol, followed by exposure to running wheels to boost their physical activity levels. Concurrently, animals received an IL-1β antagonist and agonist, and their depressionrelated behaviors were assessed through the sucrose preference test, tail suspension test, social behavior, and forced swim test.

Results and discussion: The results revealed that blocking IL-1β receptors enhanced the antidepressant effects of increased physical activity, while agonist treatment counteracted the antidepressant impact of exercise in stressed mice. In conclusion, these findings suggest that heightened physical activity can alleviate depression-related symptoms by modulating IL-1β receptors under conditions of stress in mice.

no. 52

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Spatial memory engrams in mouse hippocampus

Shimon Swer

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Memories in the brain are represented by traces. Groups of interconnected neurons fire together in response to a learning experience and their recurrent activation leads to an establishment of an engram. The hippocampus is an important region involved in the storage and consolidation of different types of memories. For example, different kinds of contextual information can influence the firing of hippocampal neurons. Activation of memory engrams during different behavioural tasks requiring hippocampal function involves molecular changes that underlie memory encoding, storage and consolidation. While studies have focussed on elucidating the transcriptomic signature of engram cells in fear memory learning experiments, less is known about the gene expression changes that accompany other forms of memory, for example, spatial memory. Therefore, one of the main objectives of this project is to elucidate the transcriptional programs of engram cells when mice learn a spatial memory task. Another aim is to investigate the different gene expression changes involved in the transition of engrams to accessible states during retrieval of memories and to analyse cell-type specific activity patterns in the hippocampus during encoding and retrieval of memories. We plan to address these aims by using a TRAP2 mouse model to tag engram cells during a behavioural task and a combination of immunohistochemistry, in-vivo electrophysiology, FACS and RNA sequencing.

no. 21

session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Glial-Secreted Factors Regulate Neuronal Gene Expression and Function

Paul Turko

Charité – Universitätsmedizin Berlin

Glial cells secrete a wide variety of proteins and metabolites to the extracellular space (Dowell et al., 2009). We and others have shown the importance of these factors for neuron survival, morphological development, and excitatory synapse formation (Banker et al., 1980; Turko et al., 2018). However, our knowledge of precisely how these factors mediate their effects is incomplete. Our aims therefore are to further investigate the effect of glial-secreted factors on neuron physiology and to identify the roles of specific protein candidates on neuron function. We have employed a combination of methods, including cell sorting, RNA sequencing and mass spectrometry to explore the regulatory effect of glial-secreted factors on neuronal gene expression, and to identify specific secreted proteins interacting with distinct neuron types (Eichelbaum et al., 2012). Our results demonstrate that glial-secreted factors can have a profound influence on gene expression levels in neurons, with hundreds of genes being significantly up or down regulated by the presence or absence of glial-secreted factors. Notably, some gene expression changes are neuron-type specific, with glial cells regulating genes associated with synapse assembly in glutamatergic but not GABAergic neurons. Interestingly, we find that the secretion of proteins by glial cells is also highly dynamic, being influenced by culture condition and injury. In conclusion, our results suggest that secreted factors are a central means by which glial cells can dynamically communicate with neurons, to regulate their gene expression and function.

no. 58

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

The relationship of sex hormone signaling and psychological stress

Clara Unger

Charité – Universitätsmedizin Berlin, Max Delbrück Center for Molecular Medicine

There is a sex-bias in stress-related psychiatric conditions, with women being more vulnerable. Especially, periods of gonadal hormone shifts – like puberty or menopause – are associated with an increased risk for depression. The fluctuations of sex hormones throughout the menstrual cycle have been suggested to predispose females for stress-related diseases. This project aims to intervene with the estrous cycling in female mice by using a hormone implant. We will study how this hormone treatment modulates the response to acute restraint stress. By applying a within animal control setup, in which the animals get tested by a number of behavioral tests before and after the stressor, it will be possible to detect intra-individual behavioral changes. In combination with home-cage tracking, a detailed behavioral phenotype can be characterized. To relate the changes in behavior to molecular mechanisms, immunostaining for cFos and receptors of the sex hormone system will be performed on several sections per brain. This enables 3D brain mapping of fluorescent signal and identification of brain regions affected by hormone treatment. Once brain regions of interest are identified, phosphoproteomics analysis will be performed on isolated synaptoneurosomes from these regions, to find out which pathways are differentially activated at the synapse. This study uses a translational and low-stress mode of hormone administration in mice and will provide a detailed behavioral and molecular characterization of stress response modulation by gonadal hormone treatment. It will thereby contribute to an improved understanding of the sex-bias in stress-associated psychiatric diseases.

no. 61

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

The Role of the Transient Receptor Potential Vanilloid 1 (TRPV1) Channel in Sharp Wave Ripples, Place Cells, and Spatial Memory

Chrystalleni Vassiliou

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Sharp-wave ripples (SWRs) are hippocampal oscillations important for memory consolidation that appear during sleep and awake immobility. During SWRs, neuronal firing patterns formed during previous exploration are reactivated, which allows strengthening of synaptic connections between the firing cells, i.e., long-term potentiation (LTP). The transient receptor potential vanilloid 1 (TRPV1) protein is a cation channel that in the hippocampus is specifically expressed in oriens lacunosum moleculare (OLM) interneurons, which participate in SWRs. Because TRPV1 knockout (KO) mice have impaired hippocampal LTP, another fundamental process of memory consolidation, we hypothesized a similar impairment in SWRs. However, both in vivo and in vitro electrophysiological recordings showed an enhancement of SWRs in TRPV1 KO mice. From recordings in behaving animals, we also examined spatial properties of hippocampal place cells and found larger and less stable place fields in TRPV1 KOs. Next, we examined spatial memory using a dry land version of the water maze, the cheeseboard maze task. Even though WT and TRPV1 KO mice learned the first reward location at similar rates, KO mice took longer to reach the new reward location when the location was switched to the opposite quadrant of the maze on all days after reversal. This was at least partly because TRPV1 KO mice visited the original reward location before going to the new one, which might hint at an impairment in memory extinction or forgetting.

no. 57

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

The impact of sleep deprivation on genome regulation in dorsal CA1 region of hippocampus

Dominika Vojtasova

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Sleep is an evolutionary conserved powerful drive that is important for brain function and often disrupted in neurological and neurodevelopmental disorders. We and others have shown that acute sleep deprivation (SD) (5-6 hours) elicits extensive changes in gene expression in the murine frontal cortex and hippocampus. The hippocampus, a key region for learning and memory, is particularly vulnerable to the effects of acute SD, however, how changes in gene expression after SD are established and how the affected mechanisms are dysregulated remain poorly understood. Here, we investigated the effects of acute SD on 3D genome architecture, chromatin accessibility and gene expression in pyramidal glutamatergic neurons of the hippocampus, one of the most affected cell types by SD. We mapped changes in chromatin topology upon SD using genome architecture mapping (GAM), and gene expression and chromatin accessibility using 10X Genomics multiome. We find extensive changes in genome architecture at all genomic scales and an overall repression of neuronal genes. Amongst the most affected genes are synapse-regulating genes (e.g Grm5, Gabrb3), ion transport associated genes (e.g. Kcnh7), learning/memory-associate genes (e.g. Satb2, Dcc), neurexin-family genes (Nrxn3, Nrxn1) and epigenetic regulators (e.g Hdac9). Our work suggests that the homeostatic response to SD involves a strong imbalance between excitation and inhibition (E-I) upon SD in all studied modalities, and reveals a role for 3D genome organisation in the physiological response to SD. As E-I imbalance is a key feature of neurodevelopmental disorders which often display chronic insomnia, our results suggest that chronic exposure to SD may contribute to their aetiology, and be connected with sleep-dependent chromatin regulation and remodelling. Furthermore, genomic regions undergoing changes in 3D genome structure, accessibility and expression, are enriched for insomnia SNPs, promising new insights on the role of sleep disturbances in neurodevelopmental disorders.

no. 45

session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

pHRoG: pH Regulating optoGenes for all-optical control of subcellular pH

Jakob Walther

Charité – Universitätsmedizin Berlin

Proton concentrations are tightly regulated in subcellular compartments like lysosomes, autophagosomes or mitochondria. For instance, prolonged changes of lysosomal pH are associated with neurodegenerative diseases such as Alzheimer's or Parkinson's Disease, cellular aging and subcellular adaptation of different types of cancer to their increased metabolic activity [1-3]. Despite the importance of subcellular pH level in the endolysosomal pathway for cell homeostasis and in different diseases, molecular tools for organelle specific, time resolved and quantitative manipulation of subcellular pH are still sparse. Generally applied chemical drugs such as bafilomycin 1A or hydroxychloriquine affect different intracellular organelles at the same time and are only slowly taken up and washed out of the cell. A promising alternative would be an optogenetic tool that firstly is exclusively expressed in the organelle membrane, secondly promotes rapid organellar alkalization or acidification and thirdly directly reports local pH changes by attached pH-sensitive reporter proteins. Targeting new families of photoreceptors to the lysosome as subcellular model organelle we generated Lyso-pHRoGs (for lysosome targeted pH-Regulating optoGenes) that fulfill all three requirements and alter lysosomal enzymatic activity.

no. 6 session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

BDNF-pHluorin imaging upon presynaptic mossy fiber potentiation

Oliver Wangler

Charité – Universitätsmedizin Berlin

Learning and memory formation in the hippocampus are thought to depend on the ability of synapses to increase their strength in an activity-dependent and long-lasting manner, known as long-term potentiation (LTP). Within the hippocampal circuitry, the giant mossy fiber (MF) synapse, which is formed between dentate gyrus granule cells and CA3 pyramidal neurons, expresses LTP differently from most other glutamatergic synapses. Its LTP is presynaptic and NMDA-receptor-independent, and depends on cAMP. One of the molecular players involved in presynaptic potentiation is the brain-derived neurotrophic factor (BDNF), which is highly expressed at mossy fibers (Conner et al., 1997). Interference with BDNF or its receptor TrkB impairs LTP (Schildt et al., 2013).

Here, we investigate the kinetics of BDNF release at the giant MF synapse upon chemical potentiation. To this end, we established a live-cell imaging workflow for the direct visualization of BDNF release from mouse autaptic granule cell cultures, utilising the pH-sensitive fluorescence reporter BDNF-pHluorin. Moreover, to identify autaptic neuron identity, we perform parallel whole-cell patch-clamp electrophysiology in the presence of L-CCG I, an mGluR2/3 agonist that specifically blocks granule cell transmitter release, but not other hippocampal pyramidal neurons in the same autaptic culture system.

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session 1 on Thursday, October 10, 2024 5:45 – 7:30 p.m.

Lysosomal control of axonal protein synthesis in Charcot-Marie-Tooth Disease type 2B

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Charcot-Marie-Tooth type 2B (CMT2B) is a peripheral sensory neuropathy caused by mutations in the late endosome/lysosome associated small GTPase Rab7A. While progress has been made in characterizing the biochemical and functional consequences of CMT2B-causing mutations, the mechanisms leading to the degeneration of neurons with very long axons are still unclear. We recently found that Rab7-positive acidic compartments are involved in axonal protein synthesis, a process that is essential for neuronal function and maintenance. These intriguing findings prompted us to better understand lysosomal function in subcellular protein synthesis and how it is affected in CMT2B neurons. We first generated a new CMT2B knock-in mouse model carrying Rab7aN161T mutation using CRISPR/Cas9 technology. Detailed characterization of the lysosomal pathway in cortical and DRG CMT2B neurons revealed changes in lysosomal morphology and trafficking. Next, we demonstrated that protein synthesis is altered in CMT2B neurons, including distal compartments, by puromycin labeling and click chemistry assays. We then identified the transcriptome associated with lysosomes in neuronal cells (N2a) and found the presence of nuclear-encoded mitochondrial mRNAs. Moreover, our preliminary evidence suggests defects in mitochondrial morphology and function in CMT2B neurons. Overall, our results support a direct role for lysosomes in controlling subcellular protein synthesis in neurons and impairments of this process could contribute to CMT2B pathogenesis.

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session 2 on Friday, October 11, 2024 5:45 – 7:30 p.m.

Neuronal membrane shape regulation through interplay of the cytoskeleton and BAR-domain proteins

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During our lifetime neurons undergo extensive membrane remodeling: starting from neurodevelopment and the growth of axons and dendrites, through synapse formation followed by selective pruning, during sustained neurotransmission, and, finally, during learning and memory formation. These complex events have to be orchestrated by elaborate signaling cascades, and locally specialized membrane remodeling machineries that are able to couple local intracellular scaffolds (like at the presynaptic active zone or the postsynaptic density) to membrane shape, trafficking organelles, and to the cytoskeleton. In this work we studied how pre- and postsynaptic plasma membrane dynamics is regulated by various classes of BAR domain proteins that couple membrane shape to the control of the assembly and disassembly of the actin cytoskeleton. To this aim we combine work in human induced neurons (iNeurons), cultured murine neurons, with a bottom-up minimal in vitro system consisting exclusively of model membranes and purified proteins.