UNIVERSITÄT LEIPZIG

Brain Dynamics Graduate School

ABSTRACT BOOK

Brain Dynamics Scientific Day

07.10.2022

Felix Klein lecture hall

Paulinum, Augustusplatz 10

1st Brain Dynamics Scientific Day

07.10.2022

Organizer:
Brain Dynamics Graduate School
Leipzig University
https://www.uni-leipzig.de/en/brain-dynamics

Speaker: Prof. Dr. Marc Schönwiesner
Co-Speaker: Prof. Dr. Stefan Hallermann
Scientific Coordinator: Dr. Saša Jovanović

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Keynote lecture I

Exploring neural dynamics in sleep and visual texture perception

Gilles Laurent
Neural Systems Department, Max Planck Institute for Brain Research, Frankfurt am Main, Germany

I will describe recent work on two systems and at different levels of investigation, both touching upon dynamics in the brain. In the first I will describe the unexpected dynamic complexity of sleep activity in the brain of a reptile, the Australian dragon, revealing competition between the two claustra during REM sleep. In the second, I will describe behavioural experiments on camouflage behavior in cuttlefish, an animal that exploits a unique skin display system controlled by the brain to match the texture statistics of visual scenes. These experiments are geared towards understanding the neural basis for texture perception in an animal whose lineage bifurcated from ours over 600 M years ago.

Keynote lecture II

Dentate gyrus circuits for encoding, retrieval and discrimination of episodic memories

Marlene Bartos
Institute of Physiology, Department I, Medical Faculty, University Freiburg, Germany

The hippocampus is the brain's center for episodic memories about our life. Its individual subregions, the dentate gyrus (DG), CA3-1, are differentially involved in the encoding and recall of episodic memories. While hippocampal principal cells represent episodic features, such as movement, space, and context, much less is known about the role of GABAergic inhibitory interneuron (IN) types in regulating information processing. We performed two-photon calcium imaging of hippocampal parvalbumin (PV)- and somatostatin (SOM)-expressing INs in the DG, CA3. 2 and 1 of head-fixed mice during foraging in virtual environments. Throughout hippocampal subfields, both IN-types showed moderate spatial tuning. PV-INs increased their activity with running-speed and reduced it in novel environments. SOM-INs displayed a dichotomy: CA1-3 SOM-INs behaved similar to PV-INs, but in the DG, their activity increased during immobility and in novel environments. Congruently, inhibition of DG SOM-INs with h4MDi designer receptors (DREADDs) caused increased activation and decreased context selectivity of DG granule cells (GC) while suppression of DG PV-INs had opposite effects, particularly in familiar environments. These data indicate a new form of novelty-dependent, dynamic routing of information through hippocampal subfields that is tailored to cognitive demands and controlled by distinct inhibitory circuits.

Symposium I

S01

Behavior-based identification of chemical mechanisms

David Leuthold, Nadia C. Herold, Tamara Tal
Helmholtz-Centre for Environmental Research – UFZ, Leipzig, Germany

Approximately 17% of US children are affected by developmental disabilities including intellectual or learning deficits. Chemical exposure can contribute to neurodevelopmental disorders, a phenomenon known as developmental neurotoxicity (DNT). It is imperative to identify chemicals causing DNT and to understand underlying adverse outcome pathways (AOPs). Behavioral alterations represent a comprehensive readout of impairment in neurodevelopment and neuronal signaling but current regulatory DNT studies are restricted to rodents. Alternative DNT new approach methods (NAMs) are needed to better protect human and environmental health. While *in vitro* DNT NAMs capture specific neurodevelopmental processes, they fail to reflect the full range of events and interactions that orchestrate nervous system development and function. To fill this gap, we developed a battery of 10 automated behavior assays for measuring visual and acoustic behaviors including habituation learning behavior in larval zebrafish, a 3R-compliant model amenable to higher-throughput chemical screens. The sequential behavior assays were optimized for photic and acoustic stimulus duration, intensity, number and sequence, and zebrafish developmental stage. The DNT NAM was evaluated against pharmaceuticals with diverse mechanisms including NMDA receptor (NMDAR) antagonism, GABA receptor antagonism and acetylcholinesterase inhibition. The battery recapitulates rodent learning deficits following acute exposure to prototypical NMDAR antagonists MK-801 and DL-2-amino-5-phosphonopentanoic acid. For the first time, we show that early life stage exposure to these compounds disrupts zebrafish learning behavior later in development. Additionally, certain US EPA ToxCast chemicals positive for NMADR perturbation *in vitro* were confirmed to cause learning deficits in larval zebrafish (e.g., clorophene). Beyond application to impaired learning AOPs, exposure to the GABA antagonist picrotoxin resembles an epileptic seizure phenotype, highlighting the applicability of behavioral phenotyping to other DNT-related AOPs. In summary, the 10-assay DNT NAM can identify chemicals with specific effects on neuronal signaling and neurodevelopment, improves our understanding of underlying AOPs, and can accelerate DNT research in an alternative test system.

S02

Area-specific differentiation of neocortical synaptic coupling distances

Max Schwarze, Grit Bornschein, Simone Brachtendorf, Jens Eilers and Hartmut Schmidt[1]

Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

[1] Correspondence: Hartmut.Schmidt@medizin.uni-leipzig.de

The physical coupling distance between presynaptic Ca^{2+} channels and transmitter-filled synaptic vesicles is a fundamental determinant of their release probability (*pv*). Investigations at different excitatory synapses in different parts of the matured brain, including brainstem, cerebellum and neocortex, indicate that highly reliable synapses processing sensory information operate with tight coupling, while highly plastic excitatory synapses in the hippocampus were found to use loose coupling. Hence, it appears that in the mature brain tight coupling is favored by reliable synapses and loose coupling by highly plastic synapses.

To probe this hypothesis at the same type of synapses within the same part of the matured brain, we focused on two functionally distinct areas of the neocortex, the prefrontal (PFC) and the somatosensory (S1) cortex and analysed coupling distances at synapses between pyramidal neurons in layer 2/3 (L2/3PNs) and layer 5 (L5PNs). We preformed whole-cell recordings from L5PNs in acute slices and stimulated connected L2/3PNs extracellularly.

Synapses in PFC showed paired-pulse facilitation, while synapses in S1 possessed paired-pulse depression, indicating that *pv* in PFC is lower than in S1. The Ca^{2+} chelator EGTA-AM decreased EPSCs in PFC significantly to 66% of the control value (P=0.03), whereas EPSCs in S1 remained unchanged (102%; P=0.9). These findings suggest that L2/3PN to L5PN synapses in PFC operate with loose coupling as opposed to tight coupling in S1. Our results show that coupling distances of the same synapses differ between cortical areas, thus, providing evidence that the presynaptic nanostructure is adapted to its cortex-area related function.

S03

Changes of brevican in animal models of dystonia

Anika Lüttig, Stefanie Perl, Angelika Richter

Institute of Pharmacology, Pharmacy and Toxicology, Faculty of Veterinary Medicine, University of Leipzig, Germany

Alterations in neuronal plasticity appear to play a critical role in dystonia. An important modulator of neuronal plasticity is represented by the perineuronal nets (PNs) located around the cell somata and proximal dendrites of neurons, particularly parvalbumin reactive (PV^+) interneurons. An important component of PN are the chondroitinsulfate proteoglycans (CSPGs) such as aggrecan and brevican. While the role of abnormal PN expression in the pathophysiology of dystonia is largely unknown, one form of canine paroxysmal dyskinesia (episodic falling syndrome) was discovered to be caused by a deletion in the brevican encoding gene. Therefore, in the present work we investigated at first whether brevican expression is altered in animal models of dystonia.

As a phenotypic model of paroxysmal dystonia, we used the *dt*^{sz} hamster, in which the maturation of PV^+ interneurons is likely delayed. In contrast, the DYT1 KI mouse is regarded as an etiologic model for a permanent form of generalized dystonia. These mice show no dystonic symptoms but moderate sensorimotor changes. We examined both animal models immunohistochemically using brevican intensity measurements and cell counting to compare dystonic (*dt*^{sz} hamster, n = 8, and heterozygous DYT1 KI mouse, n = 9, respectively) and control animals (hamster n = 5, mouse n = 8). We also added protein (Western blot) and mRNA expression (qPCR) assays.

Comparison of *dt*^{sz} and control hamsters revealed interesting differences within the basal ganglia-thalamo-cortical circuit. Thus, a lower number of brevican positive cells to the total number of PV^+ cells (percentage of $Brev^+$ in PV^+) in the motor cortex and striatal neurons with low PV reactivity became evident. Since measurements of the whole brevican immunofluorescence intensity indicated higher expression of brevican in the striatum and ventromedial thalamus, western blot and qPCR analyses are under the way. In contrast to mutant hamsters, the studies in the DYT1-KI mouse model showed only a subtle increase of $Brev^+/PV^+$ in the motor cortex.

In the *dt*^{sz} hamster model, developmental disruption of the PN could contribute to the presumed disinhibition of PV^+ neurons and abnormal plasticity within the basal ganglia circuit. However, it remains unclear whether the findings represent a cause of dystonia or the consequences of other changes. In contrast to the hamster model, the higher number of $Brev^+/PV^+$ in the motor cortex of the mouse model could represent a reason for the lack of typical dystonic symptoms in DYT1 KI mice. Together, the present data suggest that PN may play a role in both dystonia models which deserves investigations of other components of PN, such as HAPLN4 and aggrecan. Current studies on the mechanisms of deep brain stimulations (DBS) in mutant hamsters include PN, because induced PN changes may influence neuronal plasticity and thereby improve dystonia.

Funded by the DFG within the Collaborative Research Centre 1270 ELAINE.

S04

Motor neuron-driven spinal motor circuit pathology in spinal muscular atrophy with respiratory distress type

Katharina Apel, Christian Simon
Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

The group of spinal muscular atrophies can be subdivided into the classical proximal form of spinal muscular atrophy (SMA) and distal spinal muscular atrophy with respiratory distress type 1 (SMARD1). The discovery of many pathomechanisms in the classical form of SMA has resulted in promising treatment options. In contrast, little is known about the pathology of spinal motor circuits in the distal form of SMA, SMARD1, which is caused by the reduction of the DNA/RNA binding protein IGHBMP2. We applied immunohistochemistry and confocal analysis to investigate motor circuits of the most commonly used SMARD1 mouse model "Nmd^{2J}". We compared the pathology of "proximal" motor circuits consisting of the lumbar L1 spinal segment and its axial target muscles with "distal" motor circuits comprising of the L5 segment and distal muscles. We found coincidentally occurring α-motor neuron death and muscle denervation around 10 days in distal motor circuits which both extended to ~70% at 6 weeks. In contrast, the proximal motor circuit was completely resistant to degeneration, matching the distal phenotype of Nmd^{2J} mice. Next, we decipher a selective 50% loss of excitatory synapses (C-boutons and proprioceptive synapses) in the distal motor circuits around 4 weeks when first motor impairments occur, while proximal motor circuits showed no synaptic loss. Following experiments utilized a virus that conditionally overexpresses IGHBMP2 (AAV9-IGHBMP2fl/fl) upon Cre induction that restores the disease-causing IGHBMP2 protein specifically in motor neurons or proprioceptive neurons. Selective restoration of IGHBMP2 restores the entire motor circuit and NMD phenotype, identifying SMARD1 as a motor neuron-driven disease.

Symposium II

S05

Mismatch responses to sound source elevation deviants in mice

Alessandro Braga[1,2], Marc Schönwiesner[1,3]

[1] *Institute of Biology, Faculty of Life Sciences, University Leipzig, Germany,*

[2] *International Max Plank Research School NeuroCom, Max Plank Institute for Human Cognitive and Brain Sciences, Leipzig, Germany,*

[3] *International Laboratory for Research on Brain, Music, and Sound (BRAMS), Université de Montréal, QC, Canada*

Mismatch responses to sound source elevation have been shown in human EEG, but no comparable study has been performed in the rodent model. By employing a high-density rodent EEG system we were able to demonstrate the presence of attention-independent mismatch responses to elevation deviants in flip-flop oddball sequences in isoflurane-anesthetized rodents. The auditory ERP and corresponding mismatch responses observed in mice resembled those commonly obtained in human and non-human primates, with important latency differences. Furthermore, stimuli closer to midline (elevation +/- 30°) more reliably elicited mismatch responses compared to high-elevation stimuli (+90°). This might indicate that the cortical representation of sound source is a function of the distance from midline in either vertical direction, rather than being reliant on equivalent elevation-selective neuronal populations across the sagittal axis. Our results validate mice as a model for auditory deviance detection studies based on the variation of spatial features. However, similarities between human and rodent deviance detection phenomena should be investigated by taking into account inherent circuital differences in their cortical generators. To enable such translation, we are acquiring optical imaging data of the neuronal populations involved in the representation of sound source elevation.

S06

Macaca nemestrina in oil palm plantations: Changes in primate sociality under human impact

Anna Holzner[1,2,3], Nadine Ruppert[4,5], Anja Widdig[1,2,3]

[1] *German Centre for Integrative Biodiversity Research (iDiv), Halle-Jena-Leipzig, Germany*

[2] *Behavioural Ecology Research Group, Institute of Biology, University of Leipzig, Germany*

[3] *Department of Human Behaviour, Ecology and Culture, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany*

[4] *School of Biological Sciences, Universiti Sains Malaysia, Pulau Pinang, Malaysia*

[5] *Malaysian Primatological Society, Kulim Kedah, Malaysia*

Globally, wildlife is critically affected by the conversion of natural habitat into agricultural landscapes. Partially diverting foraging activities from primary forest into oil palm plantations, southern pig-tailed macaques (*Macaca nemestrina*) may benefit farmers as they actively hunt for plantation rats which cause substantial damage to the yield. Significantly reducing rat numbers, this primate can act as a biological pest control, as we previously showed. However, when ranging in plantations, macaques face multiple threats, such as an increased predation risk, conflicts with humans, and the exposure to chemical pollutants. To date, detailed knowledge on these impacts and potential behavioural adaptations is still lacking. Data on two groups of macaques inhabiting a forest-oil palm matrix in Peninsular Malaysia showed that, despite its strong dependency on the presence of nearby forest, *M. nemestrina* can partially adapt to anthropogenic habitats. However, this comes at cost of their social behaviour, the reduction of which is critical given that sociality significantly affects fitness. Specifically, we observed significant reductions of affiliative social interactions at the plantation while aggression increased. Likewise, mother-infant relationships were found to be disrupted by increased maternal protectiveness when ranging in plantations, potentially hampering population growth in this threatened species. Overall, this work improves our understanding of species' adaptability to anthropogenic landscapes, which may ultimately contribute to facilitating their coexistence with humans and preserving biodiversity.

S07

Suppression and Omission – Two of the same or totally different?

Valentina Tast[1], Erich Schröger[1], Andreas Widmann[1,2]
[1] *Institute of Psychology, Leipzig University, Germany*
[2] *Leibniz Institute for Neurobiology, Magdeburg, Germany*

The auditory N1 component is an event-related brain potential in response to acoustic transients reflecting sensory processing in auditory cortices. When a sound is self-generated by the participant, a reduction of the amplitude of the N1-component compared to externally produced sounds has been reported. This N1 suppression effect has been related to specific forward modeling allowing sensory attenuation of self-generated sensory input as well as to unspecific suppression during motor activity. When a strongly expected sound is unexpectedly omitted, a component in the N1 latency range, the so-called omission-N1 is elicited. As both the N1 suppression and the N1 omission effects are observed in a similar latency range and often assumed to reflect predictive processing, related underlying mechanisms have been suggested but so far not empirically been demonstrated. To test whether N1 suppression and omission-N1 indeed both rely on the predictability of the sound, we systematically manipulated the predictability of the sound in a self-generation paradigm in which in two conditions either 20% or 50% of the button presses did not generate a sound, inducing strong or weak expectations on sound occurrence. The resulting sound sequences from the active condition where subsequently replayed to the participants without them having to press the button in a passive condition. An omission-N1 was observed in the 20% but not in the 50% condition. A N1 suppression effect of similar amplitude was observed in both conditions. Thus, our results demonstrate a clear effect of predictability for the omission-N1, but no such difference for the N1 suppression. The results imply that the N1 suppression and the N1 omission phenomena rely on (at least partly) different mechanisms and put prediction related accounts for the N1 suppression in question.

Poster presentations

P01

Modelling the olfactory system using spiking neural networks with synaptic dynamics to study drifting in electronic noses

Ferney Beltran Velandia[1,2], Martin Bogdan[1], Nico Scherf[2], Marc Schönwiesner[3]
[1] *Department of Neuromorphic Information Processing, Faculty of Mathematics and Computer Science, University Leipzig, Germany*
[2] *Neural Data Science and Statistical Computing, Max Plank Institute for Human Cognitive and Brain Sciences, Leipzig, Germany*
[3]*Institute of Biology, Faculty of Life Sciences, University Leipzig, Germany*

Electronic noses (or e-noses) are devices to identify odors. They can be potentially applied in air quality systems, food industry, or many industrial environments. An E-nose is an array of electrochemical sensors to transduce odor molecules into electrical signals. But they suffer from a phenomenon called drifting (small non-deterministic temporal variations of the sensor response, when it is exposed to the same chemical under similar conditions). Drifting causes e-noses to have short life spans, which represents high maintenance costs for companies. Different fields have approached the drifting challenge, for example Neuromorphic Olfaction. It aims to emulate the behavior of the olfactory system in order to build technological devices (like e-noses) by using spiking neural networks (SNN). These SNN have some properties that reflect more similarities to biological neural networks than other artificial neural networks. Inspired by the robustness property of the olfactory system, short-term plasticity models (or synaptic dynamics) can be integrated into SNN to approach the drifting phenomenon. But similar to other artificial neural networks, SNN lacks clear representations to interpret and relate inputs and outputs. Therefore, neural manifolds techniques can be applied to find low-dimensional representations within high-dimensional output of SNN. These possible manifolds can help to understand how drifting can change internal representations of SNN, with and without synaptic dynamics. Additionally, the capability of biological neural networks to codify \textbf{information} in spike patterns is strongly influenced by the regulation of the network energy resources. The relationship between energy and information shapes the architecture of biological neural networks. Therefore, metrics of energy (in the synaptic level) and information (in the network level) are explored to study the proposed SNN, and to study the behavior of the possible manifolds that can represent the drifting phenomenon.

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P02

Just another new post-translational modification of α–Synuclein in Synucleinopathies?

Alexandra Bluhm[1], Maike Hartlage-Rübsamen[1], Sarah Schrempel[1], Stephan von Hörsten[2], Franziska Richter[3], Wei Xiang[4], Anja Schulze[5], Steffen Roßner[1]

[1] *Paul Flechsig Institute of Brain Research, University Leipzig, Germany*

[2] *Department for Experimental Therapy, University Clinics Erlangen and Preclinical Experimental Center, University of Erlangen-Nuremberg, Germany*

[3] *Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine Hannover, Germany*

[4] *Department Molecular Neurology, University Clinics Erlangen, Friedrich-Alexander- University of Erlangen-Nuremberg, Germany*

[5] *Department of Molecular Drug Design and Target Validation, Fraunhofer Institute for Cell Therapy and Immunology, Halle (Saale), Germany*

The so called “Bermuda triangle” (Villar-Piqué et al., 2016) between α-Synuclein (αSyn) structure, function and toxicity describes the delicate issue between loss of function and gain of function of αSyn. On one hand, the αSyn protein is implicated in physiological functions such as neurotransmitter release at the synapse and the regulation of gene expression in the nucleus. Conversely, pathological αSyn assemblies are characteristic for synucleinopathies, where αSyn aggregates can appear as Lewy bodies and Lewy neurites. Besides synucleinopathy-related mutations, post-translational modifications (PTM) can affect the complex Bermuda triangle in the direction towards toxicity and pathology. Here, we present a recently discovered pyroglutamate (pGlu) modification at Q79 of αSyn that promotes oligomer formation and neurotoxicity in synucleinopathies. The synthesis of pGlu79-αSyn requires two enzymatic reactions to generate the N-terminal Q79 residue and to subsequently catalyze glutamine cyclization into pGlu. The best candidates for these enzymes are matrix metalloproteinase-3 and glutaminyl cyclase (QC). However, why should this novel PTM of αSyn be so interesting among all those other αSyn PTMs that have been previously reported? Years ago, a similar pGlu-modification of Abeta peptides was discovered, which is also catalyzed by QC and which plays an important role in the pathogenesis of Alzheimer´s disease (AD). Intriguingly, pharmacological inhibition or genetic ablation of QC reduced the generation of toxic pGlu-Abeta and of the total Abeta load in experimental animals. As a result, there is an ongoing phase 2a/b clinical trial targeting QC for AD treatment (Vijverberg et al., 2021). We provide evidence that QC might have a similar pathogenic profile in synucleinopathies and, therefore, should be considered as a drug target for these clinical conditions as well.

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P03

Quantifying the synaptic Ca^{2+}-binding kinetics of Synaptotagmin-1, the Ca^{2+} sensor for transmitter release in the forebrain

Grit Bornschein, Simone Brachtendorf, Abdelmoneim Eshra, Jens Eilers, Stefan Hallermann, Hartmut Schmidt

Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

The Ca^{2+} sensitivity of transmitter release is a major determinant of synaptic fidelity and plasticity. Two Synaptotagmin (Syt) isoforms, Syt1 and Syt2, are the main Ca^{2+} sensors triggering fast release in the brain; however, only Ca^{2+} binding to Syt2, the dominant isoform in the hindbrain, has been studied in detail [1,2]. For Syt1, the dominating sensor in the forebrain, similar quantitative detail from brain synapses is not available at present.

To quantify the Ca^{2+}-binding kinetics of Syt1 in the context of the intact release machinery we adapted a method combining Ca^{2+}-uncaging, two-photon G/R Ca^{2+}-imaging and patch-clamp electrophysiology [1–3] to pairs of connected layer 5 pyramidal neurons in the S1 somatosensory cortex of mature mice. To define the local intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) at the release sensor, $[Ca^{2+}]_i$ was uniformly elevated in the presynaptic terminal from a caged Ca^{2+} compound by brief UV-flashes. Changes in the presynaptic G/R fluorescence were measured from individual boutons by point-mode two-photon imaging and converted to $\Delta[Ca^{2+}]_i$ based on cuvette calibrations. The corresponding EPSCs were recorded and synaptic delays and deconvolution-based release rates (RR) were quantified.

Release typically started at $\Delta[Ca^{2+}]_i$ above ~4 µM and peak RR increased until $\Delta[Ca^{2+}]_i$ of ~25 µM, saturating thereafter with no substantial further increase up to $\Delta[Ca^{2+}]_i$ of ~100 µM. Synaptic delays decreased concomitantly. In comparison to Syt2 [1,2], the cooperativity of the $[Ca^{2+}]_i$-dependency of Syt1-triggered release was similar (Hill coefficient of 4.2). However, embedded in the intact release machinery the affinity of Syt1-triggered release was two-fold lower (K_D of 20 µM) than the affinity of Syt2-triggered release. This finding has important implications for the reliability of cortical synaptic transmission. In particular influx – release coupling might be limited to smaller distances than previously thought.

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P04

Cooperational strategies and cardiophysiological correlates of maltreated youth

Angelika J. Bracher[1,2], Kai von Klitzing[1], Lars O. White[1], Jan Keil[1]

[1] *Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University Hospital Leipzig, Germany*

[2] *International Max Plank Research School NeuroCom, Max Plank Institute for Human Cognitive and Brain Sciences, Leipzig, Germany*

Behavioral research using game-theoretical paradigms has yielded conflicting evidence of hyper- and hypo-cooperative strategies with peers among children exposed to abuse and neglect (Keil et al., 2019; Pitula et al., 2017). Building on prior research, we seek to investigate potential psychophysiological mechanisms through which early life adversity impacts cooperative behaviour. Recent meta-analytic work suggests that Heart Rate Variability (HRV) may be a mediator between early life adversity and psychopathology (Sigrist et al., 2021). Additionally, high-frequency HRV is a known correlate of self-regulation and positive social engagement and may thus provide a promising candidate to further elucidate such biological mechanisms (Beauchaine & Thayer, 2015). We therefore aim to investigate hf-HRV and cooperative behaviour in youths oversampled for risk of adversity. We expect to find that at-risk adolescents show a hyper-cooperative coupled with reduced hf-HRV (i.e., greater vagal withdrawal; Young-Southward et al., 2020).

As part of a prospective longitudinal study (AMIS; White et al., 2015), 380 participants (aged 12 to 22) were divided into control and at-risk groups via a multi-source strategy drawing on reports from caregivers and official records from child protection services (e.g., Maltreatment Classification Interview). Participants played the *Pizzagame* (Keil et al., 2017), a child-appropriate computerized public goods game to assess cooperative behaviours. Additionally, for a matched subsample (n=80) we measured *local power* (Bornemann et al., 2016), a short-term estimate of hf-HRV during the task. Mixed model ANOVAs revealed significant main effects of different cooperational strategies during the *Pizzagame* but no effects of hf-HRV could be found. We also did not find evidence of hyper-cooperation or vagal withdrawal within adolescent with maltreatment experience.

P05

Mismatch responses to sound source elevation deviants in mice

Alessandro Braga[1,2], Marc Schönwiesner[1,3]
[1] *Institute of Biology, Faculty of Life Sciences, University Leipzig, Germany,*
[2] *International Max Plank Research School NeuroCom, Max Plank Institute for Human Cognitive and Brain Sciences, Leipzig, Germany,*
[3] *International Laboratory for Research on Brain, Music, and Sound (BRAMS), Université de Montréal, QC, Canada*

Mismatch responses to sound source elevation have been shown in human EEG, but no comparable study has been performed in the rodent model. By employing a high-density rodent EEG system, we were able to demonstrate the presence of attention-independent mismatch responses to elevation deviants in flip-flop oddball sequences in isoflurane-anesthetized rodents. The auditory ERP and corresponding mismatch responses observed in mice resembled those commonly obtained in human and non-human primates, with important latency differences. Furthermore, stimuli closer to midline (elevation +/- 30°) more reliably elicited mismatch responses compared to high-elevation stimuli (+90°). This might indicate that the cortical representation of sound source is a function of the distance from midline in either vertical direction, rather than being reliant on equivalent elevation-selective neuronal populations across the sagittal axis. Our results validate mice as a model for auditory deviance detection studies based on the variation of spatial features. However, similarities between human and rodent deviance detection phenomena should be investigated by taking into account inherent circuital differences in their cortical generators. To enable such translation, we are acquiring optical imaging data of the neuronal populations involved in the representation of sound source elevation.

P06

Effects of post-training transcranial direct current stimulation on motor consolidation and dorsal premotor cortex – primary motor cortex interaction: a resting-state EEG study

Alhuda Dabbagh[1], Mina Jamshidi Idaji[2], Elinor Tzvi[1,3], Vadim V. Nikulin[2], Jost-Julian Rumpf[1], Joseph Classen[1]

[1] *Department of Neurology, University Hospital Leipzig, Germany*

[2] *Research Group Neural Interactions and Dynamics, Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany*

[3] *Syte Institute, Hamburg, Germany*

Background: The process of learning a new motor skill can be divided into different phases. The initial learning phase (online) is followed by an offline phase (consolidation) during which the motor engram acquired through training is transformed into a more robust representation in the absence of further task practice. Offline (post-training) application of transcranial direct current stimulation (tDCS) to the primary motor cortex (M1) has been shown to facilitate consolidation in healthy older people. tDCS-induced modulation of neuronal oscillatory activity in the motor consolidation network, which is not fully understood, may underlie this effect on consolidation. Furthermore, previous research pointed to an especially important role of premotor-motor interaction in offline motor consolidation.

Methods: Twenty-four healthy young participants (22.9±2.9 y, 13 female) took part in two experimental sessions corresponding to a post-training sham and real tDCS intervention, which were separated by at least 14 days. tDCS was applied for 15 minutes (1 mA) with the anode over left M1 immediately following a training session of 14 blocks of an explicit sequential finger tapping task performed with the right hand. Task performance was retested (4 blocks) after 8 hours. Motor performance was assessed as the average time to perform a correct sequence within a given block. Consolidation was defined as the difference between motor speed performance at the end of the initial training session (average performance across the last two blocks of the training session) compared to the performance at the beginning of the delayed retest (average across the first two retest blocks). 64-channel "resting-state" EEG was recorded before training and after the post-training tDCS intervention to investigate beta-band power and connectivity changes by computing coherence and the phase slope index between the primary (M1) and premotor cortex (PMC, two subregions, dorsal and anterior) after reconstructing the signals in source space by using exact low resolution brain electromagnetic tomography (eLORETA; Pascual-Marqui et al. 2011).

Results: RmANOVA revealed a significant effect of *block* (14 levels, $p<0.001$), which was driven by increasing speed performance across blocks of training. There was neither a significant main effect of *session* (sham/active tDCS) nor a significant interaction of *session* and *block* indicating similar training performance before the post-training sham and active

tDCS intervention. However, consolidation following the active and sham post-training tDCS interventions did not significantly differ (p=0.342).

Post-intervention beta-band frequency power in M1 and both subregions of the PMC increased significantly (all $p<0.001$) independent of the type (active/sham) of the post-training tDCS intervention (interaction time*session, $p\geq0.48$). There were no consistent changes in connectivity between left anterior PMC and left M1. By contrast, connectivity analyses revealed decreased functional connectivity following the post-training active tDCS intervention between left M1 and left dorsal PMC ($z=-2.103$; $p=0.035$), while there was no relevant change after sham tDCS ($z=-0.852$; $p=0.394$). Furthermore, analysis of directed connectivity between M1 and dorsal PMC revealed a trend for an interaction of session and time ($p=0.056$). Post-hoc t-tests suggested that this effect was driven by a significant decrease in information flux between dorsal PMC and M1 following post-training active tDCS ($p=0.004$), whereas there was no significant decrease in sham session ($p=0.911$). Across all participants and sessions (sham and active tDCS), we found a trend for a positive correlation ($r=0.27$; $p=0.076$) of post-tDCS dorsal PMC-M1 connectivity and the extent of motor consolidation.

Conclusion: Although we found no behavioural effect of post-training tDCS on consolidation in healthy young people, post-training active tDCS appeared to modulate dorsal PMC-M1 connectivity. The trend for the association of dorsal PMC-M1 connectivity and the extent of consolidation may suggest that dorsal PMC-M1 connectivity changes play a role in motor consolidation.

P07

Cerebellar pathology in two mouse models for spinal muscular atrophy

Florian Gerstner, Christian Simon
Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

Spinal muscular atrophy (SMA) is characterized by the degeneration of spinal motor circuits resulting in impaired voluntary movement and muscle atrophy. In contrast, potential pathology of the brain contributing to the SMA phenotype has not been reported. The motor circuits in the cerebellum are critical for motor learning and voluntary movements by processing proprioceptive input and modulating motor output, which are both affected in SMA. Therefore, we investigated here the morphology of different layers of the cerebellum and Purkinje cells (PC) - the sole functional output of the cerebellar cortex - in the SMNΔ7 and Taiwanese SMA mouse models. We performed immunohistochemistry and confocal analysis of sagittal vermis section of end-stage mutants and control cerebelli. Our results showed a strongly underdeveloped cerebellum including reduced size of all cerebellar layers and PC lacking dendritic trees in Taiwanese SMA mice. SMNΔ7 mutant mice also exhibited a slightly reduced cerebellum, but while some lobuli remained resistant, others exhibit smaller cerebellar layers with vast PC death. Interestingly, vulnerable PC exhibited a strong p53 upregulation prior to their death, suggesting a role of p53 in PC pathology. Lastly, the excitatory synaptic inputs onto PC were largely reduced in SMNΔ7 mutant mice, indicating a reduced activation of PC in SMA. Taken together, our results suggest a similar pathology in the cerebellum as reported in the spinal cord of SMA mice and might suggest the cerebellum as a contributor to SMA pathology.

P08

Octopaminergic signaling during locomotion behavior of *Drosophila melanogaster* larvae

Alexandra Großjohann, Ronja Badelt, Mitra Gannadi-Khosh, Dennis Pauls, Andreas Thum

Department of Genetics, Institute of Biology, Faculty of Life Sciences, Leipzig University, Germany

Octopamine is the invertebrate equivalent of noradrenaline and acts in various physiological processes as a neuromodulator in *Drosophila melanogaster*. Identifying how octopamine is involved in one of such physiological processes – the locomotor behavior – we aim to get a more detailed understanding of the functionality of the octopaminergic system. Six octopamine receptor mutant lines and one mutant line for the synthesis enzyme tyramine β hydroxylase (Tβh) were used to examine the role of octopamine in either the whole body (Trojan Exon[1]) or only in neuronal cells of the central nervous system (tissue specific RNAi induced knockdown). In a locomotion assay the crawling behavior of *Drosophila melanogaster* larvae was imaged and tracked using FIM Imaging & FIM Track[2] and subsequent analysis identified candidate components of the octopaminergic system involved in the locomotor behavior.

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P09

Human iPSC-derived neurons have large presynaptic action potentials

Thomas Kaas, Torsten Bullmann, Andreas Ritzau-Jost, Stefan Hallermann
Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

The amplitude and the duration of presynaptic action potentials critically control neurotransmitter release. The properties of presynaptic action potentials remain poorly understood because measurements with high temporal resolution are technically challenging. Presynaptic action potentials have so far only been measured at a limited number of vertebrate but not human neurons. We therefore performed patch-clamp recordings from presynaptic boutons of cultured neurogenin2-induced human iPSC-derived neurons. To analyze human presynaptic properties, we first measured basic morphological and functional parameters of cultured neurogenin2-induced human iPSC-derived neurons after 3 to 9 weeks of culturing in four different established media.

P10

NMDA-receptor-Fc-fusion constructs neutralize anti-NMDA receptor antibodies

Toni Kirmann, Stefan Hallermann
Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common subtype of autoimmune encephalitis characterized by a complex neuropsychiatric syndrome ranging from memory impairment and psychosis to coma. Patients develop an intrathecal immune response against NMDARs with antibodies that presumably bind to the amino-terminal domain (ATD) of the GluN1 subunit. The therapeutic response to immunotherapy is often delayed and does not directly interfere with intrathecal synthesis of pathogenic antibodies. Therefore, new therapeutic approaches for fast neutralization of NMDAR antibodies are needed. Here, we developed fusion constructs consisting of the Fc part of immunoglobulin G and the ATDs of either GluN1 or GluN2B or both, GluN1 and GluN2B, subunits. Surprisingly, both subunits were required to generate high-affinity epitopes. The construct with both subunits efficiently prevented NMDAR binding of patient-derived monoclonal antibodies and of patient cerebrospinal fluid containing high-titer NMDAR antibodies. Furthermore, it inhibited the internalization of NMDARs in rodent dissociated neurons and human induced pluripotent stem cells (iPSC)-derived neurons. Finally, the construct stabilized NMDAR currents recorded in rodent neurons. Our results demonstrate that both GluN1 and GluN2B subunits contribute to the main immunogenic region of the NMDAR and provide a promising strategy for fast and specific treatment of NMDAR encephalitis, which can complement immunotherapy.

P11

The secretory pathway protein Sec31 controls composition and function of the presynaptic active zone

Marius Lamberty[1], Kerstin Reim[2], Jutta Meyer[2], Olaf Jahn[2,3,4], Robert J. Kittel[1]

[1] *Department of Animal Physiology, Faculty of Life Sciences, Leipzig University, Germany*

[2] *Department of Molecular Neurobiology, Max Planck Institute of Multidisciplinary Sciences, Göttingen, Germany*

[3] *Neuroproteomics, Max Planck Institute of Multidisciplinary Sciences, Göttingen, Germany*

[4] *Translational Neuroproteomics, Department of Psychiatry and Psychotherapy. University Medical Center Göttingen, Germany*

Information processing in the nervous system is shaped by neurotransmitter release from synaptic vesicles (SVs) at the presynaptic active zone. The cytomatrix at the active zone (CAZ) controls exocytosis by physically coupling SVs to release-sites. Correspondingly, the protein composition of the CAZ is functionally highly relevant and disrupting its molecular organization impairs synaptic transmission. However, the molecular mechanisms governing CAZ assembly are incompletely understood. The ELKS/CAST homolog Bruchpilot (Brp) is a core CAZ component in *Drosophila melanogaster*, which supports neurotransmitter release by tethering SVs and clustering voltage-gated calcium channels at the active zone. Using a short C-terminal Brp fragment as bait we found a strong enrichment of the secretory pathway protein Sec31 in affinity purification assays. Here, we further investigated this interaction by combining super-resolution microscopy and electrophysiology. Consistent with the biochemical results, Sec31 and Brp colocalize within the neuronal endoplasmatic reticulum. RNA interference mediated knock-down and mosaic knock-out of *sec31* in motoneurons reduces Brp expression at neuromuscular CAZs. This is accompanied by decreased active zone levels of voltage-gated calcium channels and the priming protein Unc13A. As a result, neurotransmitter release probability drops and synaptic efficacy is reduced. We conclude that Sec31 activity influences CAZ assembly and thereby impacts presynaptic function.

P12

The role of inefficient demyelination for axonal integrity in models of toxic and autoimmune demyelination

Maria Lehning[1], Erik Schäffner[1,2], Mar Bosch-Queralt[1], Stefan Berghoff[2], Martin Krüger[3], Tilo Reinert[1,4], Alonso Barrantes-Freer[1], Klaus-Armin Nave[2], Robert Fledrich[2,3] and Ruth Stassart[1,2]

[1]*University Clinic Leipzig, Paul Flechsig Institute of Neuropathology, Leipzig, Germany*
[2]*Max-Planck-Institute of Experimental Medicine, Department of Neurogenetics, Göttingen, Germany*
[3]*University of Leipzig, Institute of Anatomy, Leipzig, Germany*
[4]*Max-Planck-Institute for Human Cognitive and Brain Sciences, Department of Neurophysics, Leipzig, Germany*

Multiple sclerosis, an autoimmune disorder affecting more than 2 million people worldwide, is characterized by demyelinating lesions in the central nervous system. Importantly, neuronal loss rather than demyelination itself is the main contributor to long-term neurological symptoms. However, the actual implication of demyelination to axonal pathology and degeneration remains only partially understood. We here applied the toxic lysolecithin and Cuprizone demyelinating mouse models as well as the experimental autoimmune encephalomyelitis (EAE) in order to analyze axonal integrity as a function of the myelination state. Our data indicate that inefficient demyelination, in contrast to rapid and efficient demyelination, contributes to irreversible axonal damage, possibly downstream of impaired axonal support by the perturbed myelinating oligodendrocyte. In detail, upon lysolecithin-induced demyelination, large numbers of swollen axons, characterized by organelle accumulation, arise. In contrast to the rapidly demyelinating lesion center, we found an increased number of swollen axons to be still myelinated at the lesion border where demyelination kinetics are decelerated. Interestingly, in this area, we also noticed a higher number of irreversibly degenerated axons which were almost exclusively myelinated. In line, also in the cuprizone model, axons with irreversible signs of damage were found to be myelinated throughout the time course of demyelination. We further analyzed potential oligodendroglial malfunctioning and its association to axonal damage in the EAE model. Our analysis revealed that irreversible damaged axons had an enlarged inner myelin tongue, a structure which is thought to be implicated in metabolite transport. We propose that in a demyelinating condition, alterations in oligodendroglial structure might be detrimental for its function in axonal support and thus also for axonal integrity. Rapid demyelination might however be beneficial for the short-term survival. These data highlight the complexity of myelin-axon-interactions and the need to better understand involved mechanisms in demyelinating diseases.

P13

A novel battery of behavior-based assays in larval zebrafish and its potential to elucidate neurodevelopmental toxicity mechanisms with a focus on deficits in learning and memory

David Leuthold, Nadia C. Herold, Tamara Tal
Helmholtz-Centre for Environmental Research – UFZ, Leipzig, Germany

Approximately 17% of US children are affected by developmental disabilities including intellectual or learning deficits. Chemical exposure can contribute to neurodevelopmental disorders, a phenomenon known as developmental neurotoxicity (DNT). It is imperative to identify chemicals causing DNT and to understand underlying adverse outcome pathways (AOPs). Behavioral alterations represent a comprehensive readout of impairment in neurodevelopment and neuronal signaling but current regulatory DNT studies are restricted to rodents. Alternative DNT new approach methods (NAMs) are needed to better protect human and environmental health. While *in vitro* DNT NAMs capture specific neurodevelopmental processes, they fail to reflect the full range of events and interactions that orchestrate nervous system development and function. To fill this gap, we developed a battery of 10 automated behavior assays for measuring visual and acoustic behaviors including habituation learning behavior in larval zebrafish, a 3R-compliant model amenable to higher-throughput chemical screens. The sequential behavior assays were optimized for photic and acoustic stimulus duration, intensity, number and sequence, and zebrafish developmental stage. The DNT NAM was evaluated against pharmaceuticals with diverse mechanisms including NMDA receptor (NMDAR) antagonism, GABA receptor antagonism and acetylcholinesterase inhibition. The battery recapitulates rodent learning deficits following acute exposure to prototypical NMDAR antagonists MK-801 and DL-2-amino-5-phosphonopentanoic acid. For the first time, we show that early life stage exposure to these compounds disrupts zebrafish learning behavior later in development. Additionally, certain US EPA ToxCast chemicals positive for NMADR perturbation *in vitro* were confirmed to cause learning deficits in larval zebrafish (e.g., clorophene). Beyond application to impaired learning AOPs, exposure to the GABA antagonist picrotoxin resembles an epileptic seizure phenotype, highlighting the applicability of behavioral phenotyping to other DNT-related AOPs. In summary, the 10-assay DNT NAM can identify chemicals with specific effects on neuronal signaling and neurodevelopment, improves our understanding of underlying AOPs, and can accelerate DNT research in an alternative test system.

P14

Investigations on the pathophysiology of asparagine synthetase-deficiency induced microcephaly

Maximilian Liebmann, Ulrike Winkler, Dorit John, Tabea Junge, Johannes Hirrlinger
Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

Microcephaly is a neurological condition where the head circumference of a baby is more than three standard deviations below an age and sex matched population, usually associated with an underdeveloped brain (microencephaly). Patients may present with a spectrum of neurological symptoms, including hyperactivity, seizures, impaired cognitive development, and facial distortions. Mutations of different genes have been identified to cause microcephaly. Our working group identified two novel mutations in the gene of asparagine synthetase (ASNS) in two affected siblings, which were inherited in a compound-heterozygous manner (Schleinitz et al. 2018).

Asparagine synthetase (ASNS) is an enzyme synthesizing the non-essential amino acid asparagine (Asn) via the following reactions:

$$Asp + Gln + ATP \rightarrow Asn + Glu + AMP + PP_i$$

$$Asp + NH_4 + + ATP \rightarrow Asn + AMP + PP_i$$

However, the pathophysiology linking the mutation within the ASNS gene to the phenotype of microcephaly is unknown. Therefore, we generated a conditional, neuron specific ASNS knockout mouse line. We show that these mice develop microcephaly as observed in human patients. Furthermore, we analyzed multiple cell populations (NeuN, parvalbumin, calbindin-D28-K) in these mice and quantified a variety of (inter)neuronal cell parameters comparing control (WT) and knockout (KO) mice. Among the investigated markers, cortical calbindin+ cells show significant changes in size, fluorescence, and distribution. These results give further insight on the hypothesized pathomechanisms and point out potential targets for future research.

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P15

Changes of brevican in animal models of dystonia

Anika Lüttig, Stefanie Perl, Angelika Richter

Institute of Pharmacology, Pharmacy and Toxicology, Faculty of Veterinary Medicine, University of Leipzig, Germany

Alterations in neuronal plasticity appear to play a critical role in dystonia. An important modulator of neuronal plasticity is represented by the perineuronal nets (PNs) located around the cell somata and proximal dendrites of neurons, particularly parvalbumin reactive (PV^+) interneurons. An important component of PN are the chondroitinsulfate proteoglycans (CSPGs) such as aggrecan and brevican. While the role of abnormal PN expression in the pathophysiology of dystonia is largely unknown, one form of canine paroxysmal dyskinesia (episodic falling syndrome) was discovered to be caused by a deletion in the brevican encoding gene. Therefore, in the present work we investigated at first whether brevican expression is altered in animal models of dystonia.

As a phenotypic model of paroxysmal dystonia, we used the *dt*^{sz} hamster, in which the maturation of PV^+ interneurons is likely delayed. In contrast, the DYT1 KI mouse is regarded as an etiologic model for a permanent form of generalized dystonia. These mice show no dystonic symptoms but moderate sensorimotor changes. We examined both animal models immunohistochemically using brevican intensity measurements and cell counting to compare dystonic (*dt*^{sz} hamster, n = 8, and heterozygous DYT1 KI mouse, n = 9, respectively) and control animals (hamster n = 5, mouse n = 8). We also added protein (Western blot) and mRNA expression (qPCR) assays.

Comparison of *dt*^{sz} and control hamsters revealed interesting differences within the basal ganglia-thalamo-cortical circuit. Thus, a lower number of brevican positive cells to the total number of PV^+ cells (percentage of $Brev^+$ in PV^+) in the motor cortex and striatal neurons with low PV reactivity became evident. Since measurements of the whole brevican immunofluorescence intensity indicated higher expression of brevican in the striatum and ventromedial thalamus, western blot and qPCR analyses are under the way. In contrast to mutant hamsters, the studies in the DYT1-KI mouse model showed only a subtle increase of $Brev^+/PV^+$ in the motor cortex.

In the *dt*^{sz} hamster model, developmental disruption of the PN could contribute to the presumed disinhibition of PV^+ neurons and abnormal plasticity within the basal ganglia circuit. However, it remains unclear whether the findings represent a cause of dystonia or the consequences of other changes. In contrast to the hamster model, the higher number of $Brev^+/PV^+$ in the motor cortex of the mouse model could represent a reason for the lack of typical dystonic symptoms in DYT1 KI mice. Together, the present data suggest that PN may play a role in both dystonia models which deserves investigations of other components of PN, such as HAPLN4 and aggrecan. Current studies on the mechanisms of deep brain stimulations (DBS) in mutant hamsters include PN, because induced PN changes may influence neuronal plasticity and thereby improve dystonia.

Funded by the DFG within the Collaborative Research Centre 1270 ELAINE.

P16

Cortical encoding of auditory distance

Jakab Pilaszanovich[1], Marc Schönwiesner[1,2]

[1] *Institute of Biology, Faculty of Life Sciences, University Leipzig, Germany,*
[2] *International Laboratory for Research on Brain, Music, and Sound (BRAMS), Université de Montréal, QC, Canada*

The cortical encoding of sound distance is poorly understood. Several monaural cues contribute to the perception of sound source distance, including intensity, direct-to-reverberant sound energy, high-frequency attenuation, and vocal effort. Binaural cues (interaural time and intensity differences) play little to no role in this percept. Several of the distance cues are thought to be extracted in the cortex. We thus aim to measure the cortical encoding of auditory distance through a series of EEG experiments employing different acoustic features as distance cues.

Three sets of intensity equalised stimuli were generated and rendered at different distances in a simulated rectangular room (10x30x3m): 1) bursts of pink noise 2) unidentifiable sound objects compiled from anechoic recordings of impact sounds of everyday objects, and 3) anechoically recorded vocalisations with different levels of vocal effort. These stimuli are then presented in a within-subject EEG experimental design for which the subsequent analysis aims to explore variations in the amplitude of event related potentials (ERPs) as a function of perceived distance. We report systematic covariations of EEG source components with sound source distance. The comparison across stimulus conditions allows us to differentiate genuine representations of distance from representations of the underlying acoustic cues.

P17

Structure and function of larval knob sensilla

Vincent Richter[1], Anna Rist[1], Michael Laumann[2], Anton Miroschnikow[3], Michael J. Pankratz[3], Albert Cardona[4,5], Andreas S. Thum[1]

[1] *Department of Genetics, Institute of Biology, Faculty of Life Sciences, Leipzig University, Germany*
[2] *Department of Biology, Electron Microscopy Centre, University of Konstanz, Germany*
[3] *Department of Molecular Brain Physiology and Behavior, LIMES Institute, University of Bonn, Bonn, Germany*
[4] *Department of Physiology, Development, and Neuroscience, Cambridge University, UK*
[5] *MRC Laboratory of Molecular Biology, Cambridge Biomedical Campus, Cambridge, UK.*

The Drosophila melanogaster larva allows to study various aspects of behavior including taxis, kinesis and even learning and memory. All behavior that the animal exhibits is based on processing of sensory information from environmental stimuli, the internal state and acquired experience. But how do larvae actually perceive their environment and what sensory organs are they equipped with? Does the ultrastructure of these sensory organs allow for conclusions about their function? Drosophila melanogaster larvae possess external sense organs on their head, thoracic, and abdominal segments specialized to receive diverse sensory information. Besides the specialized head organs, we find three main types of external sensilla spread over the larval body wall: papilla sensilla, hair sensilla and knob sensilla. Here, we focus on the latter, as the former two are of simple organization and mainly exhibit structural properties known to serve mechanosensory function. Knob sensilla, on the other hand, were thought to serve thermo/hygrosensory function, but this is rather speculative. Therefore, we examined the ultrastructure at high resolution by serial-sectioning transmission electron microscopy and traced exemplary axonal paths to the ventral nerve cord. We created a spatial map showing the distribution of knob sensilla in the larval sensory system and compared our results with the literature, to make well-grounded predictions about their putative functions. This will serve as a basis for further molecular and functional studies.

P18

Detecting malingered memory deficits with the word completion memory test – first data of a revised German version

Juliane Riedl, G Mohr, O John, Cornelia Exner
Institute of Psychology, Leipzig University, Germany

Malingering occurs in up to 40% of neuropsychological assessments. Neither performance tests themselves nor experts are sufficiently able to identify feigned test results. For this reason a many Malingering Tests have been developed. But most of them can easily be faked, when the subject is mad aware of their rationale. The Word Completion Memory test is a new test to identify even intelligent or prepared persons malingering memory deficits. In this study, 34 amnestics and 34 experimental simulants were examined with the WCMT. Results showed, that 81,8% could be correctly classified (as Amnestic or Simulant) by the test. A ROC-Analysis also revealed high sensitivity and specificity rates. In these first results, the test proved as a valid and economical instrument. However, further validation is needed.

P19

Predicting performances in cognitive tests from fMRI data with discrete curvature

Michelle Roost, Jürgen Jost
Max Planck Institute for Mathematics in the Sciences, Leipzig, Germany

The human brain forms a complex and functional network on many scales whose regions are interconnected. We analyse the resulting network based on task-based fMRI data from 390 healthy participants of the Human Connectome Project. Using the geometric-inspired edge-based measures of Forman-Ricci and Ollivier-Ricci curvature we reduce the dimensionality of the network and predict the participants' performances in cognitive tests. The strategy for this is a partial least squares regression and cross-validation.

P20

In vivo optogenetic inhibition of striatal parvalbumin-reactive interneurons: Future perspectives for optodialysis studies in DYT1 knock-in mice

Anja Schulz, Christin Helmschrodt, Angelika Richter

Institute of Pharmacology, Pharmacy and Toxicology, Faculty of Veterinary Medicine, University of Leipzig, Germany

Abnormal striatal plasticity in the striatum plays a crucial role in the pathophysiology of dystonia - a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal postures and movements. Evidence from animal models support the loss of inhibition at circuit level and suggest a dysfunction of striatal parvalbumin-reactive interneurons (Parv+) as the main inhibitory input onto striatal projection neurons.

We investigated the effects of a loss of inhibition in the striatum on the development of dystonic signs and changes in neuronal activity. Therefore, we used *in vivo* optogenetic inhibition of Parv+ in a genetic mouse model of DYT1 dystonia. DYT1 knock-in mice (DYT1 KI) reflect a non-symptomatic human mutation carrier, but show subtle sensorimotor deficits and pattern of abnormal synaptic plasticity. While optogenetic inhibition of Parv+ did not induce abnormal movements such as dystonic signs, it revealed genotype-related differences in neuronal activity. Stimulated DYT1 KI showed decreased striatal neuronal activity and increased activation of cholinergic interneurons due to optogenetic inhibition of Parv+.

To further investigate the role of Parv+ in DYT1 dystonia, we combine optical manipulations of Parv+ with simultaneous measurement of neurotransmitters in freely behaving mice (optodialysis). Thus, a microdialysis probe is implanted in close proximity to the optical fiber and microdialysate is collected before, during, and after optogenetic inhibition of Parv+.

The effects of Parv+ inhibition on extracellular neurotransmitter levels of GABA, glutamate, acetylcholine, and dopamine are investigated in wt and DYT1 KI mice. This will provide knowledge about the basic function of striatal Parv+ and explanatory approaches for changes in neuronal activity in DYT1 KI shown in the previous study. Furthermore, ongoing micro- and optodialysis studies can provide insights into altered and unbalanced dystonia-related neurotransmitters.

Funded by a research grant for young scientists of the Faculty of Veterinary Medicine, University Leipzig

P21

Area-specific differentiation of neocortical synaptic coupling distances

Max Schwarze, Grit Bornschein, Simone Brachtendorf, Jens Eilers and Hartmut Schmidt[1]

Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

[1] Correspondence: Hartmut.Schmidt@medizin.uni-leipzig.de

The physical coupling distance between presynaptic Ca^{2+} channels and transmitter-filled synaptic vesicles is a fundamental determinant of their release probability (*pv*). Investigations at different excitatory synapses in different parts of the matured brain, including brainstem, cerebellum and neocortex, indicate that highly reliable synapses processing sensory information operate with tight coupling, while highly plastic excitatory synapses in the hippocampus were found to use loose coupling. Hence, it appears that in the mature brain tight coupling is favored by reliable synapses and loose coupling by highly plastic synapses.

To probe this hypothesis at the same type of synapses within the same part of the matured brain, we focused on two functionally distinct areas of the neocortex, the prefrontal (PFC) and the somatosensory (S1) cortex and analysed coupling distances at synapses between pyramidal neurons in layer 2/3 (L2/3PNs) and layer 5 (L5PNs). We preformed whole-cell recordings from L5PNs in acute slices and stimulated connected L2/3PNs extracellularly.

Synapses in PFC showed paired-pulse facilitation, while synapses in S1 possessed paired-pulse depression, indicating that *pv* in PFC is lower than in S1. The Ca^{2+} chelator EGTA-AM decreased EPSCs in PFC significantly to 66% of the control value (P=0.03), whereas EPSCs in S1 remained unchanged (102%; P=0.9). These findings suggest that L2/3PN to L5PN synapses in PFC operate with loose coupling as opposed to tight coupling in S1. Our results show that coupling distances of the same synapses differ between cortical areas, thus, providing evidence that the presynaptic nanostructure is adapted to its cortex-area related function.

P22

Suppression and Omission – Two of the same or totally different?

Valentina Tast[1], Erich Schröger[1], Andreas Widmann[1,2]
[1] *Institute of Psychology, Leipzig University, Germany*
[2] *Leibniz Institute for Neurobiology, Magdeburg, Germany*

The auditory N1 component is an event-related brain potential in response to acoustic transients reflecting sensory processing in auditory cortices. When a sound is self-generated by the participant, a reduction of the amplitude of the N1-component compared to externally produced sounds has been reported. This N1 suppression effect has been related to specific forward modeling allowing sensory attenuation of self-generated sensory input as well as to unspecific suppression during motor activity. When a strongly expected sound is unexpectedly omitted, a component in the N1 latency range, the so-called omission-N1 is elicited. As both the N1 suppression and the N1 omission effects are observed in a similar latency range and often assumed to reflect predictive processing, related underlying mechanisms have been suggested but so far not empirically been demonstrated. To test whether N1 suppression and omission-N1 indeed both rely on the predictability of the sound, we systematically manipulated the predictability of the sound in a self-generation paradigm in which in two conditions either 20% or 50% of the button presses did not generate a sound, inducing strong or weak expectations on sound occurrence. The resulting sound sequences from the active condition where subsequently replayed to the participants without them having to press the button in a passive condition. An omission-N1 was observed in the 20% but not in the 50% condition. A N1 suppression effect of similar amplitude was observed in both conditions. Thus, our results demonstrate a clear effect of predictability for the omission-N1, but no such difference for the N1 suppression. The results imply that the N1 suppression and the N1 omission phenomena rely on (at least partly) different mechanisms and put prediction related accounts for the N1 suppression in question.

P23

N-type calcium channels boost vesicle recruitment during sustained synaptic activity at mature parallel-fiber to Purkinje cell synapses

Magdalena Wender, Hartmut Schmidt
Carl-Ludwig-Institute of Physiology, Medical Faculty, University of Leipzig, Germany

Parallel fiber (PF) to Purkinje cell (PC) synapses in the mature cerebellum show pronounced facilitation during high-frequency activity. Their persistent facilitation is enabled by ultra-fast vesicle recruitment and overfilling. During postnatal synapse maturation N- and R-type voltage-dependent calcium channels (Ca_vs) lose their function in gating evoked release. In mature boutons, P/Q-type currents provide the almost exclusive trigger for evoked release and R-type currents are required for the induction of presynaptic long term potentiation. However, the functional significance of N-type Ca_vs remained elusive in mature boutons. Here, we addressed the hypothesis that N- and/or R-type Ca_vs are engaged in ultra-fast vesicle recruitment during repetitive evoked release. First, PFs were stimulated by brief bursts of 5 action potentials (APs) at 20 Hz and excitatory postsynaptic potentials (EPSCs) were recorded in whole-cell patch-clamped PCs. Neither EPSC amplitudes nor paired pulse ratios were affected by the N- and R-type blockers ω-conotoxin and SNX-482, respectively, indicating that vesicle recruitment during brief bursts of APs is independent of Ca^{2+} influx through N- and R-type Ca_vs. Second, synapses were activated by trains of 50 APs at 20 Hz in 6 mM extracellular Ca^{2+} concentration. Cumulative analysis of EPSC amplitudes revealed that N-type but not R-type currents significantly boosted steady-state vesicle recruitment during sustained high-frequency synaptic activity. Finally, we analyzed the recovery from steady-state by applying stimuli at increasing intervals after the train. We found that the recovery remained unaffected by blocking of N- or R-type Ca_vs These data in combination with kinetic computer simulations indicated that next to Ca^{2+}-dependent recruitment, also Ca^{2+}-independent processes are involved. To conclude, our data suggest that in mature PF boutons N-type, but not R-type Ca_vs are significant for sustaining synaptic efficacy during periods of heavy use.