Abstract Book

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NeNa Conference 2022

Neurowissenschaftliche Nachwuchskonferenz

(Conference of Junior Neuroscientists)

October 10-12, 2022
Bad Urach, Germany
From the NeNa-Team

Dear participants,

We are thrilled that you are joining us at the 23rd annual NeNa conference and we are so excited to be back in person!

This year we are at a new location here in Bad Urach and we hope that you will enjoy yourselves and the exchange with your fellow junior neuroscientists. Hopefully you will be able to meet some new people, share your work, and pick up some new ideas.

Sincerely yours,

The NeNa Organizing Committee 2022

Julia Fechner
Avani Koparkar
Emilio Pardo
Isabel Raposo
Lilian de Sardenberg Schmid
Ramona Siebert
Giulia Soto
Schedule NeNa 2022

Monday, October 10th 2022

9:30 Arrival in Bad Urach
   Check-In, Meet & Greet, Coffee Time

10:30 Introduction Blitz

11:30 Ramona Siebert
   Encoding of dynamic facial expressions in the macaque superior temporal sulcus

Foteini Tsiami
   Functional genomics identifies epigenetic regulators as novel therapeutic targets for sonic hedgehog medulloblastoma

12:30 Lunch

13:30 Zoé Bürger
   Effect of hormonal contraception on stress reactivity in women

Linus Wiora
   Label-free live cell imaging of iPSCs and iPSC-derived neural cell types by holotomography

14:30 Coffee Break

15:00 Poster Session 1
   P1-P14

16:30 Check-in into rooms

17:00 Keynote Lecture 1 – Michael Brecht
   The Biology of Grasping in Elephants

18:45 Dinner

20:30 Social Event
Tuesday, October 11th 2022

8:15  Breakfast

9:00  Morgan Hess  
*Stress Affects Central Compensation of Neural Responses to Cochlear Synaptopathy in a cGMP-Dependent Way*

**Nadine Dyszkant**  
*Functional Diversity in Degenerated and Wild-type Mouse Retina*

**Tristan Baumann**  
*Gateway identity and spatial remapping in a combined grid and place cell attractor*

10:30  Coffee Break

11:00  Workshop Part 1  
*Carolin Schwitalla, “Introduction to R”*

12:30  Lunch

13:30  Johanna Heider  
*Aberrant neuronal connectivity and activity in a human neuron-microglia co-culture model of schizophrenia*

**Ian Chong**  
*Causal Manipulation of Gaze Following in the Macaque Temporal Cortex*

**Lisa-Marie Erlandsson**  
*Gene-regulatory Networks for the Genetic Subtypes GRN, MAPT, and C9orf72 of Frontotemporal Dementia*

15:00  Coffee Break

15:30  Poster Session 2  
**P15-P28**

17:00  Keynote Lecture 2 – Lena Veit  
*Flexible Contextual Control Over Birdsong Sequencing and Structure*

18:45  Dinner

20:30  Social Event
Wednesday, October 12\textsuperscript{th} 2022

8:15  Breakfast

9:00  Yirong Xiong

\textit{Population-based cortical mapping of callosal connections in human brain}

Junya Inoue

\textit{Multidimensional cerebellar computations for flexible kinematic control of movements}

Polina Oleneva

\textit{Building a scalable pipeline for detection of blood vessels in the human brainstem using quantitative susceptibility MRI at ultrahigh magnetic fields (UHF)}

10:30  Coffee Break

11:00  Workshop Part 2

\textit{Carolin Schwitalla, “Introduction to R”}

12:30  Lunch and Awards Voting

13:30  Awards and Wrap-Up

Afterwards optional visit at the Bad Urach Therme
Speakers

Michael Brecht (Humboldt Universität zu Berlin)

“The Biology of Grasping in Elephants”

About the speaker:

Michael Brecht’s group is active in the field of cellular and systems neuroscience with the following major areas: animal play, active touch and object recognition, social and sexual touch, cortical organization, cellular basis of sensations and movement generation, hippocampal and parahippocampal activity linked to spatial navigation.

The group works on the meaning of single neuron activity, cellular mechanisms of complex somatosensory-mediated behaviors, spatial representations and social representations in forebrain.

Lena Veit (Universität Tübingen)

“Flexible Contextual Control Over Birdsong Sequencing and Structure”

About the speaker:

Lena Veit’s lab aims to understand the flexible control of complex behavior, by combining traditional neuroethological approaches with behavioral training to study the neural basis of flexible song sequencing in Bengalese finches.

The group uses a wide range of modern systems neuroscience techniques to study neural circuits involved in motor learning and flexible motor control in the avian brain.
Workshop

Carolin Schwitalla (Universität Tübingen)

“Introduction to R”

Carolin Schwitalla has a Bachelor’s degree in Biochemistry and a Master’s degree in Bioinformatics from the University of Tuebingen. She is passionate about the analysis, manipulation and visualization of biological data.

In Carolin’s workshop you will learn about the basics of programming in R with R-Studio. You will be introduced to different data types and structures, learn how to import and export data in R-Studio, and how to do simple data manipulation and visualization to help you advance your skills as a scientist.
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T1 - Encoding of dynamic facial expressions in the macaque superior temporal sulcus

Ramona Siebert*,a, Michael Settlerb, Nick Taubertb, Peter W. Dickea, Martin A. Gisebeb,#, Peter Thiera.#

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Faces of primates are a rich source of information on the identity and emotional state of the other. Whereas the neural encoding of facial identity has been extensively studied at the single-cell level, facial expressions have received relatively little interest. We took advantage of a highly naturalistic, dynamic rhesus monkey avatar [1,2], ensuring standardized and parametrized stimulus control, while recording from neurons in the macaque superior temporal sulcus (STS). The monkeys watched video clips of the avatar producing facial expressions of fear, threat or affiliative lip-smacking, as well as an artificial “blowing” expression, in different degrees of intensity. Additionally, dynamic point-light expressions, real monkey videos, moving objects, speed-matched optic flow fields and static images of faces and non-face objects were shown.

More posteriorly located STS cells seemed to correspond to “optic flow pattern” neurons, responding similarly to the full dynamic avatar and to point-light expressions lacking figural features. “Dynamic expression” neurons, located more anteriorly, were characterized by sustained responses to one expression category only, increasing almost linearly with the degree of expressivity, and only small responses to the other expressions or to other dynamic control stimuli. Most of these neurons also responded more to static faces than to static non-face stimuli but differed only little in their responses to static depictions of expressions.

It seems that neurons in the macaque STS process expression-relevant information in a hierarchical manner. Whereas more posterior neurons extract motion cues, a more anterior population integrates motion and form information in a first step towards categorizing expressions. The dynamic expression cells’ continuous increase in firing with the intensity of the expression fits a norm-referenced encoding model, which postulates that neurons are tuned to the amount of distance in face-space between a facial expression shape and a neutral reference pose [3].

References

T2 - Functional genomics identifies epigenetic regulators as novel therapeutic targets for sonic hedgehog medulloblastoma

Tsiami Foteini*\textsuperscript{a}, Federica Piccioni\textsuperscript{b}, David Root\textsuperscript{b}, Pratiti Bandopadhayhay\textsuperscript{c}, Rosalind Segal\textsuperscript{d}, Ghazaleh Tabatabai\textsuperscript{a}, Daniel Merk\textsuperscript{a}

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Medulloblastoma (MB) is among the most common malignant childhood brain tumors. It is a highly heterogeneous tumor entity that comprises four molecularly distinct subgroups: sonic hedgehog (SHH), wingless (WNT), Group 3 and Group 4. SHH subgroup constitutes 30% of all MBs and is characterized by aberrant activation of the canonical SHH signaling pathway. Although Smoothened (SMO) inhibition has proven a promising treatment approach for SHH-MB patients, de novo or acquired resistance has impeded its clinical efficiency. Therefore, novel therapeutic targets are urgently needed. Here, we conducted a genome-wide CRISPR/Cas9 knockout screen in a murine and a human SHH-MB cell line, SMB21 and DAOY, respectively, in order to decipher tumor-specific genetic dependencies. Our data demonstrate that SMB21 cells highly depend on positive regulators of the SHH pathway, such as Smo and Gli1 for their survival, as opposed to DAOY cells, suggesting that the latter does not represent a faithful model of SHH-MB. Functional genomics identified SMB21-context specific essentialities beyond the SHH pathway that include members of the epigenetic machinery such as Dnmt1 and Smarca5. Pharmacologically, we show that DNMT1 inhibition is efficacious at clinically relevant concentrations against SMO inhibitor-sensitive and resistant SHH-MB cell lines. Additionally, RNA sequencing of SMB21 cells identified early and late global gene expression alterations induced by two distinct DNMT1 inhibitors, including downregulation of mediators of SHH signaling. Of note, gene set enrichment analysis revealed that DNMT1 inhibition reduces expression of top gene sets associated with cell cycle progression, corroborating the screening results that Dnmt1 is essential for SMB21 proliferation. Finally, genetic and pharmacological inhibition of Dnmt1 and Smarca5 will be evaluated in in vivo mouse models of SHH-MB. Summarizing, our data highlight the potential of inhibitors targeting epigenetic regulators in SMO inhibitor-sensitive and resistant MB for more efficacious treatment options.
T3 - Effect of hormonal contraception on stress reactivity in women

Zoe Bürger*, Lydia Koglerb, Julia Kübbelera, Melanie Henesb, Birgit Derntlc

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With usage of hormonal contraception (HC) becoming more widespread, it is important to understand its effects on body and brain. Additionally, comprehending the mechanisms of stress reactivity is of utmost importance to understand the emergence of stress-related mental disorders like depression and anxiety. The two endocrine systems – the hypothalamic-pituitary-adrenal axis and the hypothalamo-pituitary-gonadal axis – are closely intertwined. While there are a handful of studies on oral contraceptives (OC), only one study investigated the association between stress reactivity and usage of hormonal intra-uterine devices (LNG-IUD): while OC-users showed a blunted cortisol reactivity compared to naturally cycling (NC) women, LNG-IUD-users had a potentiated reactivity. To better understand female stress reactivity and how it can be altered by HC, we apply the Maastricht Acute Stress Task (MAST) to women using LNG-IUD, OC-users and NC women in a cross-sectional design. To cover the multiple facets of stress, we measure cortisol, endogenous and exogenous sex hormones as well as subjective stress reactivity. As each participant undergoes both MAST and a non-stressful MAST-control, we have within- and between-subjects comparisons. We hypothesize to find a potentiated cortisol reactivity in LNG-IUD women, while OC-users show a blunted cortisol reactivity but presumably will not differ in terms of subjective ratings from NC women. Whether LNG-IUD-users differ in subjective stress ratings and the association of endogenous and exogenous sex hormones on stress reactivity will be explored for the first time. This project has enormous societal relevance, as women worldwide can make more informed choices as to their contraceptive method.
T4 - Label-free live cell imaging of iPSCs and iPSC-derived neural cell types by holotomography

Linus Wiora*,a,b, Lea Fischera, Milena Kornecka,b, Lena Erlebachc, Ludger Schölsa,b, Stefan Hausera,b

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The discovery and classification of disease-associated phenotypes in iPSC-derived models is a crucial step in developing new hypotheses and tackling open questions in the field. Changes in morphology and behaviour of differentiated iPSC-derived neural cell types caused by mutations or treatments are often the first hint towards a relevant phenotype worth studying in depth. However, classical "observation" techniques often lack spatial and temporal resolution (e.g. phase contrast microscopy) or require fluorescent staining, which is often inducing oxidative cell stress by photo toxicity (e.g. classical live-cell microscopy or confocal microscopy).

A new promising technique for label-free, three dimensional and high resolution live cell imaging is holotomography. Based on the distinct differences of refractive indices in cellular compartments and membranes, this technique allows label-free live cell imaging over several days. We have studied iPSCs and several iPSC-derived cell types of the brain like neural precursor cells, cortical neurons, astrocytes and microglia. Cellular processes such as mitosis, apoptosis, axonal outgrowth and cell migration have been visualized in great detail without altering the cellular environment by conventional staining. Also processes in the subcellular level such as mitochondrial transport and lipid droplet dynamics could be visualized. The identity of these organelles was verified by selective co-staining. Recently we also established neuron-microglia co-cultures to study the interactions of these cell types in vitro. Microglia showed functionality by removing cellular debris and recognized intact neurons without phagocytosing them.

In combination with classical live cell stainings this new, commercially available technique offers promising possibilities especially for in vitro disease modelling.
T5 - Stress Affects Central Compensation of Neural Responses to Cochlear Synaptopathy in a cGMP-Dependent Way

Daria Savitska\textsuperscript{a}, Morgan Hess\textsuperscript{*\textsuperscript{,}a}, Dila Calis\textsuperscript{a}, Philine Marchetta\textsuperscript{a}, Marlies Knipper\textsuperscript{a}, Wibke Singer\textsuperscript{a}

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Increasing evidence supports a link between hearing loss and dementia. We previously demonstrated in a mouse model that an age-related cochlear synaptopathy (decoupling of inner hair cell synapses from auditory nerve fibers) leads to poorer temporal auditory and memory-related processing. We could show that cochlear synaptopathy can, in some individual cases, be centrally compensated through enhanced input/output function of auditory brainstem responses (neural gain), preventing an age-dependent temporal discrimination loss. Therefore, mice can be subdivided by their compensation capacity into a group of low compensators and another group of high compensators. Low compensators also displayed an associated decrease in memory-linked processes and recruitment of activity-dependent brain-derived neurotrophic factor (BDNF) in hippocampal regions in comparison to high compensators. We aimed to identify factors capable of modifying this compensation mechanism. Animals were injected with either a cGMP-stimulating drug — the "memory-enhancing" phosphodiesterase 9A inhibitor — or a placebo. We surprisingly found that the successful central auditory- and memory-dependent adjustment to cochlear synaptopathy is a cGMP- and glucocorticoid-dependent process.
Retinitis pigmentosa (RP) is a hereditary degeneration of rod and cone photoreceptors in the retina. A model for this disease is the rd10 (Pde6brd10) mutant mouse line, in which rods change their morphology, lose their function, and eventually die, leading to complete rod degeneration around postnatal day (P) 45 (Chang et al. 2002). This is followed by a secondary cone degeneration. However, the anatomical structure of inner retinal circuits is thought to remain largely unaffected (Mazzoni et al. 2008), whereas morphological and functional re-modeling of outer retinal circuits is well documented (e.g. Strettoi et al. 2003).

In this project, we aim to investigate the functional RGC diversity during the progression of photoreceptor degeneration. To this end, we recorded light-evoked responses in the retina’s output neurons, the retinal ganglion cells (RGCs) using 2-photon calcium imaging at defined time points in rd10 and C57BL6/J mice. To analyse functional diversity, we determined the RGCs’ “functional fingerprints” (Baden et al. 2016), by measuring spatio-temporal response features. We observed that the total number of responsive RGCs and their response strength did not substantially decline in rd10 until later in degeneration (towards P180). Our preliminary analysis furthermore suggests that some response features, such as orientation- and direction-selectivity, hardly change qualitatively. Moreover, we found that all six functional groups of RGCs ([ OFF, ON-OFF, fast ON, and slow ON RGCs, and amacrine cells]) are still present in rd10 retinae, suggesting that no broad response type is lost during degeneration. Surprisingly, the distribution of cell types is strongly biased towards Off RGCs in rd10 at P180.

In summary, the fingerprinting approach allows us to track changes in retinal output during the course of photoreceptor degeneration.
T7 - Gateway identity and spatial remapping in a combined grid and place cell attractor

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The representation of space in the rodent brain is generally attributed to place cells located in the hippocampus. These cells cover the environment with location-specific firing fields ("place fields") and the population code uniquely describes each position in space. Place field shape and locations and the relative population code are subject to change if the animal enters a new compartment in the experimental maze. This effect, known as remapping, cannot be explained from grid cell-based path integration and local sensory cues alone but requires additional knowledge about the context. This is exemplified in two situations: Normally, when the animal returns to a known compartment, the place cells remap to the original pattern associated with that compartment. However, when the environment includes multiple visually identical compartments, place cells remap to the same pattern in each room and the rooms are confused. The process necessarily occurs at the gateways but not within compartments, suggesting the reactivation of a stored pattern based on cues at the entrance.

We present a model of the hippocampal-entorhinal circuit in which the activity of place and grid cells follows a joint attractor dynamic. Place cells depend on the current grid cell activity but can also reset and change the grid cell activity: The remapping process is triggered by the recognition of a gateway, where place cell patterns are retrieved from long-term memory. The joint attractor then reinstates the original grid cell pattern and path integration can proceed from there. Thereby, the pattern of active cells provides both information about the current context and the position of the animal within that context. The model is tested in various mazes from the experimental literature and reproduces the published results, and we make testable predictions for remapping in novel maze types.
T8 - Aberrant neuronal connectivity and activity in a human neuron-microglia co-culture model of schizophrenia

Johanna Heider*, a, Ricarda Breitmeyer a, Sabrina Vogel a, Richard Wüst b, Andreas J. Fallgatter b, Hansjürgen Volkmer a

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Schizophrenia is a complex neuropsychiatric disorder often related to impairments in synaptic transmission and alterations of neuronal activity patterns. Converging evidence also supports a role for inflammation and activated microglia in disease-related processes such as synaptic pruning. However, there is still only little insight into the underlying morphological and functional mechanisms in a human system. Here, we present a neuron-glia co-culture model derived from schizophrenia patient iPSC to study disease phenotypes in a humanized system in vitro.

We demonstrate that iPSC-derived glutamatergic neurons and GABAergic interneurons robustly express lineage-specific synaptic markers and develop single-cell as well as network activity when combined into co-cultures. Interneurons from schizophrenia patient iPSC show a reduction of inhibitory presynaptic terminals, which was also observed in co-cultures of glutamatergic and GABAergic neurons, highlighting the involvement of interneurons in the disease.

When patient iPSC-derived microglia were added to the neuronal cultures, an increase in the ratio of excitatory to inhibitory synapses compared to the addition of healthy microglia was observed. This finding underlines the contribution of microglial cells to the synaptic phenotype. Neuronal single-cell activity in neuron-microglia co-cultures was studied using calcium imaging. We observed an increase in amplitude and peak area of neuronal calcium traces after addition of schizophrenia microglia.

Interestingly, anti-inflammatory pre-treatment of schizophrenia microglia with the antibiotic Minocycline rescued the observed alterations of neuronal activity.

In conclusion, we generated a 2D in vitro human cellular test system to study morphological and functional signatures of neurons and microglia as well as their reciprocal interactions in schizophrenia. We observed alterations of neuronal activity and synapse formation with potential neuronal and microglial contributions. We successfully demonstrated an anti-inflammatory rescue effect of the drug Minocycline in our cultures, providing evidence for the usability of our model system to study mechanisms of disease candidate drugs.
Gaze-following, the ability to shift one’s own attention to places or objects others are looking at, is essential for social interactions. Single unit recordings from the monkey cortex and neuroimaging work on the human and monkey brain suggest that a distinct region in the temporal cortex, the gaze-following patch (GFP), underpins this ability. Since previous studies of the GFP have relied on correlational techniques, it remains unclear whether gaze-following related activity in the GFP indicates a causal role rather than being just a reverberation of behaviorally relevant information produced elsewhere. To answer this question, we applied focal electrical and pharmacological perturbation to the GFP. Both approaches, when applied to the GFP, disrupted gaze-following if the monkeys had been instructed to follow gaze, along with the ability to suppress it if vetoed by the context. By establishing a causal role of the GFP in subserving gaze-following, we suspect that dysfunction to the GFP could be a major contributing factor in disorders where gaze-following is compromised, and present a candidate cortical structure for studying joint attention.
T10 - Gene-regulatory Networks for the Genetic Subtypes GRN, MAPT, and C9orf72 of Frontotemporal Dementia

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Frontotemporal dementia (FTD) is the most common form of young-onset dementia after Alzheimer’s disease and accounts for 10-20 % of the cases under 65 years of age [1]. Contrasting to other neurodegenerative diseases, FTD has a strong genetic component as up to 40 % has a positive familial background explained for the most part by mutations in three different genes [2]. Furthermore, these genes are highly associated with aggregation of both protein tau in neurofibrillary tangles and TDP-43, which both show diverse patterns in morphology throughout different cell types, disease states, and diseases [2-3]. Current knowledge about molecular and cellular mechanisms is limited and there are no existing disease-modifying therapies that slow the process of FTD. Given the clinical, genetic, and neuropathological variation, there is a need to investigate if patients should be addressed with a common or a distinct approach for diagnosis and therapy. In human post-mortem brain tissues, we have previously identified that AMPA receptor expressing excitatory neurons are vulnerable in FTD [4]. Now, we have produced biologically comparable induced pluripotent stem cells (iPSCs)-derived excitatory neurons. With these models, we intend to expand the molecular evidence for the disease biology and to validate our findings of the genetic subgroups MAPT, GRN, and C9orf72 via multi-omics datasets. By combining different sequencing techniques (RNA-seq, smRNA-seq, ATAC-seq, CAGE-seq, and methylation-array) we will obtain multilevel information transcription and transcriptional regulation. Additionally, to get an idea of the portion of the genome that get translated into protein and about the translational regulation not explained by transcript levels we will perform quantitative proteomics. With knowledge of the biological relevance of the three genetic subgroups and how it leads to downstream dysregulation, we aim to close the loop by disease-correcting perturbation of identified genes by reversible CRISPR/Cas technology.

T11 – Population-based cortical mapping of callosal connections in human brain

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As the largest commissure bundle in the human brain, the corpus callosum contains more than 300 million fibers, mainly connecting homologous regions. Fibers in the corpus callosum have a topographic representation. An atlas of the corpus callosum is important to clarify the role of corpus callosum fibers in different cognitive processes and to understand the influence of the microstructure of white matter fibers in processing. The present study constructed a fine-grained corpus callosum projection atlas of the human brain based on a large sample dataset (~1000), which could be a critical link to address the specific function of the corpus callosum in mediating between two hemispheres. Furthermore, the atlas was embedded in a cloud server with a Web-based tool for interactive visualization. It can provide a precise map between cortical areas and the corpus callosum for researchers in studies of callosal-related disorders and is a powerful tool for revealing the role of callosal fibers in specific cognitive functions.
T12 – Multidimensional cerebellar computations for flexible kinematic control of movements

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Amid dynamic environments, we flexibly adapt our movements to multiple changes occurring simultaneously. Here we show that the cerebellum, a critical locus for sensorimotor control and learning, performs the necessary multi-dimensional computations for multiplexed encoding of different movement parameters with state-dependent flexibility. We identified a manifold-like activity in both mossy fibers (MF, network input) and Purkinje cells (PC, output), recorded from monkeys performing a repetitive saccade task, where the geometry and dynamics of PC manifolds developed exclusive representations of individual movement parameters. Error feedback-driven inputs modulated the PC manifolds to prompt highly specific, error type-dependent changes in the upcoming movements. Furthermore, the feed-forward network model that simulated MF-to-PC transformations revealed that amplification and restructuring of the lesser variability in the MF activity is a pivotal circuit mechanism. Therefore, flexible sensorimotor control and learning by the cerebellum crucially depend on its capacity for multi-dimensional computation.
Brain vessels can be observed in high resolution MRI scans, but to achieve 3D segmentation, the signal from surrounding tissues need to be suppressed and removed. Based on the inherent property of differences in magnetic susceptibility, veins can be distinguished from less paramagnetic brain tissues with quantitative susceptibility mapping (QSM) processing of 3D gradient-echo MRI. There are a number of open source algorithms for this multi-step technique. However, each algorithm relies on different parameters, and each of the parameters need to be fine-tuned to optimise vessel conspicuity.

Different QSM pipelines were optimised for GRE MRI of the human brain stem, measured at 14.1 Tesla using different sequence parameters. We found that the most robust QSM pipeline can extract veins from several brainstem samples with only minor adjustments required to cope with differences in MRI sequence parameters. Similar strategies can be used for tuning the QSM processing pipeline for different goals of MR neuroimaging.
Posters
P1 – Efficient low-dimensional coding partition of past and present states in the human prefrontal cortex

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The process of decision making is inherently biased towards previously taken actions, a phenomenon called serial dependence. It has been suggested that the brain uses serial dependences to infer moment-to-moment correlations (e.g. predictive coding). Yet, the brain frequently needs to dynamically switch between different task sets that require different actions. Within a dynamic environment, serial dependences could become maladaptive and adversely affect future behavior (e.g. cost of task-switching). Yet, the neural mechanisms underlying behavioral costs of switching remain elusive. Here, we combined a context-specific stop-signal task with human intracranial EEG recordings (iEEG) in prefrontal and motor areas to address this gap. Successfully replicating previous behavioral work on task-switching, we found that switching action requirements between two successive trials comes at a behavioral cost. By combining uni- and multivariate analysis of the iEEG data, we found that the magnitude of information present about task history in PFC, but not motor cortex, was proportional to the inter-individual cost of switch. Furthermore, the level of information present about the irrelevant task history was inversely correlated with the information present about the current relevant task-context. Thus, individuals with a high cost of switching showed high history-, but less context-coding and vice versa. Finally, we found that the overlap of coding subspaces for task history and context could be directly mapped onto the inter-individual cost of switching. Collectively, this demonstrates that the cost of task-switching underlies a form of resource competition due to conjunctive coding of the past and present in the human prefrontal cortex.

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Prior expectations, also termed beliefs, can be used to make better visual decisions. In an uncertain and constantly changing world, beliefs should be learned and updated according to the volatility of the environment. Therefore, priors need to be flexibly integrated into the decision process. The cognitive mechanisms used to integrate learned priors remain unknown. The goal of this thesis was to behaviorally dissociate the effect of beliefs in a visual decision under uncertainty using cognitive models. Combining two well-established cognitive models – Hierarchical Gaussian Filtering and the Drift Diffusion Model – replicates the well-established finding that prior expectations bias the starting point of evidence accumulation and the rate of evidence accumulation. Critically, the analyses reveal a decrease in non-decision time when belief was congruent with the outcome. Collectively, these results provide evidence for the hypothesis that prior expectations are implemented in visual decisions via multiple mechanisms that can be tested using neurophysiological data.
Olfaction is one of the most ancient senses in humans and mice, important for a large variety of innate and acquired behaviors. Clinical data reveal an early impairment of olfaction during normal aging, but the underlying cellular/molecular mechanisms remain obscure. In this study, we compare different aspects of the aging-related impairment of olfaction (i.e., odor detection, identification and olfactory memory) in humans and mice, aiming at the identification of common morbidities and biomarkers, which can be analyzed in detail in the appropriate mouse models. In the human study, we did literature research and observed a continuous increase in the prevalence of all three aforementioned aspects of olfactory impairment. There were also profound gender differences with women performing better than men in all age groups and men’s scores declining significantly faster with age. Furthermore, summarizing the human data revealed the age at which the decline in the given ability occurs. In the animal study, we use two-photon laser scanning microscopy and ratiometric in vivo Ca2+ imaging techniques to evaluate the basal Ca2+ levels and to characterize spontaneous Ca2+ signaling as well as odor-evoked responses of the olfactory bulb glomeruli, the input layer of the olfactory bulb. To monitor the level of spontaneous activity and odor-evoked responses in glomeruli of wild-type (WT) mice, we infected them with lentiviruses expressing the Förster resonance energy transfer-based Ca2+ indicator Twitch-2B. The following data are in the process to be obtained: (i) the levels of the ongoing and odor-evoked activity in dorsal glomeruli, (ii) the differences in the interglomerular odor sensitivity and (iii) the changes in the aforementioned parameters with aging. Together, our data shall provide mechanistic insight into the relationship between olfactory impairment and aging, documented in humans (Tzeng et al., 2021).
P4 – Unravelling the role of the STX1B gene in genetic epilepsy syndromes using an iPSC-derived autaptic culture system

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The majority of genes implicated in epilepsy lead to ion channel dysfunction, wherefore epilepsies are often referred to as channelopathies. However, the identification of mutations in genes encoding synaptic proteins shed light on synaptopathies as another pathophysiological mechanism of epilepsy. Mutations in STX1B, which encodes the presynaptic protein Syntaxin-1B, have been associated with various epilepsy syndromes ranging from benign generalized febrile or afebrile seizures to severe epileptic encephalopathies. The effect of STX1B mutations have already been studied in different animal models like zebrafish or mouse, while data from human model systems are still missing. Moreover, most studies on synaptic transmission rely on spontaneous activity in an uncontrolled network of neurons limiting the readout of specific synaptic properties. To overcome these limitations, we use patient-specific induced pluripotent stem cells (iPSCs) to elucidate the effects of STX1B mutations in an autaptic culture system. In that endeavour, we generated iPSC lines from patients carrying STX1B mutations in the regulatory Habc-domain or SNARE motif. Using the advantage of autaptic cultures, we examine different synaptic properties in iPSC-derived neurons by patch clamp recordings to investigate how STX1B mutations affect synaptic activity on a single cell level. Understanding the pathophysiological mechanisms of synaptic dysfunction in these patients could further help to develop adequate therapies in the future.
**P5 – Neural dynamics underlying human vocalization**

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Human speech allows to convey information via different execution forms. On the behavioral level, speech content is independent from production and execution forms. However, it remains unclear whether such a content dimension can be found on the neural level and whether it is possible to dissociate it from the motor dimension. To address this, we recorded magnetoencephalography (MEG) in human subjects that performed a rule-based vocalization task. Content (one of two vowels) and production (overt or covert) were instructed separately and in random order. Applying multivariate pattern analysis (MVPA), we found robust neural information about the content and production of vocalization several seconds before vocalization behavior. Source analysis revealed neural information in speech areas of the left hemisphere. The strength of both types of neural information correlated with the degree of motor involvement. When isolated, both types of information overlapped. Later in the trial, the neural format of production information transformed depending on the content, whereas content information remained stable independent of production type. Our results provide new insights into the neural dynamics underlying basic human vocalization and open a new window for non-invasive speech research in humans.
People learn differently under fearful and anxious conditions, especially when the environment itself is volatile. We conducted an online pilot study (as part of the functional magnetic resonance imaging project) on how emotions influence probabilistic associative learning in a volatile environment. Participants had to learn the association between two cues (colour patches) and two outcomes (images of faces or hands), while the reversals occurred at times unknown to participants. Their anxiety state and trait were measured using the ‘State-Trait Anxiety Inventory’ at the end of the experiment. Performance was compared between three different conditions: low, medium, and high fear (using scarified images). Three computational models (Rescorla-Wagner, Hidden Markov Model, and Volatile Kalman Filter) were fitted to the behavioural data in each condition. Bayesian Information Criterion, and cross-validation R-squared were used for model comparison. 

Our preliminary results suggest that fear-inducing stimuli did not influence learning performance in a volatile environment. However, we speculate that there might be individual differences in participants’ responding to our fear manipulation (bimodal distribution in high fear condition’s performance). As for anxiety, there was a positive correlation between performance and low to moderate STAI total scores (≤100) but not high STAI total scores (≥120), suggesting that moderate amount of anxiety could facilitate learning performance. Finally, model comparison result suggests that a simple model with fixed learning rate (Rescorla-Wagner Model), rather than a complex one with adaptive learning rate (Volatile Kalman Filter) most frequently explained behavioural data. In addition, task structure-related information was rarely utilized in solving our task (Hidden Markov Model).
Multidimensional data in the area of decision-making and reward processing

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In a longitudinal study combining investigation of physical effort expenditure and quantitative recordings of metabolic and hormonal states, we study sex differences in cost-benefit decision-making and reward processing in women and men. Participants perform an effort allocation task once a week for five consecutive weeks, in which they repeatedly press a button to collect food and money tokens. We analyse the motivational phases of invigoration and effort maintenance, with varying reward type (food vs. money), reward magnitude (low vs. high) and difficulty (easy vs. hard). Glucose levels are monitored continuously, and sex hormone levels are determined weekly to study whether metabolic state, sex hormone levels and the female menstrual cycle influence reward processing. Pilot data of 15 participants (6 females) have been collected so far. How can these multidimensional data best be integrated and analysed to investigate the interaction between metabolic, hormonal, and subjective data?
In healthy individuals, hypothalamus-pituitary-adrenal (HPA) axis activity shows sex dimorphism, especially in its end product cortisol, which is thought to be a mechanism underlying sex-specific disease incidence. Depression as a female susceptible psychiatric disorder, it is still unknown whether sex differences in cortisol are also obviously expressed. The aim of this study was to conduct a systematic review and meta-analysis of worldwide research that assessed cortisol reactivity in female and male depressed participants. Articles were systematically reported in the categories: (1) basal cortisol; (2) cortisol awakening response (CAR); (3) cortisol reactivity to Trier Social Stress Test (TSST) or an equivalent psychosocial stress test. According to the PRISMA statement, a total of 38 original articles were included in this review. Random effects model revealed that depressed females had no significant difference in acute basal cortisol, whereas significantly higher long term cortisol, higher CAR, and lower cortisol stress reactivity. When compared to healthy individuals, depressed females had significantly higher CAR and lower cortisol stress reactivity than healthy females. Depressed males had higher basal cortisol and CAR compared to healthy male, with no significant difference in cortisol stress reactivity. Based on the available studies, elevated cortisol and CAR, as well as reduced cortisol stress reactivity were associated with modestly increased depression risk among females, and had similar adverse effects on the onset of depression in both females and males. Further researches are needed to focus on the implications of altered cortisol concentrations in female suffering from depression, as well as the biological and social factors contributing to sex differences in cortisol reactivity.
An optimized protocol for physiological recordings in dorsal forebrain organoids

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Neocortical organoids generated from human pluripotent stem cells mimic the complexity of human brain development in vitro. Cortical organoids recapitulate early stages of human neocortical development including stem cell proliferation, differentiation, and neuronal migration in a timely manner. However, later events such as synaptogenesis, neural network formation, and maturation are yet to be studied. Until recently, many studies using cortical organoids focused on the cellular and molecular complexity of these organoids, leaving functional recordings underinvestigated. Thus, investigation of physiological properties of brain organoids is essential to support that this model system also recapitulates the in vivo development of the neural circuits. Different approaches can be used for physiological characterization of brain organoids such as calcium imaging. The aim of this study is to establish a robust protocol for calcium imaging and electrophysiological recordings in dorsal forebrain organoids to study its neural activity. For this purpose, we generated, sectioned and subsequently cultured dorsal forebrain organoids as organotypic air-liquid-interface cultures. We have adopted calcium imaging with epifluorescent and two-photon microscopes using membrane permeable calcium indicators as well as genetically encoded calcium indicators transduced virally. Optical physiological approaches allow the detection of spontaneous activity in dorsal forebrain organoids. The experimental pipeline that was used for calcium imaging can be further optimized to other genetically encoded indicators or dyes that allow for optical imaging of brain organoids. In conclusion, our protocol can be used to study the physiological activity in neocortical organoids on single cell as well as on network level to gain functional insight. Understanding the physiological properties of human pluripotent cell derived brain organoids could permit the advancement of this new model system in research.
Understanding molecular mechanisms underlying CRB1-linked retinal dystrophies

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*Crumbs homologue 1 (CRB1) is one of the major genes linked to Retinitis Pigmentosa (RP) and the more severe form Leber Congenital Amaurosis. Up to now, no treatment is available to prevent photoreceptor loss in these patients, emphasizing the necessity to further elucidate the molecular mechanisms and potential disease modifiers.

With the aim to further assess disease mechanisms underlying CRB1-linked retinal degenerations, we generated iPSC-derived retinal organoids (RO) from two RP patients carrying a homozygous CRB1 C948Y mutation. Analysis using Western blot and immunofluorescence showed a reduction of CRB1 protein levels in both C948Y patients indicating that the mutation alters protein production or stability. Using co-immunoprecipitation, we show that CRB1 and CRB2 can homo- and heterodimerize but not CRB3, which lacks the extracellular domain. This suggests that dimerization is mediated by the extracellular domain. To further elucidate CRB1 function in the retina, we investigated its retina-specific interactome using a porcine retina pull-down proteomic approach. Results showed a significant abundance of known CRB1 interacting proteins, validating the experimental approach and novel potential interactors involved, amongst others, in actin cytoskeleton dynamics. In line with these findings, using immunohistochemistry, we showed that CRB1 is located in close proximity to F-actin in control RO, which is disorganised in patient RO.

Conclusively, we provide potential novel interactors of CRB1 in the retina, which provide the basis for future validation of CRB1 function. We show that the CRB1 C948Y mutation leads to reduced CRB1 levels in patient RO and disorganised F-actin, which may affect integrity and stability of the outer limiting membrane and the corresponding area of the photoreceptor inner segment. Future work will include validation of the tentative pathways in patient-derived RO and investigation on the consequence of the C948Y mutation on the dimerization of the CRB proteins.
P11 – Clinical and electrophysiological features of SCN8A variants associated with chronic and episodic ataxia

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Mutations in sodium channels can cause ataxia, but its neuronal mechanism remain largely unknown. Here, we identified eight new mutations, which caused either progressive (N995D, K1498E, W1266C) and episodic ataxia (R847Q, E1201K, R1629H), in human SCN8A gene encoding the voltage-gated Nav1.6 channel. Electrophysiological characterization of transfected wild-type and mutant channels in neuroblastoma cell line (ND7/23 cells) revealed a genotype-phenotype correlations. For the N995D and K1498E mutation, which caused severe ataxia, we observed dramatic slowing of activation, whereas the W1266C mutation causing progressive ataxia induced mild slowing of activation. On the other hand, dominantly accelerated inactivation was found in R847Q mutation causing episodic ataxia. All the above mutations showed loss-of-function effect. However, E1201K and R1629H mutation presented both gain- and loss-of-function effect in ND7/23 cells. In our second series of experiments, we recorded these two mutations in primary neuronal cultures. E1201K decreased neuronal firing in both excitatory and inhibitory neurons. Interestingly, R1629H resulted to the decreased neuronal firing in inhibitory neurons but increased neuronal firing in excitatory neurons. These findings provide a plausible explanation for the different clinical phenotype of ataxia that occur by mutant in Nav1.6.
P12 – Uncoupling of Aβ load and neurodegeneration along disease progression in an APP-transgenic mouse model

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Genetic, pathologic and biochemical data support a primary role of amyloid-β (Aβ) aggregation in Alzheimer’s disease (AD), but clinical trials of agents targeting Aβ have not revealed robust clinical benefit. These observations are in line with the view that Aβ aggregation is the trigger of AD, but that the pathogenic cascade becomes independent of Aβ load at later and symptomatic stages. To elucidate the dependency of downstream pathologies on Aβ, we analysed brain Aβ load, Aβ seeding activity, and neurofilament light chain protein (NfL, a presumed marker of neurodegeneration) in the cerebrospinal fluid (CSF) in transgenic mice expressing AD-mutant Aβ-precursor protein (APP) and presenilin-1 (PS1) at different disease stages.

In APPPS1 mice Aβ deposition increases linearly until it reaches a plateau at a late age. In contrast, Aβ seeding activity increases more rapidly and reaches a plateau much earlier. A robust increase of CSF NfL was observed only after Aβ seeding activity had plateaued. Inhibition of Aβ generation in amyloid-laden mice reduced Aβ deposition, but failed to reduce Aβ seeding activity, and CSF NfL continued to increase. When Aβ generation was inhibited starting at pre-amylloid stages, CSF NfL no longer increased despite some Aβ deposition and robust Aβ seeding activity.

Our data indicate that neurodegeneration (as assessed by CSF NfL) starts when Aβ seeding activity is saturated, a phenomenon reminiscent of the two pathogenic phases in prion disease. Blocking Aβ deposition in AD thus is likely to be most beneficial at a much earlier time-point than that targeted in past clinical trials.
P13 – Evaluation of medin amyloid as a biomarker and therapeutic target for cerebral amyloid angiopathy and vascular dysfunction

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Aggregates of medin amyloid (a fragment of MFG-E8) are found in the blood vessels of nearly everyone over 50 years of age, making it the most common human amyloid known to date. Despite medin's exceedingly high prevalence, its pathological relevance remained largely unknown. We recently demonstrated that medin also aggregates in wild-type mice, where it impairs cerebrovascular function. Here, we demonstrate in APP transgenic animals and patients with Alzheimer’s disease (AD) that medin co-localises with vascular amyloid-β deposits and that medin-deficiency reduces vascular amyloid-β deposition in mice. Using a newly established cerebral blood vessel isolation protocol, we find that in the mouse and human brain, MFG-E8 is highly enriched in the vasculature and both MFG-E8 and medin levels increase with the severity of vascular amyloid-β burden. Altogether, these data suggest MFG-E8 or medin as potential drivers of vascular damage. To evaluate the therapeutic use of MFG-E8/medin more thoroughly, we plan to characterise novel antibodies for their detection of MFG-E8 (fragments) and medin and their potential to remove medin and/or CAA in newly generated mouse lines of human medin pathology.
Alzheimer’s disease (AD) is a neurodegenerative disease, which is characterized by slow but steady memory loss. With the continuous aging of western societies, the number of people affected by AD is increasing as well. Nevertheless, few treatment options for AD exist and none is able to halt disease progression. One possible target for drug development is the cyclic guanosine monophosphate (cGMP) pathway. cGMP is a ubiquitous second messenger and a key molecule in many important signaling cascades in the body and brain. For example, cGMP is involved in long-term potentiation, a cellular correlate of learning and memory, a process impaired in AD. The reduced CSF levels of cGMP in AD patients correlate with the degree of their memory decline, thus supporting the hypothesis of an evolution of cGMP in AD. Further, the use of cGMP-enhancing drugs such as phosphodiesterase inhibitors, reducing the breakdown of cGMP, or soluble guanylate cyclase stimulators, enhancing the production of cGMP, showed beneficial effects in AD animal models. Still, these beneficial effects could not be translated to human AD patients thus far. The current data about the Aβ- or AD-related cGMP signaling were mostly obtained in vitro or by extracellular measurements of cGMP in vivo. Recently, new FRET-based cGMP sensors have been developed, opening the possibility to investigate the AD-related changes in cGMP signaling under in vivo conditions. In this study, we have established a protocol for a stable expression of the cGMP FRET-sensor cGi500 in the mouse brain, which can be subsequently used for chronic high-resolution in vivo imaging. Further, we identified a heterogenous cGMP distribution between different cells. Besides, the cGMP production evoked by NO-donors turned out to be dependent on the baseline cGMP concentration. By tracking neurons and astrocytes, through repeated in vivo imaging, we showed that the observed heterogeneity stays constant over several months. Thus, our protocol allows tracking plaque deposition-related changes in cGMP signaling during disease development in mouse models of AD.
P15 – Tau deletion does not affect CSF neurofilament light levels in an APP transgenic mouse model

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The first pathogenic event along the Alzheimer’s disease (AD) continuum which becomes apparent is the brain deposition of amyloid β (Aβ) peptide starting at least 20 years before clinical disease onset. The link between Aβ and downstream events such as Tau pathology and neurodegeneration remains unclear – although this knowledge appears crucial at a time when clinical trials are increasingly shifted to pre-symptomatic disease phases. Neurofilament light (NfL) chain is a scaffolding protein of the neural cytoskeleton and considered as a promising biomarker of neurodegeneration in various disorders including, but not limited to AD.

In Alzheimer’s disease, levels of NfL in the cerebrospinal fluid (CSF) increase during disease progression, however, it is still not known whether the aggregation of the Aβ peptide itself or downstream processes, in particular Tau-related changes, lead to rising NFL concentrations.

To elucidate the contribution of Tau to neurodegeneration and the link to Aβ, we have bred APPPS1 x Tau knock-out mice and investigated CSF-NfL, using the highly sensitive single molecule array (SIMOA) platform. Our preliminary data indicate that in APPPS1 mice endogenous Tau is not decisive for brain Aβ and CSF-NfL levels along disease progression.
P16 – Exploring learning trajectories with infinite hidden Markov models

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Learning the contingencies of a complex experiment is no easy task for animals. Individuals learn in an idiosyncratic manner, revising their strategies multiple times as they are shaped, or shape themselves, and potentially ending up with different asymptotic strategies. This long-run learning is therefore a tantalizing target for the sort of quantitatively individualized characterization that sophisticated modelling can provide. However, any such model requires a flexible and extensible structure which can capture radically new behaviours as well as slow changes in existing ones. To this end, we suggest a dynamic input-output infinite hidden Markov model whose latent states are associated with specific behavioural patterns. This model includes a countably infinite number of potential states and so has the capacity for describing new behaviour by introducing states, while the dynamics in the model allow it to capture adaptations to existing behaviours. We fit this to data collected from mice as they learn a contrast detection task over multiple stages and around ten thousand trials each. We quantify different stages of learning via the number and psychometric characteristics of behavioural states. Our approach provides in-depth insight into the process of animal learning and offers potentially valuable predictors for analyzing neural data.
P17 – Two distinct ways to form long-term object-recognition memory during sleep and wakefulness

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Memory consolidation is promoted by sleep. However, there is also evidence for consolidation into long-term memory during wakefulness via processes that preferentially affect non-hippocampal representations. We compared in rats the effects of 2-h post-encoding periods of sleep and wakefulness on the formation of long-term memory for objects and their associated environmental contexts. We employed a novel object recognition (NOR) task, using object exploration and exploratory rearing, respectively, as behavioral indicators of these memories. Remote recall testing (after 1 week) confirmed significant long-term NOR memory under both conditions, with NOR memory after sleep predicted by the occurrence of EEG spindle-slow oscillation coupling. Rats in the sleep group decreased their exploratory rearing at recall testing, revealing successful recall of the environmental context. By contrast, rats that stayed awake after encoding showed equally high levels of rearing upon remote testing as during encoding, indicating that context memory was lost. Disruption of hippocampal function during the post-encoding interval (by muscimol administration) suppressed long-term NOR memory together with context memory formation when animals slept, but enhanced NOR memory when they were awake during this interval. Testing remote recall in a context different from that during encoding impaired NOR memory in the sleep condition, while exploratory rearing was increased. By contrast, NOR memory in the wake rats was preserved and actually superior to that after sleep. Our findings indicate two distinct modes of long-term memory formation: Sleep consolidation is hippocampus-dependent and implicates event-context binding, whereas wake consolidation is impaired by hippocampal activation and strengthens context-independent representations.
P18 – A spherical arena for naturalistic visual stimulation and 2-photon calcium imaging in zebrafish larvae

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Zebrafish have a large visual field and global motion across this field reliably triggers optomotor and optokinetic responses. However, precisely controlling the locations of visual stimulation in underwater environments is challenging. Using novel wide-field stimulation arenas, it has recently been shown that these stabilization behaviors are best driven by different parts of the visual field. For the OMR, the lower visual field is of importance, and we show that it also contains the most reliable motion cues in our recorded natural scene data. To study the underlying processing channels and their relation to natural scene statistics, stimulus arenas that cover large parts of the visual field with high fidelity are needed. A previous LED-based solution already allowed for coarse, monochromatic full-field stimulation. Here we present a novel stimulus arena, which uses a single DLP projector with four optical paths to project scenes directly onto a spherical glass arena. It enables us to present cone-optimized trichromatic visual stimuli over a large field of view of approx. 360° azimuth and 135° elevation in conjunction with calcium imaging of head-fixed larvae. Our stimulus setup will facilitate the investigation into processing of ego-motion in the zebrafish brain.
P19 – Chemogenetic restoration of epileptic circuitry in a mouse model of Dravet syndrome

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Dravet syndrome (DS) is a severe neurodevelopmental disorder mainly caused by de-novo loss-of-function mutations in the SCN1A gene, leading to functional impairment of interneurons and, consequently, network hyperexcitability. DS is characterized by severe pharmacoresistant epileptic seizures and other neurological comorbidities, altogether posing a severe clinical burden with impaired patients’ quality of life. There is currently no treatment available preempting disease onset or progression, which is why it is crucial to look for novel therapeutic strategies, such as gene therapy. Regarding epilepsy, a chemogenetic approach is a suitable option since it is minimally invasive and could be envisioned as systemic and cell-type-specific therapy, potentially making epileptic seizures more adjustable and controllable. We used one of the chemogenetic approaches, namely, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), which are activated by inert ligand – Clozapine-N-Oxide (CNO). Before studying this approach in a living animal, it was first tested in organotypic brain slices derived from wildtype mice to be established and evaluated functionally. DREADDs were delivered virally and after successful transduction, patch-clamp recordings of transduced interneurons revealed a depolarization of the resting membrane potential and/or sustained or episodic action potential firing after CNO application. These experiments established the foundation for future in vivo studies in a DS mouse model to investigate the effect of DREADDs on the firing deficit of mutated interneurons.
P20 – Characterising Epileptogenesis in a Recurrent Genetic Model of Dravet Syndrome

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Dravet syndrome (DS) is characterized as a rare form of severe developmental and epileptic encephalopathy (DEE) often caused by de-novo mutations in the SCN1A gene, encoding the Na+ subunit NaV1.1. To understand pathophysiological changes and molecular mechanisms involved in epileptogenesis of DS, we aimed to analyse changes of sodium channel gating, neuronal excitability and neuronal subnetworks caused by the recurrent human DS missense variant SCN1A_A1783V. The kinetic properties of NaV1.1-A1783V were studied by voltage-clamp recordings of transfected tsA201 cells followed by simulation in a Hodgkin-Huxley model to predict consequences on neuronal excitability. Additionally, ex vivo electrophysiology, calcium imaging and single nuclei transcriptomics were performed in hippocampal and cortical regions of wildtype and heterozygous mice at PN13-15, PN20-23 and PN37-40 to reveal vulnerable cell populations and understand seizure generation mechanisms.

SCN1A_A1783V lead to loss-of-function (LOF) of channel activation and slow-inactivation properties, resulting in a predicted shift of action potential (AP) rheobase and reduced firing in fast-spiking inhibitory neurons (IN). Recordings in cortex and hippocampus confirmed our predictions identifying transient LOF in fast-spiking neurons characterised by reduced firing frequency and increased AP half-width. Regular-spiking INs and pyramidal cells seemed less affected. Furthermore, network recordings and transcriptomic analysis displayed an imbalance of excitation and inhibition in various cell populations especially in postsynaptic compartments of excitatory cells.

In conclusion, we extend the understanding of DS further by identifying pathophysiological changes in missense variant SCN1A_A1783V similar to other nonsense variants. Additionally, we identified multiple primary and secondary mechanisms characterizing epileptogenesis in this DS model.
P21 – Establishment of an iPSC-derived co-culture model comprising glutamatergic and dopaminergic neurons to model neuropsychiatric diseases

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Schizophrenia (SCZ) is characterized by aberrant development of the central nervous system and thereby results in impairing multiple aspects of human cognitive, perceptual, emotional and behavioural functioning. The neuropsychiatric disorder is extremely complex and heterogeneous. So far, the underlying pathobiology of the disease remains elusive.

In SCZ, different neurotransmitter systems are known to be affected. The involvement of aberrant dopamine transmission in SCZ was already postulated several decades ago, proposing an imbalance between excess subcortical dopamine, leading to positive symptoms in SZ and a blunting of cortical dopamine release, leading to negative symptoms. However, the mechanistic, underlying biology of aberrant dopamine release in SCZ is so far not understood.

Human induced pluripotent stem cells (iPSC), which harbor the genetic repertoire of patients, provide a valuable tool for studying disease-relevant mechanisms. Differentiation of iPSC into the desired type of cells enable the setup of co-culture models that allow for the study of neuronal morphology and function, as well as neuron-neuron interactions. The viral overexpression of lineage-specific transcription factors allows for the rapid generation of a highly homogenous population of functional neurons.

Here, we present the establishment of a new co-culture model including glutamatergic and dopaminergic neurons, both of human origin, to study underlying disease mechanisms in SCZ. Our hiPSC-derived neurons express subtype-specific synaptic markers, release neurotransmitter and show robust single-cell activity in calcium imaging, respectively.

In conclusion, we generated a humanized 2D in vitro model system to study the reciprocal interaction of different neuronal cell types affected in SCZ. These systems can be employed for the study of molecular mechanisms underlying neuropsychiatric diseases and may be helpful for future drug development.
P22 – Porcine cone-enriched retinal explants as a model to explore proteostasis modulation

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Degeneration of cone photoreceptors due to retinal degenerative diseases and complex maculopathies causes a major impact on the quality of life. The study of cone degeneration using murine models is complex since cones only represent a small percentage of all photoreceptors in the mouse retina. The porcine retina presents an advantage in this regard, as it possesses the cone-rich visual streak where the cone photoreceptors density reaches up to 40,000 cones/mm² (Hendrickson and Hicks, 2002) and resembling in some way to the human macula. Modulation of proteostasis through the inhibition of Valosin-Containing Protein (VCP) has proven to be protective for rods in different models of autosomal dominant retinitis pigmentosa (Arango-Gonzalez et al., 2020; Sen et al., 2021), and we have preliminary data suggesting that this protection is accomplished by a mutation independent mechanism. This study aims to assess the progress of cone degeneration in organotypic porcine retina cultures and test the effect of VCP inhibition in this model.

Porcine eyes were obtained from the local slaughterhouse from six-month-old pigs. Eyes were dissected, removing the anterior part, lens, and vitreous body. The cone-enriched areas of the retina were identified by the pattern of blood vessels of the retina and dissected using 6mm diameter punches. Cone-enriched retinal explants were transferred to transwell membranes for culture in an air-medium interphase approach and maintained in serum-free conditions for up to eight days. Retinas were treated with VCP inhibitors (ML240 or NMS-873) added in the medium every two days. General retina morphology, cell death, and cone-photoreceptor survival were assessed using immunostaining, TUNEL assay, and ONL cell row quantification.

From day 0 to day 8 in culture, progressive degeneration of the porcine explants can be observed, with a considerable increase in TUNEL positive cells at day 6 and a degeneration of cones and cones outer segments starting at day 7-8. Interestingly, after VCP inhibition, we observed an increased cell survival reflected in a reduction in the number of TUNEL positive cells. Furthermore, there was also an improvement in the morphology of the photoreceptor outer segments and the opsin expression. Our preliminary results suggest that VCP inhibition is a good therapeutic approach to delay cell degeneration in porcine retinal explants and encourage us to explore the potential of VCP inhibition in more complex “AMD-like” models.
P23 – Juxtacellular opto-tagging of hippocampal CA1 neurons in freely moving mice

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Neural circuits are made of a vast diversity of neuronal cell types. While immense progress has been made in classifying neurons based on morphological, molecular, and functional properties, understanding how this heterogeneity contributes to brain function during natural behavior has remained largely unresolved. In the present study, we combined the juxtacellular recording and labeling technique with optogenetics in freely moving mice. This allowed us to selectively target molecularly defined cell classes for in vivo single-cell recordings and morphological analysis. We validated this strategy in the CA1 region of the mouse hippocampus by restricting Channelrhodopsin expression to Calbindin-positive neurons. Directly versus indirectly light-activated neurons could be readily distinguished based on the latencies of light-evoked spikes, with juxtacellular labeling and post hoc histological analysis providing ‘ground-truth’ validation. Using these opto-juxtacellular procedures in freely moving mice, we found that Calbindin-positive CA1 pyramidal cells were weakly spatially modulated and conveyed less spatial information than Calbindin-negative neurons – pointing to pyramidal cell identity as a key determinant for neuronal recruitment into the hippocampal spatial map. Thus, our method complements current in vivo techniques by enabling optogenetic-assisted structure–function analysis of single neurons recorded during natural, unrestrained behavior.
Humans can implicitly learn complex perceptuo-motor skills over the course of large numbers of trials. This likely depends on our becoming better able to take advantage of ever richer and temporally deeper predictive relationships in the environment. Here, we offer a novel characterization of this process, fitting a non-parametric, hierarchical Bayesian sequence model to the reaction times of human participants' responses over ten sessions, each comprising thousands of trials, in a serial reaction time task involving higher-order dependencies. The model, adapted from the domain of language, forgetfully updates trial-by-trial, and seamlessly combines predictive information from shorter and longer windows onto past events, weighing the windows proportionally to their predictive power. As the model defines a prior over window depths, we were able to determine the extent to which the internal predictions of individual participant depended on how many previous elements.

Already in the first session, the model showed that participants had begun to rely on two previous elements (i.e., trigrams), thereby successfully adapting to the most prominent higher-order structure in the task. The extent to which local statistical fluctuations influenced participants' responses waned over subsequent sessions, as subjects forgot the trigrams less and evidenced skilled performance. By the eighth session, a subset of participants shifted their prior further to consider a context deeper than two previous elements. Finally, participants showed resistance to interference and slow forgetting of the old sequence when it was changed in the final sessions. Model parameters for individual subjects covaried appropriately with independent measures of working memory. In sum, the model offers the first principled account of the adaptive complexity and nuanced dynamics of humans' internal sequence representations during long-term implicit skill learning.
The increasing number of people suffering from stress-related diseases such as depression, anxiety or PTSD, and the rather poor success of treatment, increases the necessity of getting more profound knowledge about the molecular mechanisms underlying such diseases. The reasons for imbalance of excitatory and inhibitory activity in these illnesses might be due to synaptic aberrations. Several receptor kinases are relevant regarding synaptic plasticity and stability such as the BDNF binding tropomyosin related kinase TrkB. It is not only relevant for neuronal survival, differentiation and synaptic plasticity but also highly susceptible to stress hormones. Preliminary investigations of a partial knockdown of TrkB in vivo revealed a specific decrease in the density of inhibitory synaptic marker gephyrin located in the perisomatic area of principle neurons. Since gephyrin is essential for the clustering of GABAergic receptors at the postsynaptic sites of inhibitory synapses, this finding demonstrates the role of BDNF-signaling for inhibitory synaptic stability. We modified the respective induction sites of the three major TrkB signaling cascades PLCγ-, MAPK- and Pi3K-Akt to further investigate pathway specific mechanisms regarding the inhibitory synaptic stabilization in principal neurons. Functional validation of the generated TrkB variants confirms individual pathway induction due to the point mutations. Transduction of primary hippocampal neurons further revealed pathway dependent changes in somatic synapse density, indicating a differential role of the individual TrkB signaling pathways regarding the stability of synapses.
Birdsong is a learned vocal behaviour composed of sequences of individual elements called syllables. As most neuroscience research on songbirds focuses on one species with relatively stereotyped songs, the zebra finch, the neuronal mechanisms underlying the formation of songs from variable syllable sequences remain poorly understood.

Here, we test whether cortical nucleus mMAN (medial magnocellular nucleus of the anterior nidopallium) contributes to the variable sequencing of adult Bengalese finch (Lonchura striata) song. mMAN is part of a basal ganglia-thalamo-cortical loop that projects to motor nucleus HVC. Bengalese finch song contains branch points, where one syllable can be succeeded by multiple following syllables in a probabilistic manner and chunks, where multiple syllables are sung in stereotypical order. After mMAN lesion, sequencing became more random: 1) Transition probabilities at branch points became less predictable (for example ab-c 70% and ab-d 30% became ab-c 60% and ab-d 40%), characterised by an increase in total transition entropy. 2) We observed breaking of previously stereotyped chunks, and introduction of new transitions between syllables. 3) Repeat phrases, where the same syllable is repeated multiple times, increased in length and variability after the lesion. These changes were apparent as soon as singing resumed after the lesion and persisted after the song had stabilised. mMAN lesions in adult zebra finches have previously been found to have little influence on song production. In contrast, our results suggest that nucleus mMAN contributes to the variable sequencing of Bengalese finch song, and suggests that models of song production may need to include areas upstream of premotor song nucleus HVC for species with more complex song syntax.
P27 – Interactions of Prenatal and Postpartum Depression and Infants’ Temperament Trajectories: From Age 6 Weeks to 18 Months

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Background: Infant temperament is one of the earliest indicators of later developmental difficulties. The interaction between maternal depression and anxiety and the developmental course of infant temperament over time is not well explored. This study identified trajectories of infant temperament from 6 weeks after delivery to 18 months, and the association between maternal symptoms of depression and anxiety in pregnancy and the postpartum period and infant temperament trajectories.

Method: Data from 1687 mother-infant dyads from the Uppsala (Sweden) BASIC cohort (“Biology, Affect, Stress, Imaging and Cognition in pregnancy and puerperium”) and the follow-up study (U-BIRTH) was used. Maternal depressive and anxiety symptoms were assessed via the Edinburgh Postnatal Depression Scale (EPDS & EPDS-3A) during pregnancy at gestational weeks 17 and 32 and postpartum at week 6. Difficult infant temperament was defined from the Infant Characteristics Questionnaire (6 weeks), subscales of the Toddler Behavior Questionnaire (TBQ) (12 months) and the very short form of the Early Childhood Behavior Questionnaire (18 months). Difficult infant temperament trajectories were calculated via Group-Based Trajectory Modeling. Multinomial regression was employed for the associations between maternal variables and temperament trajectories.

Results: Trajectories stable low, stable medium and high rising were identified. Higher anxiety scores (EPDS-3A) prenatally were associated with the high rising difficult temperament trajectories, the depressive/anhedonia subscale was associated with the stable medium temperament trajectory. The association between prenatal anxiety and the high rising trajectory stayed significant after introduction of postpartum anxiety, while the association of depression/anhedonia got attenuated when postpartum depression/anhedonia was introduced to the model. Sex specific effects were found for girls being more vulnerable towards maternal anxiety during pregnancy and boys towards maternal postpartum depression.

Conclusion: Effects on infant temperament by maternal mood vary, depending on the timing (pre- or postpartum), type of symptoms (depression/anhedonia vs. anxiety) and sex of the infant.
P28 – Investigating the neuron-glial metabolic coupling in iPSC-derived models of HSP

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In the central nervous system, glial cells, in particular astrocytes, are considered to play a major supportive role for neurons through the tight coupling of metabolic processes. Defective neuroglial communication is implicated in the pathophysiology of many neurodegenerative diseases including Hereditary Spastic Paraplegia (HSP), a heterogeneous disorder leading to the progressive degeneration of upper corticospinal motor neurons. The three most common forms of autosomal dominant HSPs, SPG4 (Spastin), SPG3A (Atlastin-1), and SPG31 (REEP1), result from distinct mutations in proteins directly implicated in the shaping and distribution of tubular endoplasmic reticulum (ER) and the formation of lipid droplets (LDs). While the ER plays a central role in the intracellular synthesis, metabolism, and distribution of lipids, LDs are highly dynamic intracellular organelles that primarily store and transport neutral lipids such as cholesterol esters and triacylglycerols. Astrocytes are closely involved in the lipid metabolism, they are the primary providers of lipids to neurons through lipoprotein-mediated transfer and play a key protective role by buffering/metabolizing excess neuron-derived lipids to mitigate lipotoxic neuronal damage. A better understanding of how ER-resident HSP proteins regulated lipid metabolic pathways in astrocytes and neurons may provide new insights into the pathogenesis of HSP. Here we report the implementation of disease-specific iPSC-derived astrocytes and introduce a set of cell-based and molecular methods with a specific focus on lipid metabolism (ER morphology and LD dynamic) to further characterize neuron-glial crosstalk in health and disease. On this basis, neuronal-glial co-cultures might provide a comprehensive approach to study intercellular transport and metabolism of lipids (lipid metabolism) and to identify a potential disease-relevant role of astrocytes in the pathology of HSP.
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