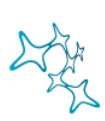


Munich Brain Day 2025 | May 16th 2025

Abstract booklet



Graduate School of
Systemic Neurosciences
LMU Munich



Welcome to the Munich Brain Day 2025!

Welcome to the 3rd Munich Brain Day, an initiative of the Munich Center for Neurosciences (MCN). Our goal is to bring the local neuroscience community together, fostering the exchange of ideas, and catalyzing innovative interdisciplinary research. The Munich Brain Day serves as a forum for molecular, cellular, developmental, computational, cognitive, and evolutionary neuroscientists to present their latest work. We hope that new interactions will lead to new ideas and exciting new discoveries in Munich. We will raise the profile of early career scientists, with a particular emphasis on increasing diversity. All disciplines, nationalities, ethnic groups, genders and sexualities are welcome at the Munich Brain Day. Put simply - we aim to be more than the sum of our parts.

Today's program includes 13 dynamic speakers, each of whom will give a 20 min talk to introduce the community to their research. A two-hour poster session over lunch will enable students and post-docs to present their work and persuade the judges that they are deserving of a poster prize! This will be preceded by a 30 min data blitz, where 10 students and postdocs will have an opportunity to present their work to the audience. The day will conclude with a social event supported by Coherent.

We wish to say a special thanks to our Gold sponsors TOPTICA and SyNergy who support the poster session. We are also indebted to our Silver Sponsors Campden Instruments, Coherent, Inotiv, Laser 2000, Merck, Prospective Instruments, and TRR274. Finally, we would also like to thank the Max Planck Institute for Biological Intelligence for hosting our symposium, as well as all volunteers who helped organize this event.

Have fun!

The organizing committee

Oliver Behrend | LMU/MCN
Silvia Cappello | LMU
Lisa Fenk | MPI BI
Angelika Harbauer | MPI BI

David Keays | LMU
Oriane Mauger | MPI PSY
Gregory Nordmann | MPI BI
Ruben Portugues | TUM

Program

08:00 Registration

09:00 Opening remarks

Session 1 – Cellular and Developmental Neuroscience

Chair: David Keays | Biology Department, LMU

09:10	Jovica Ninkovic Helmholtz Munich Unveiling the Intricate Dance: Glioblastoma and Surrounding Reactive Glial Cells
09:30	Antje Grosche Biomedical Center, LMU Focus on glial cells: New gene therapy approaches for retinal diseases
09:50	Elisabeth Binder Max Planck Institute of Psychiatry Molecular and Cellular Mechanisms of Prenatal Risk Factors in Psychiatric Disorders
10:10	Fabian Theis Department of Mathematics, TUM Generative AI for learning Cellular state & response

10:30 Coffee Break

Session 2 – Brain and Circuit Evolution

Chair: Gregory Nordmann | Max Planck Institute for Biological Intelligence

11:00	Richard Merrill Biology Department, LMU Brains, behaviour and butterfly speciation
11:20	Maude Baldwin Max Planck Institute for Biological Intelligence Evolution of sensory and digestive systems in birds
11:40	Veronica Pravata Biomedical Center, LMU <i>DCHS1</i> Modulates Forebrain Proportions in Modern Humans via a Glycosylation Change

↖ Data Blitz ↘

12:00

Chair: Angelika Harbauer | Max Planck Institute for Biological Intelligence

12:30 **Lunch | Poster Session | Trade exhibition**

Session 3 – Neurodegeneration

Chair: Oriane Mauger | Max Planck Institute of Psychiatry

14:30

Dominik Paquet | Institute for Stroke and Dementia Research, LMU
Building novel human 3D brain tissue models to investigate neurodegenerative diseases

14:50

Thomas Misgeld | Institute of Neuronal Cell Biology, TUM
Mitochondrial dynamics, diversity and damage in the CNS

15:10

Günter Höglinger | MCN
Towards a biological definition of Parkinson's disease

15:30

Sabina Tahirovic | DZNE
Neuronal-Glial Crosstalk in Niemann Pick Type C Disease

15:50

Coffee Break & Photo | sponsored by Campden Instruments

Session 4 – Systems Neuroscience

Chair: Ruben Portugues | TUM

16:30

Laura Busse | Biology Department, LMU
Effects of corticothalamic feedback on neural responses in visual thalamus

16:50

Anna Schröder | Biology Department, LMU
Neural circuit mechanisms of internal state driven behavioral flexibility

17:10

Final remarks and Poster awards

17:30

Social hour | sponsored by Coherent

Posters

1 ♂	VAPB-RMDN3 mito-ER contact sites persist upon mitochondrial damage to recruit autophagy mediators Alina Rühmkorf, Alexander Zorn, Christian Behrends, Angelika Harbauer
2	Decoding Temporal Features of Birdsong Through Neural Activity Analysis Amirmasoud Ahmadi, Hermina Robotka, Frederic Theunissen, Manfred Gahr
3	Extracellular Vesicle Transport of Primate-Specific MicroRNAs in brain development Andrea Forero, Kiril Tuntevski, Kyrania Christofi, Davide Pietri Tonelli, Silvia Cappello
4	Dynamic Modulation of Auditory Cortex Activity: Distinct Effects of Task Engagement and Locomotion on Neuronal Population Response Andrey Sobolev, Miguel Bengala, Valentin Winhart, Dardo Ferreiro, Benedikt Grothe, Anton Sirota, Michael Pecka
5	Quantitative analysis of temporal activity in medial entorhinal cortex Arseniy Veselov, Martin Stemmler, Andreas Herz
6	Mouse frontal cortical dopamine transients during cue-action-outcome association learning Righetti, B., Bernklau, T.W., Jacob, S.N.
7	Investigating the Molecular Interplay in c9orf72 ALS/FTD: Uncovering Novel Pathways and Therapeutic Targets Berkcan Isilgan, Dieter Edbauer
8 ♂	State-dependent neural dynamics in the visual system Berkutay Mert, Emmalyn S.P. Leonard, Liya Niv, David A. McCormick, Christopher M. Niell, Dennis B. Nestvogel
9	Interplay between TDP-43 and Progranulin (PGRN) Buse Özbaykent, Julia Schneider, Milos Ninkovic, Jovica Ninkovic
10	Assessment of synapse loss in an animal model of multiple sclerosis using [18F] UCB-H Sv2a PET tracer: A step towards clinical translation Carla Ares Carral, Emily M. Ullrich Gavilanes, Laura M. Bartos, Diego Ruiz Navarro, Doron Merkler, Matthias Brendel and Martin Kerschensteiner
11	Tracing neuronal connectivity in the developing mouse with barcoded monosynaptic rabies virus Connor Lynch, Rachel Bandler, Dan Doyle, Alex Hennrich, Karl-Klaus Conzelmann, Christian Mayer
12	Investigating Oligodendrocyte Pathology in Familial Alzheimer's Disease Courtney McQuade, Seiji Kaji, Stefan Berghoff, Francesca Drummer, Charlene Hurler, Thomas Arzberger, & Sarah Jäkel
13	Does Print Exposure Moderate the Relationship Between Affective and Cognitive Empathy? Daniel Lee, Ciara Egan

14	Exploring the ontogenesis of adult neural stem cells across species Daniela Cimino, Virginia Fernández, Annina Denoth-Lippuner, Anna Danese, Tatiana Simon-Ebert, Sebastian Jessberger, Victor Borrell, Magdalena Götz
15	TECPR2 neuropathy mice reveal endo-lysosomal dysfunction in neurons and microglia Debjani Bhattacharya*, Patricia da Silva-Buttkus*, Karsten Nalbach, (...) Christian Behrends
16	Epigenetic mechanisms of innate immune memory in the brain at single cell level Desirée Brösamle, Xidi Yuan, Rebekka Scholz, Marc Beyer, Jonas J. Neher
17	Action without Visual Awareness: The Role of Visual Awareness for the Control of Visually Guided Actions Didem Taskiran
18	Characterization of novel recombinant adeno-associated virus (rAAV)- capsid variants in the mouse brain for future use in seizure therapy E. Arslantas, P. Lorenz, Dr. V. Mehlfeld and Prof. M. Biel
19 ↗	Neural basis underlying following in Drosophila courtship Eduardo Gallego, Inês M.A. Ribeiro
20	Beyond Univariate Envelope Modeling: EEG Response Prediction with the Multivariate Amplitude-Binned TRF Model Elnur Imamaliyev, Thorge Haupt
21	The effects of respiration-locked TMR on the consolidation of memories Esteban Bullón Tarrasó, Fabian Schwimmbeck, Marit Petzka, Bernhard P. Staresina & Thomas Schreiner
22 ↗	Epigenetic modulation with decitabine reduces C9orf72-associated toxic pathologies via heterochromatinization Eszter Katona, Berkcan Huseyin Isilgan, Ashutosh Dhingra, (...) Dieter Edbauer
23	“Natreshka” - Recoverable Neuropixel 2.0 implant for chronic recordings Evgeniia Bukina, Andrey Sobolev, Anton Sirota
24	Direct neuronal reprogramming of Oligodendrocyte progenitor cells Fabio Laredo, Oleksandra Pavlovska, Magdalena Götz, Giacomo Masserdotti
25	Nuclear function of the cytoskeletal protein MAP1B in neural stem cells drives neurogenesis Florencia Merino, Lucas Miranda, Yiling Li, (...) Magdalena Götz
26	CRISPR-Cas13 mediated DMPK Knockdown in Myotonic Dystrophy Type 1 (DM1) Hanseul Oh, Aline Huguet, Stefan Hintze, Geneviève Gourdon, (...) Peter Meinke
27	Topological Data Analysis Enhances fMRI-Based Classification Performance of Obsessive-Compulsive Disorder Hanyang Ruan, Daniela Rodriguez Manrique, Deniz Gürsel, Benita Schmitz-Koep, Götz Berberich, Claus Zimmer, Kathrin Koch

28	Investigation of axonal membrane resealing regulation in an animal model of spinal cord injury Ioanna Emmanouilidis, Hsiu-Hsin Cheng, Yi-Heng Tai, (...) Thomas Misgeld
29	Understanding the Role of Pink1 mRNA Transport and Localization in Parkinson's Disease Isabel Geelhaar, Dr. Inmaculada Segura Vitutia, Prof. Dr. Angelika Harbauer
30	Systematic analysis of meta-learned synaptic plasticity rules reveals degeneracy and fragility Jan-Erik Huehne, Nikos Malakasis, Dylan Festa, Julijana Gjorgjieva
31	Uncovering sexual dimorphism in human microglia using organoid-based platforms Janina Kaspar, Irene Santisteban Ortiz, Lucía Rodríguez Martínez, (...) Simon Schafer
32	Medin amyloid: Exploring its role in vascular ageing and Alzheimer's disease Jessica Wagner, Karoline Degenhardt, Nathalie Beaufort, (...) Jonas J. Neher
33	Spontaneous and sensory-evoked arousal fluctuations engage a specific brain activity wave Jose Maria Martinez de Paz, Johanna Mayer, Paulina Wanken, Beatriz Rodrigues Apgaua, Emilie Macé
34	Integration of spatial transcriptomics into existing 3D mouse brain atlases Katia Berr, Jakob König, Hannah Spitzer
35	Acute changes in neurosteroid levels in brain and plasma following mild traumatic brain injury (mTBI) Kosisochukwu E. Umeasalugo; Igor Khalin; Burcu Seker; Philippe Liere; Michael Schumacher; Inga Koerte; Nikolaus Plesnila
36	Investigation of Region-specific Interactions Between Neural Progenitors and Microglia During Development Kyrania Kaarina Christofi, Maria Veronica Pravata, Silvia Cappello
37	40 Hz Steady-State Visually Evoked Potentials Recorded During Oscillating Transcranial Electrical Stimulation Laura Hainke, Manuel Spitschan, Josef Priller, Paul Taylor, James Dowsett
38 ↗	Large-scale extracellular recordings reveal right-hemispheric language processing in aphasia Laura Schiffli & Lisa M. Held, Arthur Wagner, Bernhard Meyer, (...) Simon N. Jacob
39	Identification of proteomic clusters in the CSF of sporadic ALS patients Laura Tzeplaeff, Xuan Liu, Clara Meijs, Lucas Caldi Gomes, (...) Paul Lingor
40	Lipid Metabolism in the Ependymal Cells of the Brain Lennart Schlaphoff, Mikael Simons
41	A spatial transcriptomics workflow to investigate molecular signatures of learning in the striatum of humanized foxp2 mice Leonhard Schaffmayer, Wolfgang Enard

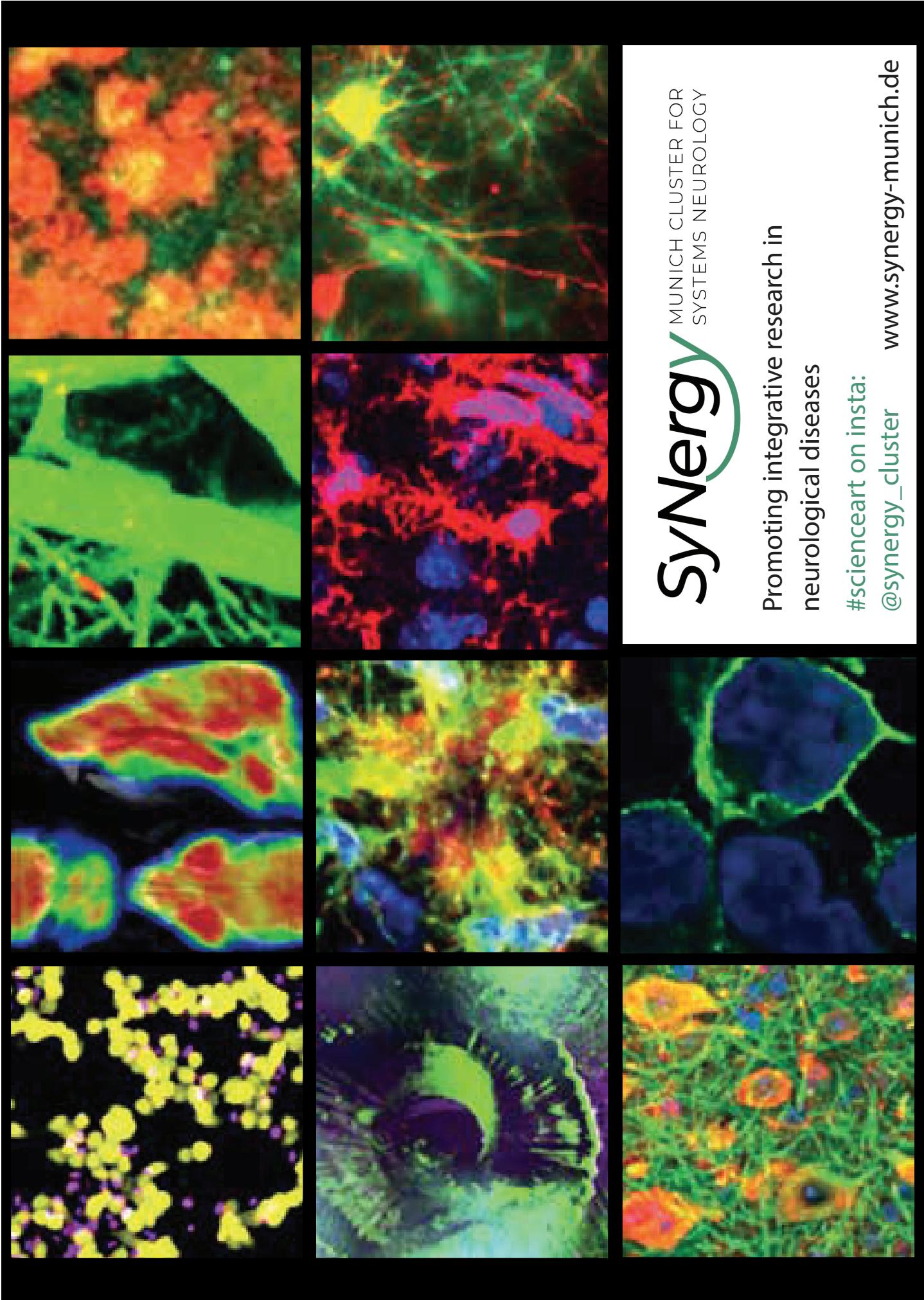
42	Dynamics of inflammation in retinitis pigmentosa disease progression Leonie Pauline Kugel and Susanne Friederike Koch
43	Sex-specific & Ever-changing: Long-term recordings after acute restraint reveal sex-specific and dynamic stress behavior in mice London Aman, Benjamin Jurek, Mathias Schmidt
44	Anatomically resolved oscillatory bursts reveal dynamic motifs of thalamocortical activity during naturalistic stimulus viewing Lukas S. Meyerolbersleben, Anton Sirota, Laura Busse
45	Temporal precision of the LSO neurons and their input Luna A. Studer, Jonas Fisch, Eckhard Friauf and Conny Kopp-Scheinpflug
46	Investigating the neural correlates of the magnetic sense in the pigeon Marco Numi, Simon Nimpf, David Keays
47	The pathophysiological relevance of MCUGR1 and its function in glial cells Margarita Chudenkova, Hilda Carolina Delgado, Yiming Cheng, Safal Walia, Monika Leischner-Brill, Tito Cali', Fabiana Perocchi
48	EGFR activation correlates with intracranial pressure and survival in a mixed intracranial bleeding porcine model Marica Pagliarini, Zongren Zhao, Burak Özkan, Tamara Merz, (...) Francesco Roselli
49	EVs-derived microRNAs and Their Potential Involvement in EPM1 Pathogenesis Ianni M, Forero A, Tuntevski K, Christofi K K, Pravatà M V, De Pietri Tonelli D, Cappello S and Di Giaimo R
50	Decoding Auditory Attention from Brain Activity in a Two-Speaker Environment Maryam Bajool, Bernhard U. Seeber
51	Molecular pathology of the late-onset Alzheimer's disease risk variant S209F ABI3 Matteo Rovere, Michele Albertini, Molly Streich, Ignasi Forné, (...) Christian Haass
52	Behavioral and Neuronal Correlates of Exploration and Goal-Directed Navigation Miao Wang, Fabian Stocek, Justin Graboski, Adrian Duszkiewicz, Joseph González, Adrien Peyrache, Anton Sirota
53	JAXLEY: Differentiable simulation enables large-scale training of detailed biophysical models of neural dynamics Michael Deistler, Kyra L. Kadhim, Matthijs Pals, Jonas Beck, Ziwei Huang, Manuel Gloeckler, Janne K. Lappalainen, Cornelius Schröder, (...) Jakob H. Macke
54	Differential effects of acoustic trauma on auditory onset and offset responses Mihai Stancu, Ezhilarasan Rajaram, Joseph Kroeger, Benedikt Grothe, and Conny Kopp-Scheinpflug
55	Divergent subcortical connectivity patterns during sleep/wake transitions and isoflurane-induced loss of responsiveness in mice Monika Vadkertiova, Leesa Joyce, Rachel Nuttall, Matthias Kreuzer, Gerhard Rammes, Gerhard Schneider, Thomas Fenzl

56	Modulation of Visual Avoidance by Environmental Conditions Mrudula Gangur, Weiqi Chen, Inês M.A. Ribeiro
57	Preclinical Validation of a Novel Drug Target for Amyotrophic Lateral Sclerosis Identified Through Multiomic Analysis Natalie Dikwella, Lucas Caldi Gomes, Paul Lingor
58	Pathogenesis of Morbus Stargardt in an Abca4 KO Mouse Model and in Retinal Disease Organoids Natalie Klippel, Verena Mehlfeld, Martin Biel
59	The effects of daytime napping on the ability to retrieve memories in humans Nicolas D. Lutz, Iris Köller, Tobias Staudigl, Susanne Diekelmann, Luciana Besedovsky
60	Paradoxical Excess Dopamine upon Locus Coeruleus Axon Loss in the Hippocampus drives Cognitive Impairment in LBD Nicolas Landgraf*, Weilin Chen*, Paul Feyen, Thomas Köglspurger, (...) Lars Paeger
61	Vocal Strategies for Territorial Defense and Mate Attraction in Nightingales Niels Hein, Giacomo Costalunga, Daniela Vallentin
62	Hif1a regulates microglial phenotype and cognitive function in mouse models of Alzheimer's Disease Pathology Nina Hermann, Desirée Brösamle, Jonas J. Neherw, Lisa Steinbrecher, Ann-Christin Wendeln, Katleen Wild, Heidi Theis, Marc Beyer, Joachim Schultze
63	A behavioural response to magnetic stimuli in Pigeons? Aaron T. Denton, Spencer D. Balay, and David A. Keays
64	Human retinal organoids mimick the cholesterol sotrage disease Niemann-Pick type C in vitro Patricia Hoffelner, Oliver Bludau, Valerio Zenatti, Lina Dinkel, Laura Sebastian Monasor, Dominik Paquet, Matthias Prestel, Sabina Tahirovic, Antje Grosche
65	Selective vulnerability of Pvalb Neuron Axon Bifurcations in Tauopathy Paul Feyen, Yuxiao Zhang, Lars Paeger, Theresa Niedermeier, Jochen Herms
66	Ocular dominance columns in mouse visual cortex Pieter M Goltstein, David Laubender, Tobias Bonhoeffer, Mark Hübener
67	iPSC-Derived Monocytes Modulate the Glioblastoma Microenvironment and Inhibit Tumor Progression Polyxeni Moysidou, Jovica Ninkovic
68	The role of synchronous motion in perceiving agency in inanimate entities Rebecca Geiselmann, Lasana T. Harris, Ophelia Deroy
69	Neural Correlates of Social Metacognition Mattes, Rebekka S.; Vural, Gizem; Drexler, Sarina; (...) Soutschek, Alexander
70	Contrastive representation learning for neural system identification Rodrigo Gonzalez Laiz, Tobias Schmidt, Steffen Schneider

71	Subregion-Dependent Insular Coupling with Heart Rate and Its Derivative in Aversive and Appetitive States Ronja Brinkmann, Mira Erhart, Dr. Nadine Gogolla, Dr. Victor Spoormaker
72	Canaries differentially modulate solo and overlapping singing during the transition to the breeding season Santhosh Totagera, Pepe Alcami
73♀	Brain-wide networks for category learning in the mouse Selina Majaj, Sandra Reinert, José-Maria Martinez de Paz, Mark Hübener, Pieter M Goltstein, Emilie Macé, Tobias Bonhoeffer
74	Energetic costs of brain connectivity in Behavioural Variant Frontotemporal Dementia Shuqi Xie, Yifan Mayr, Igor Yakushev
75	Neural representation of color in the pigeon brain Simon Nimpf, Ann H. Kotkat, Andreas Genewsky, Laura Busse, David A. Keays
76	Functional and molecular mechanisms underlying plasticity-mediated CNS recovery after spinal cord injury in adulthood and aging Adna Smajkan, Hannah Peedle, Florence Bareyre
77	Human cerebral assembloids as a model to study the interaction of glioblastoma with resident glial cells S Kalpazidou, P. Moysidou-Tsiorva, B. Özbaykent, (...) J. Ninkovic
78	Sex-specific outcomes of developmental stress exposure and psilocybin intervention S. Narayan, R. Florea, J. Bordes, S. Mitra, B. Silva, C. Castoldi, B. Dal Bianco, S. Röh, D. Czamara, E.B. Binder, M.V. Schmidt
79	Emotion state representations in the mouse insular cortex Stoyo Karamihalev, Lisa Rottenfußer, Yanko Arevalo, Rosa-Eva Huettl, Nadine Gogolla
80	Unraveling Human Brain Cross-Regional Complexity Through Integrative snRNA-seq Profiling Su Han Cho; Eva M.G. Viho; Anna S. Fröhlich; Elisabeth B. Binder
81	Early changes in glial cells in INSC94Y pig model for diabetic retinopathy Sweetu Susan Sunny, Lew Kaplan, Oliver Bludau, Kirsten Wunderlich, Patricia Hoffelner, Cornelia A. Deeg, Simone Renner, Eckhard Wolf, (...) Antje Grosche
82	Induction of Tau Pathology in Wild-Type Mice: A Model to Study Seeding and Spread in Tauopathies T. Nazarenko, S. Kaji
83♀	Studying mitochondrial dynamics with in vivo acousto-optic two photon imaging – focus on Locus Coeruleus vulnerability Theresa Niedermeier, Paul Feyen, Katharina Ochs, Jochen Herms, Lars Paeger
84	Multi-tracer PET monitoring of an immunomodulatory therapy in 4R tauopathy: Evaluating a novel drug's impact on glial function and protein pathology Tim Bathe, Svetlana Salomasova, Manvir Lalia, Lea H. Kunze, Giovanna Palumbo, Rosel Oos, Emanuel Joseph, Matthias Brendel

85	Axolotl: ready-to-go program to achieve successful brain regeneration? Zahra Yaghoobi, Sophie Antesberger, Alberto Joven Araus, Elif Eroglu, Jonas Huber, Martin Heß, Hans Straka, and Rosario Sanchez-Gonzalez
86	painless mediated stiffness-sensing of oviposition substrates in <i>D. melanogaster</i> Vijayaditya Ray, Lasse Bräcker, Alexandros Kourtidis, Charlotte Rosher, Gesa F. Dinges, Ansgar Büschges, Kevin M. Cury, Nicolas Gompel
87	Neural Circuits Regulating Avoidance and Tracking Weiwei Chen, Ines M.A. Ribeiro
88	Neuronal signatures of contextual decision-making in mouse prefrontal cortex and mediodorsal thalamus Xuanyu Wang, Daniel Hähnke, Ajit Ranganath, Tobias W. Bernklau, Simon N. Jacob
89	Generalizable emotion state inference from facial videography in mice Yanko Arévalo, Stoyan Karamihalev, Nadine Gogolla
90	Evolution of the olfactory system during the radiation of Heliconiini butterflies Yi Peng Toh, Francesco Cicconardi, Richard M Merrill & Stephen H. Montgomery
91	Distractor Suppression Mechanisms in Differing Sensory Volatilities: Implications for Predictive Coding in Autism Spectrum Disorder Yun Wai Foo, Sonja Coenen, Irene Sophia Plank, (...) Christine M. Falter-Wagner
92	Cell-cell communication in retinal homeostasis and disease Zeynep Okutan, Michelle Jentzsch and Susanne F. Koch
93	All-optical exploration of emotion state representations in the mouse insular cortex Lisa Rottenfußer, Stoyan Karamihalev and Nadine Gogolla

↳selected for Data Blitz



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Poster abstracts

1 VAPB-RMDN3 mito-ER contact sites persist upon mitochondrial damage to recruit autophagy mediators

Alina Rühmkorf, Alexander Zorn, Christian Behrends, Angelika Harbauer

>Neurons strongly rely on processes mediating cellular homeostasis. One critical process for cellular self-renewal is autophagy, which requires interaction between mitochondria and the ER. In neurodegenerative diseases such as Amyotrophic lateral sclerosis (ALS), damaged mitochondria accumulate in neurons before cell death. Additionally, mutations of mitochondria-ER contacts sites (MERCS) can be present, including mutations of Vesicle-associated membrane protein-associated protein B (VAPB), an ER-resident protein, interacting with Regulator of microtubule dynamics 3 (RMDN3), a protein located on the outer mitochondrial membrane. Together, this hints at defects in mitochondrial autophagy (mitophagy). This study investigates the functional implications of the mitochondria-ER tether pair VAPB-RMDN3 in mitophagy. Using the proximity ligation assay (PLA), VAPB and RMDN3 were found to increase their interaction upon mitochondrial damage, while interaction of another mitochondria-ER tether pair decreases. Additional proximity proteomic analyses, where split APEX is coupled to the VAPB-RMDN3 tether proteins and combined with mass spectrometry analyses in HEK293 cells, revealed several autophagy and ALS associated proteins being recruited towards the interacting tether proteins. One of these proteins is SAC1, a phosphoinositol phosphatase, previously described to be implicated in autophagosome formation. This study further evaluates the role of SAC1 in mitophagy and how this might differ in somatic cells compared to neurons. Altogether, this study underscores the importance of functional MERCS and unravels their underlying molecular mechanism mediating mitophagy, ultimately providing important insights for the progression of neurodegeneration.

2 Decoding Temporal Features of Birdsong Through Neural Activity Analysis

Amirmasoud Ahmadi, Hermina Robotka, Frederic Theunissen, Manfred Gahr

>Segmenting vocalizations into distinct units, a process called auditory temporal decoding, is essential for interpreting sounds. Songbirds, especially the zebra finch with its hierarchical song structure, provide valuable models for studying neural representations of complex sounds. In this study, we recorded zebra finches' auditory activity during song processing using a movable electrode array, collecting data from 51 recording sites. We employed stacked bidirectional long short-term memory (BiLSTM) deep neural networks to decode the amplitude envelope and time-locked envelope features of the songs. To evaluate how effectively neural activity segments continuous songs into units and decodes amplitude, the networks were trained using local field potential (LFP) and multi-unit activity envelope (MUAe) data. Our results demonstrate that both amplitude envelope and time-locked features can be accurately decoded from ensemble responses using LFP and MUAe. While the performance of LFP and MUAe was similar, MUAe provided slightly better results for envelope decoding. We observed temporal information is not uniformly present across the auditory pallium. By analyzing the information rate of

recorded neurons and the decoding performance of our networks, we identified specific brain regions that code the temporal aspects. Most of these regions are located in the primary auditory area, Field L. Notably, we found a linear correlation between neurons' mean information rate at recording sites and the decoding performance achieved using MUAe. Our high-performance decoding of temporal features illustrates how neural representations facilitate the segmentation of songs. We found that the temporal features of songs are also coded at the single-neuron level and that zebra finches employ region-specific encoding strategies within their auditory processing network. These findings provide valuable insights for future research into the intricate neural processes involved in vocal communication.

3 Extracellular Vesicle Transport of Primate-Specific MicroRNAs in brain development

Andrea Forero, Kiril Tuntevski, Kyrania Christofi, Davide De Pietri Tonelli, Silvia Cappello

>Extracellular vesicles, consisting of secreted vesicles that transfer nucleic acids, lipids, and proteins between cells, have recently been identified as potential modulators in neuronal development and function. Although it is a known fact that microRNAs (miRNAs) are trafficked via extracellular vesicles, a systematic categorization of the miRNA content of EVs released by human neural progenitor cells, neurons and astrocytes is still lacking. Therefore, the aim of this project is to study transcriptional regulation via EV-miRNAs in the context of neurodevelopment. By collecting EVs from both 2D neural cultures and 3D cerebral organoids, we identified both well conserved miRNAs, such as miR-9, as well as less conserved primate-specific miRNAs, such as miR-6825. Following target prediction analysis, we then focused on one human-specific and three primate-specific miRNAs that have yet to be studied in human brain cells and are predicted to target genes relevant for processes such as generation of neurons and neuronal migration. Our results highlight the importance of recognizing human/primate-specific elements mediating human brain development.

4 Dynamic Modulation of Auditory Cortex Activity: Distinct Effects of Task Engagement and Locomotion on Neuronal Population Response

Andrey Sobolev, Miguel Bengala, Valentin Winhart, Dardo Ferreiro, Benedikt Grothe, Anton Sirota, Michael Pecka

>A significant limitation in current research on sensory processing is the assumption that behavioral and cognitive states are stationary, often reducing them to simplistic categories such as "active" or "passive." This overlooks the dynamic and fluctuating nature of these states, especially in naturalistic settings, and leads to a loss of crucial real-time information about the joint evolution of both internal brain state and external sensory processing. Furthermore, the influence of cognitive states, such as attention and engagement, and behavioral states, such as locomotion on auditory processing remains a topic of significant debate. Using the freely-moving experimental paradigm (SIT) and continuous periodic auditory stimulation we investigated the dynamic effects of different voluntary behavioral states on the evoked and sustained neuronal responses in the primary auditory cortex (A1). Our findings revealed that cognitive states requiring increased auditory processing such as task engagement selectively

reduce sustained neuronal activity while maintaining stable evoked responses, suggesting an optimization of sensory processing. In contrast, behavioral states characterized by high locomotion lead to increased sustained activity without affecting evoked responses. Our generalized linear model analysis confirmed that task engagement and locomotion are significant predictors of sustained neuronal activity, in line with existing evidence that sustained activity is a key driver of variance in sensory cortex responses. These results underscore the need to consider the instantaneous interaction between internally-driven behavioral states and externally-driven sensory inputs to understand auditory cortical function in dynamic environments.

5 Quantitative analysis of temporal activity in medial entorhinal cortex

Arseniy Veselov, Martin Stemmler, Andreas Herz

>Grid cells in the medial entorhinal cortex (MEC) are crucial for spatial navigation. This study compares the temporal activity of grid cells in rats and mice using multiple datasets to characterise and classify their activity patterns. We apply principal component analysis (PCA) and K-means clustering algorithm to autocorrelograms of grid cell spike trains to identify distinct firing behaviours. Our results reveal three major activity patterns: sparsely bursting, bursty without peaks, and bursty with peaks. These clusters align with previous findings in rodent grid cell research. Further, we analyse how these activity patterns shift between wakefulness and sleep, revealing systematic transitions that suggest state-dependent reorganisation of grid cell activity. By extending this analysis to include mice, we compare interspecies differences and similarities in grid cell temporal dynamics. Our findings indicate conserved activity motifs across species. This study provides insights into the temporal structure of grid cell activity and its modulation across behavioural states.

6 Mouse frontal cortical dopamine transients during cue-action-outcome association learning

Righetti, B., Bernklau, T.W., Jacob, S.N.

>As a neurotransmitter with wide-ranging neuromodulatory effects, dopamine is essential for brain functions such as cognition, motivation, and reward. Studies show that midbrain dopamine neurons projecting to the medial prefrontal cortex (mPFC) and lateral orbitofrontal cortex (IOFC) influence high-level cognitive processes. These regions receive dopamine transients which are believed to be fundamental for reinforcement learning. Here, we examined the time course of dopaminergic transients in mouse mPFC and IOFC during abstract associative learning in order to investigate how frontal dopaminergic signatures evolve with increasing task competency. We trained mice ($n = 23$) on an auditory decision-making task with implicit rule switches, requiring the forming of associations between auditory cues (tones varying along the dimension of location and frequency) and motor responses to obtain rewards. Using the fluorescent dopamine sensor GRAB DA3h, we conducted subsecond measurements of dopaminergic signals with fiber photometry over the course of several months while the animals learned the different rules. Dopamine responses during cue presentation and reward

consumption varied with the animals' task proficiency. In both regions, reward-triggered dopaminergic transients were largest in novice animals and decreased as the animals became experts. This effect was strongest for the first task rule. In contrast, omission of rewards in error trials triggered a reduction of dopamine levels, which also scaled with performance. This suggests that frontal dopamine contributes to modifying behavior based on feedback and reinforces learning. Dopamine activity was also triggered by auditory cues, particularly in the mPFC. After rule switches, cue triggered-dopamine transients were indicative of reward anticipation in the mPFC but, interestingly, not in the IOFC. In summary, our results suggest differential involvement of the mPFC and IOFC in cue-action association learning.

7 Investigating the Molecular Interplay in c9orf72 ALS/FTD: Uncovering Novel Pathways and Therapeutic Targets

Berkcan Isilgan, Dieter Edbauer

>Neurodegenerative diseases, characterized by the progressive degeneration of neurons in the central nervous system, remain a significant medical challenge. Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) exemplify two distinct yet interconnected disorders within this category. Despite extensive research, these diseases' triggers are poorly understood. Notably, over 30 gene mutations, including the prevalent C9orf72 repeat expansion, are linked to these diseases in which mutations result in disrupted protein and RNA regulation, culminating in characteristic neuronal TDP-43 inclusions. This project aims to uncover the link between ALS/FTD genes and how they act on TDP-43 eventually. Using functional assays in reporter cell lines and iPSC-derived neurons, I will investigate how gene knockdown affects the endolysosomal pathway, TDP-43 cytoplasmic mislocalization and phosphorylation, and cryptic exon expression. Initial siRNA validation and screening of 34 individual ALS-related genes revealed no impact on DPR levels in iPSC-derived neurons. Subsequent combinatorial siRNA screenings targeting disrupted pathways in C9/ALS also showed no effect. Similarly, these screenings did not influence TMEM106b levels or staining patterns. Conversely, siRNA screening identified two ALS/FTD-related genes that modulate cryptic exon expression without altering TDP-43 levels or localization. These findings suggest an alternative mechanism affecting ALS-associated pathways independently of TDP-43. The ultimate goal of this project is to identify molecular mechanisms behind the unexpected interactions of ALS-associated genes, such as poly-GA/C9orf72 and TBK1 [1]. Unraveling these pathways may uncover novel, druggable targets, offering new therapeutic pathways for both familial and sporadic ALS.

8 State-dependent neural dynamics in the visual system

Berkutay Mert, Emmalyn S.P. Leonard, Liya Niv, David A. McCormick, Christopher M. Niell, Dennis B. Nestvogel

>To meet their basic needs and to adequately interact with their environment, animals must integrate external signals from their surround together with internal signals from their body. External signals are detected by sensory organs, such as the eye, while internal signals constitute information about the physiological, cognitive, emotional and bodily state of the animal. The mechanisms by which sensory signals are integrated together with internal signals are poorly understood, but accumulating evidence indicates that the thalamus plays a crucial role in this process. Recent studies in head-fixed animals have demonstrated that the sensory thalamus strongly encodes state-related signals, such as arousal levels and motor movements. These signals, in turn, significantly influence how sensory information is transmitted to and between cortical regions. While experiments under head-fixed conditions offer precise control over sensory input and facilitate neural recordings, they limit the subject's ability to exhibit a range of states typical in more naturalistic, real-world conditions. Consequently, our understanding of how thalamic neurons encode state-related information and integrate it with external sensory signals remains limited. To overcome these limitations, we have performed high-density neural recordings in freely moving mice while monitoring changes in their physiological and bodily state via videography. Specifically, we recorded signals from the dorsolateral geniculate nucleus (dLGN) – the primary sensory thalamic nucleus for vision – and assessed changes in the physiological and bodily state of the animal by monitoring pupil size, orofacial movements, locomotion, and the position of the head, body, and eyes. Preliminary results from our experiments support previous findings that dLGN neurons strongly encode arousal- and motor movement-related signals. Furthermore, by making use of a simple neural network in our data analysis, we demonstrate that these signals explain a significant proportion of the neural variance of the average dLGN population activity in freely moving mice. Additionally, we identified different clusters of dLGN neurons that differentially encode positional signals of body parts. Overall, our results lend strong support to the hypothesis that the visual thalamus encodes a diverse array of state-related signals and integrates those together with sensory information to guide behavior.

9 Interplay between TDP-43 and Programulin (PGRN)

Buse Özbaykent, Julia Schneider, Milos Ninkovic, Jovica Ninkovic

>Preventing chronic inflammation and tissue scarring necessitates the inactivation of pathology-activated microglia. Injury-induced or disease-associated microglial states are characterized by the accumulation of lipid droplets, cytoplasmic TDP-43 condensates, and metabolic reprogramming. Programulin (GRN)-mediated clearance of lipid droplets and TDP-43 condensates is crucial for restoring microglia to their homeostatic state, promoting scarless regeneration in a zebrafish model. Notably, in traumatic brain injury patients, activated microglia also accumulate TDP-43 condensates, suggesting a conserved regulatory mechanism in humans. In this study, we investigate the cellular activation responses and metabolic alterations associated with pathological TDP-43 aggregation using induced pluripotent stem cell (iPSC)-derived human microglia (i-Micros). After successfully differentiating and

characterizing GRN WT and KO i-Micros, we optimized external activators such as H₂O₂, which is elevated in humans after spinal cord injury and heat shock, a well-established microglial activator. Our single-cell transcriptomics data revealed that GRN KO i-Micros inherently exhibit ER stress and an unfolded protein response (UPR). Upon activation, they developed phosphorylated TDP-43 aggregates colocalized with the ER membrane, accompanied by fragmented Golgi, disrupted ER-Golgi coupling, and decreased translation. Given the impaired lysosomal function in GRN KO microglia, we hypothesize that these ER-localized aggregates are not efficiently cleared via ER-phagy thus leading to prolonged cellular stress. Additionally, our single-cell data identified a metabolic shift in GRN KO i-Micros from oxidative phosphorylation (OXPHOS) to glycolysis. Since mitochondria closely interacts with the ER through mitochondria-associated membranes (MAMs), we propose that ER stress induced by pTDP-43 aggregation also disrupts mitochondrial functions, contributing to the observed metabolic shift. This hypothesis was further validated using Fluorescence Lifetime Imaging Microscopy (FLIM) metabolic imaging of GRN WT and KO i-Micros before and after activation. These findings suggest a novel link between TDP-43 aggregation, cellular stress responses, and metabolic adaptations. Within the scope of this project, we aim to determine whether these mechanisms constitute a transient microglial activation response or drive persistent neuroinflammation in human disease.

10 Assessment of synapse loss in an animal model of multiple sclerosis using [18F] UCB-H Sv2a PET tracer: A step towards clinical translation

Carla Ares Carral, Emily M. Ullrich Gavilanes, Laura M. Bartos, Diego Ruiz Navarro, Doron Merkler, Matthias Brendel and Martin Kerschensteiner

>Although initially considered a white matter disease, time has proven the relevance of grey matter pathology in the development of multiple sclerosis (MS). Synaptic loss, which arises early in the disease course, widely occurs in the grey matter, and this process has been previously identified as a key pathological feature. Despite their importance in the development of cognitive impairment, MRI detects only a small fraction of gray matter lesions. Consequently, the aim of the present study was to assess whether [18F] UCB-H as a synaptic vesicle glycoprotein 2A (Sv2a) tracer, could be a valuable tool for quantifying the synapse loss observed in MS pathology.

11 Tracing neuronal connectivity in the developing mouse with barcoded monosynaptic rabies virus

Connor Lynch, Rachel Bandler, Dan Doyle, Alex Hennrich, Karl-Klaus Conzelmann, Christian Mayer

>To understand how neurons network with each other at the neonatal developmental stage, we have developed a tracing strategy using an EnvA-pseudotyped rabies virus to transmit RNA barcodes to a neuron's immediate presynaptic partner. Neurons present in these networks are profiled by single-cell RNA sequencing to determine the identity and molecular state of cells, while recovery of the RNA barcodes allows for network reconstruction. We employed a transgenic mouse that expresses the avian TVA receptor under the excitatory neuronal transcription factor Neurod6 to achieve seeding of rabies

tracing in cortical excitatory neurons at birth, with collection between 6-8 days later. We recovered tens of thousands of cells participating in hundreds of distinct circuit networks, which reveal patterns of neuronal inputs to the prefrontal cortex present in the developing mouse brain. Notably, we observe overwhelming inputs from cajal-retzius cells, likely describing transient interactions during cortical layer establishment. Additional inputs to cortical cells were observed from sub-cortical structures, demonstrating the technique's power to reveal individual neuronal circuits, and when analyzed en-masse, to describe the complex patterns of cell-type connectivity in the developing brain.

12 Investigating Oligodendrocyte Pathology in Familial Alzheimer's Disease

Courtney McQuade, Seiji Kaji, Stefan Berghoff, Francesca Drummer, Charlene Hurler, Thomas Arzberger, & Sarah Jäkel

>Alzheimer's disease (AD) research has been neuron-centric for decades, but in recent years, glial cells such as oligodendrocytes (OLs) have been identified as key players in disease progression. OLs are not just the myelinating cells of the central nervous system, they also provide trophic support to neurons. Accumulating evidence suggests that OLs play an active pathogenic role in AD, which has not yet been fully elucidated. To better understand the involvement of OLs in AD, we have performed a thorough characterization of OLs in postmortem human brain tissue of familial AD (fAD) cases with a mutation in the APP gene (APPLondon), and respective non-diseased controls. We found unexpected accumulations of oligodendrocytes, which occur more often in cortical brain regions with greater disease burden, but are not spatially correlated with amyloid plaques. In addition, we identified intracellular protein aggregation in oligodendrocytes, as well as what appear to be early-stage A β -plaques originating from oligodendrocytes. To complement our observations in the human brain, we are using a 2D human iPSC-derived oligodendrocyte in-vitro model carrying three well-studied mutations in the APP gene: the Swedish (NL), Iberian (G) and Arctic (F) mutations. This system allows us to study how AD-associated mutations impact OL physiology and will help us identify OL-mediated mechanisms which may contribute to the pathogenesis and progression of AD. We aim to shed new light on a prevalent neurodegenerative disorder with our fresh perspective, and hope that the knowledge we gain contributes to the development of novel therapeutic approaches in the future.

13 Does Print Exposure Moderate the Relationship Between Affective and Cognitive Empathy?

Daniel Lee, Ciara Egan

>Affective empathy (feeling as others) and cognitive empathy (knowing what others are feeling) work in tandem to facilitate social interaction, yet are dissociable. While affective empathy is likely a stable trait, cognitive empathy may be a skill that can be enhanced. Reading is suggested to be one such method to enhance cognitive empathy, with print exposure correlated with enhanced social cognitive skills. It is possible, then, that print exposure is a moderating variable that enables trait affective empathy to be "translated" into cognitive empathy. The current research explored the relationship between affective

empathy and cognitive empathy, hypothesising that this relationship is moderated by print exposure, such that the effect of affective empathy on cognitive empathy is stronger for individuals with higher levels of print exposure compared to those with lower levels. 50 participants read emotion-inducing vignettes, and their affective empathy was measured via subjective self-report and objective pupillometry measures. Participants also completed the Reading the Mind in the Eyes Test (RMET) to assess their cognitive empathy, and the Author Recognition Test (ART) to assess their level of print exposure. Consistent with prior research, a positive correlation was found between print exposure and scores on the RMET. However, no correlation was found between self-report emotion and pupil size. Print exposure was also not found to moderate the prediction of RMET scores by either self-report or pupillometry measures of affective empathy. These results are discussed in relation to previous theory, and the implications for the connection(s) between affective and cognitive empathy is discussed.

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14 Exploring the ontogenesis of adult neural stem cells across species

Daniela Cimino, Virginia Fernández, Annina Denoth-Lippuner, Anna Danese, Tatiana Simon-Ebert, Sebastian Jessberger, Victor Borrell, Magdalena Götz

>Initial evidence for adult neurogenesis in the mammalian brain was already obtained in the 60s of the last century, when newly generated neurons were first described in the rat brain. Since then, numerous studies have provided experimental evidence of adult neurogenesis in several mammalian species, from rodents to non-human primates and humans. Despite the extensive characterization of neural stem cells (NSCs) in the adult brain, still relatively little is known about their origin. Here, we investigate the regulatory mechanisms underlying adult NSCs (aNSCs) specification in the mouse Ventricular Sub-Ventricular Zone (V-SVZ) and explore the ontogeny of aNSCs across different mammalian species. The majority of the aNSCs in the mouse V-SVZ are set aside during a specific window of the embryonic development (E13.5-E16.5) from slowly dividing progenitor cells. To characterize the embryonic ancestors of aNSCs, we isolated slowly and fast dividing LGE progenitors from the iCOUNT mouse line and profiled their transcriptome via single-cell RNA sequencing. We identified distinct clusters of stem/progenitor cells. Via differential gene expression analysis, we detected a set of transcripts enriched in slowly versus fast dividing progenitors. We selected several candidates and explored their function in aNSCs specification via loss of function analysis, which will be presented at the meeting. Finally, to address whether the establishment of aNSCs occurs similarly in other mammals, we performed cross-species comparison of single-cell datasets from the mouse, ferret and human embryonic brain, with the aim to identify a common molecular signature of the embryonic ancestors of aNSCs. Taken together, our work aims to identify the molecular mechanisms specifying aNSCs with the long-term aim to possibly elicit their specification also in other brain regions lacking adult neurogenesis.

15 TECPR2 neuropathy mice reveal endo-lysosomal dysfunction in neurons and microglia

Debjani Bhattacharya*, Patricia da Silva-Buttkus*, Karsten Nalbach, (...) Christian Behrends

>Tectonin β-propeller repeat containing protein 2 (TECPR2) mutation causes hereditary sensory and autonomic neuropathy type 9 (HSAN9), a fatal autosomal recessive neurodevelopmental and neurodegenerative disorder. TECPR2 functions as a scaffold protein, functioning in trafficking and sorting of proteins. Previous studies using TECPR2 disease mutant (L440fs) proximity proteomics, secretome, membranome and lysosome profiling revealed altered abundance of secreted, membrane-bound, and lysosomal proteins. To have a better understanding of the disease, this study established a TECPR2 mutation knock-in (KI) mouse model (L1139fs). Behavioral analysis displayed neurodegenerative gait phenotypes as TECPR2 knockout (KO) mice confirming a loss of function mechanism in the disease. Immunohistochemistry of KI mice brain revealed regional neuronal loss and localized microglial activation. Electron microscopy of the affected area in KI mice brain showed aberrant axonal morphologies further suggesting neurodegeneration. Whole brain transcriptomics, cerebrospinal fluid and primary microglia proteomics identified disease associated microglia with a dysfunctional endo-lysosomal system which is further confirmed in TECPR2 KO cells. These cells exhibit defective clearance of endocytosed cargo due to loss of TECPR2 interaction with membrane tethering HOPS

complex and early endosomal protein Rab5. Our findings establish that TECPR2 is essential for endolysosome maintenance with potential relevance for neuron-microglia crosstalk and disease pathogenesis.

16 Epigenetic mechanisms of innate immune memory in the brain at single cell level

Desirée Brösamle, Xidi Yuan, Rebekka Scholz, Marc Beyer, Jonas J. Neher

>Epidemiological and experimental studies have demonstrated that an activation of the peripheral immune system, for example through infections, influences the development or progression of neurological diseases. As every person is exposed to such inflammatory events throughout their life (e.g. bacterial and/or viral infections, chronic illnesses), this is particularly relevant for the aging population. Microglia, as the primary resident immune cells of the brain have a major influence on the immunological status of the CNS and can be immunologically activated by peripheral inflammatory processes. Notably, changes in microglial responses, that result from peripheral immune activation, can persist for a long period of time given rise to the concept of innate immune memory in microglia. In this regard, our lab previously demonstrated for the first time that at cell population level, microglia develop immune memory in response to peripheral inflammatory insults, and is driven by epigenetic reprogramming that persists for at least 6 months in the mouse brain. However, the specific mechanisms that regulate immune memory responses, if all microglia or only a subpopulation can develop immune memory and whether our previous results can be generalized to different immune stimuli remains unclear. Therefore, in this project, we optimized a methodology to generate paired epigenetic and transcriptomic profiles of single microglia. Using large scale single cell profiling, we now investigate the mechanisms of immune memory in the brain in response to a range of peripheral immune insults.

17 Action without Visual Awareness: The Role of Visual Awareness for the Control of Visually Guided Actions

Didem Taskiran

>Motor movements often require corrections, some of which may be triggered by environmental changes that we are not perceptually aware of. In their study, Goodale et al. (1986) demonstrated that despite being unaware of the changes in target position during saccadic eye movements, participants pointing movements adjusted to account for those changes. This implies a robust visuomotor system operating independently of conscious awareness and cognitive resources. The current study aims to test these implications, by examining the performance of the visuomotor system under single-task and dual-task conditions. In order to achieve this, participants undergo pointing tasks with gaze-contingent target shifts, combined with an auditory n-back task, while their hand and eye movements are recorded. Since secondary tasks are known to impair performance on primary tasks, namely the dual-task interference, we test whether saccadic and corrective pointing movements to unperceived target shifts are resistant to such interference. Hand and eye movement metrics, such as pointing and saccade accuracy, along with n-back performance, are compared across conditions. A separate two-alternative

forced-choice (2AFC) task evaluates participants' perceptual awareness to gaze-contingent target shifts, enabling analysis of its relationship with corrective movements. This approach aims to determine whether motor corrections rely on central cognitive resources and to clarify the role of perceptual processes in these adjustments.

18 Characterization of novel recombinant adeno-associated virus (rAAV)- capsid variants in the mouse brain for future use in seizure therapy

E. Arslantas, P. Lorenz, Dr. V. Mehlfeld and Prof. M. Biel

>AAV vectors have become a powerful tool in gene therapy for brain disorders, offering targeted and long-lasting therapeutic effects. Despite challenges such as immune response and limited vector capacity, ongoing research and advances in AAV technology continue to improve the prospects for treating complex neurological disorders. New capsid variants with improved cell specificity and reduced immunogenicity are of great interest for neuropathological therapeutic approaches. In this context, the Hyperpolarization-activated cyclic nucleotide-gated channel 2 (HCN2) knockin mice with a point mutation in the nucleotide-binding site (HCN2EA) serves as a model of generalised epilepsy with absence seizures (AS). The fact, that HCN mutations also cause epilepsy in humans, makes the HCN2EA mouse an interesting animal model to test new gene therapy approaches for HCN channelopathies. We tested novel vectors with the AAV9 capsid (WT, GL and NN) encoding eGFP under the control of different promoters in the mouse brain. In vitro studies revealed that all capsid variants using the CMV promoter resulted in eGFP expression in neurons and astrocytes. Using the neuron-specific hSyn promoter, eGFP expression was restricted to neurons. Based on these results, we injected the viral capsids into the thalami of WT mice by stereotaxic surgery. After three weeks, eGFP expression was quantified in different brain regions using RT-qPCR and Western blotting. All capsid variants were most prominent in the thalamus. AAV9GL was also able to express eGFP in thalamo-cortical neurons, which are the main target for AS therapy. Therefore, a gene supplementation strategy using the AAV9GL capsid is currently being investigated for functional studies in the HCN2EA mouse model. Stereotactic injection of AAV9GL-CMV-HCN2-HA in the thalami of HCN2EA mice resulted in higher HCN2 expression, which was quantified by RT-qPCR and Western blotting. Preliminary EEG measurements of treated HCN2EA mice may indicate a reduction in the number of seizure per day compared to control mice. Taken together, our study provides an important basis for the generation of a novel gene therapy for AS.

19 Neural basis underlying following in *Drosophila* courtship

Eduardo Gallego, Inês M.A. Ribeiro

>Proximity to a prospective mate is essential for reproductive success in animals with internal fecundation, like insects. *Drosophila melanogaster* males rely on vision to orient towards, approach and track a female during courtship behavior. A courting male is exposed to diverse combinations of visual features emanating from the female as the behavior progresses from detection of a discrete object to

maintaining a short distance from the female during chasing or following. The visual information from the female during following is a large angular size in the male visual field. The male attempts to maintain this large angular size constant to sustain the same, short distance from the female, characteristic of following. How this is achieved remains incompletely understood. To find the neural basis of following, previous work used large collections of GAL4 driver lines to block neurotransmitter release in different sets of neuron types, and tested male behavior in single pair courtship assays. Several driver lines led to a decrease in the median distance to the female and a reduction in the percentage of time spent following. We used these sets of driver lines as an entry point to uncover the neural circuits underlying following. Furthermore, we developed a group assay to test male courtship behavior in a more naturalistic environment. The naïve male was placed in an arena with droplets of fly food and several starved, virgin females. The starved females settled on food patches to eat but started walking when the male approached to court, and triggered following. Our results show that chase is thus part of the courtship ritual, even in the presence of more than one female. Ongoing research will uncover the neural circuits and mechanisms underlying female chase during *Drosophila* male courtship behavior.

20 Beyond Univariate Envelope Modeling: EEG Response Prediction with the Multivariate Amplitude-Binned TRF Model

Elnur Imamaliyev, Thorge Haupt

>Accurately predicting neural responses to naturalistic auditory stimuli remains a key challenge in auditory neuroscience. In this study, we used an Amplitude-Binned (AB) envelope model that partitions the continuous auditory envelope into discrete amplitude segments, thereby capturing the nonlinear aspects of neural processing. Electroencephalography (EEG) data were collected from participants immersed in a complex, real-world auditory environment during a 3D Tetris task, where concurrent speech, alarm, and beep sounds created variable attention demands. Using a multivariate Temporal Response Function (mTRF) framework, we optimized different binning strategies and normalization protocols to evaluate the performance of our AB envelope model against conventional Standard Envelope approaches. Our results indicate that discretizing the auditory signal into amplitude bins markedly improves the prediction of EEG responses. Notably, when participants maintained focused attention, our AB model produced significantly higher prediction accuracies, especially in frontal and temporal cortical areas, and exhibited a robust linear association between stimulus intensity and neural response amplitude. In conditions where attention was more diffusely distributed, the distinction between model performances diminished, implying that selective focus enhances the neural encoding of sound intensity variations. The careful calibration of bin parameters and normalization timing provide critical insights into the optimal design of neural encoding models. Furthermore, augmenting the AB model with an onset-based envelope to capture rapid auditory transitions further increased prediction accuracy by accounting for fast temporal dynamics absent in traditional methods. Statistical evaluation, including permutation tests and paired comparisons, confirmed the reliability of these improvements. These findings show the potential of multivariate envelope representations for improving neural response prediction in naturalistic settings and lay the groundwork for advanced neural encoding models applicable to real-world auditory processing.

21 The effects of respiration-locked TMR on the consolidation of memories

Esteban Bullón Tarrasó, Fabian Schwimmbeck, Marit Petzka, Bernhard P. Staresina & Thomas Schreiner

>Recent evidence shows that respiration serves as a pacemaker for memory-related sleep oscillations during sleep. However, the extent to which the respiratory phase impacts memory consolidation remains poorly understood. In this study, we analysed EEG and respiratory recordings acquired in an overnight experiment where participants' memory (N = 26) was assessed before and after a closed-loop Targeted Memory Reactivation (TMR) session during NREM sleep. For TMR, previously encoded memories (consisting of audio verbs paired with images of scenes or objects) were divided into three different categories depending on the respiratory phase at which cues were replayed: cues presented during the preferred coupling phase between sleep oscillations and respiration, as extracted from a previous habituation nap (in-phase), cues presented in the opposite phase (antiphase), and cues that were not presented during the TMR (uncued). Behavioural results demonstrate that memory performance is enhanced for cues presented in-phase with respect to the ones presented in antiphase. Future analyses will include differences in the event-related potential (ERP) and memory reactivation between cue phase categories.

22 Epigenetic modulation with decitabine reduces C9orf72-associated toxic pathologies via heterochromatinization

Eszter Katona, Berkcan Huseyin Isilgan, Ashutosh Dhingra, Verena Bopp, (...) Dieter Edbauer

>An intronic (G4C2)n repeat expansion in the C9orf72 gene causes amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) through three synergistic mechanisms: C9orf72 protein haploinsufficiency, accumulation of RNA foci, and toxic dipeptide repeat (DPR) protein translation. Recently, antisense oligonucleotides (ASOs) targeting sense RNA failed in multiple clinical trials despite achieving target engagement, due to a lack of clinical improvement. This highlights the need to investigate and potentially target repeat toxicity at the DNA level. We screened a library of 1,430 FDA-approved drugs in C9orf72 patient-derived iPSC neurons and identified decitabine as a potent inhibitor of DPR toxicity. Unlike failed ASOs, decitabine inhibits both (G4C2)n and (C4G2)n repeat expression, reduces sense and antisense RNA foci, and lowers repeat-containing C9orf72 transcript levels with minimal effects on global gene expression. Importantly, decitabine shows no toxicity in postmitotic neurons, and short-term high-dose therapy reduces pathology in C9orf72 BAC transgenic mice. Decitabine, a cytidine analogue, typically incorporates during DNA replication, leading to DNA methyltransferase (DNMT) inhibition and demethylation. However, we found that DNMT inhibition is neither sufficient nor required for the effects of decitabine in postmitotic neurons. Instead, we identified active DNA damage and repair at the repeat locus in postmitotic neurons, facilitating decitabine incorporation. This incorporation induces heterochromatinization and transcriptional silencing. While heterochromatinization has been linked to C9orf72 haploinsufficiency, our study reveals its protective role against repeat toxicity. Interestingly, in dividing C9 patient fibroblasts, decitabine upregulates C9orf72 expression while reducing heterochromatin, suggesting cell-type-specific epigenetic regulation.

Our findings highlight active DNA damage at the repeat locus as a key contributor to repeat toxicity and reveal differential epigenetic regulation between dividing and non-dividing cells, providing insight into neuronal vulnerability in C9orf72 ALS/FTD.

23 “Natreshka” - Recoverable Neuropixel 2.0 implant for chronic recordings

Evgeniia Bukina, Andrey Sobolev, Anton Sirota

>Recent advances in electrophysiology, particularly Neuropixels probes, have revolutionized neural recordings by enabling high-resolution monitoring of hundreds of neurons simultaneously. While acute probe implantations are common, they do not allow long-term recordings in freely moving animals - essential for studying behaviors like navigation, learning, and memory. Here, we introduce Natreshka, an open-source implantation system for Neuropixels 2.0 designed for chronic recordings. We focused on making the assembly simple, robust, and fast (~20 min on average), requiring no special skills - any student can do it without prior experience. The system's core is a payload that securely holds the probe, flex cable, and headstage. It slides into a protective shell with guiding rails for precise manual mounting. The shell features grips for cementing and allows implantation at various angles. A cap module encloses the shell, isolating the payload, with a window for cable connection and an integrated nut for implantation and recovery. A protective lid covers the cable window when the animal is at rest. The protection module has multiple functions: it safeguards the shanks during assembly, enables manual stereotax-free probe recovery, and allows long-term implant storage. Additional accessories include a cable adapter for easy headstage connection in unrestrained animals and a stereotaxic holder for precise implantation. Natreshka consists of 3D-printed parts and standard M1/M3 nuts and screws, eliminating the need for specialized components. It is compact (14.6 × 14.2 × 26 mm) and lightweight (3.8 g), allowing for a full range of natural behaviors. Successfully tested in freely moving gerbils and rats, it simplifies Neuropixels 2.0 workflows, reduces surgery time, and enhances animal welfare by streamlining implantation and recovery.

24 Direct neuronal reprogramming of Oligodendrocyte progenitor cells

Fabio Laredo, Oleksandra Pavlovská, Magdalena Götz, Giacomo Masserdotti

>Direct neuronal reprogramming is a promising avenue for cell-based therapies: it aims at replacing neurons lost in neurodegenerative diseases or traumatic brain injuries with newly generated ones via the direct conversion of resident, non-neuronal cells into functional neurons. Various somatic cells have been successfully converted into neurons both *in vitro* and *in vivo*. Among brain-resident somatic cells, oligodendrocyte progenitor cells (OPCs) are a poorly investigated yet interesting population to target. OPCs are the only cell type that proliferate in the adult brain parenchyma under physiological and pathological conditions, and therefore their direct conversion would not cause their irreversible depletion. To investigate if, and how, OPCs can be reprogrammed into neurons, we established a protocol to isolate and culture OPCs from the cortical gray matter of mice at postnatal age. Subsequently, primary cultures of OPCs were transduced with retroviruses encoding for different transcription factors, such as

Neurogenin2, Ascl1, NeuroD1 and Dlx2. Interestingly, at 7 days all factors besides Ascl1 generated neuronal cells, which matured over time into functional neurons, as assessed by electrophysiological analysis. We then investigated the molecular mechanisms underlying the direct reprogramming of OPCs using different factors via single RNA sequencing and CUT&RUN, and will present preliminary results on the different programs induced by the TF considered. To translate these findings into a human context, we will also present a protocol to differentiate induced pluripotent stem cells (iPSC) into OPCs, and the preliminary results on the direct conversion of hIPSC-derived OPCs into neurons, using the above-mentioned reprogramming factors. Together, these data provide compelling evidence that OPCs can be reprogrammed into neurons, paving the way for investigating their direct neuronal conversion *in vivo*.

25 Nuclear function of the cytoskeletal protein MAP1B in neural stem cells drives neurogenesis

Florencia Merino, Lucas Miranda, Yiling Li, Deepak Kumar Sundaramoorthy (...) Magdalena Götz

>Cellular differentiation and morphogenesis rely on both the dynamic remodelling of the cytoskeleton and transcriptional programs to drive cell fate decisions and growth. However, how these processes communicate to shape cellular specification, particularly how the cytoskeleton feeds back into differentiation, remains poorly understood. Here, we uncover a nuclear role for the cytoskeletal protein MAP1B in regulating neurogenesis during brain development. We choose to study MAP1B given its high abundance and enrichment in neural stem cells, and its link to neurodevelopmental diseases. We demonstrate that MAP1B localizes to the nucleus in NSCs, where it interacts with the SWI/SNF chromatin remodeling complex to maintain NSC identity and regulate differentiation. Its nuclear translocation is dynamically regulated and depends on microtubule state. Disrupting MAP1B's effects in neurogenesis leads the generation of an ectopically located subpopulation of neurons in the mouse cerebral cortex, as found in patients harboring MAP1B mutations. Notably, patient iPSC-derived cerebral organoids show enrichment of the mutant MAP1B protein in the nucleus along with neuronal heterotopia. This study demonstrate how cytoskeletal elements can drive differentiation during neurodevelopment and how disruption of this process can lead to brain disorders.

26 CRISPR-Cas13 mediated DMPK Knockdown in Myotonic Dystrophy Type 1 (DM1)

Hanseul Oh, Aline Huguet, Stefan Hintze, Geneviève Gourdon, Benedikt Schoser, Peter Meinke

>Myotonic Dystrophy Type 1 (DM1) is the most common adult-onset muscular dystrophy, caused by a CTG-repeat expansion in the 3' UTR of the DMPK gene. This expansion sequesters key splicing regulators, disrupting normal gene expression and affecting muscle, respiratory, and cognitive functions. Our project leverages CRISPR-Cas13 to selectively knock down the repeat-containing DMPK gene, aiming to free splicing regulators and restore normal transcriptomic profiles. The system is delivered via an AAV vector and tested in patient-derived immortalized myoblasts and the DMSXL DM1 mouse model to evaluate its efficacy in correcting pathological changes.

27 Topological Data Analysis Enhances fMRI-Based Classification Performance of Obsessive-Compulsive Disorder

Hanyang Ruan, Daniela Rodriguez Manrique, Deniz Gürsel, Benita Schmitz-Koep, Götz Berberich, Claus Zimmer, Kathrin Koch

>Background: Functional magnetic resonance imaging (fMRI) has revealed brain function alterations in obsessive-compulsive disorder (OCD) patients. However, traditional fMRI features like functional connectivity (FC) and graph theory metrics often show limited classification power. Topological Data Analysis (TDA) provides an alternative by characterizing high-dimensional data's topological features, offering potential for improved functional imaging and machine learning classification. This study investigates whether TDA-derived features outperform traditional methods in classifying OCD patients versus healthy controls. Method: Resting-state fMRI data from 49 OCD patients and 41 healthy controls were acquired using a 3T Philips MRI scanner. Time series were extracted using the Schaefer 400_7 networks atlas. Functional features included ROI-to-ROI functional connectivity (FC), fractional amplitude of low-frequency fluctuations (fALFF), network-level FC, and network-level fALFF. Additionally, three sets of graph theory features—betweenness centrality, eigenvector centrality, and local efficiency—were derived. Four topological descriptors calculated in two dimensions—Betti curves (BC), persistent landscapes (PL), persistent images (PI), and persistent silhouettes (PS)—were also obtained from the time series data. All features were normalized, reduced to 50 principal components, and input into an AutoGluon classifier for machine learning classification. Results: Topological descriptors outperformed conventional functional features, achieving the highest classification accuracy of 0.87. Among TDA features, PI and BC had the highest classification performance. Conclusion: TDA enhances fMRI classification by capturing non-linear patterns and preserving high-dimensional features. This suggests TDA's potential in improving diagnostic tools for psychiatric conditions like OCD in future functional imaging studies.

28 Investigation of axonal membrane resealing regulation in an animal model of spinal cord injury

Ioanna Emmanouilidis, Hsiu-Hsin Cheng, Yi-Heng Tai, Martin Kerschensteiner, Thomas Misgeld

>Axon degeneration is a critical determinant of neurological disability in central nervous system diseases or trauma. Previous work from our lab indicates that, upon mechanical or neuroinflammatory injury, a key predictor of axonal fate is acute calcium influx through damaged axonal membranes. Persistent elevation of calcium then triggers overt axon degeneration. This, however, can be averted by re-establishment of calcium homeostasis, likely via membrane resealing. Therefore, the mechanisms by which axons can repair their membranes are in the focus of this study. Indeed, the understanding of membrane resealing in mammalian axons *in vivo* remains poor, as membrane repair research is so far mainly performed in cell culture systems and invertebrate model organisms. Our aim is to optimize tools to study the mechanisms of axonal membrane repair in the mouse spinal cord. Thus far, we have established a two-photon imaging approach to the dorsal column, which allows assaying intraaxonal calcium levels and axonal fate -degeneration vs. recovery – over periods of several hours after mild

spinal cord contusion. This we now combine with neonatal intraventricular viral injections to generate general and neuron-specific CRISPR/Cas-9 knock-outs in marked axonal subsets. As a proof of principle, our approach yields a successful reduction in protein level of molecules known to regulate axonal membrane organization and repair and demonstrates the efficient coupling of calcium imaging with CRISPR manipulations *in vivo*. We are currently performing a small scale screen of the effects of depleting molecules previously implicated in membrane repair (such as Dysferlin, Synaptotagmin 7 or regulators of the ESCRT-III pathway), some of which have also been linked to progression e.g. of multiple sclerosis, where axon degeneration is a key driver. Our current approach thus opens a unique window into the largely unknown, but highly disease-relevant biology of axonal membrane maintenance.

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29 Understanding the Role of Pink1 mRNA Transport and Localization in Parkinson's Disease

Isabel Geelhaar, Dr. Inmaculada Segura Vitutia, Prof. Dr. Angelika Harbauer

>Mitochondrial quality control (MQC) is central to cellular health and particularly relevant in high-energy demanding cells such as neurons. Accordingly, mitochondrial dysfunction plays a major role in the neuronal loss observed in neurodegenerative diseases, such as Parkinson's disease (PD). PINK1 (PTEN induced kinase 1) is a key regulator of MQC in neurons, and its mutations are linked to early-onset PD. The Pink1 mRNA hitchhikes on mitochondria to be transported along axons in a tethering complex formed by Synaptojanin 2a (SYNJ2a) and its binding partner SYNJ2BP. Coupled with local translation, this ensures a constant supply of the short-lived PINK1 protein at the periphery of neurons. Using advanced live-cell imaging tools such as MS2/PP7-split Venus system for mRNA visualization, the SunTag reporter for active translation visualization, and mKeima for assessing mitochondrial health, we evaluate mRNA localization, protein translation, and mitochondrial function, respectively, in cultured mouse hippocampal neurons and CRISPR-Cas9 engineered iPSC-derived neurons. We have studied the PD-associated PINK1 mutation Q126P. The Pink1-Q126P mRNA shows an altered localization with enhanced mitochondrial recruitment. Analysis of the secondary RNA structure predicts the destabilization of a stem-loop, potentially influencing relevant RNA-protein interactions. Interestingly, the effect on mitochondrial tethering can be reversed by mimicking the wild-type Pink1 structure. To evaluate the underlying mechanisms of these observations, we aim to characterize mRNA binding conditions and dynamics in neuronal health and upon induction of mitochondrial stress. Furthermore, we investigate correlating changes in PINK1 protein synthesis, localization and function. Our data suggests that the single nucleotide mutation results in structural disruption of a defined Pink1 region and increases its association with mitochondria. Thus, negatively influencing translation and protein availability, consistent with previously observed reductions in cellular protein expression. Understanding these interaction-mediated mechanisms provides new insights into neuron-specific regulation of RNA transport and highlights its importance in the pathogenesis of PD.

30 Systematic analysis of meta-learned synaptic plasticity rules reveals degeneracy and fragility

Jan-Erik Huehne, Nikos Malakasis, Dylan Festa, Julijana Gjorgjieva

>Plasticity rules governing synaptic changes vary widely across species, brain regions, and brain states. Despite this variability, these rules often give rise to neural circuits with similar structural motifs and functional properties, a phenomenon known as degeneracy. While functional degeneracy—where different plasticity rules result in similar network functions—has been widely studied, the structural aspects of degeneracy remain underexplored. Structural degeneracy refers to cases where distinct plasticity rules produce neural circuits with similar connectivity patterns, such as comparable weight distributions across the network. To investigate emergent structural properties, we performed a comparative analysis of the relationships between plasticity rules and their resulting network structures. Specifically, we compared the similarity between plasticity rules to the similarity between the network

structures resulting from the respective plasticity rules. Using filter simulation-based inference (fSBI) to generate a large dataset of spike timing-dependent plasticity (STDP) rules optimized for stabilizing recurrent spiking neural networks, we examined how these rules shape network architectures over time. Our findings confirm that distinct plasticity rules can give rise to highly similar network structures, exemplifying structural degeneracy. In contrast, we also identify a phenomenon we term fragility, where nearly identical plasticity rules lead to drastically different network structures. These two phenomena—degeneracy and fragility—highlight the diverse and complex interplay between plasticity rules and network architectures, offering new insights into the mechanisms underlying synaptic plasticity.

31 Uncovering sexual dimorphism in human microglia using organoid-based platforms

Janina Kaspar, Irene Santisteban Ortiz, Lucía Rodríguez Martínez, Monique Pena, Simon T. Schafer

Microglia, the brain's resident immune cells, play critical roles in development and adulthood by safeguarding neuronal tissue from harmful stimuli. However, uncontrolled microglial activation can trigger pro-inflammatory states, potentially disrupting brain development and contributing to neurodevelopmental disorders. Emerging evidence highlights sex-specific differences in microglial function, yet the mechanisms underlying this early heterogeneity and its implications for human brain development remain poorly understood. To address this, we developed sex-specific ImmunoBrain organoid models using human subject-derived induced pluripotent stem cells to investigate microglial diversity during human brain development. Single-cell RNA sequencing uncovered a female-enriched microglial subpopulation with heightened responsiveness to environmental stimuli. Notably, male and female microglia exhibited distinct reactions to immune challenges, with female microglia displaying a response that was confined to this specific subpopulation. To disentangle whether these differences arise intrinsically or are shaped by the surrounding environment, we engineered gender-mismatch models by combining male microglia with female brain organoids and vice versa. Our findings revealed that the sexual dimorphism in microglial behavior is environmentally instructed, suggesting a profound influence of the brain's niche on microglial phenotype and function. The approach developed here will allow to gain new insights into how female microglia might modulate the brain's susceptibility to environmental perturbations, with implications for understanding sex-specific risks in neurodevelopmental disorders.

32 Medin amyloid: Exploring its role in vascular ageing and Alzheimer's disease

Jessica Wagner, Karoline Degenhardt, Nathalie Beaufort, (...) Jonas J. Neher

>Medin, an internal fragment of MFG-E8, aggregates in the aorta and large arteries of nearly everyone above ~50 years of age. Independent genetic studies report a possible role of medin in cardiovascular aging and disease. Recently, elevated levels of medin were observed in the cerebral arterioles of patients with Alzheimer's disease (AD) and have been suggested as a reliable predictor for AD and cognitive decline. However, the question whether these elevated medin levels are a cause or consequence of AD pathology has not yet been answered. Building upon our previous research

demonstrating that medin forms aggregates in the aorta and cerebral arteries of ageing wildtype mice, leading to arterial stiffening and consequential vascular dysfunction, we explored medin deposition in the brains of APP transgenic mice. We employed immunohistochemical and biochemical techniques to examine its influence on A β deposition and vascular damage. To understand the underlying disease mechanism, we studied the interaction between medin and A β through genetic knockout of the medin-containing domain of MFG-E8 as well as seeding assays. Notably, we found that medin does not only co-localize with A β deposits but also alters plaque pathology in these transgenic mice upon genetic deletion or exogenous addition of medin. Interestingly, in line with its primary vascular localization in humans, elevated levels of MFG-E8 and medin correlate strongly with CAA severity, i.e. A β deposition within blood vessels. Furthermore, genetic medin deficiency significantly reduced CAA and vascular damage. Additionally, in human brain tissue, we found evidence that MFG-E8 and medin can predict vascular A β pathology and cognitive decline in AD patients. Current work now focusses on proteomic and cellular alterations in isolated human and mouse cerebral vessels. Our findings unveil a novel mechanism underlying age-associated vascular disease and amyloid deposition, highlighting medin as a potential CAA-specific therapeutic target and candidate for biomarker development.

33 Spontaneous and sensory-evoked arousal fluctuations engage a specific brain activity wave

Jose Maria Martinez de Paz, Johanna Mayer, Paulina Wanken, Beatriz Rodrigues Apgaua, Emilie Macé

>Arousal state has a major impact on perceptual ability, task performance, and diverse aspects of physiology and behavior. During wakefulness, spontaneous fluctuations in arousal state strongly modulate neural activity in numerous brain regions in mice, but the lack of large-scale, deep imaging methods has prevented testing whether these fluctuations affect the entire brain uniformly. Moreover, it remains unclear whether spontaneous and sensory-evoked fluctuations in arousal state engage the same brain circuits or are fundamentally distinct processes. To address this gap, we used functional ultrasound imaging in awake, head-fixed mice and correlated the recorded whole-brain activity with pupil size fluctuations, known to track arousal. We characterized a large-scale arousal 'wave' of activity from specific brain regions showing a distinct temporal dynamic. Next, we compared this spontaneous arousal wave to the brain-wide wave elicited by arousing stimuli (mild air-puffs) and found a large overlap between the two, the main difference being that external stimuli also activate sensory areas. Finally, we assessed how the arousal wave is affected by manipulations in the tonic levels of noradrenaline, a well-established regulator of arousal, using optogenetics and pharmacology. We found that the cortical component, but not the subcortical component, of the arousal pattern was sensitive to the noradrenergic tone. Our work refines the role of arousal as a global modulator of neural activity by identifying a specific brain network that responds to spontaneous and evoked fluctuations in arousal, and by characterizing its constitutive components across sustained arousal states.

34 Integration of spatial transcriptomics into existing 3D mouse brain atlases

Katia Berr, Jakob König, Hannah Spitzer

>Spatial transcriptomics enables the study of gene expression patterns within the brain, providing critical insights into cellular organization and function. A challenge in this field is mapping spatial transcriptomic data onto existing 3D brain atlases. This mapping would facilitate multimodal atlas creation, enable brain area label transfer from the atlas to the spatial transcriptomics sample, and hence unify brain area annotation across different experiments. Existing approaches primarily rely on image registration, which performs well for 2D-to-2D or 3D-to-3D alignment. However, spatial transcriptomics often requires 2D-to-3D mapping, where a single transcriptomics slide must be integrated into a full-brain 3D atlas. To address these limitations, we propose an alternative deep learning-based, feature-driven approach to map spatial transcriptomics data to 3D atlases. Our overall strategy for integrating transcriptomics data into histology atlases starts by creating unimodal encodings for each modality. For histology, we use a pretrained foundation model. For transcriptomics, we compare PCA with a Point Cloud Transformer, evaluating how well these embeddings can classify brain areas of the transcriptomics data at the patch or even single-cell level. To map the unimodal transcriptomics embeddings to the histology embeddings, we then apply optimal transport, aiming to enable the transfer of brain area labels from histology to transcriptomics. Preliminary results for the unimodal spatial transcriptomics embeddings indicate that both PCA and Point Cloud Transformer perform well at classifying brain areas at the patch level, but the Point Cloud Transformer achieves better accuracy at the single-cell level. However, further evaluation is necessary to assess how well these models generalize to new datasets with different gene panels. The multimodal optimal transport approach for mapping transcriptomics to histology currently enables a coarse matching of brain areas. Future work will focus on refining the unimodal embeddings, improving alignment accuracy, and comparing our method to classical registration techniques.

35 Acute changes in neurosteroid levels in brain and plasma following mild traumatic brain injury (mTBI)

Kosisochukwu E. Umeasalugo; Igor Khalin; Burcu Seker; Philippe Liere; Michael Schumacher; Inga Koerte; Nikolaus Plesnila

>Mild traumatic brain injury (mTBI) accounts for 80% of all TBI, may be associated with chronic impairments, and is difficult to diagnose due to a lack of objective markers. In this study, we investigated whether neurosteroids can serve as blood biomarkers for mTBI. Neurosteroids include allopregnanolone and $3\alpha,5\alpha$ -tetrahydrodeoxycorticosterone (THDOC), and their 3β -enantiomers isopregnanolone and $3\beta,5\alpha$ -tetrahydrodeoxycorticosterone (ISODOC). Two cohorts of C57BL/6 mice were subjected to a model of mTBI combining impact with rotational acceleration or sham surgery. The first cohort underwent neurological testing for anxiety, balance, and locomotion before and after mTBI. For the second cohort, brains and plasma were collected 6 or 24 h after mTBI to measure steroid and neurosteroid levels by gas chromatography-tandem mass spectrometry. Traumatized mice exhibited significantly prolonged wake-up time from anesthesia, transiently increased beam-walk time, and mild astrogliosis compared with their control counterparts, but did not suffer from skull fractures, intracranial

hemorrhage, or mortality. Isopregnanolone and ISODOC were significantly decreased by more than 50% in brain parenchyma at 6 and 24 h after mTBI, while ISODOC was also significantly reduced in plasma (-75%). Therefore, ISODOC may be a candidate diagnostic biomarker for mTBI.

36 Investigation of Region-specific Interactions Between Neural Progenitors and Microglia During Development

Kyrania Kaarina Christofi, Maria Veronica Pravata, Silvia Cappello

>Microglia is a unique cell type that has been studied extensively in the adult brain, due to the implication in disease and physiological brain homeostasis. Deriving from the yolk sac, microglia is one of the first glial cell types to colonize the developing neuroepithelia, preceding the peak of neurogenesis in the developing telencephalon. Previous studies have shown that during early development of the telencephalon, microglia appear to colonize heavily the proliferative zones of the primate cortex. Microglia shows one of the highest regional heterogeneity in the brain, on a morphological, transcriptional and proteomic level. Until now, little is known about the communication between microglia and neural progenitors during development. We therefore ask if microglia show similar heterogeneity during development, specifically during telencephalic development and what are the effects of the presence of developing microglia in the neural progenitor pools of different regions of the developing neuroepithelia. We have developed a model system in which we can incorporate hematopoietic progenitor cells (HPCs) derived from induced pluripotent stem cells(iPSCs) in patterned cerebral organoids of two different identities: dorsally patterned and ventrally patterned cerebral organoids. HPCs are then differentiated to microglia-like cells in the organoids, allowing the investigation of direct and indirect interactions of microglia-like cells and the neuronal population in environments of different cellular composition. We performed proteomic profiling and scRNAseq analysis of patterned organoids with different identities, with the presence and absence of microglia-like cells at an early developmental stage. Through comparative analysis we aim to underline how the profile of microglia can change when embedded in different neuronal environments. We further aim to decipher the effects that microglia-like cells can mediate in environments with different cellular identities and how this cell population can affect neuronal differentiation and identity acquisition during early developmental stages.

37 40 Hz Steady-State Visually Evoked Potentials Recorded During Oscillating Transcranial Electrical Stimulation

Laura Hainke, Manuel Spitschan, Josef Priller, Paul Taylor, James Dowsett

>Transcranial Electrical Stimulation and Visual Stimulation in the gamma range (30-100 Hz, especially 40 Hz) are non-invasive tools to investigate and modulate human cognition. Combining both techniques would open the door to new research questions and clinical applications. Importantly, this would require Steady-State Visually Evoked Potentials (SSVEPs) to be measured concurrently to determine any neuronal effects of the electrical brain stimulation – a substantial methodological challenge. We aimed to demonstrate the feasibility of recording visually evoked 40 Hz activity with EEG during electrical brain

stimulation and to explore whether they may interact. We tested if a potential interaction could depend on the brain areas electrically stimulated (Experiment 1; N=25) and on how closely the respective frequencies match (Experiment 2; N=25). Experiment 3 (N=25) investigated how effectively the data processing pipeline can attenuate artefacts from electrical stimulation and recover evoked neuronal activity. SSVEPs were processed and analysed in the time domain following an improved adaptive template subtraction approach. In summary, we successfully recorded 40 Hz SSVEPs during frequency-matched electrical stimulation applied between occipital and central regions. Waveform correlations revealed that SSVEPs from combined visual and electrical stimulation were more similar in shape to baseline SSVEPs from visual stimulation alone than to control data from electrical stimulation alone. In line with this finding, during combined stimulation, the recovered signals were higher in amplitude than the electrical control data. The electrical and visual stimulation did not seem to interact. Our results show that 40 Hz SSVEPs can indeed be reliably measured with EEG during frequency-matched electrical brain stimulation, using a pipeline capable of distinguishing rhythmic neuronal activity from electrical or physiological confounds. This method enables fundamental and clinical researchers to combine rhythmic sensory and electrical stimulation in the gamma band and concurrently assess neuronal effects.

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38 Large-scale extracellular recordings reveal right-hemispheric language processing in aphasia

Laura Schiffl & Lisa M. Held, Arthur Wagner, Bernhard Meyer, Jens Gempt, Simon N. Jacob

>The human language system is predominantly associated with the left hemisphere. Damage to left brain regions typically results in language impairment (aphasia). As patients regain language abilities, linguistic functions potentially redistribute to other brain regions, for example in the right hemisphere. To gain an in-depth understanding of the right hemisphere's role in residual language following brain injury, we chronically implanted a patient with stroke-induced aphasia with four intracortical micro-electrode arrays (totaling 256 channels) in right hemispheric regions homotopic to the language network, namely the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), supramarginal gyrus (SMG) and angular gyrus (AG). Over several months, the patient performed word repetition, comprehension and naming tasks while we recorded large-scale extracellular neuronal activity from more than 10.000 single and multi-units. In line with symptoms of non-fluent aphasia, behavioral performance was high in comprehension and repetition, yet low in naming. The majority of recorded units (60% in IFG, 77% in MFG, 57% in SMG, and 80% in AG) showed modulations of their activity with regard to the performed language task. These modulations were region- and event-specific, i.e. varied with electrode and task epoch and carried information about the individual word being processed. Furthermore, the neuronal responses were dissociable from purely sensorimotor-driven activity by triangulating response profiles across the three language tasks. For example, clusters of units in SMG encoded word information in naming, but not when repeating or viewing the same stimuli in the comprehension task. Overall, our findings lend unique insights into the right hemisphere's role in post-stroke language functions. Understanding the neuronal mechanisms of language reorganisation will pave the way for novel treatments for language disorders. Our findings also highlight the potential of right-hemispheric neuronal resources to be leveraged for verbal communication in individuals with aphasia.

39 Identification of proteomic clusters in the CSF of sporadic ALS patients

Laura Tzeplaeff, Xuan Liu, Clara Meijis, Lucas Caldi Gomes, Ana Galhoz, (...) Paul Lingor

>Background: ALS heterogeneity poses challenges in understanding and comprehensively treating the disease. Recent studies, including our own, demonstrated that ALS patients can be divided into different clusters according to their gene expression level in post-mortem tissue. Clustering based on cerebrospinal fluid (CSF) proteins might therefore hold great promise towards personalized medicine for ALS. In this study, we aim to determine if molecular clusters can be identified from the CSF of ALS patients, and if so, characterize them with proteins and pathways. Methods: We collected clinical information and conducted a proteomic analysis (label-free nanoLC-MS/MS) of the CSF from 50 ALS patients and 52 controls. Four clustering approaches (hierarchical, model-based, k-means, and partitioning around medoids) were used to identify ALS clusters, and gene set enrichment analyses was performed on the differentially abundant proteins. Results: The ALS cohort consisted of 68% males, mean age of 65 years and 28% bulbar disease onset. Demographics were not significantly different from the control cohort. Clustering analyses identified two robust clusters, exhibiting distinct pathway

alteration patterns. Focusing on each cluster, one showed prominent upregulation of the immune and coagulation pathways, including immunoglobulins, complement activation proteins, and fibrinogens. The other cluster demonstrated an increased abundance of proteins involved in synaptic and cell junction/adhesion pathways, including members of the tyrosine protein phosphatase receptor family, members of the cadherin and collagen family and growth-associated proteins. Interestingly, the immune response and coagulation cluster shows significant younger age of onset compared to the other cluster. We are currently validating our finding in a new CSF cohort. Interpretation: Our study demonstrated that ALS heterogeneity can partially be explained by distinct proteomic patterns in the CSF of ALS patients. Stratification by CSF clusters may open avenues for clustering in clinical trials to select efficacy-expected subpopulations.

40 Lipid Metabolism in the Ependymal Cells of the Brain

Lennart Schlaphoff, Mikael Simons

>Cells can neutralize excess lipids by storing them in lipid droplets. Lipid droplets are specialized, dynamic organelles with a complex surface proteome and a neutral lipid core. While specialized lipid storing cells can be found in the periphery in form of adipocytes, cells of the brain are also capable of storing lipids. Most glia only store significant amounts of lipids under specific conditions, ependymal cells on the other hand constantly harbour lipid droplets at any given time after birth. Ependymal cells are specific epithelial cells which line the ventricle of the brain and are mostly recognized for causing CSF flow by their cilia beating and for contribution to the brain-CSF-barrier (BCB). That ependymal cells do harbour lipid droplets has been observed in the past by several researchers. Nonetheless, the reason for these significant lipid droplet formations are still unknown. Here, we try to elucidate the reason for this storage, the molecular mechanism behind it and the consequences of deregulation.

41 A spatial transcriptomics workflow to investigate molecular signatures of learning in the striatum of humanized foxp2 mice

Leonhard Schaffmayer, Wolfgang Enard

>Foxp2 was the first gene directly linked to the human ability of vocal learning. Additionally, it was shown that Foxp2 has two unique amino acid substitutions across the human lineage. Introducing the humanized version of Foxp2 in mice facilitates altered transcriptomes in the striatum and better performance in learning-based assays compared to their wild-type counterparts. The plasticity of neuronal connections in the brain enables the process of learning. Intermediate early genes bridge neuronal activation to the adjustment of synaptic strengths by ultimately altering transcription or protein states in neurons. This enables experience-dependent neural circuit remodeling, which is necessary for plasticity and learning. Therefore, we aim to analyze the spatial expression patterns of intermediate early genes in the temporal context of learning in mice carrying the human version of Foxp2. Consequently, we developed an end-to-end image-based spatial transcriptomics workflow with single-cell resolution. It utilizes multiplexed hybridization chain reaction RNA fluorescence in situ hybridization

and machine learning algorithms as well as a new powerful transcript classifier, Transcriptor, to investigate a large number of samples precisely and cost-effectively. This allows us to understand how the molecular changes in the brains of humanized Foxp2 mice result in their increased learning performances, potentially leading to crucial insights into the complexity of learning.

42 Dynamics of inflammation in retinitis pigmentosa disease progression

Leonie Pauline Kugel and Susanne Friederike Koch

>Retinitis pigmentosa (RP) is characterized by photoreceptor degeneration, leading to progressive tunnel vision and central vision loss at later stages of the disease. Rod cells are primarily affected, whereas cones degenerate secondarily. Photoreceptor degeneration triggers a chronic immune response characterized by the activation of microglia and Müller glia cells, which in turn activate multiple inflammatory pathways. We hypothesize that increased inflammation in RP accelerates the rate of photoreceptor cell death, and reducing this inflammation by targeting multiple pathways may slow retinal disease progression. To assess this, a Pde6b-deficient mouse model was used to establish a retinal explant culture. After 3 and 6 days of culturing, the retina morphology and inflammatory response were analyzed by immunohistochemistry. Preliminary data indicate Müller glial and microglial cell activation in our RP retinal explant culture. An increased retinal expression of the inflammatory key regulators IL-1 β , NF- κ B, and caspase-1 accompanies these changes. This project aims to assess the pathways underlying immune response activation and identify therapeutic checkpoints that interfere with the detrimental aspects of inflammation.

43 Sex-specific & Ever-changing: Long-term recordings after acute restraint reveal sex-specific and dynamic stress behavior in mice

London Aman, Benjamin Jurek, Mathias Schmidt

>Stress responses in rodent models further understanding of the underlying causes and potential treatments of highly prevalent stress-related psychiatric disorders. Studying animal behavior provides insight into stress response systems, drug discovery, and treatment exploration, and can be expanded upon to investigate mechanisms driving this behavior when combined with molecular and proteomic analysis. Classically these models involve simple, behavior-only tasks run during the inactive phase of mice and usually provide only a snapshot of altered behavioral states, while overlooking the dynamics of the stress response. Utilizing long term behavioral recordings of freely moving mice and deep neural network-based animal pose estimation software enables stress-induced behavior to be compared continuously over the full acute stress response. Paired with proteomic analysis of extracellular vesicles (EVs) released into the cerebrospinal fluid (CSF) of these mice, behavioral changes and CSF EV protein levels may be sampled and compared across time. Using DeepOF, a tool allowing for deep phenotyping of longer behavioral recordings, we found the response after an acute restraint stress exposure to be dynamic over a full activity cycle (24 hours) in a sex-specific manner. We also found a heightened variability in stressed mice related to arousal triggers, such as during light cycle phase switches and

interaction with the stress apparatus. With a more inclusive, dynamic behavior profile and preliminary analysis of EV content indicating multiple candidate proteins, related to stress-response mechanisms such as FKBP_s and HSP90, our model suggests that parallel analysis of EV content and behavior may provide a more comprehensive picture of the stress response, and therefore an improved model translatability to psychiatric disorders and their treatment.

44 Anatomically resolved oscillatory bursts reveal dynamic motifs of thalamocortical activity during naturalistic stimulus viewing

Lukas S. Meyerolbersleben, Anton Sirota, Laura Busse

>Natural vision requires circuit mechanisms which process complex spatio-temporal stimulus features in parallel. In the mammalian forebrain, one signature of circuit activation is fast oscillatory dynamics, reflected in the local field potential (LFP). Using data from the Allen Neuropixels Visual Coding project, we show that local visual features in naturalistic stimuli induce in mouse V1 retinotopically specific oscillations in various frequency bands and V1 layers. Specifically, layer 4 narrow-band gamma was linked to luminance, low-gamma to optic flow, and L4/L5 epsilon oscillations to contrast. These feature-specific oscillations were associated with distinct translaminar spike-phase coupling patterns, which were conserved across a range of stimuli containing the relevant visual features, thus suggesting that they might constitute feature-specific circuit motifs. Our findings highlight visually induced fast oscillations as markers of dynamic circuit motifs which may support differential and multiplexed coding of complex visual input and thalamo-cortical information propagation.

45 Temporal precision of the LSO neurons and their input

Luna A. Studer, Jonas Fisch, Eckhard Friauf and Conny Kopp-Scheinpflug

>The mammalian auditory system uses interaural time differences (ITD) and interaural intensity differences (ILDs) to determine the location of a sound. Conventionally, neurons in the lateral superior olive (LSO) that are excited by sound from the ipsilateral ear and inhibited by sound from the contralateral ear are called EI neurons and are known to encode ILDs. However, in recent years there is growing evidence that LSO EI neurons are also sensitive to temporal disparities between the two converging inputs. Current-clamp recordings in brain slices have shown that LSO neurons have a transient response to prolonged current injections and that this response is sensitive to the 1) rate of depolarization as well as to 2) noise arising from temporal jitter in the converging inputs. Here, we are exploring the influence of both parameters *in vivo* by presenting mice with transposed tone pulses that allow modifying the sound envelope independently from the pulse rate to increase the sharpness of the stimulus (e.g. changing from a 100 Hz sinus amplitude modulated sound to a 100 Hz click-like train). So far, 17 identified LSO EI neurons have been tested for this stimulus paradigm. Correlating temporal response characteristics (PSTH, jitter, cv) to the neurons' sensitivity to envelope changes for high- vs low-frequency neurons will contribute to our understanding of LSO interaural coding strategies.

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46 Investigating the neural correlates of the magnetic sense in the pigeon

Marco Numi, Simon Nimpf, David Keays

>Magnetoreception is a widespread sensory modality that enables animals to detect the Earth's magnetic field. While behavioral evidence strongly points towards the importance of this sensory system for different animals (including many avian species), there are many aspects which are still not understood: 1) Where is the dedicated sensory organ located? 2) How is magnetic information encoded in the brain of these animals? Our lab has previously identified regions in the pigeon brain that show a significant increase in neural activity to the presentation of magnetic stimuli. Our aim is to investigate the neuronal representation of the magnetic sense in two of these areas in the pigeon forebrain: the mesopallium and the hippocampus. To achieve this, we employ high-density, multi-channel Neuropixels probes and developed a pipeline to identify neurons that show a significant response to the stimuli presented.

47 The pathophysiological relevance of MCUGR1 and its function in glial cells

Margarita Chudenkova, Hilda Carolina Delgado, Yiming Cheng, Safal Walia, Monika Leischner-Brill, Tito Cali', Fabiana Perocchi

>The functionality of glial cells heavily relies on the proper regulation of calcium activities. Mitochondria actively shape and buffer cytosolic calcium transients through the activity of a calcium channel located at the inner mitochondrial membrane, named MCUC. Analysis of publicly available scRNA sequencing datasets predicted MCUGR1 (Mitochondrial Calcium Uniporter Glia Regulator 1) as a glia-specific regulator of MCUC. While MCUGR1 interacts with MCUC and is highly expressed in oligodendrocytes and astrocytes, its role in the physiology of glial cells remain elusive. Here, we show that MCUGR1 loss in immortalized cells leads to an increase of mitochondrial calcium uptake and concomitant deregulation of cell cycle progression. Proteomics analysis of MCUGR1-depleted cells also points to its role in cell death and DNA synthesis and gives clues concerning its involvement in cell cycle progression. Although MCUGR1 is normally localized in the cytosol, we show that it can relocate to mitochondria based on the cell cycle stage. Overall, our data suggest MCUGR1 plays a crucial role in cell proliferation, and we are currently addressing its role in glial cell differentiation and maturation using iPSC-derived models and their analysis with immunostaining and proteomics.

48 EGFR activation correlates with intracranial pressure and survival in a mixed intracranial bleeding porcine model

Marica Pagliarini, Zongren Zhao, Burak Özkan, Tamara Merz, Peter Radermacher, Francesco Roselli

>The pig model is an advanced system for studying human brain trauma due to its anatomical similarities with the human brain, such as brain size, gyrencephalic structure, skull shape, and white-to-gray matter ratio. Ischemia, a common feature in fatal acute intracranial hemorrhage cases, occurs when brain tissue compression obstructs vasculature, reducing cerebral blood flow. This ischemia-driven injury is central to brain injury pathophysiology. This study investigates the role of receptor tyrosine kinases

(RTKs) in the injury response and clinical outcomes, focusing on their potential as therapeutic targets for edema and reperfusion control after injury. To this end, we developed a sustained, resuscitated pig model of acute mixed intracranial hemorrhage with ICP, providing a robust system for in-depth examination of brain injury. Multimodal brain monitoring and neurological assessments offered valuable insights into the progression of the injury. Macroscopic postmortem analysis, transcriptional evaluations combined with western blotting and protein arrays, allowed the the assessment of RTK pathway activation. Our findings showed that 44-54 hours post-injury, animals exhibited signs of hypoxia, neuroinflammation, and extensive tissue damage. Elevated HIF1- α expression in the ipsilateral hemisphere confirmed local hypoperfusion. Inflammatory markers such as TNF- α , CD68, and MMP-9 were upregulated in both hemispheres, reflecting a generalized neuroinflammatory response. Gene expression analysis revealed increased markers of vascular, astrocytic, and neuroimmune activation, particularly related to endothelial integrity and astrocyte activation. RTK expression analysis showed increased levels of VEGFR1, VEGFR2, Tie-2, EGFR, and Axl in the injured cortex, with activation of EGFR/ErbB4 and HGFR/Met pathways. Hierarchical clustering of intrand astrocytic markers revealed distinct patterns of activation, highlighting the relationship between ICP severity and astrocyte response. Elevated EGFR phosphorylation correlated with astrocyte activation and ICP severity, survival, and Glasgow Coma Scale outcomes. These findings suggest that modulating EGFR signaling may offer a therapeutic approach for managing ICP and improving outcomes in traumatic brain injury.

49 EVs-derived microRNAs and Their Potential Involvement in EPM1 Pathogenesis

Ianni M, Forero A, Tuntevski K, Christofi K K, Pravatà M V, De Pietri Tonelli D, Cappello S and Di Giaimo R

>Progressive Myoclonic Epilepsy Type1 (EPM1) is a rare genetic form of epilepsy, characterised by early onset, myoclonus seizures and neurological symptoms. The neurodevelopmental disorder is linked to a loss-of-function of Cystatin-B (CSTB). Human Cerebral Organoids (hCOs) generated from EPM1 patient-derived iPS cells, showed altered proliferation and differentiation in neural progenitors. Moreover, CSTB levels modulated interneuron migration via cell-non-autonomous mechanisms. More recently, we demonstrated that pathologically low levels of CSTB altered progenitor cell identity and consequently neuronal output and electrophysiological properties in ventrally patterned hCOs. Extracellular Vesicles (EVs) are cell-derived vesicles containing biologically active molecules such as nucleic acids, proteins and lipids, which can influence and regulate neighbouring cells, therefore working as a form of short- and long-distance intercellular communication. microRNAs (miRNAs) are small non-coding RNAs involved in post-transcriptional regulation of gene expression, which can be released from cells encapsulated in small EVs, namely microvesicles and exosomes. EPM1-hCOs showed altered secretion of EVs that affected gene expression of the receiving cells. Here, our focus is to identify miRNA content in EPM1-EVs which might be involved in EPM1 cell-non-autonomous mechanisms in ventrally patterned hCOs. To this end, we collected dorsally and ventrally patterned EVs secreted by control- and EPM1-hCOs and characterized their miRNA content. Then, we analyzed unique and differentially expressed miRNAs derived from EVs according to their origin (control and patient) and brain area (dorsal and ventral). miRNA molecules were selected according to their biological function and will be

overexpressed in Neural Progenitor Cells (NPCs). Our final goal is to investigate the role of the selected miRNA in either rescuing the disease phenotype in EPM1-hCOs or mimicking it in control-hCOs by modulating gene expression.

50 Decoding Auditory Attention from Brain Activity in a Two-Speaker Environment

Maryam Bajool, Bernhard U. Seeber

>Humans possess a remarkable ability to selectively focus on a desired speaker in multi-speaker scenarios and noisy environments while effectively filtering out competing voices. This phenomenon, known as the 'cocktail party problem', highlights the brain's remarkable capacity for selective auditory attention. However, the neural mechanisms underlying this selective processing remain an open question, leading to the development of auditory attention decoding (AAD). AAD tackles the challenge of directly decoding auditory attention from neural activity, aiming to determine which speaker a listener is focusing on. It has been shown that neural activity contains information regarding incoming speech features. A common approach to decoding the attended direction is stimulus reconstruction from brain activity. We present the preliminary TUM dataset, which includes EEG recordings of five subjects while they were exposed to two concurrent audio streams played from loudspeakers positioned at $\pm 20^\circ$ azimuth in an anechoic chamber, informed to focus on one of the audio stimuli. Using linear regression, we demonstrate that for one-minute decision windows, attended stimulus envelopes exhibit a stronger correlation with the original stimulus compared to the unattended speech features. However, these correlations remain relatively weak, as linear models fail to account for the non-linear processing of acoustic signals along the auditory pathway. When narrowing the decision window, which is crucial for fast switching of attention, the accuracy of the model drops. Additionally, clean speech references are not always available in real-world applications. Inspired by recent studies suggesting that the spatial locus of auditory attention is neurally encoded, we change the problem from stimulus reconstruction to EEG classification by proposing a deep neural network to classify the direction of auditory attention from the short window of one second. We anticipate that auditory attention decoding at closer angles of $\pm 20^\circ$ compared to other implementations, e.g., $\pm 90^\circ$ and $\pm 60^\circ$, be more challenging.

51 Molecular pathology of the late-onset Alzheimer's disease risk variant S209F ABI3

Matteo Rovere, Michele Albertini, Molly Streich, Ignasi Forné, (...) Christian Haass

>Alzheimer's disease (AD) is the foremost cause of dementia and, despite recent breakthroughs, there is still no established disease-modifying therapy against it. Multiple genome-wide association studies have identified a number of AD risk variants in genes related to microglial physiology, which could in turn emerge as druggable targets. Among these is ABI3, a cytoskeleton-associated gene whose S209F mutation has been linked to an increased risk of late-onset AD, though its physiological and pathological roles remain largely unknown. Our goal is a detailed molecular characterization of ABI3's interaction and post-translational modification landscape, in order to understand its molecular mechanism of action in health and disease. Through the use of various biochemical methods, including immunoprecipitation,

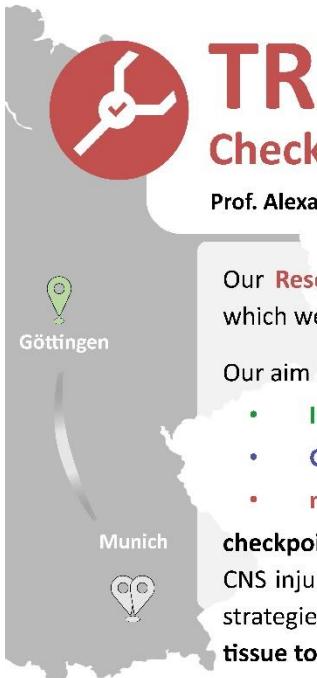
blue native gel electrophoresis, and size-exclusion chromatography, we establish ABI3 as an integral component of the WAVE regulatory complex (WRC). We demonstrate that the incorporation of ABI3 in the WRC is regulated by phosphorylation, identifying phosphosites at S213 and S216 which are disrupted by the S209F mutation. We also show how the ABI3 WRC is a soluble entity, in contrast to the “canonical” ABI1 WRC. MultiFOLD-based structural predictions and molecular phylogenetics identify a T-to-A variant in the ABI3 WRC which could explain its diminished recruitment to the membrane by way of a reduced binding affinity towards the WIRS motif. Lastly, we demonstrate how overexpressed exogenous ABI3 can replace endogenous ABI1 in the WRC, mimicking the hypothesized stoichiometric regulatory action of ABI3. We propose a model in which the S209F mutation, by depleting phospho-ABI3, shifts ABI3 outside of the WRC and results in a loss-of-function phenotype. Further work will corroborate these findings via molecular docking studies, immunofluorescence, and immunogold electron microscopy.



TRR 274

Checkpoints of Central Nervous System Recovery

Prof. Alexander Flügel (UMG), Prof. Martin Kerschensteiner (LMU), Prof. Mikael Simons (TUM)



Göttingen

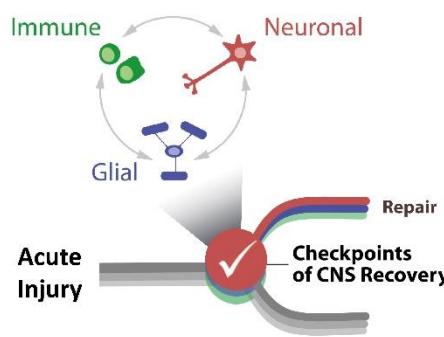
Munich

Our Research Consortium 274 is a collaboration between **Göttingen** and **Munich** in which we study the **multi-cellular response** that determines **recovery after CNS injury**.

Our aim is to define:

- **Immunological**
- **Glial**
- **neuronal**

checkpoints that predict the outcome of CNS injuries, and to develop intervention strategies that **guide an injured CNS tissue towards recovery**.



Find for an overview of our ongoing projects and measures at Sfb274.de

52 Behavioral and Neuronal Correlates of Exploration and Goal-Directed Navigation

Miao Wang, Fabian Stocek, Justin Graboski, Adrian Duszkiewicz, Joseph González, Adrien Peyrache, Anton Sirota

>The balance between exploration and exploitation is crucial for an animal's survival, guiding the transition between gathering and using information. However, the behavioral features that characterize these states and their neural correlates have remained elusive. Extending previous studies, in our prior work, we identified a set of behavioral features associated with exploratory states: sniffing, rhythmic head movements, and low head pitch. Conversely, the departure from this default "low" state of intense orofacial sampling to a "high" state is associated with slower breathing and high head pitch. Interestingly, these two states give rise to remapping of the hippocampal spatial representation. In this study, we extend this work in two directions. First, we analyzed rat behavioral features in a spatial memory task to identify the functional correlates of the two states. Multiple trajectory features distinguished between exploratory and goal-directed phases of the task, which, in turn, were predominantly associated with the "low" and "high" states. Second, we extended the analysis of the neural correlates of these behavioral states to a different allocentric spatial representation—the head direction system in the Postsubiculum of the mouse. We found similar remapping of head-direction cells between exploration and goal-directed states. We demonstrate this both at the single-neuron level, in terms of firing rate and preferred direction, and at the population level via Bayesian decoding and low-dimensional manifold analyses. Our results demonstrate that distributed allocentric spatial representations spontaneously fluctuate between exploration and goal-directed states in behaving rodents. Understanding this relationship provides new insights into the link between animal behavior, learning, and spatial cognition.

53 JAXLEY: Differentiable simulation enables large-scale training of detailed biophysical models of neural dynamics

Michael Deistler, Kyra L. Kadhim, Matthijs Pals, Jonas Beck, Ziwei Huang, Manuel Gloeckler, Janne K. Lappalainen, Cornelius Schröder, Pedro J. Gonçalves, Philipp Berens, Jakob H. Macke

>Biophysical neuron models provide mechanistic insight underlying empirically observed phenomena. However, optimizing the parameters of biophysical simulations is notoriously difficult, preventing the fitting of these models to physiologically meaningful tasks or datasets. Backpropagation of error (backprop) has enabled deep neural networks to scale to millions of parameters and large datasets. Unfortunately, no current toolbox for biophysical simulation can perform backprop, limiting any study of whether backprop could also be used to construct and train large-scale biophysical neuron models. We built a new simulation toolbox, JAXLEY, which overcomes previous limitations in constructing and fitting biophysical models. JAXLEY implements numerical solvers required for biophysical simulations in the machine learning library JAX. Thanks to this, JAXLEY can simulate biophysical neuron models and compute the gradient of such simulations with backprop. This makes it possible to optimize thousands of parameters of biophysical models with gradient descent. In addition, JAXLEY can parallelize simulations on GPUs, which speeds up simulation by two orders of magnitude. We applied JAXLEY to a range of datasets and models. First, we applied JAXLEY to a series of single neuron tasks and found

that it outperforms gradient-free optimization methods. Next, we built a simplified model of the mouse retina and optimized synaptic and channel conductances on dendritic calcium recordings. Third, we built a recurrent neural network with biophysically-detailed neurons and trained this network on working memory tasks. Finally, we trained a network of morphologically detailed neurons to solve MNIST with 100k biophysical parameters. Overall, JAXLEY makes it possible to construct and optimize biophysical models with thousands of parameters. We designed JAXLEY to be easy to use and we provide extensive documentation, which will make it easy for the community to adopt the toolbox. JAXLEY bridges systems neuroscience and biophysics and will enable new opportunities for multiscale neuroscience.

54 Differential effects of acoustic trauma on auditory onset and offset responses

Mihai Stancu, Ezhilarasan Rajaram, Joseph Kroeger, Benedikt Grothe, and Conny Kopp-Scheinflug

>Prolonged exposure to loud sounds can damage the auditory system and lead to increased neuronal firing in auditory pathways. Such an increase in firing rate is suggested to be caused by either increased intrinsic excitability or decreased neuronal inhibition. However, to our knowledge, the effects of acoustic trauma on neuronal firing have been investigated exclusively in neurons that respond to the onsets of sounds. The contribution of neurons that respond to the offset of sound to auditory perception and speech processing has only recently become a major topic of investigation. Knowing that acoustic trauma causes difficulties in understanding speech in noisy environments, we now ask the question of whether neurons firing at sound offset are differentially affected by acoustic trauma compared to neurons firing at sound onset. We took advantage of two synaptically connected nuclei in the auditory pathway, one receiving predominantly excitatory input (Medial Nucleus of the Trapezoid Body: MNTB) and the other receiving primarily inhibitory input (Superior Paraolivary Nucleus: SPN) and investigated changes in cellular, synaptic and circuit properties in response to acoustic trauma.

55 Divergent subcortical connectivity patterns during sleep/wake transitions and isoflurane-induced loss of responsiveness in mice

Monika Vadkertiova, Leesa Joyce, Rachel Nuttall, Matthias Kreuzer, Gerhard Rammes, Gerhard Schneider, Thomas Fenzl

>Non-rapid eye movement sleep (NREMS) and general anesthesia (GA) are two different processes, however, they share some similarities. In order to gain a better understanding of both phenomena, it is important to research their underlying mechanisms. This study focused on the functional connectivity between the sleep-promoting ventrolateral preoptic nucleus (VLPO) and the wake-promoting locus coeruleus (LC) during transitions between wakefulness (WAKE) and NREMS, as well as during isoflurane-induced loss (LOR) and recovery (ROR) of responsiveness to investigate the involvement of sleep/wake-promoting pathway in isoflurane-induced GA. Twelve male C57BL/6N mice were implanted with local field potential electrodes in VLPO and LC, as well as EEG electrodes to monitor vigilance states. Chronic recordings included two baseline days and GA. WAKE/NREMS/WAKE transitions were identified and functional connectivity between VLPO and LC was calculated and compared to LOR and

ROR. As measures for functional connectivity, coherence, inter site phase clustering (ISPC), and Granger causality (GC) were used. Coherence between VLPO and LC increased during WAKE to NREMS transition and decreased during NREMS to WAKE, while it decreased during LOR, with no significant change during ROR. ISPC during WAKE/NREMS/WAKE transitions was similar to coherence, LOR and ROR showed no significance. GC from VLPO to LC increased during WAKE to NREMS transition, as well as during LOR at low frequencies, while it decreased during NREMS to WAKE transition. GC from LC to VLPO decreased during WAKE to NREMS transition and increased after ROR. Functional connectivity between VLPO and LC showed different patterns during sleep and GA. While the results do not disregard the involvement of both nuclei in LOR and ROR, they point to at least partially different mechanisms underlying both processes. Current research in our lab uses targeted neuronal manipulation to better understand the role of the sleep/wake pathway in LOR and ROR.

56 Modulation of Visual Avoidance by Environmental Conditions

Mrudula Gangur, Weiqi Chen, Inês M.A. Ribeiro

>Vision is a fundamental sensory modality in many species, including humans and flies. Visual cues along with chemosensory cues and environmental conditions play a critical role in regulating many social behaviours. Courtship in *Drosophila melanogaster* is one such complex behaviour guided by visual cues with fewer magnitude of neurons, compared to mice or humans. Despite its small size, a large part of the *Drosophila* brain is allocated to processing visual information. Being a powerful neurogenetic model organism with its connectome mapped out, flies help us unravel the visual circuits involved in social interactions. Previous research has demonstrated the importance of LC10-group neuron types in avoidance and tracking behaviour. To identify the neural circuits mediating avoidance of visual objects devoid of chemosensory cues, but displaying naturalistic visual features, we use a behavioural assay known as the two floor assay. In this assay, a male and a female are placed in two chambers stacked vertically and separated by acrylic glass that allows exchange of visual cues, but not chemosensory or auditory cues, between the two flies. In this setting, changes in walking speed of the male lead to positioning the female away from the male frontal visual field, in what we call avoidance behavior. We serendipitously found that avoidance in two floor assays at different temperatures showed an increase in avoidance at both 21°C and 29°C, and less avoidance at the preferred temperature of 25°C. Moreover, neural circuits downstream of thermosensory receptor neurons can be traced to LC10-group neuron types, suggesting that temperature might modulate visual neurons involved in avoidance. Overall, our current research aims to unravel the neural circuitry mechanisms behind modulation of avoidance levels by environmental factors, such as temperature.

57 Preclinical Validation of a Novel Drug Target for Amyotrophic Lateral Sclerosis Identified Through Multiomic Analysis

Natalie Dikwella, Lucas Caldi Gomes, Paul Lingor

>Introduction: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease and effective therapeutic options are lacking. Despite substantial research efforts, no effective disease-modifying therapies are currently available. Through a multiomic analysis of human post-mortem prefrontal cortex (PFC) and PFC from four transgenic ALS mouse models, we identified a novel drug target (NDT), a protein kinase C (PKC) activator, as a promising candidate for neuroprotection in ALS. Methods: To validate selected molecular targets, we established primary cortical neuron cultures from P0 C57/Bl6 mice. To determine the concentration range for subsequent investigations, NDT was tested at concentrations ranging from 1–1000 nM in primary cortical neurons using the Toxilight assay, a luminescent assay for detecting cell viability and cytotoxicity. Then, to investigate the therapeutic potential of NDT, we used in vitro toxin models mimicking known disease pathways in ALS, such as glutamate excitotoxicity and arsenite-induced stress granule formation. Western blots for PKC were performed to evaluate the effects of NDT on PKC expression in the two in vitro toxin models. Neuroprotective effects were investigated by immunocytochemistry (for cleaved caspase 3) and analysis of neurite outgrowth using Image J. Results: Western blot analysis revealed a reduction in PKC expression in the sodium arsenite and glutamate excitotoxicity models upon NDT treatment, suggesting a potential regulatory role of PKC in ALS-related pathways. In glutamate treated neurons, NDT at 10 nM and 100 nM significantly increased neurite length and, at 10 nM, significantly reduced apoptotic cell death, indicating neuroprotection against excitotoxicity. Similarly, in sodium arsenite-treated neurons, neurite length was significantly enhanced at both 10 nM and 100 nM. However, while apoptosis showed a decrease, the effect was not significant. Notably, stress granule formation remained unchanged upon NDT treatment. Conclusion: Given its neuroprotective effects and modulation of key ALS-related pathways, NDT represents a promising candidate for further preclinical development and evaluation as a potential ALS therapy.

58 Pathogenesis of Morbus Stargardt in an Abca4 KO Mouse Model and in Retinal Disease Organoids

Natalie Klippe, Verena Mehlfeld, Martin Biel

>Morbus Stargardt is one of the most common forms of inherited retinal degeneration characterized by varying degrees of visual impairment. The ATP binding cassette subfamily A member 4 (ABCA4) is a transmembrane protein of the ABCA subfamily that is mainly expressed in the outer segments of photoreceptors and in the retinal pigment epithelium (RPE). It plays an essential role in the recycling and removal of components of the visual cycle, thereby preventing the aggregation of cytotoxic bis-retinoids. Mutations in the ABCA4 gene are the predominant cause of Stargardt's disease. Patients exhibit bilateral central vision loss, dyschromatopsia and central scotomata, including macular atrophy and yellow-white flecks on the RPE at the posterior pole. To date, there is no satisfactory therapy to halt or mitigate retinal degeneration in patients with Stargardt's disease. To gain a comprehensive

understanding of the pathogenesis of Morbus Stargardt, an Abca4 KO mouse model was characterized using electroretinography (ERG), optical coherence tomography (OCT) and blue autofluorescence (BAF) of the fundus. Given the role of glial cells in many degenerative eye diseases, the investigation of gliosis was also of particular interest. Increased inflammatory processes were identified by a larger GFAP-positive area in cryosections and flatmounts of Abca4 KO mice compared to WT animals. Our findings suggest that Abca4 KO mice exhibit significant photoreceptor degeneration, as evidenced by reduced retinal layer thickness, diminished photoreceptor activity and increased gliosis. To establish and evaluate a human disease model of Morbus Stargardt in parallel, ABCA4 KO retinal organoids were developed and compared to WT retinal organoids by measuring their circularity, area, and perimeter over time.

59 The effects of daytime napping on the ability to retrieve memories in humans

Nicolas D. Lutz, Iris Köller, Tobias Staudigl, Susanne Diekelmann, Luciana Besedovsky

>While it is well established that sleep benefits memory encoding and, particularly, memory consolidation, the role of sleep in memory retrieval remains unclear. According to the Synaptic Homeostasis Hypothesis (SHY), down-selection of weak synapses during sleep desaturates the brain's ability to encode new information and improves memory consolidation by increasing signal-to-noise ratios. Based on SHY, we hypothesized that sleep-dependent changes in synaptic strength continue after the consolidation period, potentially contributing to processes improving memory retrieval following sleep. To investigate the role of sleep in memory retrieval, healthy participants took part in two conditions in a within-subjects design. Following encoding of new information, they spent a one-week consolidation period at home and then returned to the sleep laboratory for retrieval testing, which took place either following an afternoon nap or an equivalent period of daytime wakefulness. Additionally, we recorded polysomnography and wake electroencephalography during and following the sleep/wake manipulation to investigate electrophysiological correlates of sleep-dependent memory retrieval. Our preliminary behavioral results ($n = 20$) indicate a beneficial effect of sleep on memory retrieval in both declarative and procedural memory tasks. Particularly, we found an effect of daytime napping on retrieval of word-pair associations and their accessibility from long-term memory. Furthermore, we found a significant sleep-dependent improvement in correctly typed sequences in a procedural finger-tapping task. Together, our preliminary results provide first evidence for an active role of sleep in retrieval of previously encoded memories.

60 Paradoxical Excess Dopamine upon Locus Coeruleus Axon Loss in the Hippocampus drives Cognitive Impairment in LBD

Nicolas Landgraf*, Weilin Chen*, Paul Feyen, Thomas Köglspurger, Jochen Herms*, Lars Paeger*

>Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, characterized by motor symptoms such as resting tremor, bradykinesia, and rigidity. Pathologically, misfolded α -synuclein (α -syn) aggregates into Lewy bodies, leading to neurodegeneration. Early diagnosis remains

challenging, often occurring after substantial dopaminergic neuron loss in the substantia nigra pars compacta (SNc), highlighting the need for earlier diagnostic methods to slow disease progression. Prodromal symptoms, including hyposmia, sleep disturbances, and psychiatric manifestations, are critical for identifying patients in the premotor stage. Notably, the locus coeruleus (LC), a small noradrenergic brainstem nucleus, controls physiological function impaired at early PD stages, suggesting a potential link between LC dysfunction and prodromal PD. Here, we established a mouse model of prodromal PD by virally inducing A53T- α -synuclein expression in the LC. We utilized behavioral tests, immunohistochemistry and *in vivo* imaging techniques including fiber photometry, two-photon microscopy and microendoscopy to investigate LC involvement in non-motor symptoms PD stages. Our findings reveal behavioral impairments in the A53T animals, particularly in working memory and spatial learning during the Y-maze test. In the dorsal hippocampus, dopamine is predominantly released from LC NA axons. We hypothesize that altered dopamine release from the LC to the hippocampus underlies these deficits, supported by significant reductions in LC cell count, LC axonal degeneration in hippocampal CA1/CA3 regions and changes in local dopamine concentration in CA1 observed *in vivo*. Paradoxically, we prove increased DA release despite LC axon loss. These results suggest that A53T- α -synuclein overexpression in the LC induces neuronal loss and axonal degeneration in the hippocampus, potentially contributing to early cognitive impairment in PD via disrupted dopamine signaling. Further investigations are ongoing to elucidate the mechanisms linking LC degeneration to cognitive decline in PD.

61 Vocal Strategies for Territorial Defense and Mate Attraction in Nightingales

Niels Hein, Giacomo Costalunga, Daniela Vallentin

>The rapid and accurate interpretation of vocal signals in different behavioral contexts is central to producing an appropriate behavioral response. Songbirds, for instance, demonstrate this capability by recognizing different behavioral contexts through vocalizations used for territorial defense, mate attraction, signaling danger, and individual identification. The common nightingale provides a compelling example of how a large repertoire of vocalizations can be strategically utilized in a vast number of different scenarios. During the breeding season in Europe, male nightingales engage in intense nocturnal counter-singing duels with neighboring males to establish and defend territories. Simultaneously, males attract females by singing their songs. Since females search for potential mates during the darkness of the night, they use acoustic signals, so called 'huit' calls, to indicate their presence. These 'huit' calls have been suggested to be used as contact calls or even luring calls. Differentiating rivalling male songs from 'huit' calls is of utmost relevance for the male birds during the breeding season. Here, we investigated the influence of these two distinct acoustic contexts on vocal behavior in wild male nightingales, by exposing the birds to either male songs or 'huit' calls. During exposure to rival male song, male nightingales engaged in counter-singing and regularly exhibited their typical song matching behavior - listening to and repeating the same song that was just presented. During 'huit' call playback, male nightingales sang faster compared to normal counter singing and introduced new elements into their vocal repertoire that were not observed during male-male song

interactions. These findings indicate that nightingales can categorize auditory signals and in turn tailor their vocalizations accordingly.

62 Hif1a regulates microglial phenotype and cognitive function in mouse models of Alzheimer's Disease Pathology

Nina Hermann, Desirée Brösamle, Jonas J. Neherw, Lisa Steinbrecher, Ann-Christin Wendeln, Kathleen Wild, Heidi Theis, Marc Beyer, Joachim Schultze

>Microglia, the resident tissue macrophages of the brain, have come into focus as important drivers and modulators of Alzheimer's Disease pathology. In response to A β plaques, microglia adopt a so-called disease-associated (DAM) phenotype, including activation of the transcription factor HIF-1 α , a master regulator of cell metabolism and pro-inflammatory responses in peripheral macrophages. However, it remains unclear, how HIF-1 α regulates microglia metabolism and response to plaque pathology, and whether modulation of the HIF-1 α pathway could affect cognition and behavior. Therefore, this study focuses on the role of HIF-1 α in driving the molecular and functional microglia response to cerebral β -amyloidosis and its effect on cognitive functions in animal models. Behavioral tests were conducted in APP23 or APPPS1 transgenic animals harbouring either Hif1a knockout or wildtype microglia (using Cx3cr1-CreER mediated recombination). Brain tissue of these animals was then used to perform immunohistochemistry and single-cell RNA sequencing. Microglial Hif1a KO results in an enhanced microglial coverage of A β plaques and reduced neuritic damage. Furthermore, the loss of microglial Hif1a leads to transcriptomic changes in specific microglial subpopulations, and regulates a subset of DAM-associated genes. These changes were reflected also on protein level. Finally, preliminary results suggest that Hif1a KO mice show behavioral changes in general locomotion, anxiety and short-term memory. Altogether, this study suggests that microglial HIF-1 α triggers a detrimental microglial response that is mediated by a distinct set of DAM genes. This response impairs the microglial plaque barrier function and contributes to cognitive deficits caused by cerebral β -amyloidosis. Thus, this work highlights the potential of targeting HIF-1 α as an immuno-modulatory approach for Alzheimer's disease.

63 A behavioural response to magnetic stimuli in Pigeons?

Aaron T. Denton, Spencer D. Balay, and David A. Keays

>The remarkable navigation abilities of pigeons (*Columba livia*) are facilitated by a sensory system that detects the Earth's magnetic field. While there is compelling behavioural evidence for magnetoreception, the mechanisms by which magnetic information is sensed and integrated into neural circuits remain poorly understood. One hypothesis states that animals detect magnetic fields by electromagnetic induction within the semicircular canals of the inner ear, which contain sensitive electroreceptors. In support of this, preliminary data from the Keays lab has shown that the vestibular nuclei and nucleus abducens in the brain are activated by magnetic stimuli. As these areas are components of the vestibular-ocular pathway, we theorised magnetic fields may trigger the vestibular-ocular reflex (VOR). The VOR is responsible for stabilizing gaze during head movements by inducing eye movements in the

opposite direction. Our primary goal was first to develop a novel avian eye-tracking method and then to test this hypothesis by investigating pigeons' eye movements when exposed to magnetic stimuli. We successfully adapted the pre-existing pose-estimation deep learning software, DeepLabCut, to track eye movements. However, our experiments found no experimental evidence of a rotating magnetic field having a significant effect on head fixed pigeon's eye movements (n=3 birds). Further experimentation should focus on increasing the sample size and optimizing the stimulus and experimental conditions.

64 Human retinal organoids mimick the cholesterol sotrage disease Niemann-Pick type C in vitro

Patricia Hoffelner, Oliver Bludau, Valerio Zenatti, Lina Dinkel, Laura Sebastian Monasor, Dominik Paquet, Matthias Prestel, Sabina Tahirovic, Antje Grosche

>Introduction. Niemann-Pick type C (NPC) disease is caused by a malfunction of either of the two cholesterol transporters NPC1 (95 % of patients) or NPC2 (5 % of patients). NPC1 dysfunction in patients leads to intracellular accumulation of cholesterol in lipid vesicles and mitochondria with brain and liver being the most affected tissues resulting in neurodegeneration, visual impairment and ultimately premature death. We aim to mimic a retinal phenotype in NPC1-deficient human retinal organoids (hRO) co-cultured with iPSC-derived microglia. Methods. hRO were generated from a healthy human iPSC line as well as a NPC1 mutant line (NPC1mut) derived from the latter. As neuroepithelial-derived hRO do not contain hematopoietic lineage-derived microglia, we co-cultured hRO with iPSC-derived microglia from the same cell line. By morphometric analysis of different cell populations using immunolabeling, the cellular composition of hRO and the activation state of iMicroglia was investigated. Results. First results indicate a shift in the cellular composition or differentiation pattern/timing upon NPC1 mutation. While there were more photoreceptors in NPC1mut hRO (indicated by an increased recoverin intensity and a thicker ONL), there is a tendency to less neurons of the INL (indicated by less calretinin and calbindin positive cells). In contrast, no differences between both lines were found for Müller cells (Vimentin) and VGlut1 (Synapses). 18 kDa translocator protein (TSPO), which is hypothesized to be a mitochondrial cholesterol transporter in Müller cells, is upregulated in NPC1mut hRO at later time points, indicating a possibly altered cholesterol shuttling upon NPC1 mutation. In co-culture experiments, microglia readily integrate into hROs regardless of the genotype and could be maintained for up to 60 days. Cholesterol accumulation in microglia soma, a hallmark of NPC, was confirmed by filipin staining. Conclusion and Outlook. Although initial retinogenesis and microglia integration appears to be unaffected by NPC1mut hROs, there may be an effect on the maturation and/or survival of distinct cell populations at later developmental time points. Since cell number does not necessarily indicate cell functionality, we will characterize hRO glial cells in terms of their functionality upon NPC1 loss in live cell assays already established in the lab.

65 Selective vulnerability of Pvalb Neuron Axon Bifurcations in Tauopathy

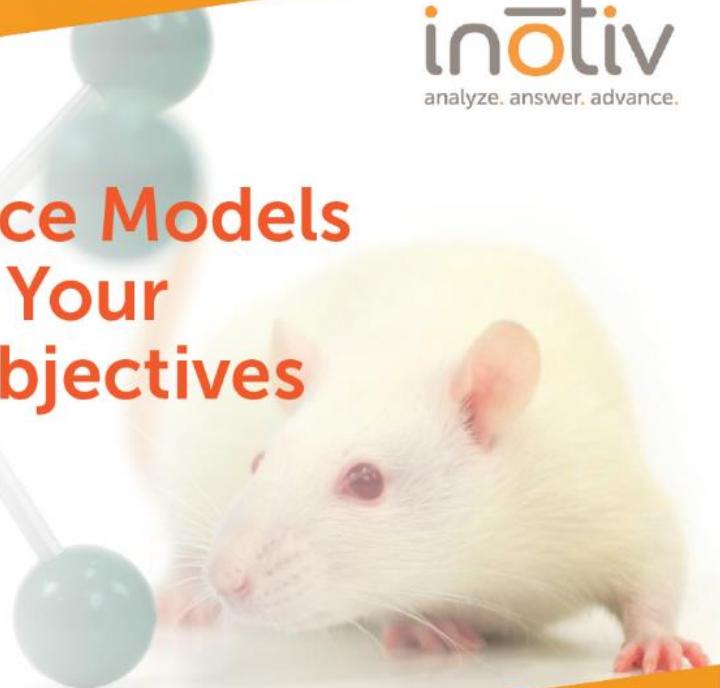
Paul Feyen, Yuxiao Zhang, Lars Paeger, Theresa Niedermeier, Jochen Herms

>Parvalbumin neurons are known for their extensive, highly myelinated axonal arbors, which enable their critical role in regulating cortical and hippocampal network oscillations. Their axons comprise multiple subcompartments—the axon initial segment, synapses, and bifurcation points—any of which could be differentially susceptible to Tau-induced damage by virtue of their geometry and molecular composition. To determine whether and how PV+ axons respond in tauopathies, we employed a 2N4R Tau expression model targeted to the largest GABAergic subpopulation: the PV+ interneurons. In this accelerated tauopathy paradigm, we observed pronounced neuronal loss that was preceded by severe, focal axonal dystrophy. Surprisingly, this damage was enriched at axon bifurcation points, suggesting a specialized microdomain-specific vulnerability within PV+ neurons. Longitudinal *in vivo* two-photon microscopy further revealed secondary oligodendrocytic pathology, manifested as dystrophic glial processes in direct contact with—and in the vicinity of—these focal lesions. We also provide corroborating evidence from human post-mortem brain tissue, indicating that PV+ axonal tauopathy and bifurcation dystrophy are features of human tauopathy. Collectively, our findings highlight that axonal damage in tauopathy is far from uniform. Instead, PV+ axonal branch points appear to be hypervulnerable sites where local Tau accumulation triggers an early cascade of structural and glial-mediated pathology. Understanding these compartment-specific mechanisms of axonal degeneration in PV+ neurons could help clarify not only how inhibitory network dysfunction arises in diseases such as AD, CBD, and PSP, but also how novel therapies might be aimed at stabilizing critical axonal domains to prevent broader circuit failure.



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66 Ocular dominance columns in mouse visual cortex

Pieter M Goltstein, David Laubender, Tobias Bonhoeffer, Mark Hübener

>The primary visual cortex (V1) of higher mammals such as cats and monkeys shows columns for stimulus features like orientation preference and ocular dominance, but such columns are not found in all groups of mammals. Models suggest that the afferent sampling density in V1 could be a key factor determining whether a columnar organization is established or not. Accordingly, in rodent V1, which – in comparison to other animals – has a low sampling density, there appear to be no orientation columns. However, the situation is less clear for ocular dominance. So far, *in vivo* imaging studies in mice have not reported an obvious functional clustering for ocular dominance, while experiments in rat V1 revealed eye-specific patches by activity mapping with immediate early genes. Here we use a mouse line with widespread expression of a genetically encoded calcium indicator (GCaMP6s.Niell) to test whether mice show a functional organization for ocular dominance. We performed wide field-of-view, cellular-resolution two-photon calcium imaging throughout cortical layers 2/3, 4 and 5 of binocular V1. In most animals, we observed a patchy organization of eye preference within layer 4, with clear clusters of neurons that preferentially responded to the ipsilateral eye, surrounded by a contiguous region of contralateral eye dominance. Extending vertically into layer 2/3 and layer 5, these clusters resembled ocular dominance columns. The observation of ocular dominance columns in the minute binocular visual cortex of mice sets a new boundary condition for computational models explaining the emergence of a columnar organization in the brain.

67 iPSC-Derived Monocytes Modulate the Glioblastoma Microenvironment and Inhibit Tumor Progression

Polyxeni Moysidou, Jovica Ninkovic

>Glioblastoma (GBM) is a highly aggressive brain tumor characterized by a profoundly immune-infiltrated tumor microenvironment (TME), which plays a critical role in driving tumor progression and recurrence. The complexity of the TME—arising from intricate interactions between immune cells, glial cells, and neurons—has made it challenging to dissect the specific contributions of individual cell types. To address this, we developed a modular human cerebral assembloid (hc-assembloid) system that enables the study of defined cellular interactions within a human-relevant context. Using this platform, we investigated the role of monocytes by integrating iPSC-derived monocytes (i-monocytes) into hc-assembloids containing GBM foci. Strikingly, i-monocytes infiltrated the GBM core, whereas resident microglia predominantly remained in the peritumoral area. Importantly, i-monocyte invasion led to a significant reduction in tumor size, with the effect varying depending on the GBM subtype. This tumor regression was accompanied by a marked decrease in glial reactivity within the TME. Together, these findings reveal a novel role for monocytes in reshaping the GBM microenvironment and suppressing tumor growth, offering new insights into immune-mediated modulation of GBM and potential avenues for therapeutic intervention.

68 The role of synchronous motion in perceiving agency in inanimate entities

Rebecca Geiselmann, Lasana T. Harris, Ophelia Deroy

>Perceiving agency from motion cues is fundamental to social cognition. While goal-directed motion is a well-known agency cue, the role of synchronous motion between inanimate entities remains underexplored. This study examines whether synchrony contributes to agency perception, enhances goal-directed motion cues, and influences metacognitive confidence. In Experiment 1, 78 U.S.-based neurotypical participants watched videos of pre-programmed disc movements, judged whether the discs were chasing, and rated their confidence. Experiment 2 (78 participants) extended the investigation to purposeful interactions beyond chasing. Findings demonstrate that synchrony plays a fundamental role in agency perception, shaping judgments of chasing and purposeful interaction. While chasing perception requires cue integration, with synchrony amplifying directed motion effects, purposeful interaction perception is shaped independently by each factor. Response times and confidence ratings reveal cue integration, suggesting that even when categorical judgments treat cues separately, the perceptual system processes both. Data was collected in August 2024. Age and gender were balanced, but the sample was predominantly White, highly educated, and U.S.-raised, limiting generalizability. While perceptual mechanisms are likely universal, cultural, developmental, and neurocognitive factors may shape higher-level judgments. These findings inform social cognition and human-AI interaction, highlighting synchrony as key to perceived agency.

69 Neural Correlates of Social Metacognition

Mattes, Rebekka S.; Vural, Gizem; Drexler, Sarina; Xia, Hongmei; Soutschek, Alexander

>Metacognition research has explored domains such as perception, memory, and value-based decision-making. However, less is known about metacognition in social decision-making. This is especially interesting in the context of the domain specificity vs. generality debate surrounding metacognition: it has been suggested that different neural networks may underlie metacognition in different domains, but so far few studies directly compared the neural correlates of metacognition in different domains. To close these gaps, the present study investigated the neural correlates of social metacognition and examines whether they differ from the well-established neural mechanisms of perceptual metacognition. To this end, participants performed a social and a perceptual metacognition task inside the fMRI scanner. Both tasks required a task-dependent decision and subsequent confidence rating about the accuracy of the decision. On the behavioural level, we found that both metacognitive bias and metacognitive efficiency differ significantly and are not correlated between the metacognition tasks. For both tasks, the fMRI analyses revealed neural correlates for confidence in the FPC but task-specific connectivity patterns of the FPC with other brain regions. This research sheds light on the neural substrates of social metacognition and contributes to the ongoing debate on whether metacognition operates as a domain-general or domain-specific process.

70 Contrastive representation learning for neural system identification

Rodrigo Gonzalez Laiz, Tobias Schmidt, Steffen Schneider

>Inferring and describing neural dynamics is a key challenge in systems neuroscience. While many models have been proposed, robust solutions for inferring non-linear dynamics in the absence of auxiliary variables remain limited. Among machine learning methods for time-series data, self-supervised contrastive learning approaches have brought tremendous success across many tasks and domains. It has been argued that these successes can be attributed to a link between self-supervised and identifiable representation learning: Temporal structure and auxiliary variables ensure that latent representations are related to the true underlying generative factors of the data. We substantially extend this connection by showing that contrastive learning can perform system identification in latent space. We propose a new framework to model linear, switching linear, and non-linear dynamics under a non-linear observation model, allow external inputs, and provide theoretical guarantees for identifying both the latent space and underlying dynamics. We verify these guarantees in extensive simulations and show consistent latent dynamics identification on real-world electrophysiology and calcium imaging datasets.

71 Subregion-Dependent Insular Coupling with Heart Rate and Its Derivative in Aversive and Appetitive States

Ronja Brinkmann, Mira Erhart, Dr. Nadine Gogolla, Dr. Victor Spoormaker

>Introduction: The insula cortex functions as a central hub in autonomic regulation, including the modulation of heart rate. In both human and animal research, experiments have demonstrated that insular activity is closely linked to cardiovascular control, and elicits both heart rate increases and decreases. Additionally, a posterior-to-anterior functional organization within the insula has been proposed: the posterior insula is generally associated with sympathetic activation, whereas the anterior insula appears more involved in parasympathetic regulation. Complementary animal studies have supported these mechanisms by mapping insular projections to key brainstem autonomic centers, thereby providing causal evidence for its role in heart rate modulation. Expanding on these findings, we investigate how this heart rate-insula coupling varies across different emotionally arousing paradigms. Specifically, we examined heart rate-insula interactions both during an aversive and an appetitive context. This approach allows us to explore whether the affective valence of a stimulus modulates the coupling. Method: We analyzed a subset of the BeCOME dataset ($n = 84$ healthy participants), of simultaneous fMRI and heart rate recordings, while participants performed the modified Montreal Imaging Stress Task, and the Reward Anticipation Task. In our analyses, we examine the parametric modulation of insula activation by heart rate and its derivative. Results: In both the stress and the reward task, we find similar heart rate-insula coupling during the valent conditions, compared to control ones. We additionally find intra-insula differences in the coupling of heart rate and heart rate derivative with the insula, in both tasks. Discussion: Our findings demonstrate a similar coupling of the insula with both heart rate and heart rate derivative across arousing tasks with different valences. The direction of this coupling, however, differs between sub-regions within the insula.

72 Canaries differentially modulate solo and overlapping singing during the transition to the breeding season

Santhosh Totagera, Pepe Alcami

>Songbirds sing different song types depending on the social context. Songs can be categorized into two types based on their timing relative to other birds' songs: solo and temporally-overlapping songs. Overlapping songs have been typically characterized in the breeding season, in which they are associated with an aggressive social context. However, whether both song types occur year long, and whether they show differential modulation of their rate of production and properties during the transition between the non-breeding and the breeding season has been rarely studied. Here we investigate, the production of both song types in a group of domesticated canaries (*Serinus canaria*), at the transition between the nonbreeding and the breeding season. We found that both song types were present outside the breeding season. Whereas for solo songs, duration and its variability, fraction of time singing and number of songs increased as the breeding season approached, overlapping songs showed opposite trends. Furthermore, both song types were distributed more homogeneously as the daylength increased. Overall, the differential changes of both song types at the seasonal time scale suggest differential underlying mechanisms and functions.

73 Brain-wide networks for category learning in the mouse

Selina Majaj, Sandra Reinert, José-Maria Martinez de Paz, Mark Hübener, Pieter M Goltstein, Emilie Macé, Tobias Bonhoeffer

>Learning to group objects and experiences into categories is an important cognitive ability that helps us to efficiently respond in complex and unfamiliar situations. Multiple regions in the neocortex, hippocampus and subcortex have been identified to underlie category learning in many species. However, most of these studies have focused on one brain region at a time or the interaction between two regions. Thus, there is a need to investigate the spatial and temporal interactions of brain regions involved in category learning in an unbiased manner. Here we present an approach utilizing functional ultrasound imaging (fUSI) to record brain-wide dynamics while mice are engaged in a category learning task. The principle of fUSI is to detect cerebral blood volume changes induced by neuronal activity. We used this method over a period of several months during which mice learned to discriminate visual categories in a head-fixed 2-alternative forced choice (2-AFC) paradigm. Our initial data show that we achieved sufficient spatiotemporal resolution to examine brain-wide activity during task trials across different stages of category learning. We identify distinct sensory and motor neural correlates representing instructed task variables (visual categories, licks, reward and running). Additionally, our data show changes in brain-wide dynamics with different spatial and temporal profiles following learning. Using this approach, we aim to characterize the learning related recruitment of specific brain regions to constitute functional networks that process and generalize visual categories.

74 Energetic costs of brain connectivity in Behavioural Variant Frontotemporal Dementia

Shuqi Xie, Yifan Mayr, Igor Yakushev

>Despite a growing interest in brain connectivity, energetic costs of brain connectivity remain unknown. Because dementia disorders are considered as syndromes of brain disconnection, regionally well-defined behavioural variant frontotemporal dementia (bvFTD) can be a useful model to study pathological brain connectivity in general and its energetic costs in particular. A group of healthy subjects (HC, n = 19) and patients with bvFTD (n = 19) underwent diffusion-weighted imaging and functional magnetic resonance imaging, simultaneously with ¹⁸F-fluorodeoxyglucose positron emission tomography. Three sets of non-linear regression models were fitted, with a) structural connectivity (SC), b) resting state functional connectivity (rsFC), and c) both SC and rsFC as predictors of glucose consumption. At the whole brain level, SC explained an average of 75% and 55% variance in glucose consumption in HC and in bvFTD respectively, with a significant group difference in adjusted R² for each non-linear model. The corresponding values for rsFC were 32% and 29%, with no significant group difference. For frontal lobe as major affected region in bvFTD SC explained 54% and 17% variance in glucose consumption in HC and in bvFTD respectively, again showing a significant group difference. The corresponding values for rsFC were 0% and 0%. For occipital lobe as presumably unaffected region in bvFTD SC explained 33% and 36% variance in glucose consumption in HC and in bvFTD, respectively, with no group difference. The corresponding values for rsFC were 28% and 22%, with no group difference. None of the c) models outperformed a) models. In sum, SC explained 2/3 less variance in frontal glucose consumption in bvFTD than in the healthy state. No difference in explained variance was found for occipital glucose consumption. Predictive power of rsFC differed between bvFTD and healthy state neither at the regional nor at the whole brain level. In neither model, rsFC added to the predictive power when combined with SC. These results strongly support the decoupling between SC and glucose metabolism in bvFTD.

75 Neural representation of color in the pigeon brain

Simon Nimpf, Ann H. Kotkat, Andreas Genewsky, Laura Busse, David A. Keays

>For many animals, color vision is important for survival, contributing to critical behaviors such as identifying food, detecting predators and recognizing mates. How colors are processed in the central nervous system of di- and trichromatic vertebrate species (2-3 color cones) has been a topic of considerable research over the last decades. In contrast, the neuronal circuits supporting color vision in tetrachromatic vertebrates (4 color cones), such as birds, remain poorly understood. Through a combination of LED display engineering, Neuropixels recordings and computational methods, we here provide a comprehensive characterization of the neuronal representation of color in the pigeon visual Wulst, the functional homologue of the mammalian primary visual cortex. We presented full-field colors on a custom 5-channel LED display covering the avian visual spectrum while recording single unit responses in the visual Wulst of awake, head-fixed pigeons. To quantify the diverse response profiles of individual units to the colors, we used a combination of non-linear dimensionality reduction and a two-step unsupervised clustering approach. This allowed us to identify ~100 unique response types, which could be broadly categorized as color-selective, color-opponent or achromatic. To investigate the neural

encoding of color within the visual Wulst, we used CEBRA, a new machine learning algorithm, to find a low-dimensional embedding of responses to the different colors. A classifier trained on the resulting embeddings was able to decode color with high accuracy (~80%, 100 repeats), demonstrating that visual Wulst population activity profiles are distinct between different colors. Together, our functional survey highlights the extraordinary diversity and complexity of color responses in the pigeon's visual Wulst. Ultimately, our findings will allow investigating commonalities and divergences between the evolutionary ancient visual system of birds and our own visual sense.

76 Functional and molecular mechanisms underlying plasticity-mediated CNS recovery after spinal cord injury in adulthood and aging

Adna Smajkan, Hannah Peedle, Florence Bareyre

>Although plasticity is restricted in the adult mammalian CNS, recent findings suggest an increasing amount of evidence that this plasticity can change in response to injury. One such instance is the reorganization of spinal circuits following dorsal hemisection, aiming to compensate for the loss of supraspinal input deriving from the motor cortex. The corticospinal tract (CST) is one of the neural pathways that undergo injury-induced plasticity. This involves sprouting of CST axons rostral to the injury site, leading to the establishment of new connections with relay neurons unaffected by the lesion, ultimately contributing to the restoration of motor function. While the formation of detour circuits has been a well-established model demonstrating functional recovery in young animals, there is a lack of data in older animals. This question is of particular importance as the increase in the geriatric population over recent years has led to an increase in the median age of patients experiencing spinal cord injury. Our objective is to examine the anatomical basis of worsened recovery in older animals. A crucial aspect to investigate involves the role of microglial cells, which are already acknowledged for engulfing synapses during the post-remodeling process. We have already demonstrated that these cells excessively engulf synapses in older animals, potentially contributing to the observed deterioration in recovery. Moving forward, we aim to identify the key molecular pathways that regulate microglial-mediated synaptic engulfment in the injured spinal cord. By targeting these pathways, our goal is to develop strategies that protect synapses from excessive pruning and ultimately restore motor function in older animals.



77 Human cerebral assembloids as a model to study the interaction of glioblastoma with resident glial cells

S Kalpazidou, P. Moysidou-Tsiorva, B. Özbaykent, (...) J. Ninkovic

>Glioblastoma multiforme (GBM) is a highly lethal brain cancer, yet the role of GBM-induced glial reactivity in tumor progression remains unclear. To investigate glia-GBM interactions, we developed human cerebral organoids with innately integrated microglia and macroglia, then transplanted them with GBM cells to model tumorigenesis. Our model recapitulates key tumor features, including tumor stiffness, GBM-associated methylation, and glial reactivity, mirroring *in vivo* conditions. scRNA-seq analysis of reactive glia in hc-assembloids revealed a previously unrecognized enrichment of extracellular vesicles (EVs) in reactive glial cells, validated in GBM patient samples, highlighting novel regulatory pathways in the GBM microenvironment. Additionally, this modular system enables co-culturing of GBMs with defined immune and stromal cells, as we exemplified with monocytes, allowing the study of immune-tumor interactions. Thus, iPSC-derived cerebral organoids offer a versatile platform to model GBM-induced glial reactivity and its role in tumor progression.

78 Sex-specific outcomes of developmental stress exposure and psilocybin intervention

S. Narayan, R. Florea, J. Bordes, S. Mitra, B. Silva, C. Castoldi, B. Dal Bianco, S. Röh, D. Czamara, E.B. Binder, M.V. Schmidt

>Stress exposure during neurodevelopment is an established risk factor for the onset of psychiatric disorders in adulthood, which are known to differ in symptomatology depending on sex, and are difficult to treat due to their heterogeneity. A more holistic biological perspective of the adult brain after stress exposure during development is needed, to provide new avenues of intervention options. Despite an explosion of neuroscience knowledge in recent decades, psychiatric treatments remain largely ineffective for many patients, indicating a need for preclinical neuroscience research to better reflect the clinical setting. Recently, there has been renewed interest in using psychedelic drugs like psilocybin as treatments for mental illnesses. However, sex-specific effects of psilocybin on different behavioral domains, and the potential of psilocybin to rescue negative effects of developmental stress, have yet to be characterized. To this end, this work uses a mouse model to characterize alterations in the adult brain and behavior due to prior exposure to stress early in life, on different levels of brain organization. We investigate transcriptomics and network connectivity, and use robust phenotyping to efficiently characterize a wide variety of behaviors associated with stress-related disorders. We show that many adulthood behavioral and physiological outcomes of developmental stress are distinct between sexes, driven in the brain by alterations in processes highly active during neurodevelopment. Psilocybin broadly altered the behavioral profile in a direction opposing effects of developmental stress, but via social behaviors in females and internalizing behaviors in males, opening new interpretations of behavioral phenotypes. Through this work, we display the necessity of considering sex as a biological variable, encourage enhanced translational validity of pre-clinical work, and characterize a vast range of lasting effects of developmental stress on the brain and psilocybin on behavior, which can be used to aid the progress of finding targeted treatments for stress-related disorders.

79 Emotion state representations in the mouse insular cortex

Stoyo Karamihalev, Lisa Rottenfussler, Yanko Arevalo, Rosa-Eva Huettl, Nadine Gogolla

>Emotions are complex internal states that shape actions across the behavioral repertoire of individuals. There is overall agreement that emotion states exhibit many common characteristics, such as persistence and scalability, while also being distinct in crucial ways. Yet, the brain-level implementations of commonalities and differences across emotions remain elusive. Here we address this by focusing on the anterior insular cortex, a brain area implicated in emotion modulation and interoception. We take advantage of facial expressions and postural dynamics to obtain a comprehensive description of an individual's internal state across a range of evoked and spontaneous emotions. Using *in vivo* cellular resolution imaging and photostimulation, we attempt to resolve how neurons in the insular cortex represent and contribute to characteristics of emotional expression. This work may help uncover organizing principles of emotion state representation and control.

80 Unraveling Human Brain Cross-Regional Complexity Through Integrative snRNA-seq Profiling

Su Han Cho; Eva M.G. Viho; Anna S. Fröhlich; Elisabeth B. Binder

>Single-nucleus RNA sequencing (snRNAseq) is a powerful method for investigating the transcriptomic complexity of tissues and their diverse cell types. To enhance statistical power in studies involving human samples, increasing the sample size is essential, which often involves integrating multiple datasets. However, the integration of heterogeneous datasets introduces several methodological challenges. It is crucial to carefully manage biological and technical confounders to avoid biases and distorted analytical outcomes. In this study, we investigate the molecular and cellular mechanisms underlying brain aging by applying snRNAseq to post-mortem tissue samples from 99 donors across the orbito-frontal cortex (OFC), the hippocampus, and the amygdala. The OFC data generation was performed in several experimental and sequencing batches. For the integration, we applied stringent statistical thresholds accounting for variations such as sequencing depth, the number of nuclei captured, and batch effects that may affect each sample differently. Using Scanpy (v1.10.3), we implemented quality control measures and corrections, including ambient RNA removal (SoupX v1.6.2), cell and gene filtering via z-score transformation, and doublet removal (DoubletDetection v4.2). This resulted in a robust dataset of over 950,000 high-quality nuclei. Label transfer using scArches(v0.6.1) enabled mapping of 21 distinct cell types, which matched our previous published findings. The insights gained from the integration of multiple sequencing batches will inform our approach to integrate data from the hippocampus and amygdala, enhancing the statistical validity and biological relevance of future comparative studies.

81 Early changes in glial cells in INSC94Y pig model for diabetic retinopathy

Sweetu Susan Sunny, Lew Kaplan, Oliver Bludau, Kirsten Wunderlich, Patricia Hoffelner, Cornelia A. Deeg, Simone Renner, Eckhard Wolf, Stefanie M. Hauck, Antje Grosche

>Purpose: Diabetic retinopathy (DR) is a leading cause of visual impairment in adults, with its prevalence increasing globally. This study utilizes the INSC94Y pig model of neonatal diabetes to investigate DR, chosen for its similarity in eye size, cone density, and its ability to closely mimic the symptoms of late-stage disease. The study focused on the role of glial cells, particularly Müller glial cells, in the dysregulation of the neurovascular unit. Methods: The study was conducted using 5-7 month-old and 2-3 year-old wild-type and INSC94Y pigs. Glial cell activation was assessed through immunostaining for GFAP (Müller cells) and Iba1 (microglia). Mitochondrial fitness of Müller cells was measured using the JC-1 assay. The volume regulation function of Müller glial cells was evaluated by measuring cell soma swelling in retinal slices subjected to hypo-osmotic stress. Proteomic profiling was performed on acutely isolated Müller cells, microglia, and neurons, enriched via magnetic-activated cell sorting. Results: INSC94Y pigs exhibited retinal thickening compared to age-matched wild-type controls, indicative of edema formation similar to what is observed in human patients suffering from diabetic macular edema. A substantial upregulation of glial fibrillary acidic protein (GFAP) marked the onset of Müller cell gliosis, and an increase in Iba1-positive microglia/macrophages with reduced territory indicated microglial activation specifically in inner retinal layers of the central visual streak. Functional assays revealed decreased mitochondrial fitness and impaired osmotic stress response in Müller glial cells of INSC94Y retinas compared to wild-type controls. Proteomic analysis of glial cells revealed dysregulation of mitochondrial metabolism associated proteins. Conclusions: Our results confirm alterations in retinal architecture in the INSC94Y pig model of DR. Early-stage disease progression in these pigs was marked by molecular and metabolic changes in Müller cells and microglia. These findings suggest that glial cell dysfunction develops early in the course of the disease potentially playing a key role in DR.

82 Induction of Tau Pathology in Wild-Type Mice: A Model to Study Seeding and Spread in Tauopathies

T. Nazarenko, S. Kaji

>Tau, a microtubule-associated protein, assembles into insoluble filaments that accumulate as neurofibrillary tangles in Alzheimer's disease (AD) and other tauopathies. Tau fibrils can be transmitted from cell to cell and can initiate the aggregation of soluble tau. Widely accepted tools to investigate the development and propagation of tau are transgenic models that overexpress tau. However, these models may be limited in studying tau seeding and can be inaccurate due to artifacts from overexpression. Dr. Virginia Lee's group developed a protocol that induces tau seeding in the brains of non-transgenic mice through inoculation with tau fibrils purified from the brains of AD patients. For our project, we decided to use this model. Therefore, we began by optimizing the protocol to reduce the amount of human material used.

83 Studying mitochondrial dynamics with in vivo acousto-optic two photon imaging – focus on Locus Coeruleus vulnerability

Theresa Niedermeier, Paul Feyen, Katharina Ochs, Jochen Herms, Lars Paeger

>The study of mitochondria is often restricted to in vitro assays or cytochemical analysis, limiting conclusions about dynamics and progression over time. Here we present a novel in vivo two-photon imaging method utilizing acousto-optics to study mitochondrial dynamics. Region-specific mitochondrial GFP expression allowed for selectively imaging mitochondria in Parvalbumin (PV) interneurons, CamKIIα excitatory neurons and Locus Coeruleus (LC) brainstem neurons. The presence of a significant number of moving mitochondria in adult mammals has been discussed controversially in the past. Here, we show the abundance of mobile mitochondria in adult and aged animals across these cell-types and identify cell-specific characteristics of mitochondrial transport dynamics. The LC specifically is of special interest in the context of neurodegenerative diseases such as Alzheimer's disease (AD), where it is one of the first regions to show hyperphosphorylated 'pretangle' tau. While this region-specific vulnerability is not fully understood, mitochondria have been proposed to be linked to this pathology due to the bioenergetic needs of the tonically active LC neurons with their extensive unmyelinated axonal projections throughout the entire forebrain. We use our novel method to show mitochondrial velocity in LC, but not in PV and CamKIIα neurons, in a tauopathy model is significantly reduced, correlating with a significant loss of LC axonal projections in the cortex. Furthermore, mitochondrial velocity in LC axons was also decreased in a model of α-synucleinopathy and aging, emphasizing the vulnerability of the cell type. This highlights the importance and possibilities of further investigations of the role mitochondria play in diseases such as AD.

84 Multi-tracer PET monitoring of an immunomodulatory therapy in 4R tauopathy: Evaluating a novel drug's impact on glial function and protein pathology

Tim Bathe, Svetlana Salomasova, Manvir Lalia, Lea H. Kunze, Giovanna Palumbo, Rosel Oos, Emanuel Joseph, Matthias Brendel

>Background: The prevalence of neurodegenerative diseases (ND), including Alzheimer's disease (AD) and non-AD tauopathies, is projected to rise significantly by 2050 due to an aging global population. Chronic neuroinflammation, driven by glial activation in response to protein pathologies, is a major contributor to disease progression. Targeting glial dysfunction through immunomodulatory therapies offers a promising approach to mitigate the effects of tauopathies and other ND. Objective: The research scope is to monitor the efficacy of GV1001 in a transgenic tau mouse model (PS19) with an early-intervention biomarker study using molecular biology and neuroimaging techniques including TSPO (microglia) PET, deprenyl (astroglia) PET, tau PET (perfusion and retention) and CSF markers of inflammation (e.g. sTREM2) and neurodegeneration (NfL). Methods: PS19 mice receive chronic treatment with GV1001 over 5 months. Serial neuroimaging techniques, including PET scans targeting tau protein, microglial activation, and astrocytic responses, are employed to assess treatment effects in vivo (Fig. 1). Postmortem validation is performed using immunohistochemistry and biochemical methods, comparing treated mice to placebo and non-transgenic controls. Results: Preliminary findings,

expected to be presented at the event day, will provide insights into the drug's ability to modulate glial activity, restore homeostasis, and reduce tau pathology. Conclusions: This study highlights the potential of monitoring immunomodulatory strategies to address the complex interplay between chronic neuroinflammation and protein aggregation in ND. If successful, these findings could inform the development of novel therapeutic approaches for AD and related disorders, bridging the gap between preclinical research and clinical application.

85 Axolotl: ready-to-go program to achieve successful brain regeneration?

Zahra Yaghoobi, Sophie Antesberger, Alberto Joven Araus, Elif Eroglu, Jonas Huber, Martin Heß, Hans Straka and Rosario Sanchez-Gonzalez

> The differential regenerative capacity of vertebrates raises the question whether the ability to functionally regenerate is genetically hardwired but subsequently lost during evolution in amniote vertebrates such as mammals. Our group believes that the true regenerative potential of a given species is not fixed and is susceptible to regulation. The challenge resides in understanding the molecular and cellular basis of the biological process intended to be modified. Our research aims to identify and characterize the mechanisms that facilitate functional recovery following traumatic brain injury (TBI). To this end, we have developed a novel TBI model in the *Ambystoma mexicanum* (Axolotl), that resemble the classical stab wound injury previously used in zebrafish and rodents. Our findings demonstrate that Axolotl performs a "bona fide" scarless wound healing upon TBI, recapitulating the extraordinary regenerative capacity observed after spinal cord injury and limb amputation. Moreover, comparative analysis across amphibian species reveals that regenerative-competent salamanders (Axolotl and Pleurodeles) exhibit, under physiological conditions, a more permeable blood-brain barrier (characterized by increased paracellular diffusion and macropinocytosis) compared to *Xenopus*, a species with limited regenerative capacity. We hypothesize that the increased blood-brain barrier permeability provides a metabolic advantage during regeneration, rapidly increasing the energy supply, which potentially promotes cell survival and contributes to the scarless wound closure.

86 painless mediated stiffness-sensing of oviposition substrates in *Drosophila melanogaster*

Vijayaditya Ray, Lasse Bräcker, Alexandros Kourtidis, Charlotte Rosher, Gesa F. Dinges, Ansgar Büschges, Kevin M. Cury, Nicolas Gompel

>Evolutionarily, the distinct textural properties of fruits and the varying stages of ripening - present unique ecological niches that have shaped egg-laying decisions across various species of fruit flies. For instance, *D. melanogaster* choose to oviposit on soft, decaying fruits whereas *D. suzukii* prefer hard, ripe ones. How a female fly gauges the stiffness of a potential surface and then prioritizes it for oviposition, is still not very well understood. In this study, we systematically dissect the texture-sensing modality at body-part, sense-organ, neuro-genetic and molecular levels to elucidate how substrate-texture impacts oviposition decision-making in gravid females. Via a genetic screen, we identified the

TRPA channel painless, as a mechanoreceptor of textural stiffness. By combining organ-ablation experiments and genetically disrupting neurotransmission in a tissue-specific manner, we recognized tarsi in legs as the body-parts that accommodate painless-expressing sensory neurons, perceptive to surface stiffness. We next visualized painless expression in the tarsi using a fluorescent reporter and identified painless-expressing neurons innervating mechanosensory and chemosensory bristles, and campaniform sensilla. Silencing leg-specific mechanosensory neurons innervating campaniform sensilla, stationed dorsally at the joints, and ventrally positioned mechanosensory bristles, resulted in reduced oviposition preference for softer substrates, emphasizing their stiffness-sensing functions. Moreover, RNAi-induced downregulation of painless in mechanosensory neurons innervating campaniform sensilla and mechanosensory bristles also diminished the perception of softer substrates. By overexpressing specific pain isoforms that differ in both structure and function, we observed that pain60 isoform, lacking N-terminal ankyrin repeats, preferably acts as a molecular sensor for the transduction of light tactile information in pain-expressing leg neurons. Based on our results, we hypothesize that encountering a stiffer substratum, results in a strong dorsal compression of campaniform sensilla and possible bending of mechanosensory bristles in the legs, thus functioning as peripheral sensory detectors, that use specific isoforms of painless to receive and transduce substrate-stiffness information.

87 Neural Circuits Regulating Avoidance and Tracking

Weiqi Chen, Ines M.A. Ribeiro

>Animals survive and reproduce by responding appropriately to environmental stimuli, relying on rapid and accurate information processing for tasks such as predation, evasion, and courtship. In *Drosophila*, vision is a major sensory modality, constituting more than half of the inputs to the central brain. During social behavior, visual input enhances the probability of successful copulation by facilitating the close proximity to the mobile female. LC10a neurons mediate female tracking during courtship, whereas LC10d neurons mediate avoidance of visual objects deprived of a chemosensory signature. Both LC10a and LC10d project to the central unit of the anterior optic tubercle (AOTu), the largest retinorecipient area in the central brain that receives input from different neuron types and maintains the spatial organization of its inputs. How AOTu-output neural circuits orchestrate avoidance and tracking behaviors remains unknown. In this study, we explored the downstream targets of LC10a and LC10d in the AOTu to identify neuron types mediating avoidance or tracking. We employed single-pair behavior assays together with blocking neurotransmission of single AOTu-output neuron types with specific driver lines. We found that specific AOTu-output neuron types were required for avoidance or distinct steps of tracking, with the major phenotypic categories: early courtship initiation, increased latency to initiate courtship, and a modest decrease in female tracking. Our findings suggest the presence of intricate relationships in AOTu-output circuits that result in high robustness in the ability of the male to maintain close proximity to the female when courting on one hand, and more straightforward roles in the transition from avoidance to tracking on the other. The central unit of the AOTu thus appears to function as a hub processing visual cues subserving different behavioral modules in evasion and courtship.

88 Neuronal signatures of contextual decision-making in mouse prefrontal cortex and mediodorsal thalamus

Xuanyu Wang, Daniel Hähnke, Ajit Ranganath, Tobias W. Bernklau, Simon N. Jacob

>The ability to modify behavior in the face of varying task demands is a central component of cognitive flexibility. In situations with insufficient evidence, one should refrain from premeditated actions and collect additional evidence. To isolate a state of cognitive flexibility, we trained head-fixed mice on a two-alternative forced-choice task in which animals rotated a response ball to the left or right. An auditory context cue that was either predictive or not predictive for the upcoming instruction was followed by an auditory instruction cue signaling which side to rotate to. As expected, animals performed better and faster in predictive contexts than in the non-predictive context. Decomposition of sub-movements following the context cue (indexing the animals' 'state of mind') revealed a preparatory bias towards the animals' preferred response side before the actual instructed movement. We hypothesized that this behavioral strategy might draw upon executive centers of the prefrontal cortex (specifically, the prelimbic cortex, PL) and the interconnected mediodorsal thalamus (MD). Therefore, we extracellularly recorded single-neuron activity in these regions (1049 total units across 4 animals; 629 in PL and 420 in MD) as the animals performed the task. During the context epoch, non-predictive and non-preferred cues induced stronger neuronal responses than the preferred cue in both regions. In non-predictive trials, PL responded to the context cue earlier than MD, while MD responded earlier in predictive trials. During the instruction epoch, instruction to the preferred side elicited stronger activity than to the non-preferred side in both regions. MD encoded the instructed side more stably than PL but did not show context-dependent changes in neuronal responses as opposed to PL. Notably, neuronal functional connectivity in PL distinguished between contexts, while in MD it distinguished between response sides. These findings suggest that mice employ optimized asymmetric behavioral strategies, supported by prefrontal-driven executive control over thalamus-driven movement planning.

89 Generalizable emotion state inference from facial videography in mice

Yanko Arévalo, Stoyo Karamihalev, Nadine Gogolla

>Quantifying emotional expression in animal models is essential for behavioral neuroscience, yet standardized and scalable methods remain limited. We introduce MIME (MIME Interprets Mouse Emotions), a computational tool for extracting facial information from video recordings of mice across diverse experimental conditions. MIME operates robustly across variations in lighting, camera angles, and recording setups with minimal user intervention. By leveraging the stereotypy of mouse facial expressions, MIME provides a consistent and automated approach to tracking facial features relevant to emotion assessment. We present a large, multi-laboratory dataset encompassing a wide range of imaging conditions and emotionally salient stimuli, enabling robust model training and validation. MIME offers a scalable, high-throughput solution for researchers seeking to analyze facial dynamics in mice, facilitating standardized emotion research across laboratories.

90 Evolution of the olfactory system during the radiation of Heliconiini butterflies

Yi Peng Toh, Francesco Cicconardi, Richard M Merrill & Stephen H. Montgomery

>Sensory system evolution plays a crucial role in shaping species' interactions with their environment, yet the extent to which olfactory system diversity reflects ecological and evolutionary pressures at a macroevolutionary scale remains unclear. Here, we investigate the evolution of the olfactory system across the Heliconiini butterfly tribe, an ecologically diverse but closely related group. Using a comparative approach, we examined variation in antennal lobe morphology and its constituent structures, the glomeruli and antennal lobe hub, as well as olfactory receptor repertoires across species. We found that antennal lobe size variation is driven by independent shifts in glomerular and antennal lobe hub volumes, with species-specific differences occurring against a backdrop of broader phylogenetic stability. While no direct associations with ecological traits were observed, certain species showed large expansion in glomerular volume and olfactory receptor numbers, warranting further investigation into unmeasured ecological or behavioural factors. Additionally, comparisons between wild-caught and insectary-reared individuals revealed a surprising pattern of developmental plasticity, with antennal lobe hub volumes increasing and glomeruli volumes decreasing in captivity, highlighting the influence of environmental conditions on neural development. These findings suggest that olfactory evolution in Heliconiini is shaped by both evolutionary divergence and developmental plasticity, emphasizing the need to integrate phylogenetic, ecological, and developmental perspectives to fully understand sensory system adaptation.

91 Distractor Suppression Mechanisms in Differing Sensory Volatilities: Implications for Predictive Coding in Autism Spectrum Disorder

Yun Wai Foo, Sonja Coenen, Irene Sophia Plank, Zhuanghua Shi, Christine M. Falter-Wagner

>Background: The predictive coding theory proposes that the brain compares incoming sensory information with predictions based on experience (priors). If there is a mismatch between the prediction and sensory input, a prediction error occurs, which can be incorporated into prior adjustment. This incorporation can be influenced by volatility of the sensory environment. Studies have shown atypical predictive processing in individuals with autism spectrum disorder (ASD), affecting the balance of precisions placed on priors, sensory information, and prediction errors. However, the specific mechanism underlying this imbalance remains unclear. Studies involving probability learning of distractor suppression have shown that autistic individuals required increased effort in attaining target information when the target appeared in distractor-rare locations. This points to an overregulation of parameters in post-selective decision-making when attempting to control surprise. Method: We wanted to understand how autistic individuals implicitly learn to suppress irrelevant information in different volatilities. To achieve this, we adopted a behavioural paradigm – an additional singleton visual search task with pre-cue – where we manipulated sensory volatility by changing distractor prevalences. We measured behavioural responses and gaze patterns to gain insights into distractor interference and eye-movement patterns during visual search. Results: We found that controls implicitly learn the cue to suppress salient distractors. In contrast, the ASD group exhibited notable distractor interference, with

longer fixation durations to the distractor. The ASD group also showed an increased number of saccades, which mirrors the distractor interference effect, and increased target refixation. Implications: Drawing from presented findings enables us to understand the mechanisms underlying distractor suppression in sensory environments of differing volatilities. On the backdrop of our results, we suggest an autistic signature characterised by attenuated disengagement from salient sensory information and, maybe as a compensation mechanism, a more conservative decision threshold for target identification.

92 Cell-cell communication in retinal homeostasis and disease

Zeynep Okutan, Michelle Jentzsch and Susanne F. Koch

>Retinitis pigmentosa (RP) is a group of inherited retinal disorders characterized by the progressive degeneration of photoreceptor cells, leading to vision loss. Rod cells are primarily affected by mutations in rod-specific genes, such as Phosphodiesterase 6b (PDE6B). In an RP mouse model (Pde6bSTOP/STOP), PDE6B expression was partially rescued via Pax6αCre, preventing rod degeneration only in the retina's periphery. Pax6 is a transcription factor expressed in retinal progenitor cells at embryonic stages in the retina's periphery. The Cre recombination was visualized using ROSAnT-nG or ROSAmT-mG mice. To confirm the effects of the partial rescue, immunofluorescence, *in situ* hybridization, qRT-PCR, and western blotting techniques were employed. It was observed that the PDE6B expression was progressively extended from the peripheral to the central retina at both RNA and protein levels. Due to these findings, this study investigates whether material transfer between photoreceptor cells contributes to retinal function and disease progression. Accordingly, potential mechanisms and transport pathways will be analyzed to gain insights into the role of the communication between photoreceptors in retinal homeostasis. As potential means for material transfer, extracellular vesicles (EVs) will be investigated by isolating them for characterization and cargo analysis at DNA, RNA, and protein levels. Moreover, EV release and uptake mechanisms within the retinal environment will be studied to better understand the role of EV-based communication. An important question to be answered is whether the transfer happens in a way that meets the specific needs of recipient cells.

93 All-optical exploration of emotion state representations in the mouse insular cortex

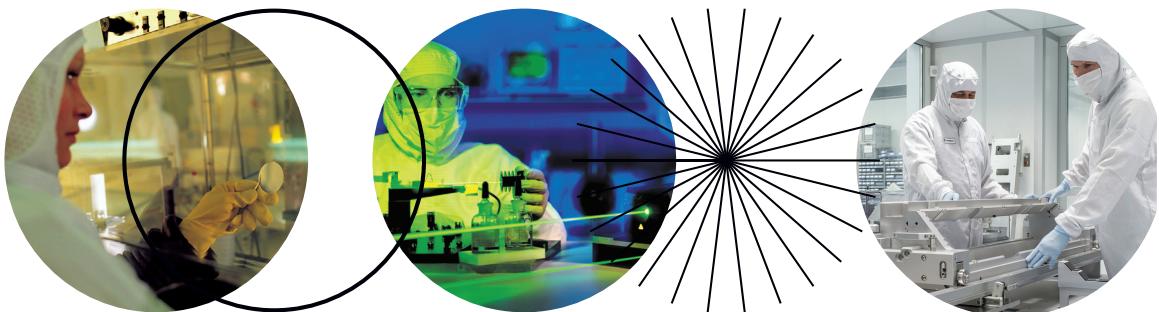
Lisa Rottenfußer, Stoyo Karamihalev and Nadine Gogolla

>Emotions are essential functional states that play a crucial role in adaptive behavior. They are a feature across humans and other animals. Our research focuses on exploring how emotional states are represented within the neural circuits of the mouse insular cortex (IC). The IC is a highly interconnected region of the brain, adept at integrating sensory information with interoceptive signals, making it ideally suited for regulating emotions. In our study, we employ an all-optical approach to dissect the neural underpinnings of emotional states. By combining targeted optogenetic manipulation with functional calcium imaging, we aim to monitor and elucidate the causal roles of cortical representations in emotion regulation. Furthermore, we evaluate emotional states through their observable behavioral manifestations, namely facial expressions, body posture, and changes in pupil size (pupillometry). To

experimentally evoke various emotional states—such as pleasure, disgust, anxiety, and pain—we expose mice to stimuli that are emotionally salient. Here, we share preliminary findings from an experiment designed to assess the impact of inhibiting the anterior insular cortex (aIC) on the expression of an emotion state. Following the presentation of emotionally salient stimuli, we inhibited the aIC at different stages of the emotional response while closely observing the animals' behaviors.

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