# IZN Retreat 2023
# Kloster Schöntal
# July 16-17

IZN

Interdisziplinäres Zentrum für
Neurowissenschaften der
Ruprecht-Karls-Universität Heidelberg


# Program and Abstract Book

## Sunday, July 16

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|---|---|---|---|
| **Welcome Reception** | **10:00** | Banquet hall | |
| **Welcome Address** | 10:20 | **Hilmar Bading**<br>Managing Director of the IZN, Heidelberg University<br>Heidelberg, Germany | |
| **Introduction** | 10:30 | **Andreas Draguhn**<br>Heidelberg University<br>Heidelberg, Germany | |
| **Session 1**<br>Chairs: Jonas Schimmer and Max Ingo Thurm | 10:40 | **Matthew Larkum**<br>Humboldt University<br>Berlin, Germany | *What's in a spike?* |
| | | **Memming Park**<br>Champalimaud Foundation<br>Lisbon, Portugal | *Persistent learning signals and memory in recurrent networks* |
| **Session 2**<br>**"Poster Jam"**<br>Chair: Nathalie Couturier | 11:50 | **Quirin Krabichler**<br>AG Grinevich | *Oxytocin action in the periaqueductal gray is involved in social habituation by heterospecific play in rats* |
| | | **Janina Kupke**<br>AG Oliveira | *DNA methylation promotes memory persistence by facilitating systems consolidation and cortical engram stabilisation* |
| **Lunch** | **12:20** | | |
| **Free Time** | **Canoeing** (meet at 13:15 at the parking lot next to the former train station)<br>*or*<br>**Walk 'n' Talk**<br>*or*<br>**Guided tour through the monastery** (meet at 14:00 at the baroque staircase) | | |
| **Dinner** | **18:00** | | |
| **Session 3**<br>**Plenary Lecture**<br>Chair: Raquel Perez Fernandez | 19:15 | **Pascal Fries**<br>Ernst Strüngmann Institute<br>Frankfurt, Germany | *Brain rhythms serve the definition and learning of functional neuronal networks* |
| **Posters & Drinks** | 20:15 | Rooms 203, 204, 219, and the hallway | |

## Monday, July 17

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|---|---|---|---|
| **Breakfast** | **7:00** | *Please check out of your room prior to the first session, if possible.* | |
| **Session 4**<br>Chairs: Emilio Isaías-Camacho and Max Ingo Thurm | 9:00 | **Rodrigo Quian Quiroga**<br>University of Leicester<br>Leicester, United Kingdom | *A unique coding of memories in the human brain* |
| | | **Simon Jacob**<br>Technical University of Munich (TUM)<br>Munich, Germany | *The stuff of thought: neuronal representations, neuronal implementations, and neuronal revelations* |
| **Posters & Coffee** | **10:10** | Rooms 203, 204, 219, and the hallway | |
| **Session 5**<br>Chair: Janina Kupke | 11:15 | **Eisuke Koya**<br>University of Sussex<br>Sussex, United Kingdom | *The modulation of cue-evoked food seeking: Prefrontal cortex ensemble mechanisms* |
| **Meetings** | 11:50 | IZN Investigator Meeting: Room TBA<br>Students' Meeting / Science Pub Quiz: Banquet Hall | |
| **Lunch** | **12:50** | | |
| **Session 6**<br>Chair: Danny Baltissen | 14:15 | **Michael Pecka**<br>Ludwig Maximilian University (LMU)<br>Munich, Germany | *Dynamic sound source presentations during active sensing* |
| **Awards Ceremony** | 14:50 | **IZN Students' Poster Prize**<br>*Recipient TBA*<br>Laudatio: Omar Ramirez<br><br>**Foundation BrainAid IZN Master's Award**<br>*Rangeet Manna* (AG Schlesiger)<br>Laudatio: Christoph Schuster<br><br>**Foundation Brain Aid IZN Dissertation Award**<br>*Jose Ricardo da Cruz Vieira* (AG Ruiz de Almodóvar)<br>Laudatio: Andreas Draguhn<br><br>**IZN / Chica and Heinz Schaller Young Investigator Neuroscience Award**<br>*Alexander Hodapp and Martin Kaiser* (AG Both)<br>Laudatio: Ana Oliveira<br><br>**Neuroscience Art Contest Winner**<br>*Recipient TBA*<br>Laudatio: Anna Hertle | |
| **Group Picture** | 15:15 | baroque staircase | |
| **Coffee** | **15:25** | | |
| **Session 7**<br>Chair: Debanjan Chowdhury | 15:55 | **Konrad Kording**<br>University of Pennsylvania<br>Philadelphia, Pennsylvania, USA | *Why do we love the word "representation" so much?* |
| **Closing Remarks** | 16:30 | **Hilmar Bading**<br>Managing Director of the IZN, Heidelberg University<br>Heidelberg, Germany | |
| **Bus Departure** | 17:00 | from the parking lot next to the train station | |

# Poster Presentations

| Nr. | Authors | Group | Title |
|---|---|---|---|
| 1 | **Darshana Kalita**, Amit Agarwal | Agarwal | Analysis of glial mosaics in a mouse model of X-linked disorder |
| 2 | **Ram Dereddi**, Carolin Wust, Irena Dikic, Darshana Kalita, Anthony Hill, Annarita Patrizi, Angela Wirth, Wiebke Möbius, Marc Freichel, Amit Agarwal | Agarwal | OCaR1 is a novel regulator of myelination in the central nervous system |
| 3 | **Pascal Klein**, Beate Throm, Kevin Allen | Allen | Contribution of head-direction cells to path integration within grid cell networks |
| 4 | **Felix Jose Kavarayil**, Kevin Allen | Allen | Grid cell integrity as a neural resource for navigation and episodic memory |
| 5 | **Zihong Zhang**, Celia García Vilela, Anna M. H. Hertle, Yan Jing, Hilmar Bading | Bading | Unraveling the role of calpain and the NMDAR/TRPM4 complex in NMDA-induced neurotoxicity |
| 6 | **Aisha R. Ravenhorst**, Anna M. H. Hertle, Hilmar Bading | Bading | Influence of nuclear calmodulin buffering on the generation of calcium signals in striatal neurons |
| 7* | **Weixia Duan**, Cong Liu, Jie Zhou, Qin Yu Yu Duan, Tian Zhang, Yuanyuan Li, Guanyan Fu, Yapei Sun, Jiacheng Tian, Zhiqin Xia, Yingli Yang,Yongseng Liu, Shangcheng Xu | Bading | Upregulation of mitochondrial calcium uniporter contributes to paraquat-induced neuropathology linked to Parkinson's disease via imbalanced OPA1 processing |
| 8 | **Berin Boztepe**, Jessica Hunger, Manuel Fischer, Yannik Streibel, Jonas Scheck, Dennis Agardy, Kianush Karimian-Jazi, Hannah Fels-Palesandro, Ina Weidenfeld, Sabine Heiland, Martin Bendszus, Michael Platten, Katharina Schregel, Michael O. Breckwoldt | Breckwoldt | Assessing the immune microenvironment in glioma models by correlative high field MRI and optical microscopy |
| 9* | Jessica Hunger, Ina Weidenfeld, Katharina Schregel, Berin Boztepe, Kianush Karimian-Jazi, Lennart Heinz, Manuel Fischer, Michael Platten, Martin Bendszus, **Michael O. Breckwoldt** | Breckwoldt | Correlated MRI and light sheet microscopy to dissect immune cell dynamics of the glioma microenvironment during immunotherapy |
| 10 | **Märt Rannap**, Andreas Draguhn, Alexei V. Egorov | Draguhn | Hippocampal output signals to medial entorhinal cortex layer VI are preferentially mediated by the ventral hippocampus |
| 11 | **Matthias Klumpp**, Lee Embray, Justus Simon, Andreas Draguhn, Martin Both | Draguhn | Syntalos: A software for precise simultaneous multi-modal data acquisition and closed-loop interventions |
| 12 | **Zeynab Razzaghpanah**, Zahra Monfared, Martin Fungisai Gerchen, Georgia Koppe, Daniel Durstewitz | Durstewitz | Multimodal assesment of nonlinear brain activity dynamics with fMRI and MEG |
| 13 | **Angela Serian**, Jamila Andoh, Simon Desch, Herta Flor | Flor | Changes in brain activity as possible predictors for phantom limb pain in leg amputees – a longitudinal pilot study |
| 14 | **Mina Kandić**, Francesca Zidda, Katrin Usai, Martin Löffler, Michaela Ruttorf, Frauke Nees, Herta Flor | Flor | The superior longitudinal fasciculus is a biomarker of resilience to chronicity in back pain |
| 15 | **Zhou Zhou**, Annette Loeffler, Stefano Silvoni, Dieter Kleinböhl, Herta Flor | Flor | Association between tactile processing and memory performance in participants with mild cognitive impairment |
| 16 | **Jonas Schimmer**, Stephanie Küppers, Julia Lebedeva, Marina Eliava, Valery Grinevich | Grinevich | Oxytocin facilitates sexual partner preference in male rats acting at the ventral hippocampus |
| 17 | **Stephanie Küppers**, Arthur Lefevre, Alan Kania, Marina Eliava, Valery Grinevich | Grinevich | An oxytocin-sensitive cortical circuit facilitating sociability of female rats |
| 18* | **Quirin Krabichler**, Eduard Maier, Leonie Bechthold, Hshin-Jui Liu, Ana Zovko, Michael Brecht, Shimpei Ishiyama, Valery Grinevich | Grinevich | Oxytocin action in the periaqueductal gray is involved in social habituation by heterospecific play in rats |
| 19 | **Ana Zovko**, Elena Munoz, Daniel Sierra Garcia, Sandra Horschitz, Quirin Krabichler, Philipp Koch, Valery Grinevich | Grinevich / Koch | Generation of iPSCs derived Oxytocin specific hypothalamic organoids and transplantation into rat brains |
| 20 | **Josephine Timm**, **Nadin Mari Saluti**, Filippo Heimburg, Tim Kreuziger, Matthias Klumpp, Lee Embray, Thomas Kuner, Alexander Groh | Groh | The role of the posterior thalamic nucleus in somatosensory processing in freely moving mice |

| Nr. | Authors | Group | Title |
|---|---|---|---|
| 21 | Katharina Ziegler, **Ross Folkard**, Antonio Gonzalez, Jan Burghardt, Sailaja Antharvedi-Goda, Jesus Martin-Cortecero, Emilio Isaías-Camacho, Sanjeev Kaushalya, Linette Liqi Tan, Thomas Kuner, Claudio Acuna, Rohini Kuner, Rebecca Audrey Mease | Groh | Primary somatosensory cortex bidirectionally modulates sensory gain and nociceptive behavior in a layer-specific manner |
| 22 | **Isaias-Camacho Emilio Ulises**, Martin-Cortecero Jesus Maria, Groh Alexander | Groh | A cortico-collicular pathway for defence modulation |
| 23 | **Diptyajit Das**, Marnie E. Shaw, Matti S. Hämäläinen, Andrew R. Dykstra, Laura Dolla, and Alexander Gutschalk | Gutschalk | A role for retro-splenial cortex in the task-related P3 network |
| 24 | **Laura Doll**, Andrew R. Dykstra, Alexander Gutschalk | Gutschalk | Perceptual awareness of near-threshold tones scales gradually with pupil dilation and auditory cortex activity |
| 25 | **Amr Elgez**, Andrea Lewen, Babak Khodaie, Lennart Soeder, Oliver Kann | Kann | Exploring the mechanisms underlying microglia-mediated inflammatory neurodegeneration |
| 26 | **Lennart Söder**, Babak Khodaie, Amr Elgez, Andrea Lewen, Oliver Kann | Kann | Dissecting the roles of lactate as energetic fuel and signaling molecule in neuronal network activity |
| 27* | **Babak Khodaie**, Elke Edelmann, Volkmar Leßmann | Kann | Distinct GABAergic modulation of spike timing-dependent plasticity in mouse CA1 pyramidal cells across the longitudinal axis of the hippocampus |
| 28 | **Marina R. Hesse**, Steffen Sass, Maja Klevanski, Thomas Kuner | Kuner, T. | Uncovering the molecular active zone nano-organization of the mammalian central synapse using multiplex 3D – super resolution microscopy |
| 29 | **Ivo Sonntag**, Avi Adlakha, Thomas Kuner | Kuner, T. | Activity of the neurons in the infralimbic cortex of rats during reward seeking |
| 30 | **Catello Guida**, Fabio Marsoner, Anne Hoffrichter, Philipp Koch, Julia Ladewig | Ladewig | Unraveling the functions of the transcription factor TBR2 In human neurodevelopment |
| 31 | **Annasara Artioli**, Lea Zillich, Eric Poisel, Fabio Marsoner, Anne Hoffrichter, Julia Ladewig, Philipp Koch | Ladewig | Human cortical brain organoids to study adaptive changes in alcohol addiction |
| 32 | **Raquel Pérez Fernández**, Marco Siekmann, Annasara Artioli, Philipp Koch, Julia Ladewig | Ladewig | Modeling reward and addiction: development of an *in vitro* reward neurocircuitry |
| 33 | **Yassin Harim**, Chunxuan Shao, Heike Alter, Changwen Wang, Yue Zhuo, Gözde Bekki, Asya Sayin, Nadja Stöffler, Giulia Di Muzio, Katharina Hartmann, Anna Neuerburg, Weijun Feng, Hai-Kun Liu | Liu | The chromatin remodeler Chd7 acts as a chromatin hub coordinating differentiation of multiple cell lineages during hippocampal development |
| 34 | **Jana Franziska Tegethoff**, Moritz Mall | Mall | Active maintenance of neuronal cell fate prevents brain dysfunction |
| 35 | **Jule Truberg**, Jana Tegethoff, Bettina Weigel | Mall | Loss of neuronal cell fate and function in pluripotent stem cell-derived neurons from MYT1L syndrome patients |
| 36 | **Martina Braun**, Lukas Kremer, Santiago Cerrizuela, Simon Anders, Ana Martin-Villalba | Martin-Villalba | Detection of differentially methylated regions in single-cell bisulfite sequencing data by scbs diff |
| 37 | **Merve Akan**, Ivan Skorodumov, Marcus Meinhardt | Meinhardt | Psilocybin tolerance disrupts hallucinogenic pause and quipazine-induced head twitches |
| 38 | **Ivan Skorodumov**, Yelena le Prieult, Merve Akan, Marcus Meinhardt | Meinhardt | Ibogaine restores control over compulsive alcohol drinking in addicted rats |
| 39 | **Sofiya Zbaranska**, Debanjan Chowdhury, **Katharina Held**, Duncan Archibald Allan MacLaren, Hannah Monyer | Monyer | Characterization of septal somatostatin-positive neurons and their projections to the hippocampus |
| 40 | **Debanjan Chowdhury**, Duncan MacLaren, Beate Throm, Magdalene Schlesiger, Nina Bieber, Hannah Monyer | Monyer | Identifying mechanisms involved in acute alcohol-induced amnesia |
| 41 | **Danny Baltissen**, Charlotte S. Bold, Lena Rehra, Marija Banicevic, Justus Fricke, Jennifer Just, Susann Ludewig, Christian Buchholz, Martin Korte, Ulrike C. Müller | Müller | APPsα rescues CDK5 and GSK3β dysregulation and restores normal spine density in Tau transgenic mice |
| 42 | **Lena Rehra**, Lelia Wagner, Vicky Steubler, Tobias Köthe, Philipp Uhl, Gundula Braun, Gert Fricker, Christian Buchholz and Ulrike Müller | Müller | Investigating the therapeutic potential of the APPsα-derived CTα16 peptide |

| Nr. | Authors | Group | Title |
|---|---|---|---|
| 43 | **Lara Kilian**, Marija Banicevic, Susanne Erdinger, Dominique Fäßler, Verena Bengelsdorff, Ulrike Müller | Müller | Characterization of novel APP-knockin mutants lacking important functional domains for secretion or cell adhesion |
| 44 | **Verena Bengelsdorff**, Lena Rehra, Dominique Fäßler, Susanne Erdinger, Lara Kilian, Danny Baltissen, Martina Braun, Ulrike C. Müller | Müller | Establishing an injection protocol for tamoxifen-inducible knockdown of the amyloid precursor protein (APP) gene family in mice |
| 45 | **Dominique Fäßler**, Susanne Erdinger, Vicky Steubler, Michaela K Back, Susann Ludewig, Max Richter, Kang Han, Lutz Slomianka , Irmgard Amrein, Jakob von Engelhardt, David P Wolfer, Marc Busche, Martin Korte & Ulrike C Müller1 | Müller | Characterization of mice that lack APP family members |
| 46 | **Stefanos Loizou**, Harrison Gabel, Ana M.M. Oliveira | Oliveira | Characterization and reversibility of cognitive deficits in a mouse model of Tatton-Brown-Rahman syndrome |
| 47 | **Janina Kupke**, Stefanos Loizou, Carsten Sticht, Ana MM Oliveira | Oliveira | DNA methylation promotes memory persistence by facilitating systems consolidation and cortical engram stabilisation |
| 48* | **Janina Kupke, Lisa M. Spänig** | DNO | Introduction to the Deutsche Neurowissenschaften-Olympiade (DNO) and all the ways that passionate neuroscientists like YOU can contribute |
| 49 | **Lisa M. Spänig**, Robert Reinhardt, Sinem Saka, Stefan M. Pfister, Lena M. Kutscher | Kutscher | Investigating the development of unipolar brush cells, a glutamatergic interneuron of the cerebellum and cell-of-origin of medulloblastoma |
| 50 | **Jing Chen**, Yifeng Zheng, Bahardokht Tolou-Dabbaghian, Melanie Motsch, Norbert Weidner, Radhika Puttagunta | Puttagunta | The modulatory effects of activity-based interventions on spinal cord injury-induced neuropathic pain: exploring sex differences |
| 51 | **Bahardokht Tolou-Dabbaghian**, Jing Chen, Jarred Griffin, Melanie Motsch, Norbert Weidner, Radhika Puttagunta | Puttagunta | The role of the α2-δ2 subunit of the voltage-gated calcium channel in nociceptors in spinal cord injury-induced neuropathic pain in mice |
| 52 | **Sarah Hörner**, Nathalie Couturier, Daniele Gueiber, Roman Bruch, Mathias Hafner, Rüdiger Rudolf | Rudolf | Human iPSC and 3D-bioprinting technologies for the development of neuromuscular tricultures including glia cells |
| 53* | **Nathalie Couturier**, Sarah Janice Hörner, Mathias Hafner, Rüdiger Rudolf | Rudolf | Towards a human iPSC-derived model to address neuromuscular development and disorder |
| 54 | **Julia Dyckow**, Celine Geywitz, Torben Ruhwedel, Hannah Kapell, Wiebke Möbius, Klaus-Armin Nave, Lucas Schirmer | Schirmer | Investigating the function of Piezo proteins in the oligodendrocyte lineage |
| 55 | **Rangeet Manna**, Duncan Archibald Allan MacLaren, Magdalene Isabell Schlesiger | Schlesiger | Lateral entorhinal spatial coding in a conditioned place preference task |
| 56 | **Kalaivani Manibarathi**, Tam Pham, Emma Katharina Fürtsch, Sophie Schäfer, Katrin Bratl, Maike Nagel, Klaus Dittmann, Rebecca Schüle | Schüle | RNA therapies for ultrarare diseases: development of a mutation-specific ASO therapy for POLR3A-associated spastic ataxia |
| 57 | **Francesco Giannone**, Arian Hach, Magda Chrószcz, Marion Friske, Marcus Meinhardt, Rainer Spanagel, Wolfgang H. Sommer, Anita C. Hansson | Spanagel | Generalized habitual tendencies in alcohol dependent rats |
| 58 | **Armin Drusko**, Julian Reichert, Prof. Dr. Jonas Tesarz | Tesarz | Computational modeling of aberrant pain perception within a Bayesian framework |
| 59 | **Cedric Stahl**, Christian Thiel | Thiel | Towards understanding the impact of ALG5 impairment on protein N-glycosylation |
| 60 | **Giulia Di Muzio**, Hsin-Jui Lu, Franciscus van der Hoeven, Brittney Armstrong, Lorenzo Corazzi, Yassin Harim, Li-Chin Wang and Pei-Chi Wei | Wei | Cycling plasticity of neuronal progenitor cells during neuronal development |
| 61 | **Isabel Loss**, Rüstem Yilmaz, Rosanna Parlato, Carsten Sticht, Babak Loghmani, Axel Freischmidt, Johannes Wilbertz, Loic Cousin, Philipp Koch, Jochen Weishaupt | Weishaupt | Modelling ALS caused by KIF5A mutations in patient-derived motor neurons |
| 62 | **Ketrin Dimco**, Rosanna Parlato, Rüstem Yilmaz, Jochen Weishaupt | Weishaupt | Myorg protein quality control dysfunction in primary familial brain calcification |
| 63* | **Alexander Dieter**, Lena Eschholz, Chantal Wissing, Maxime Maheu, Simon Wiegert | Wiegert | Investigating the neuromodulation of learning and memory |

| Nr. | Authors | Group | Title |
|---|---|---|---|
| **64*** | **Andrey Formozov**, **Alexander Dieter**, J. Simon Wiegert | Wiegert | A flexible and versatile system for multi-color fiber photometry and optogenetic manipulation |
| **65*** | **Andrey Formozov**, J. Simon Wiegert | Weigert | Neurobiological computing and all-optical brain interfacing |
| **66** | **Lena Eschholz**, Chantal Wissing, Maxime Maheu, Fabio Morellini, Alexander Dieter, J. Simon Wiegert | Wiegert | Targeting noradrenergic neurons of the locus coeruleus: A comparison of model systems and strategies |
| **67** | **Sophie Stichert**, Jürgen Haas, Sven Jarius, Brigitte Fritz, Katharina Mattes, Mirjam Korporal-Kuhnke, Brigitte Wildemann | Wildemann | Impaired X-chromosomal inactivation—a key mechanism for female predisposition to MS and NMOSD? |
| **68** | **Viktoria Greeck**, Cornelia Würthwein, Richard Fairless, Jürgen Haas, Brigitte Wildemann | Wildemann / Fairless | Reduced Treg suppressive capacity exacerbates B cell dysfunction in Multiple Sclerosis |
| **69*** | **Matthia A. Karreman**, Nils R. Hebach, Varun Venkataramani, Chanté D. Mayer, Linh C. Nguyen, Cedric Tehranian, David Hausmann, Lukas Geckeler, Theresa Kraft, Michael Seifert, Dana Westphal, Thomas Kuner, Wolfgang Wick, Frank Winkler | Winkler | Cancer networks in brain metastases |
| **70*** | Anne K. Thomann, **Mike M. Schmitgen**, Kristina Szabo, Matthias P. Ebert, Wolfgang Reindl, Robert C. Wolf | Wolf | Structural correlates of extraintestinal symptoms in Crohn's disease in active and remitted patients |
| **71** | **Yéléna Le Prieult**, Marie-Luise Otte | Wolf | Structural integrity of the language network in patients with borderline personality disorder with and without auditory verbal hallucinations |
| **72** | **Marton Istvan Molnar**, J. Simon Wiegert, Andrey Formozov | Wiegert | New optical approaches for the manipulation and read-out of hippocampal circuits at multiple time scales |
| **73** | **Maryam Najafian Jazi**, Adrian Tymorek, Ting-Yun Yen, Felix Jose Kavarayil, Moritz Stingl, Sherman Richard Chau, Benay Baskurt, Celia García Vilela and Kevin Allen | Allen | Hippocampal firing fields anchored to a moving object predict homing direction during path-integration-based behavior |

*** Posters marked with an asterisk do not qualify for the IZN students' poster prize.**

# Poster Abstracts

**1** **Darshana Kalita**, Amit Agarwal

### Analysis of glial mosaics in a mouse model of X-linked disorder

X-chromosome inactivation (XCI) is an epigenetic process unique to female mammals occurring early during embryonic development and creates a mosaic of cells expressing either the maternal or paternal X-chromosome. Females heterozygous for genes leading to X-linked neurodevelopmental disorders, such as Fragile X Syndrome (FXS), exhibit a variety of phenotypes, with much of the variability presumably due to variability in the ratio and location of cells expressing the mutant vs wild type (WT) X-chromosome. FXS is one of the most common causes of intellectual disability, implicated by the epigenetic silencing of the FMR1 gene, usually severely affecting males. FXS carrier females exhibit variable and milder disease symptoms due to mosaic neural circuits generated by XCI. To investigate the pathophysiology of mosaic neural circuits in X-linked genetic disorders we have developed a Cre-loxP based dual-color X-linked cell labelling system in mice enabling us to fluorescently label WT and mutant cells in the brain of FMR1+/- heterozygous female mice *in vivo*. Using our dual-colored model, we focused on studying the role of oligodendrocyte lineage cells (OLCs) in the pathophysiology of FXS. We performed extensive *in vivo* fate-mapping studies on the differentiation, maturation and proliferation patterns of OLCs, and the functional and structural characterization of mature oligodendrocytes in the heterozygous female brain as well as in the homozygous WT and mutant male brain. Our results suggest that WT and mutant OLCs in the heterozygous FXS female brain might exhibit reciprocal adaptive responses– i.e., mutant OLCs adapt in response to WT OLCs and vice versa.

**2** **Ram Dereddi**, Carolin Wust, Irena Dikic, Darshana Kalita, Anthony Hill, Annarita Patrizi, Angela Wirth, Wiebke Möbius, Marc Freichel, Amit Agarwal

### OCaR1 is a novel regulator of myelination in the central nervous system

OCaR1 (Organellar Calcium Regulator1), also known as Tmem63a, is widely expressed in several organ systems. OCaR1 is thought to be a mechanotransduction channel, which on activation can conduct cations such as calcium (Ca2+). Also, OCaR1 has been shown to be expressed on the membranes of lysosomes and secretory vesicles, and potentially regulate Ca2+ signals in these intracellular compartments. In this study, we characterized the expression of OCaR1 and its function in the mouse central nervous system (CNS) using transgenic mouse lines expressing endogenous OCaR1 protein tagged with enhanced yellow fluorescent protein (OCaR1-eYFP), and OCaR1 null mutant (OCaR1-/-) mice. Our extensive immunohistochemical analysis revealed OCaR1 is mainly expressed by oligodendrocytes in both grey- (motor cortex) and white-matter (corpus callosum), with almost no expression in neurons and astrocytes. In OCaR1-/- mice, we observed severe developmental hypomyelination at postnatal days (P) 11, which persisted at the juvenile stage (P21) but was resolved while mice reached adulthood (P35). A detailed electron microscopic analysis of axonal myelination in the motor cortex and corpus callosum, revealed aberrant myelination of small caliber axons, and hypomyelination of large caliber axons, indicating that OCaR1 might play a crucial role in fine-tuning myelin sheath thickness on individual axons. Next, to test whether ultrastructural deficits in myelin could result in motor dysfunction, we performed a systematic motor behavior analysis in adult (7-8 weeks old) OCaR1-/- mice. Although, OCaR1-/- mice didn't have any major movement dysfunction (e.g., rotarod test and beam balance test), mutants exhibited deficits in fine motoric functions such as gait, motor coordination, and grip strength. To gain mechanistic insights into intracellular signaling regulated by OCaR1 in oligodendrocytes, we performed bulk-RNA sequencing on enriched oligodendrocytes isolated from the cortex of OCaR1-/- and littermate controls at P11 and P35. Our preliminary analysis of differentially expressed genes between P11 and P35 stage indicates that OCaR1 might regulate secretory, and vesicular transport pathways in oligodendrocytes. To identify the key mechanism by which OCaR1 can regulate the process of myelination in the brain, at present, we are preforming a thorough immunocytochemistry and calcium imaging experiments on oligodendrocytes cultures derived from OCaR1-/- and control mice. We believe that our study has an immense potential to decode the underlying cellular mechanism by which loss-of-function mutation of OCaR1 in patients leads to transient hypomyelination. In the long-run we foresee that our study can provide novel targets for developing a treatment strategy for these patients.

**3** **Pascal Klein**, Beate Throm, Kevin Allen

### Contribution of head-direction cells to path integration within grid cell networks

The neuronal representation of space and one's own current position is processed by cells, referred to as spatially selective cells, which are active as a function of an animal's position or orientation. Examples are head-direction cells (HD) in the postsubiculum (POS) coding for the animal's head direction, or grid cells (GC) in the medial entorhinal cortex cortex (MEC) firing at vertices of equilateral shaped triangles. These two navigational cell systems share geometric properties to encode for orientation of the ambient space. However, it still remains unclear in how far they are functionally connected. In this project, we study whether the preferred firing direction of POS head-direction cells and the orientation of MEC grid cells is coupled. Exposing the animal to a series of different environments equipped with visual landmarks

caused a global remapping of GC and reanchoring of HD in every transition which we could show to be each explained by a simultaneous rotation of GC and HD. This remapping and reanchoring is stable in so far as reverting to the initial environment caused a resetting to the initial state of HD and GC activity. In darkness, both the grid pattern and head-direction sensitivity is disrupted, as no visual cues are available and relying on only self-motion cues causes accumulation of error. On a higher temporal resolution during darkness, we want to demonstrate that these cell systems remain coupled despite not coding for the actual orientation.

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**4** **Felix Jose Kavarayil**, Kevin Allen

### Grid cell integrity as a neural resource for navigation and episodic memory

Spatial navigation is a vital cognitive process underlying individuals' ability to navigate their physical environment. This research project focuses on investigating the integrity of grid cells, specialized neurons in the entorhinal cortex, as a neural resource for navigation and memory, with a particular emphasis on understanding individual differences. The study aims to achieve three key objectives: (1) identifying critical inputs maintaining grid cell stability, (2) examining the impact of replay events during rest on grid cell integrity, and investigating manipulations targeting replay events to enhance both grid cell integrity and memory performance, and (3) examining the relationship between grid cell integrity and the preservation of cognitive abilities in older adults, termed SuperAgers. To assess the influence of visual landmarks on grid cell stability and variability, a novel behavioral task is being developed. This task utilizes a custom-built instrument controlled through a robotic operating system, ensuring precise control and automation. Rodent electrophysiology serves as the primary method for assessing grid cell integrity, measuring changes in mean orientation stability and the strength of the characteristic hexagonal firing pattern. The outcomes of this interdisciplinary research provide valuable insights into the neural mechanisms underlying spatial navigation and episodic memory. These findings have implications for enhancing navigation skills and preserving cognitive function in aging populations. Additionally, the development of a new behavioral task and a custom-built instrument offers controlled and automated approaches to investigate the impact of visual landmarks on grid cell activity, enhancing research methodology. This research project contributes to a deeper understanding of spatial navigation, grid cell function, and their significance in cognitive processes. By addressing individual differences and leveraging technological advancements, it opens novel avenues for investigating and improving spatial navigation abilities, with potential applications in translational approaches for human studies. Keywords: spatial navigation, episodic memory, grid cells, individual differences, neural integrity, SuperAgers, behavioral task, electrophysiology, visual landmarks.

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**5** **Zihong Zhang**, Celia García Vilela, Anna M. H. Hertle, Yan Jing, Hilmar Bading

### Unraveling the role of calpain and the NMDAR/TRPM4 complex in NMDA-induced neurotoxicity

N-methyl-D-aspartate receptors (NMDARs) are glutamate-gated calcium-permeable channels that are composed of two GluN1 subunits and two GluN2 subunits. NMDARs dependent excitotoxicity depend on the location of NMDARs: stimulation of synaptic NMDARs results in the formation of a neuroprotective ‘shield,’ whereas stimulation of extrasynaptic NMDARs promotes cell death. The previous study of our lab uncovers transient receptor potential melastatin 4 (TRPM4) expressed at the extrasynaptic site can bind to the NMDA receptors leading to cell death. We found extrasynaptic NMDARs activation leads to cleavage of GluN2A and GluN2B subunits, while GluN1 subunits and TRPM4 remain unaffected. Here, we propose the existence of a third protein that can only lead to GluN2A and GluN2B cleavage when activated extrasynaptic NMDARs and focus on m-calpain as a candidate. Calpains, non-lysosomal cysteine proteases, play essential roles in brain function: activation of m-calpain downstream of extrasynaptic NMDARs induces neurotoxicity. Our findings demonstrate that inhibiting calpain activity via inhibitors or gene knockdown effectively prevents NMDARs cleavage. Additionally, disrupting the NMDAR/TRPM4 complex impedes NMDARs cleavage and reduces calpain-mediated breakdown product generation. Furthermore, knockdown of m-calpain, but not μ-calpain, protects hippocampal neurons from NMDA-induced loss of mitochondrial membrane potential. Intriguingly, in NMDA-induced cell death assay (24 hours), this neuroprotective effect is limited to the early 12-hour window, as its effectiveness diminishes thereafter. These findings highlight the critical role played by the interplay between calpain and the NMDAR/TRPM4 complex in NMDA-induced neurotoxicity.

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**6** **Aisha R. Ravenhorst**, Anna M. H. Hertle, Hilmar Bading

### Influence of nuclear calmodulin buffering on the generation of calcium signals in striatal neurons

Addictive drugs like cocaine are known to hijack the brain’s reward processing circuitry and can induce persistent changes in excitatory transmission, also referred to as drug-evoked synaptic plasticity, resulting in behavioral changes. Synaptic plasticity requires synapse-to-nucleus communication leading to changes in gene expression. A key player in this signal propagation is intracellular calcium. Two of the most common calcium-dependent pathways are the extracellular-signal regulated kinase (ERK) pathway and nuclear calcium-dependent activation of resident signaling intermediates such as the calcium-calmodulin-dependent kinases IV. It has been shown that drugs of abuse activate

the ERK pathway, providing a pathway for the transition from casual drug intake towards addiction. However, little is known about the role of nuclear calcium signaling in addiction. To better understand the role played by nuclear calcium signaling in the processes of drug addiction, our colleagues infected medium-sized spiny neurons (MSN) of the striatum with the nuclear calcium-calmodulin buffer, CaMBP4 and examined its influence on addiction-related neuropathological changes. The aim of this project was to investigate whether the expression of CaMBP4 might influence the generation of calcium signals involved in ERK activation in response to cocaine. To these ends, we aimed to perform calcium imaging in striatal neurons *in vitro* using genetically encoded calcium indicators located either within the nucleus or the cytoplasm and to investigate the influence of nuclear calcium-calmodulin buffering on calcium transients in these compartments. Identifying the role of cocaine-induced nuclear calcium signals in adaptations to cocaine on molecular, cellular, and behavioural levels might lead to a discovery of new therapeutic targets for improved addiction treatment.

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**Weixia Duan**, Cong Liu, Jie Zhou, Qin Yu Yu Duan, Tian Zhang, Yuanyuan Li, Guanyan Fu, Yapei Sun, Jiacheng Tian, Zhiqin Xia, Yingli Yang,Yongseng Liu, Shangcheng Xu

**Upregulation of mitochondrial calcium uniporter contributes to paraquat-induced neuropathology linked to Parkinson's disease via imbalanced OPA1 processing**

Paraquat (PQ) is the most widely used herbicide in agriculture worldwide and has been considered a high-risk environmental factor for Parkinson's disease (PD). Chronic PQ exposure selectively induces dopaminergic neuron loss, the hallmark pathologic feature of PD, resulting in Parkinsonian-like movement disorders. However, the underlying mechanisms remain unclear. Here, we demonstrated that repetitive PQ exposure caused dopaminergic neuron loss, dopamine deficiency and motor deficits dose-dependently in mice. Accordingly, mitochondrial calcium uniporter (MCU) was highly expressed in PQ-exposed mice and neuronal cells. Importantly, MCU knockout (KO) effectively rescued PQ-induced dopaminergic neuron loss and motor deficits in mice. Genetic and pharmacological inhibition of MCU alleviated PQ-induced mitochondrial dysfunction and neuronal death *in vitro*. Mechanistically, PQ exposure triggered mitochondrial fragmentation via imbalance of the optic atrophy 1 (OPA1) processing manifested by cleavage of L-OPA1 to S-OPA1, which was reversed by inhibition of MCU. Notably, the upregulation of MCU was mediated by miR-129-1-3p posttranscriptionally, and overexpression of miR-129-1-3p could rebalance OPA1 processing and attenuate mitochondrial dysfunction and neuronal death induced by PQ exposure. Consequently, our work uncovers an essential role of MCU and a novel molecular mechanism, miR-MCU-OPA1, in PQ-induced pathogenesis of PD, providing a potential target and strategy for environmental neurotoxins-induced PD treatment.

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**8**

**Berin Boztepe**, Jessica Hunger, Manuel Fischer, Yannik Streibel, Jonas Scheck, Dennis Agardy, Kianush Karimian-Jazi, Hannah Fels-Palesandro, Ina Weidenfeld, Sabine Heiland, Martin Bendszus, Michael Platten, Katharina Schregel, Michael O. Breckwoldt

**Assessing the immune microenvironment in glioma models by correlative high field MRI and optical microscopy**

Background: Gliomas are malignant brain tumors with an immunosuppressive tumor microenvironment (TME). We have recently implemented the Toll like receptor 7 agonist, CDNP-R848 to efficiently treat preclinical glioma by inducing a proinflammatory shift of the TME. Magnetic resonance imaging (MRI) is the main clinical modality for treatment monitoring of glioma. However, visualizing the immunological key components of the TME is not possible in clinical practice. We hypothesize that light sheet microscopy (LSM) combined with whole brain immunostaining of myeloid and T cells can provide information on immune cell influx, cellular distribution and perturbations that occur after therapy induction. Methods: Preclinical GI261 glioma were intracranially xenografted and after baseline MRI mice were treated with 3 doses of intravenous CDNP-R848 or CDNP vehicle control. Followed by correlative tissue clearing (iDISCO for CD3, IBA1 and CD31), LSM and immunohistochemistry. Results: We have recently shown that CDNP-R848 potently induces regression of established gliomas (ORR: 75%). This was based on macrophage activation during the effector phase (week 3) after CDNP-R848 treatment. To examine spatial patterns of immune cells of the TME we investigated cleared mouse brains with immuno-stained macrophages (Iba1) and T-cells (CD3). Whereas T cell accumulation occurred mainly around peritumoral microvessels, preliminary data showed additional "non-classical" recruitment pathways of myeloid cells with pronounced macrophage accumulation at the ipsilateral choroid plexus, in the corpus collosum and the leptomeninges. We propose that the recruitment pathways of myeloid and T cells play an important role for the development of response and resistance towards glioma immunotherapy which can be assessed by correlated by MR-LSM.

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**9***

Jessica Hunger, Ina Weidenfeld, Katharina Schregel, Berin Boztepe, Kianush Karimian-Jazi, Lennart Heinz, Manuel Fischer, Michael Platten, Martin Bendszus, **Michael O. Breckwoldt**

**Correlated MRI and light sheet microscopy to dissect immune cell dynamics of the glioma microenvironment during immunotherapy**

Immunological processes play pivotal role in a variety of neurological diseases, including neoplastic conditions. Gliomas are highly malignant brain tumors which actively suppress antitumor immune responses. Another hallmark of glioma is their infiltrative nature into the adjacent parenchyma and to the contralateral hemisphere. Magnetic resonance imaging (MRI) is the main modality for initial diagnosis and treatment monitoring for many neurological disorders including glioma.

However, visualizing the immunological cellular origins and thus the catalysts of disease is not possible in clinical practice. Clinical imaging is mainly restricted to assess morphological information (e.g. tumor size, extent of edema and gliosis) but does not provide “functional” information on immune cell influx, cellular distributions and perturbations that occur after therapy induction and which mediate treatment. This, however, would be crucial to better understand and eventually treat neurological disorders associated with innate and adaptive immune responses. Furthermore, novel therapies that modulate the tumor microenvironment (TME) and tumor cell invasion are entering clinical practice and require advanced treatment monitoring – an unmet clinical need for all solid cancer entities. Advanced imaging of inflammatory processes can also foster mechanistic insights into disease mechanisms and facilitate therapy development. My group uses innovative nanoparticle formulation to visualize and modulate immune responses for direct tracking of effector cells. This facilitates preclinical therapy development and allows treatment monitoring. Despite a number of proof of principle studies, the concept of immuno-imaging has not yet entered clinical practice. Major limitations of MRI include the resolution (~50µm to 1mm) and lack of specificity of conventional MR sequences. Optical imaging can overcome both limitations. Recent developments of tissue clearing and light sheet microscopy (LSM) allow the generation of 3D datasets at single cell resolution which can constitute a “ground truth” for MRI biomarker development. The presentation shows how light sheet microscopy can dissect innate and adaptive immune cell dynamics of the glioma microenvironment during immunotherapy.

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**10** **Märt Rannap**, Andreas Draguhn, Alexei V. Egorov

### Hippocampal output signals to medial entorhinal cortex layer VI are preferentially mediated by the ventral hippocampus

The deep layers (V/VI) of the entorhinal cortex form an important interface for relaying hippocampal output signals to telencephalic structures. Recently, we found marked dorsoventral differences in the structural and functional organization of hippocampal projections to layer V (LV) of the medial entorhinal cortex (MEC) (Ohara, Rannap et al., Cell Rep. 2023). In comparison, little is known about the dorsoventral topography of the hippocampal output to MEC layer VI (LVI) and how LVI neurons are integrated into the MEC micro-network. Here, we performed whole-cell patch-clamp recordings from MEC LVI neurons in horizontal mouse brain slices. Reciprocal connections between excitatory LVI neurons in paired recordings were relatively sparse (7/119, 6%) and no interconnections between LVI and LVb (0/97) glutamatergic neurons were found. Weak connectivity was also observed between LVa and LVI neurons using an optogenetic approach where we selectively infected LVa neurons with a ChR2-expressing AAV using the Rbp4-Cre mouse line. To study hippocampal-MEC LVI projections along the dorsoventral axis, we injected the ChR2-expressing AAV into the dorsal or ventral hippocampus (CA1/subiculum). Dorsal hippocampal projections were confined to the dorsal MEC and their activation elicited weak monosynaptic responses in only half of recorded LVI neurons (10/22). In contrast, ventral hippocampal projections innervated both dorsal and ventral MEC and elicited strong monosynaptic responses in nearly all recorded LVI neurons (30/31). Our findings reveal a specific functional architecture of MEC LVI and suggest that MEC LVI-mediated signal propagation is preferentially controlled by the ventral hippocampus.

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**11** **Matthias Klumpp**, Lee Embray, Justus Simon, Andreas Draguhn, Martin Both

### Syntalos: A software for precise simultaneous multi-modal data acquisition and closed-loop interventions

Complex experimental protocols often require multi-modal data acquisition with precisely aligned timing, as well as state- and behavior-dependent interventions. Tailored solutions are mostly restricted to individual experimental setups and lack flexibility and interoperability. We present an integrated software solution, called ‘Syntalos’, for simultaneous acquisition of data from an arbitrary number of sources, including multi-channel electrophysiological recordings and different live imaging devices, as well as closed-loop, real-time interventions with different actuators. Precisely matching timestamps for all inputs are ensured by continuous statistical analysis and correction of individual devices’ timestamps. New data sources can be integrated with minimal programming skills. Data is stored in a comprehensively structured format to facilitate comparison pooling or sharing data between different laboratories. Syntalos enables precisely synchronized multi-modal recordings as well as closed-loop interventions for multiple experimental approaches. Preliminary experiments with different research questions show the successful performance and easy-to-learn structure of the software suite.

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**12** **Zeynab Razzaghpanah**, Zahra Monfared, Martin Fungisai Gerchen, Georgia Koppe, Daniel Durstewitz

### Multimodal assesment of nonlinear brain activity dynamics with fMRI and MEG

Research in computational neuroscience has provided ample evidence that information processing in the brain is implemented via the dynamics. Meaning, a dynamical systems view of the brain and the evolution of possible states it assumes over time can provide information about various computational properties of the information processing carried out. Recurrent neural networks have been mathematically proven to be adaptive models possessing sufficient

expressive power to approximate any function regardless of specific function characteristics such as linearity. In addition to this, activation functions which provide global non-linearity but are locally linear (called piece-wise linear) provide more ease in modeling complicated and non-linear functions. The use of such activation functions also facilitates the training of RNN and helps avoid common pitfalls such as exploding or vanishing gradients (SVG). Another advantage of these piece-wise linear recurrent neural networks (PLRNN) is their accessible dynamics and possibility for analytic derivation of corresponding dynamical objects such as fixed points and limit cycles. Seeing as PLRNN can take any dynamical system with one or more dimensions describing the system state at different points in time, they can be trained on different timeseries modalities, be it behavioral observations, recorded activity of individual neurons (single neuron recordings) or population activity as recorded by fMRI and MEG. Therefore, in this project, we use same-day recordings of brain activity in the resting state (first MEG followed by fMRI) as the dynamical systems to be reconstructed. We fine-tune the specific PLRNN internal model components, training, optimisation, regularization and inference schemes as well as the corresponding hyper-parameters separately for fMRI and MEG data of each subject and perform model-based analysis of the inferred dynamical systems in terms of the number and types (stable, unstable, virtual or non-virtual) of fixed points as well as bifurcations. In order to ensure that the PLRNN capture and represent sufficient and accurate dynamical properties of the systems they model, we follow general principles derived from PLRNN models which were fine-tuned and demonstrated to be effective in capturing the dynamics of benchmark systems well-known for being particularly challenging.

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**13** **Angela Serian**, Jamila Andoh, Simon Desch, Herta Flor

### Changes in brain activity as possible predictors for phantom limb pain in leg amputees – a longitudinal pilot study

Phantom limb pain (PLP) describes chronic pain that occurs after severe peripheral nerve injury in the missing body part in up to 80% of amputees. PLP has been associated with brain changes. However, the causality of the neuronal and perceptual changes is still unclear. Therefore, we conducted a longitudinal study to examine brain excitability in leg amputees longitudinally. We examined nine leg amputees within the first six month (Time 1) and followed them up 1.5 years (Time 2) after amputation and gender- and age-matched healthy controls. Five participants suffered from phantom limb pain and 4 were pain-free. The activation of brain regions involved in the processing of pain after painful heat stimulation was examined using functional magnetic resonance imaging (fMRI). Based on the brain activation of the healthy controls, we extracted brain masks within our regions of interest: somatosensory cortex, the posterior Insula and the anterior ACC. In early stages after amputation we found differences between amputees with and without PLP: neural activity was increased in S1, Insula and ACC using acute painful stimulation adjacent to the side of amputation in amputees with PLP and adjacent to the intact limb in amputees without PLP. In late stages after amputation we found a decreased neural activity in S1, Insula and ACC at Time2 compared with Time1 in amputees with PLP and an increased neural activity in Insula and ACC in amputees without PLP. In summary, it can be assumed, that the respected brain regions might be involved in pain chronicity.

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**14** **Mina Kandić**, Francesca Zidda, Katrin Usai, Martin Löffler, Michaela Ruttorf, Frauke Nees, Herta Flor

### The superior longitudinal fasciculus is a biomarker of resilience to chronicity in back pain

Previous research proposed that white matter changes in prefrontal-limbic circuits are predictive of the development of chronic back pain (CBP). In the current study, we collected diffusion imaging data of patients with subacute back pain (SBP, N=48) at baseline and their pain patterns at baseline and at a 6-month follow-up, and in individuals with CBP (N=21) and age- and gender-matched healthy controls (HC, N=23). We used tract-based spatial statistics to derive white-matter indices of structural integrity. In a longitudinal approach, we used multiple linear regression to predict the severity of chronicity as well as receiver operating characteristic curves to classify patients who recovered (SBPr) and those whose pain persisted (SBPp). Additionally, we examined white-matter differences between HC and patients with CBP in a cross-sectional manner. Whole-brain analysis revealed a cluster in the right superior longitudinal fasciculus (SLF) tract significantly greater in SBPr than in SBPp. Fractional anisotropy (FA) baseline values in this cluster were predictive of chronicity at the 6-month follow-up and predicted pain severity change from baseline to follow-up. Healthy controls had significantly higher FA values versus CBP patients across several brain regions, partially confirming the previous findings on structural alterations in CBP. In the SBP sample, we identified a white-matter brain biomarker of resilience to CBP. Our results suggest that the integrity of the right SLF, linked to visuospatial attention and proprioception, could serve as an important predictor in the early stage of the development of CBP.

**15** **Zhou Zhou**, Annette Loeffler, Stefano Silvoni, Dieter Kleinböhl, Herta Flor

### Association between tactile processing and memory performance in participants with mild cognitive impairment

Patients with Mild Cognitive Impairment (MCI) face the dilemma of multifaceted cognitive decline, the first to be affected is episodic memory, especially visuospatial, which is not only closely related to the quality of daily life but is also a valid indicator to monitor the progression of the disease, for example to predict the transition to Alzheimer's disease (AD). Recent neural models suggest that cognitive decline is due to a combination of altered peripheral input and central processing. The aim of this work is to predict visuospatial memory function in MCI by examining tactile function and central processing patterns of touch. The creation of an integrated tactile model may open up new insights into mechanisms and treatment directions for the pathological memory dilemma of MCI.

**16** **Jonas Schimmer**, Stephanie Küppers, Julia Lebedeva, Marina Eliava, Valery Grinevich

### Oxytocin facilitates sexual partner preference in male rats acting at the ventral hippocampus

The hypothalamic neuropeptide oxytocin (OT) modulates a plethora of socio-sexual behaviors. In this study we focused on OT signaling in the ventral hippocampus (vHippo), a central hub of social memory. In our preliminary experiments, implementing cell-type specific adeno-associated viruses (AAVs) we first found substantial innervation of the vHippo from the hypothalamic OT-ergic nuclei. Next, using a combination of OTR-IRES-Cre knock-in rats and viral-based vectors, we identified 3 types of neurons expressing OT receptors (OTR) in the vHippo: 1) Parvalbumin-positive GABAegic neurons, 2) Excitatory radiatum giant cells (RGS) and 3) A sub-population of pyramidal cells, residing in CA1 principal cell layer. External application of an OT agonist on acute vHippo slices resulted in generation of EPSCs in both types of OTR-expressing pyramidal neurons and simultaneous IPSPs in OTR-negative pyramidal cells. By chemogenetic activation and inhibition of vHippo OTR expressing cells we found that male rats show higher interest in urine of their respective mating partner compared to urine of an unknown female in a reference-based olfactory hole-board test when the vHippo OTR system is manipulated. Our results suggest that OTR neurons of the vHippo facilitate male sexual partner preference likely via modulation of the local circuit via OTR interneurons which control the signal to noise ratio. We also found various long range outputs of OTR neurons to forebrain regions, which might play a role in behavioral modulation of this and other paradigms.

**17** **Stephanie Küppers**, Arthur Lefevre, Alan Kania, Marina Eliava, Valery Grinevich

### An oxytocin-sensitive cortical circuit facilitating sociability of female rats

The infralimbic cortex (ILC) is a forebrain region modulating social behavior in its function as a command center for top-down regulation of sensory-affective experiences. We aim to investigate how the pro-social neuropeptide oxytocin (OT) influences social behavior through signaling in the ILC. In order to describe the underlying circuitry of OT action in the ILC, we employed cell-type specific recombinant adeno-associated viruses (rAAVs) in transgenic OTR-Cre female rats. We identified direct axonal projections of OT-neurons originating in the hypothalamus to the ILC. Additionally, we described two populations of OT-receptor (OTR) expressing neurons within the ILC: GABAergic interneurons in layer 2/3, and a small population of principal cells (PCs) in layer 5, which almost exclusively innervate the nucleus accumbens. Modulatory action of OT was verified by optogenetic stimulation of OT release in the ILC, which increased sociability in female rats during social interaction behavioral experiments. Recording ILC OTR-neuron firing via fiber-photometry, we observed social-behavior-dependent activation of OTR neurons in the ILC during social interaction. Chemogenetic manipulation of OTR-neurons in the ILC bidirectionally increased and decreased sociability after activation or inhibition, respectively. Further investigations of the impact of the two distinct OTR-neuron populations revealed OTR-interneurons to be the main modulator driving sociability. We hypothesize, that OTR-interneurons in the ILC preferentially inhibit neurons projecting to the amygdala, thereby reducing social anxiety and increasing sociability. Our work demonstrates that OTR-sensitive neurons in the ILC are necessary for facilitating sociability in female rats, furthering our understanding of underlying mechanisms modulating this multi-sensory and integrative behavior.

**18*** **Quirin Krabichler**, Eduard Maier, Leonie Bechthold, Hshin-Jui Liu, Ana Zovko, Michael Brecht, Shimpei Ishiyama, Valery Grinevich

### Oxytocin action in the periaqueductal gray is involved in social habituation by heterospecific play in rats

Social habituation involves building trust, and play behaviour is a potent driver for this in young individuals. Playing is not limited to conspecific interactions but can also occur heterospecifically, such as between humans and animals. In rats, human experimenters can imitate conspecific play by “tickling” young rats over repeated sessions, which leads to increased emission of hedonistic 50 kHz ultrasonic vocalizations (USVs). Rat tickling is emerging as a powerful paradigm to study the neural substrate of social habituation, play behaviour and trust-building. However, many aspects of human-rat play behaviour remain little understood. We analyzed spectro-temporal characteristics of over 100,000 USVs from

20 rats across repeated tickling sessions. We found a gradual increase of the overall rate of USVs and a change of their spectral characteristics with a proportional decrease of “neutral” flat USVs and an increase of “positive” frequency-modulated USVs. Our behavioral analysis furthermore suggested a transition from a less to a more playful state. We hypothesized that these changes were facilitated by the hypothalamic neuropeptide oxytocin (OT), a ‘master regulator’ of social behavior, acting on the periaqueductal gray (PAG), a known center for play-related behaviors (arousal, USVs, approach and avoidance). We chemogenetically inhibited PAG OT-receptor neurons in play-habituated rats and found a decrease of the rate of USVs as well as their proportion of “positive” vs. “neutral” types. Taken together, we show that social habituation by playing in rats is characterized by distinct spectro-temporal USV patterns, which in turn appear to be modulated by OT action in the PAG.

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**19** **Ana Zovko**, Elena Munoz, Daniel Sierra Garcia, Sandra Horschitz, Quirin Krabichler, Philipp Koch, Valery Grinevich

### Generation of iPSCs derived Oxytocin specific hypothalamic organoids and transplantation into rat brains

Oxytocin (OT), a neuropeptide produced in the hypothalamus, is a potent modulator of emotions and social behavior acting via numerous brain-wide projections. The OT system is known to be dysregulated in many psychiatric diseases, such as anxiety, depression, PTSD, schizophrenia, autism spectrum disorder. So far, no therapeutic approach exists to target the brain’s OT system in order to rescue the healthy behavioral phenotype. In recent years, a promising tool for targeted treatment of neuropathologies has emerged from the field of stem cell research: By applying instructive signals to human-derived induced pluripotent stem cells (hiPSCs), structures resembling specific regions of the brain can be generated and could in the future be transplanted as xenografts into the brain of patients. Here, we show first results of successful production of hiPSC-derived OT neurons in ventral hypothalamic organoids, using a “self-patterning” approach based on natural propensity of hiPSC to develop towards anterior brain regions with addition of ventralizing inductive signals. We observed the expression of region-specific progenitor markers Rax1, Nkx2.1. and transcription factors necessary for adopting the identity of OT progenitors – Otp, Sim1 and Brn2. Due to high diversity of neuropeptidergic neurons present in this brain region, we are establishing a 2-step selection process to obtain higher yields of OT producing neurons, based on CRISPR/Cas9-gene-edited transgenic cell lines and OT-specific viral vectors. Our study will pave the way towards individualized cell-culture generation of neuroendocrine hypothalamic cells, which one day could be implanted into the brains of patients suffering from neurologically impaired hormone systems.

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**20** **Josephine Timm**, **Nadin Mari Saluti**, Filippo Heimburg, Tim Kreuziger, Matthias Klumpp, Lee Embray, Thomas Kuner, Alexander Groh

### The role of the posterior thalamic nucleus in somatosensory processing in freely moving mice

Functional neuronal ensembles in the posterior medial nucleus (POm) in the rodent whisker system (higher-order thalamus) are likely generated by motor, sensory and context-dependent variables such as whisking, locomotion, or salience. Preliminary work suggests that POm specifically responds to tactile stimuli that are unpredicted and/or behaviorally relevant and that POm is involved in sensory discrimination and learning. Our goal is to understand the function of these “higher-order ensembles” in behavior. They could play a role in detecting salient stimuli and preparing appropriate motor responses. To test this hypothesis, we established a tactile discrimination task in which we can manipulate POm activity. Mice run between two lick ports, located at opposite ends of a linear maze, which alternately dispense a reward (sweetened milk) or deliver a punishment (noise). To reach the lick ports, mice must pass through a narrowing in which two wings with variable distances from each other are presented to the whiskers. Each visit (=one trial) mice touch the wings and decide whether to lick or not. POm activity is systematically inhibited at specific time points via a pharmacogenetic approach using DREADDs. Our preliminary results show, that once the rules are learned, POm inhibition does not affect the performance of the animals. However, if we change the rules, DREADD animals need significantly longer to relearn the new rule, compared to control animals.

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**21** Katharina Ziegler, **Ross Folkard**, Antonio Gonzalez, Jan Burghardt, Sailaja Antharvedi-Goda, Jesus Martin-Cortecero, Emilio Isaías-Camacho, Sanjeev Kaushalya, Linette Liqi Tan, Thomas Kuner, Claudio Acuna, Rohini Kuner, Rebecca Audrey Mease

### Primary somatosensory cortex bidirectionally modulates sensory gain and nociceptive behavior in a layer-specific manner

The primary somatosensory cortex (S1) is a hub for body sensation of both innocuous and noxious signals, yet its role in somatosensation versus pain is debated. Despite known contributions of S1 to sensory gain modulation, its causal involvement in subjective sensory experiences remains elusive. Here, in mouse S1, we reveal the involvement of cortical output neurons in layers 5 (L5) and 6 (L6) in the perception of innocuous and noxious somatosensory signals. We find that L6 activation can drive aversive hypersensitivity and spontaneous nocifensive behavior. Linking behavior to neuronal mechanisms, we find that L6 enhances thalamic somatosensory responses, and in parallel, strongly suppresses L5 neurons. Directly suppressing L5 reproduced the pronociceptive phenotype induced by L6 activation, suggesting an anti-nociceptive function for L5 output. Indeed, L5 activation reduced sensory sensitivity and reversed

inflammatory allodynia. Together, these findings reveal a layer-specific and bidirectional role for S1 in modulating subjective sensory experiences.

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**22** **Isaias-Camacho Emilio Ulises**, Martin-Cortecero Jesus Maria, Groh Alexander

### A cortico-collicular pathway for defence modulation

Animals can quickly react to sudden events in their environment, i.e. orienting towards a stimulus or escaping a threat. The superior colliculus (SC) is a phylogenetically old brain structure initiating swift orientation and defence movements to achieve these tasks. We recently described the whisker-related connectivity to SC involving the motor cortex (MC), the barrel field of S1 (BC) and the brainstem (Bs) by using an intersectional viral approach. Building on this work, we next tested whether top-down cortical pathways can augment or suppress SC-mediated behaviours. To achieve our goal, we investigated the functional role of MC inputs by terminal excitation or inhibition, as well as by activating different recipient neuron populations in SC (MC-RNs). I developed a behavioural paradigm to quantify mice's SC-dependent defence behaviour upon an unpredictable tactile stimulation of mice's whiskers. This setup allowed us to study the ability of MC and different MC-RN populations to modulate the animal's defence behaviour. Manipulations of MC terminals in SC had a congruent effect on defence behaviour: excitation led to a slight increase, whereas silencing significantly decreased the behaviour. Similarly, exciting inhibitory RNs (MC-iRNs) also significantly reduced the defence behaviour of mice, while general RNs tend to have the opposite effect. Our results reveal that top-down modulation of innate defence behaviours is achieved through specific neural populations in SC, controlled by MC layer 5 inputs. The efficacy of these pathways might undergo Hebbian plasticity through the individual's experiences thus attaining behaviour adaptability/flexibility.

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**23** **Diptyajit Das**, Marnie E. Shaw, Matti S. Hämäläinen, Andrew R. Dykstra, Laura Dolla, and Alexander Gutschalk

### A role for retro-splenial cortex in the task-related P3 network

The P3 is an event-related response observed in relation to task-relevant sensory events. Despite its ubiquitous presence, the neural generators of the P3 are controversial and not well identified. We compared source analysis of combined magneto- and electro–encephalography (MEG and EEG) data with fMRI and simulation studies to better understand the sources of the P3 in an auditory oddball paradigm. Our results suggest that the dominant source of the classical, postero-central P3 lies in the retro-splenial cortex of the ventral cingulate gyrus. A second P3 source in the anterior insular cortex contributes little to the postero-central maximum. Multiple other sources in the auditory, somatosensory, and anterior middle cingulate cortex are active in an overlapping time window but can be functionally dissociated based on their activation time courses. These results provide a new perspective for the interpretation of the extensive research based on the P3 response.

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**24** **Laura Doll**, Andrew R. Dykstra, Alexander Gutschalk

### Perceptual awareness of near-threshold tones scales gradually with pupil dilation and auditory cortex activity

Perceptual awareness of near-threshold sounds shows stronger inter-trial variability than expected based on cochlear processing. Here, we used MEG, EEG, and pupillometry to explore the roles of attention and arousal on inter-trial perceptual variability of near-threshold tones embedded in noise. In experiment 1, participants first detected amplitude modulations of white noise and retrospectively denied having heard task-irrelevant, near-threshold tones. Such tones failed to elicit significant tone-evoked pupil dilation or activity in auditory cortex. In contrast, when task-relevant, detected tones elicited strong pupil dilation and activity in auditory cortex, and both measures, though smaller, were still present for missed tones. In experiment 2, participants rated how confident they were in their perception of the near-threshold tones on a six-level scale, permitting multiple decision criteria. Decreasing confidence in tone perception was associated with a gradual decrease in auditory-cortex activity and pupil dilation across the whole range of ratings. This gradual decrease was modeled well by the signal strength assumed in signal detection theory based on the behavioral data. These results support a model of perceptual awareness where activity in sensory cortices, modulated by subcortical attention systems, is closely coupled to conscious perception, and which is consistent with classical signal detection theory.

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**25** **Amr Elgez**, Andrea Lewen, Babak Khodaie, Lennart Soeder, Oliver Kann

### Exploring the mechanisms underlying microglia-mediated inflammatory neurodegeneration

Currently, it is widely acknowledged that strongly activated microglia can release proinflammatory mediators and oxidants, such as nitric oxide (NO) and superoxide, inducing an extensive inflammatory neurodegeneration. However, the putative synergy between microglial activation and concomitant pathological neuronal network activity, which may

exacerbate neuronal energetic and oxidative stress in the neurodegenerative process, remains poorly understood. In this study, the first experimental group involved the exposure of organotypic hippocampal slice cultures from rats to a combination of interferon-gamma (IFN-γ) and lipopolysaccharide (LPS) for 48 hours, known to induce severe neurodegeneration. In the second group, the slice cultures were additionally treated with a combination of the Na+ channel blocker tetrodotoxin (TTX), the AMPA receptor blocker CNQX, and the NMDA receptor blocker D-AP5 to suppress neuronal excitation. After the exposure period, the release of NO and lactate dehydrogenase (LDH) was assessed in the slice culture supernatant. Proinflammatory cytokines (TNF-α and IL-6) were measured using ELISA. Additionally, local field potential (LFP) recordings were performed to evaluate neuronal activity states in slice cultures. The results showed that LDH levels in the untreated group (IFN-γ+LPS only) and the treated group (TTX, CNQX, D-AP5, IFN-γ+LPS) were comparable indicating similar levels of cell death. Notably, the treated group exhibited significantly higher NO release. There was no significant impact on the release of TNF-α and IL-6. LFP recordings revealed severe disturbances in neuronal network activity in both groups. These findings suggest that inhibiting neuronal excitation neither mitigates nor prevents microglia-mediated neurodegeneration. Interestingly, the release of NO from microglia appears to be partially influenced by neuronal activity.

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**26** **Lennart Söder**, Babak Khodaie, Amr Elgez, Andrea Lewen, Oliver Kann

### Dissecting the roles of lactate as energetic fuel and signaling molecule in neuronal network activity

In recent years, there has been a growing recognition that lactate not only serves as a potential energy substrate for neurons but may also function as a signaling molecule, capable of modulating synaptic transmission. However, the specific details underlying this signaling function remain widely unknown. Particularly, the acute effects of lactate on neuronal network activity, such as gamma oscillations (30-70 Hz), have not been sufficiently explored. Therefore, our research aims to investigate the role of lactate in greater depth through electrophysiological measurements of local field potentials in organotypic hippocampal slice cultures. In our initial experiments utilizing acute applications via the bath solution, we found no significant differences in the properties of gamma oscillations recorded in artificial cerebrospinal fluid (ACSF) containing 5 mM glucose and in ACSF containing 10 mM glucose. This suggests that 5 mM glucose is sufficient, and an increase to 10 mM glucose does not provide additional energetic benefits. Interestingly, when we replaced ACSF containing 5 mM glucose with ACSF containing 5 mM glucose plus 2 mM lactate a significant increase in peak frequency of the gamma oscillations by about 3 Hz was observed. Taken together, these findings indicate that this effect might imply a signaling mechanism rather than being related to energy metabolism. To further investigate this phenomenon, our next steps involve the application of inhibitors targeting the monocarboxylate transporter 2 (MCT2), which is the responsible transporter for neuronal lactate uptake, as well as the administration of agonists known to activate the lactate receptor HCAR1 in neurons.

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**27*** **Babak Khodaie**, Elke Edelmann, Volkmar Leßmann

### Distinct GABAergic modulation of spike timing-dependent plasticity in mouse CA1 pyramidal cells across the longitudinal axis of the hippocampus

The hippocampus and its associated medial temporal lobe structures develop as a complex micro-network of excitatory and inhibitory synapses to process learning and memory formation. The longitudinal hippocampal axis spans from dorsal to ventral poles, which are differentially involved in spatial and emotional learning. Along this axis GABA, glutamate, and neuromodulatory receptors are differentially expressed, providing diverse synaptic regulation mechanisms. GABAergic inhibition balances excitatory responses and neuromodulatory transmitter release. Due to the non-uniform expression of GABAA and GABAB receptors along the longitudinal axis, synaptic plasticity might be differently modulated by this diverse GABAergic inhibition. STDP is a paradigm based on precise ms delays of action potentials (APs) in pre- and postsynaptic neurons. Patch clamp recorded CA1 neurons were subjected to canonical (1 presynaptic: 1 postsynaptic AP) or burst t-LTP protocols (1:4), repeated 6 times @0.5 Hz in acute mouse hippocampal slices taken from dorsal (DH), intermediate (IH), or ventral (VH) hippocampus to test timing-dependent LTP (t-LTP) induction under diverse settings for GABAergic inhibition. We used either intact GABAergic inhibition, fully blocked inhibition using co-applied GABAAR (100µM picrotoxin) or GABABR antagonists (10µM CGP55845), or recorded in the presence of only picrotoxin. We found a complex association of excitatory and inhibitory responses depending on stimulation protocols (canonical or burst) and studied regions (DH or VH). While the 6x 1:1 protocol lost its dependency on GABAergic signaling to induce robust t-LTP from DH to VH pole, our 6x 1:4 protocol mainly depended on active GABABR signaling during t-LTP induction.

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**28** **Marina R. Hesse**, Steffen Sass, Maja Klevanski, Thomas Kuner

### Uncovering the molecular active zone nano-organization of the mammalian central synapse using multiplex 3D – super resolution microscopy

Synapses are pivotal for transmitting action potential-encoded information in the nervous system. The presynaptic active zone (AZ) orchestrates neurotransmitter release through a series of intricate steps. Voltage-gated calcium channels

facilitate calcium influx (1), vesicle docks guided by AZ proteins (2), cell-adhesion molecules align pre- and post-synapse (3), and presynaptic plasticity is mediated by AZ (4). During exocytosis, membrane fusion relies on specific v-SNARE and t-SNARE proteins, while regulatory proteins such as liprin, ERC, piccolo, and bassoon, coordinate the recruitment of calcium channels and vesicles to the AZ plasma membrane and AZ structure. Alongside endocytosis markers like endophilin and amphiphysin coordinate vesicle recycling. However, the intricate nano-architecture and mechanisms underlying AZ constitution, and vesicle recycling remain incompletely understood. To gain valuable insights into synaptic communication, we employed direct stochastic optical reconstruction microscopy (dSTORM), a cutting-edge super-resolution technique capable of visualizing structures at the nanoscale. By utilizing maS3TORM, a multiplexing method, we successfully identified multiple proteins within the same sample, enhancing our resolution and comprehensiveness. Our study focused on the major AZ proteins in the calyx of Held, a mammalian central synapse, providing unprecedented molecular insights into their nano-organization, which not only facilitate the structural integrity of the AZ but also play a crucial role in mediating exocytosis. These findings significantly advance our understanding of synaptic organization and provide a solid foundation for future investigations into the functional aspects of these proteins at the intricate nanoscale level.

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**29** **Ivo Sonntag**, Avi Adlakha, Thomas Kuner

### Activity of the neurons in the infralimbic cortex of rats during reward seeking

The medial prefrontal cortex (mPFC) is responsible for emotional, decision-making and reward-processing behaviours. Out of the mPFC, specifically the infralimbic cortex (IL) is often associated with reward-seeking and punishment-avoiding behaviours. It has been shown to also play a crucial role in the regulation of emotions and their extinction related to these tasks. However, the representation of the neural network in the infralimbic cortex remains elusive. In this study, we imaged the infralimbic cortex of rats using 1-photon calcium imaging in a freely moving setup. The data was acquired using a GRIN lens and miniaturized head-mounted fluorescence microscopes (miniscopes). The paradigm consisted of conditional behaviour training and was further divided into learning, extinction and reinstatement phases. The data obtained from the miniscope was analysed using Minian and was further classified and matched with the behavioural data with the help of MATLAB. It was found that there were a few cells that would reliably fire a significant amount of time before the behavioural motor outcome and could be a part of “preparatory cells” found in the PFC of other animals. The cells were matched across the sessions, and it was found that while some cells restricted their activity to a particular session, others kept showing up across the sessions.

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**30** **Catello Guida**, Fabio Marsoner, Anne Hoffrichter, Philipp Koch, Julia Ladewig

### Unraveling the functions of the transcription factor TBR2 in human neurodevelopment

The human brain is remarkably complex, both structurally and functionally and clearly represents the organ with the greatest progression during evolution. The human neocortex is greatly expanded and exhibits increased complexity. Several neuronal progenitor types are present during development e.g. radial glial (RG) cells, intermediate progenitors (IPs) and outer (o)RGC. An increase in progenitor cell number and diversity is thought to contribute to the increase in cortical size and complexity during evolution. The developmental mechanisms underlying the evolutionary changes are, however, poorly understood. With the advent of efficient gene editing technologies in human cells in combination with the ability to generate human pluripotent stem cells (PSC) and organotypic PSC-derived brain organoids we are now technologically equipped to decipher the molecular basis of the changes between our brain and that of our ancestors. In this project we apply gene editing in PSC and thereof derived organoids to study the function of TBR2, a transcription factor selectively expressed in IPs and functionally required for SVZ neurogenesis, during early human cortical development. Using CRISPR/Cas9 mediated gene editing we generated PSC-TBR2-knockout (KO) lines. Following validation we applied a standardized forebrain-type organoid protocol. When analysing the transgenic organoids and isogenic controls by single nuclei sequencing and successively by immunofluorescence analysis, we found that TBR2 is impacting on the proliferation of progenitor cells together with their differentiation into cells positive for the neuronal markers TBR1 and SATB2. Furthermore, our sequencing data suggests a role of the transcription factor in the development of the cortical preplate and subplate.

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**31** **Annasara Artioli**, Lea Zillich, Eric Poisel, Fabio Marsoner, Anne Hoffrichter, Julia Ladewig, Philipp Koch

### Human cortical brain organoids to study adaptive changes in alcohol addiction

Alcohol use disorder (AUD) is a global problem causing 2.5 million deaths per year and accounts to the world’s third largest risk factor for premature mortality and disability. Although it poses major challenges to public health care systems, the medical needs of the patients are largely unmet and underlying neurobiological causes only poorly understood. Most of our understanding of the molecular changes in the brain evoked by alcohol addiction is based on post mortem human tissue or animal models. Induced pluripotent stem (iPS) cell-derived brain organoids represent an attractive and innovative tool to decipher adaptive changes during disease onset caused by genetic or environmental challenges

(including noxious substances) in a human setting and an unbiased forward approach. We set out to analyze how acute and chronic alcohol exposure changes transcriptional and epigenetic programs in the human cortex. We generated forebrain-type organoids applying iPS cells from healthy controls and alcohol addicts. We developed protocols allowing us to generate organoid slices cultured for >100 days, which develop a cell composition and histoarchitecture mimicking late stages of corticogenesis of the human brain. We performed a combinatorial single nuclei sequencing approach for the simultaneous detection of the cells' transcriptome and chromatin accessibility. Acutely and chronically treated organoids showed an increased expression of inflammatory, metabolic and ROS genes as well as alcohol-induced immune system activation biomarkers as SIM2. Differential expression of epigenetic modifiers have been observed in the treated conditions, whose among the targets are genes implicated in neuronal migration, synapses formation, neuroglia interactions and genes involved in AUD predisposition and behaviors regulation, such as CNR1, PSD3 and PDE4B. Particularly the acute condition shows an upregulated expression of acetyltransferases and demethylases and an increased accessibility of the chromatin compared to the chronic condition, suggesting that epigenetic adaptations in forebrain-type organoids could be induced by long-term EtOH treatment. We expect that this project will help to define critical contributors in the pathogenesis of alcohol addiction, eventually leading to new therapeutic paradigms.

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**32** **Raquel Pérez Fernández**, Marco Siekmann, Annasara Artioli, Philipp Koch, Julia Ladewig

### Modeling reward and addiction: development of an *in vitro* reward neurocircuitry

Rewarding stimuli are processed by the brain mesocortico-limbic dopaminergic (DA) pathways. These circuits arise at the ventral tegmental area (VTA), and the neurons project towards diverse brain regions, such as the cortex and the ventral striatum respectively. Dysregulation in their signaling is associated with maladaptive behaviors potentially leading to pathologies, like substance use disorder (SUD) and addiction. However, our knowledge regarding how this comes to be, is hindered by the limited availability of human specific models. The advent of human induced pluripotent stem cells (hiPSCs) and thereof derived brain organoids have offered a platform to overcome these limitations. Here, we aim to establish an organoid-based system to model the development of the reward circuitry and investigate its function in health and disease. We have developed and characterized human midbrain organoids (hMOs) composed of DA progenitor cells (FOXA2+/LMX1+/OTX2+) that mature into mesencephalic DA neurons (TH+), some of them characteristic of the VTA (CALB+). Similarly, we have generated organoids resembling the ventral striatum area (hVSOs) containing progenitors with ganglionic eminence identity (FOXG1+/ GSH2+) and mature GABAergic medium spiny neurons (CTIP2+/ DARP32+/ GAD1+). Subsequently, we have fused the hMOs organoids with already established human cortical organoids and hVSOs to investigate the development of mesocorticolimbic interactions. The fused cultures revealed the establishment of TH+ axonal projections from the hMOs to the cortical and striatal regions. Our results open the possibility to analyse in-vitro how this system reacts to different substances of abuse and to identify mechanisms involved in the onset of SUD.

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**33** **Yassin Harim**, Chunxuan Shao, Heike Alter, Changwen Wang, Yue Zhuo, Gözde Bekki, Asya Sayin, Nadja Stöffler, Giulia Di Muzio, Katharina Hartmann, Anna Neuerburg, Weijun Feng, Hai-Kun Liu

### The chromatin remodeler Chd7 acts as a chromatin hub coordinating differentiation of multiple cell lineages during hippocampal development

Chromatin remodeling plays an essential role in development, for instance by controlling gene expression during cell differentiation. Mutations of chromatin remodelers are often implicated in developmental diseases such as CHARGE syndrome, in which a heterozygous mutation of the chromatin remodeler CHD7 is the major driver of the disease. To investigate the role of Chd7 during brain development, we used a dorsal telencephalon-specific Chd7 loss of function mouse model and discovered Chd7 acts as a multi-lineage coordinator. Histological analysis of Chd7 mutant mice shows that upon ablation of Chd7, the hippocampus, a key region for learning and memory in both humans and rodents, displays a patterning defect. Importance of Chd7 for forebrain development is furthermore underlined by its expression in Cajal-Retzius neurons, a small, transient population of cells which orchestrate spatial organisation of the cortex and hippocampus. Integrative analysis of single-cell RNA and ATAC sequencing as well as histological data of the developing mouse brain suggests that Chd7 is essential for the migration, differentiation and maturation of multiple cell lineages during hippocampal development. Mechanistically, Chd7 is required for shaping the chromatin landscape, which allows a coordinated activation of lineage-specific gene expression programs and subsequent fine-tuning of gene expression during cell differentiation. Altogether, our data suggest an emerging role of Chd7 as a central chromatin coordinator of multiple lineages during development. This novel concept of a chromatin remodeler as a pivotal hub during development provides new insights into the essential role of chromatin remodeling in development and disease.

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**34** **Jana Franziska Tegethoff**, Moritz Mall

### Active maintenance of neuronal cell fate prevents brain dysfunction

How neurons differentiate has been broadly studied during the past years. However, comparably little is known about how postmitotic neurons maintain their cell fate throughout life, thereby preventing neurodegeneration and associated

diseases. Unlike many neurodevelopmental regulators, the transcription factor Myelin Transcription Factor 1-Like (MYT1L) is not only expressed during development but also in adulthood, suggesting a potential role in maintaining neuronal fate. Interestingly, low levels of MYT1L are associated with various brain disorders, including Alzheimer's disease. Here, we investigate the role of MYT1L in lifelong maintenance of the neuronal fate and function. Postnatal depletion of Myt1l caused hyperactivity and social impairment *in vivo*, a phenotype that we previously reported in the context of neurodevelopmental disorders caused by Myt1l germline depletion. To further understand the molecular changes underlying the functional defects *in vivo*, we analysed transcriptomic changes in the prefrontal cortex upon conditional postnatal depletion of Myt1l in mice. Surprisingly, non-neuronal gene programs were upregulated in knockout mice whereas neuronal genes were downregulated. Genes associated with cognition, memory and learning were also downregulated while genes involved in cell death were upregulated, suggesting a potential link of MYT1L loss and neurodegeneration. Finally, we showed that postmitotic MYT1L depletion also causes functional defects in human induced neurons. Taken together, these results show that MYT1L depletion in postmitotic neurons causes functional defects in mice *in vivo* and in human neurons *in vitro* which mimics phenotypes associated with neurodevelopmental disorders caused by MYT1L germline depletion, strengthening the role of MYT1L in neuronal fate maintenance.

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**35** **Jule Truberg**, Jana Tegethoff, Bettina Weigel

### Loss of neuronal cell fate and function in pluripotent stem cell-derived neurons from MYT1L syndrome patients

Neurodevelopmental disorders (NDDs) such as autism are a significant challenge worldwide. Despite advancements in understanding the intricate workings of the brain, the cause of many NDDs is still unclear, leading to a lack of effective treatment options. Numerous transcriptional regulators are linked to NDDs. However, unlike other regulators, MYT1L, a neuron-specific transcription factor, drives and maintains neuronal cell fate by suppressing non-neuronal genes rather than activating neuronal ones. Patients with MYT1L loss-of-function mutations are often diagnosed with MYT1L syndrome consisting of symptoms including autism spectrum disorder, intellectual disability but also other phenotypes like seizures and obesity. Engineered MYT1L-deficient human neurons and primary mouse neurons exhibit MYT1L-target upregulation, delayed neurogenesis, and neuronal hyperactivity, which were normalized by the FDA-approved drug lamotrigine. Although the engineered MYT1L mutations are similar to patient mutations, the disease-specific background is missing. Hence, we used patient-derived stem cell induced neurons carrying different MYT1L mutations to investigate whether the type (missense/nonsense) or the genetic region (different functional domains) of the mutation affects the functional phenotype and the gene regulatory capacity of MYT1L. We found that MYT1L mutations in patient neurons cause similar hyperactivity phenotypes which can be rescued by the treatment with lamotrigine. In order to learn more about the molecular mechanisms in which MYT1L affects the neuronal function, RNA-seq and ATAC-seq were performed. My project showed the loss of neuronal cell fate and function in stem cell-derived neurons from MYT1L syndrome patients and has the potential to pave the way to new treatment options for MYT1L syndrome

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**36** **Martina Braun**, Lukas Kremer, Santiago Cerrizuela, Simon Anders, Ana Martin-Villalba

### Detection of differentially methylated regions in single-cell bisulfite sequencing data by scbs diff

DNA methylation can now be measured at single-base pair and single-cell resolution using single-cell bisulfite sequencing (scBS-seq). An essential goal in studies performing scBS-seq is to identify genomic regions that differ in methylation between distinct cell types, tissues, or conditions, so-called differentially methylated regions (DMRs). DMRs provide valuable insights into unique epigenetic and gene regulatory characteristics, as methylation plays a significant role in gene expression. Currently, software solutions to calculate DMRs of variable size are only available for bulk methylation data, therefore the standard approach for scBS-seq still relies on using pre-defined genomic regions such as CG islands, CG shores, and gene bodies. However, this approach is limited to targeted settings, and the location of differential methylation is often unknown in advance. Here I offer a solution by presenting a method that defines candidate DMRs of variable size and subsequently explicitly evaluates statistical significance at the regional level. I validated the method's performance using vSVZ neuroblasts and oligodendrocytes from a published dataset, demonstrating its ability to detect biologically relevant DMRs with a putative regulatory role. The procedure is implemented as the scbs diff command in the scbs package, a comprehensive software toolkit for scBS data analysis.

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**37** **Merve Akan**, Ivan Skorodumov, Marcus Meinhardt

### Psilocybin tolerance disrupts hallucinogenic pause and quipazine-induced head twitches

Tolerance is a compensatory biological mechanism for repeated drug exposure which can also occur between different drugs as cross-tolerance. The present study investigates the behavioural effects of psilocybin tolerance in operant lever pressing and pharmacological effects with quipazine cross-tolerance in head twitch response. Adult male Wistar rats were trained for lever pressing with a reward of sweet water for one week. After the shaping phase, psilocybin group received 1 mg/kg and 4 mg/kg (i.p.) psilocybin while control group was receiving saline for 5 consecutive days of operant

lever pressing. On the 6th day, both groups were given 2 mg/kg quipazine to assess the psilocybin cross-tolerance on quipazine-induced head twitch response. Psilocybin tolerance resulted in the disruption of hallucinogenic pause in operant lever-pressing on the 2nd day with significantly higher presses in psilocybin group compared to the number of presses on the 1st day. Saline group did not show significant change in the number of presses between the days. This result shows the quick emergence of behavioural tolerance to psilocybin. On the 6th day of quipazine challenge, saline group showed significantly higher number of head twitches compared to psilocybin group. This result indicates the cross-tolerance of psilocybin to quipazine-induced head twitch response.Overall, repeated psilocybin administration was coupled with repetitive operant conditioning sessions caused an acute behavioural tolerance with the disruption of hallucinogenic pause as well as a pharmacological cross-tolerance to quipazine.

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**38** **Ivan Skorodumov**, Yelena le Prieult, Merve Akan, Marcus Meinhardt

### Ibogaine restores control over compulsive alcohol drinking in addicted rats

Alcohol addiction, characterized by a compulsive desire to drink alcohol despite knowledge or evidence of its harmful consequences, affects about 23 million Europeans and creates a large health burden worldwide. Although substantial research has been done into possible therapies, currently available pharmacological treatments demonstrate limited efficacy. In the scope of recent resurgence of interest in psychedelic drugs, one particularly promising candidate is ibogaine, a psychoactive alkaloid present in Tabernanthe iboga that consistently reduces opioid withdrawal symptoms, and in many cases promotes abstinence in individuals addicted to alcohol. Based on these data, we performed a study to assess ibogaine's efficacy in a model of alcohol dependence that is predominantly driven by negative reinforcement. In this model, Wistar rats undergo chronic intermittent alcohol vapor exposure for 14 h/day over the period of 7 weeks, as a result, animals reach clinically relevant blood alcohol levels, develop physical withdrawal signs and long-lasting neuroadaptations. Before and after the vapor exposure, rats are trained in daily 30 min operant sessions to self-administer 10% ethanol coupled with orange smell serving as odor cue. We administered ibogaine 24h before quinine-adulterated alcohol self-administration session and cue-induced reinstatement and assessed motivation for reward in both sessions. Ibogaine significantly reduced alcohol self-administration in taste aversion test and motivation for obtaining reward in cue-induced reinstatement, suggesting a long-lasting effect on addiction memory. We conclude that ibogaine demonstrates promising results in our model of alcohol addiction that warrant further research into its mechanism of action and translational potential for use in pharmacotherapy.

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**39** **Sofiya Zbaranska**, Debanjan Chowdhury, **Katharina Held**, Duncan Archibald Allan MacLaren, Hannah Monyer

### Characterization of septal somatostatin-positive neurons and their projections to the hippocampus

The medial septum (MS) is a thin subcortical structure in the rostral forebrain, which maintains numerous functions. It generates theta rhythm and relays it to the hippocampus and medial entorhinal cortex, thereby supporting spatial coding and memory formation, modulates attention, and even processes emotions. This functional diversity is achieved by heterogeneous cell types harbored within the MS. Three main neuronal types comprise cholinergic, GABAergic, and glutamatergic cells. GABAergic neurons can be further subdivided into calbindin (CB)-, parvalbumin (PV)- and somatostatin (SOM)-positive cells. Previous studies have shown that CB- and PV-expressing neurons send long-range projections targeting interneurons in the medial entorhinal cortex and hippocampus. The nature of targeted interneurons differs resulting in distinct behavioral effects. While the physiology and long-range connectivity of septal CB and PV cells have been addressed before, the portrait of SOM-expressing neurons has remained obscure. Recent discovery in the Monyer lab revealed that septal SOM neurons might innervate the hippocampus and led us to investigate the functional role of these projections. The aim of the present project encompasses the characterization of SOM neurons in the MS, in particular their electrophysiological properties, local connectivity as well as elucidation of a functional projection to the hippocampus. To achieve this, *in vivo* electrophysiological recordings have been performed in the MS or hippocampus along with optogenetic activation of MS SOM-positive neurons or their projections to the hippocampus. Understanding the hippocampal targets of SOM neurons could shed light on whether and how these neurons affect spatial coding and memory.

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**40** **Debanjan Chowdhury**, Duncan MacLaren, Beate Throm, Magdalene Schlesiger, Nina Bieber, Hannah Monyer

### Identifying mechanisms involved in acute alcohol-induced amnesia

Alcohol intoxication can impair episodic (autobiographical) and spatial (navigational) memory. These memories are formed in different subareas of the hippocampal formation, including the hippocampus proper (HC) and the medial entorhinal cortex (MEC). The rhythmic activity within these regions is orchestrated by GABAergic projection neurons of the medial septum (MS). The effects of alcohol on these systems are unexplored. My project aims to examine the effects of acute alcohol intoxication on functional cell types and network-level activity in and between these regions by combining optogenetics with *in vivo* electrophysiological recordings in behaving mice. Alcohol administration at a dosage of 1.5 g/kg intraperitoneally leads to a reduction in the firing rate of fast-spiking cells in the MS, MEC (strongest effect),

and HC. The firing rate of grid cells in the MEC, but not of place cells in the HC, is reduced following alcohol administration. At the network level, alcohol administration causes a reduction of the LFP theta frequency in both the MEC and HC. Phase precession, a temporal coding property of spatially selective cells, is affected by alcohol in grid cells in the MEC, but not in place cells in the HC. Stimulation of PV+ septal cells reliably paces the theta frequency in the MEC and HC, and stimulating CB+ septal cells recovers the alcohol-induced reduction in the firing rate of fast-spiking cells in the MEC. Hence, we infer that the MEC is more susceptible to alcohol than the HC. Thus, the present study investigates the neural circuits involved in alcohol-induced memory deficits.

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**41** **Danny Baltissen**, Charlotte S. Bold, Lena Rehra, Marija Banicevic, Justus Fricke, Jennifer Just, Susann Ludewig, Christian Buchholz, Martin Korte, Ulrike C. Müller

### APPsα rescues CDK5 and GSK3β dysregulation and restores normal spine density in Tau transgenic mice

Alzheimer's disease (AD) is characterized by the accumulation of hyperphosphorylated Tau species as neurofibrillary tangles, which are a major hallmark of the disease. Another characteristic of AD is the presence of extracellular Aβ plaques, which are derived from the β-amyloid precursor protein APP. APP processing along the competing non-amyloidogenic pathway results in the secretion of neurotrophic and synaptotrophic APPsα. Recently, we demonstrated that APPsα has therapeutic effects in transgenic AD model mice and rescues Aβ-dependent impairments. In this study, the potential of APPsα to regulate two major tau kinases, GSK3β and CDK5, was examined in THY-Tau22 mice, a widely used mouse model of tauopathy. Immunohistochemistry revealed a dramatic increase in pathologically phosphorylated Tau and misfolded Tau species in the hippocampus of THY-Tau22 mice between 3-12 months of age. Using a highly sensitive radioactive kinase assay, an increase in GSK3β and CDK5 activity in the hippocampus of Thy-Tau22 mice was demonstrated. However, AAV-mediated intracranial expression of APPsα in THY-Tau22 mice efficiently restored normal GSK3β and CDK5 activity. Furthermore, AAV-APPsα reduced misfolded Tau species, particularly in somatodendritic compartments of CA1 pyramidal neurons. Finally, it was shown that AAV-APPsα normalized PSD95 expression and deficits in spine density of THY-Tau22 mice. These findings suggest that APPsα may hold therapeutic potential to mitigate Tau-induced pathology in AD.

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**42** **Lena Rehra**, Lelia Wagner, Vicky Steubler, Tobias Köthe, Philipp Uhl, Gundula Braun, Gert Fricker, Christian Buchholz and Ulrike Müller

### Investigating the therapeutic potential of the APPsα-derived CTα16 peptide

The development of senile plaques is a key feature of Alzheimer’s disease. These plaques are extracellular protein aggregates mainly consisting of the β-amyloid peptide (Aβ), which arises by proteolytic cleavage of the amyloid precursor protein (APP). While the role of APP as a precursor of Aβ is well established, its physiological functions remain elusive. Studies have shown that APPsα and APPsβ fragments, generated by non-amyloidogenic or amyloidogenic processing of APP, serve distinct roles. AAV-mediated overexpression of APPsα by stereotactic injections has proven to efficiently rescue spine density, synaptic plasticity and spatial reference memory deficits in knockout mouse models. Furthermore, the C-terminal 16 amino acids of APPsα (which are lacking in APPsβ) are sufficient to produce similar rescue effects. In this project, we want to establish different administration procedures to further test the therapeutic potential of CTα16 while aiming at minimally invasive routes instead of stereotactic injections into the brain. On the one hand, we use surface-modified liposomes for blood-brain barrier transfer of the peptide. On the other hand, we would like to induce AAV-mediated CTa16 overexpression by using the AAV2-BR1 capsid, which specifically targets brain endothelial cells after intravenous injections.

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**43** **Lara Kilian**, Marija Banicevic, Susanne Erdinger, Dominique Fäßler, Verena Bengelsdorff, Ulrike Müller

### Characterization of novel APP-knockin mutants lacking important functional domains for secretion or cell adhesion

The amyloid precursor protein (APP) plays a pivotal role in Alzheimer’s Disease, as sequential cleavages of APP by the β- and γ-secretase first form the soluble fragment APPsβ and finally the neurotoxic peptide Amyloid-β (Aβ). Alternatively, cleavage by the a-secretase disrupts the Aβ domain and releases the soluble fragment APPsα. Adeno-associated overexpression of APPsα could partially rescue deficits in peripheral and central nervous system of conditional APP/APLP2 double knockout mice. As a type I transmembrane protein, APP can form homo- and heterotypic dimers in cis- and trans-orientation via its E1 domain. This could be shown to mediate presynaptic differentiation. In line with this, APP mutations diminishing its trans-dimerizing properties led to reduced synaptogenic activity in neuronal cell culture studies. Notably, inhibition of APP processing strongly enhanced cell adhesion and promoted its synaptogenic activity. However, the interplay between the dimerized and the secreted APP has been examined so far only *in vitro* and lacks *in vivo* validation. I continue dissecting the two different modes of APP signaling as a soluble ligand and/or as a synaptic adhesion molecule (SAM) in novel secretion deficient (APPΔS622) and dimerization deficient (APPΔE1) knockin mice. APP expression and proteolytic processing is assessed predominantly via western blot and immunohistochemistry (IHC) in comparison to wildtype mice. This will be followed by a detailed phenotypic analysis including evaluation of spine

plasticity, synaptic transmission and cognitive properties. Together, we hope to better understand the physiological role of APP and its complex signaling via soluble fragments or cell-cell interaction.

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**44** **Verena Bengelsdorff**, Lena Rehra, Dominique Fäßler, Susanne Erdinger, Lara Kilian, Danny Baltissen, Martina Braun, Ulrike C. Müller

### Establishing an injection protocol for tamoxifen-inducible knockdown of the amyloid precursor protein (APP) gene family in mice

This project aims to explore the consequences of acute loss of the amyloid precursor protein (APP) and its homolog amyloid precursor like protein 2 (APLP2) *in vivo* using the Tamoxifen (TAM)-inducible CreERT2/loxP system. A three-week Tamoxifen administration protocol was used to achieve a global APP/APLP2 double knockout in adult mice. Although APP expression was significantly reduced in peripheral organs, APP expression was only slightly reduced in the spinal cord, not at all, in the brain. Changing the TAM solvent to Miglyol-812 resulted in severe adverse events and early termination of Tamoxifen application after two weeks. However, Western blot results showed a significant reduction in APP in the hippocampus, rest brain, and spinal cord. Compared to the two-week injection protocol, the three-week protocol yielded a more significant APP reduction in peripheral tissues. To analyze the limited knockdown of APP in the CNS, Cre activity was evaluated using Ai14 and HPRT-tdTomato reporter mice that were crossed to ROSA26-CreERT2 mice and injected with Tamoxifen following the 3-week injection protocol. Immunohistochemical investigation of brain and spinal cord slices suggests Cre-mediated recombination rarely occurred in neurons and mainly in nonneuronal cells, potentially endothelial cells. In summary, both established Tamoxifen injection protocols provide a valuable tool to investigate the physiological functions of APP in various contexts, such as the role of APP in peripheral organs like the heart and liver, as well as its functions at the neuromuscular junction, potentially uncovering new APP functions in complex biological processes.

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**45** **Dominique Fäßler**, Susanne Erdinger, Vicky Steubler, Michaela K. Back, Susann Ludewig, Max Richter, Kang Han, Lutz Slomianka , Irmgard Amrein, Jakob von Engelhardt, David P. Wolfer, Marc Busche, Martin Korte, Ulrike C. Müller

### Characterization of mice that lack APP family members

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease in humans. It is characterized by two hallmarks, Tau tangles and amyloid plaques, made up of aggregates of the amyloid precursor protein (APP). The key role of APP in the pathogenesis of Alzheimer's disease is well established. However, the physiological function of APP and its family members APLP1/2 are not jet fully understood. In order to analyze the physiological function of the APP family, conditional triple KO (cTKO) were generated. These animals are fully, viable but showed altered brain morphology with agenesis of the corpus callosum and impaired lamination of the hippocampus. Further, electrophysiological recordings in the hippocampus of adult cTKO mice indicated a strong synaptic phenotype with pronounced deficits in the induction and maintenance of hippocampal LTP and impairments in paired pulse facilitation, indicating a possible presynaptic deficit, as well as severe behavioral abnormalities including cognitive decline and stereotypical- and impulsive-behavior traits. Moreover, *in vivo* calcium imaging of cortical neurons revealed an increase in the abundance of silent neurons which may disturb the excitation/inhibition balance. Here we used scRNAseq as well as nCounter experiment to determine the genetic makeup of our cTKOs in comparison to their corresponding littermate animals. In order to validate the sequencing data a RNAscope was carried out.

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**46** **Stefanos Loizou**, Harrison Gabel, Ana M. M. Oliveira

### Characterization and reversibility of cognitive deficits in a mouse model of Tatton-Brown-Rahman syndrome

A *de novo* mutation in the DNA methyltransferase 3A gene (DNMT3A) causes Tatton-Brown-Rahman syndrome (TBRS), a recently described genetic neurodevelopmental disorder that currently has no treatment. Patients display tall stature, macrocephaly and intellectual disability. Dnmt3a encodes for the enzymes DNMT3A1 and DNMT3A2. These enzymes, according to literature as well as published and unpublished work from our lab, play a crucial role in memory formation in the adult hippocampus. However, how brain and neuronal function is affected in TBRS remains poorly understood. This project aims to bridge this gap of knowledge by using a novel mouse model. Our pilot studies have revealed differences in line with cognitive deficits at the behavioural level. Morphological differences at distinct developmental stages are currently being investigated. Additionally, we will investigate for differences in the transcriptional and cellular level, as well as if engram reactivation is impacted. Recent gene replacement approaches have yielded positive results for other neurodevelopmental disorders in which replacing the dysfunctional gene reversed some of the pathology. Thus, in a next step, DNMT3A will be restored in adult TBRS animals to observe if deficits are ameliorated and cognitive function is improved. Should the process prove effective, TBRS research will greatly benefit, allowing for the development of more acute, and perhaps even definitive, treatments moving forward. Furthermore, it would serve to challenge the notion that neurodevelopmental disorder derived cognitive deficits are irreversible in adulthood.

**47** **Janina Kupke**, Stefanos Loizou, Carsten Sticht, Ana M. M. Oliveira

### DNA methylation promotes memory persistence by facilitating systems consolidation and cortical engram stabilisation

Persistence is a key characteristic of memory that relies on systems consolidation, a process classically defined as the gradual transfer of information from the hippocampus to the cortex for long-term memory storage. However, the underlying molecular mechanisms are unknown. DNA methylation can act as a long-term regulatory signal, therefore being a prime candidate to regulate memory duration and stabilisation within engrams– the physical substrate of a memory. Using contextual fear conditioning (CFC) and engram tagging tools in mice, we showed that reactivation of cortical engrams reflects systems consolidation. We found higher engagement of cortical engrams selectively in persistent fear memory. To address whether DNA methylation underlies persistent memory storage and neuronal ensemble reactivation, we overexpressed a DNA Methyltransferase (Dnmt3a2) in the dorsal hippocampus of mice during CFC. Strikingly, we found a conversion of short-lasting into long-lasting memory. Moreover, we found an improved reactivation of cortical engrams and increased fear generalisation, mimicking the engram dynamics and behavioural trait of remote memory, respectively. Further, using chemogenetic inhibition of the cortical engram, we proved that the memory trace resides in the cortex. These findings demonstrate that DNA methylation processes facilitate the transfer of information from the hippocampus to the cortex for long-term storage. To gain further mechanistic insight we uncovered, using RNA-Sequencing, Dnmt3a2 target genes that may underlie the memory persistence. In summary, we found that DNA methylation in dorsal hippocampus converts a short-lasting into a persistent memory by the facilitation of systems consolidation and associated stabilisation of cortical engrams.

**48*** **Janina Kupke, Lisa M. Spänig**

### Introduction to the Deutsche Neurowissenschaften-Olympiade (DNO) and all the ways that passionate neuroscientists like YOU can contribute

The Deutsche Neurowissenschaften-Olympiade e.V. (DNO) is a non-profit organization dedicated to inspiring the next generation of young neuroscientists. Inspired by the International Brain Bee (IBB), our program promotes the study of life-sciences by directly reaching out to high school students via neuroscience competitions aimed to drive critical thinking and foster new ideas in young minds. These competitions serve as platforms that not only showcase their knowledge but also encourage critical thinking, problem-solving, and the development of innovative ideas.

We are seeking passionate minds like **yours** to join us on this inspiring journey. As a member of our team, you will have the incredible opportunity to contribute to the discovery of new talent, inspire the next generation of neuroscientists, and make meaningful and long-lasting connections with likeminded individuals. Your expertise, guidance, and mentorship will play a crucial role in igniting their curiosity, fostering their passion, and nurturing their potential.

Together, we can create an environment that empowers young minds to excel in the field of neuroscience. We believe in the transformative power of education and the immense impact it can have on individuals and society as a whole.

Our motto, “Driving Connectivity,” refers to the multiple organizational and functional levels of neuronal activity within the human brain. It also refers to our desire to encourage national and international exchange among young students on their way towards a scientific career. Join us at the DNO and be part of the driving force shaping tomorrow’s scientific discovery.

**49** **Lisa M. Spänig**, Robert Reinhardt, Sinem Saka, Stefan M. Pfister, Lena M. Kutscher

### Investigating the development of unipolar brush cells, a glutamatergic interneuron of the cerebellum and cell-of-origin of medulloblastoma

Medulloblastoma is one of the most common malignant tumors of the central nervous system in children and develops in the cerebellum. Four distinct molecular groups of medulloblastoma have been identified: wingless activated (WNT), sonic hedgehog activated (SHH), Group 3 and Group 4. Of all medulloblastoma cases, 40% of medulloblastoma patients are diagnosed with Group 4 medulloblastoma. Although Group 4 medulloblastoma is the most prevalent group, its pathogenesis remains poorly understood, mainly because of the lack of good preclinical models. Recently, it was discovered that the unipolar brush cell (UBC) lineage of the cerebellum is the lineage-of-origin for Group 4 medulloblastoma. While it is known that UBCs play a role in balance and movement, their development is less understood. To better understand UBC biology, we are investigating the role of UBCs in the developing mouse cerebellum. Based on previous studies, the transcription factors Tbr2 and Lmx1a may be essential for UBC development. We find that TBR2 and LMX1A are co-expressed in early progenitor cells and later in development in UBCs. The master regulator Atoh1 is co-expressed with Tbr2 and Lmx1a at the mRNA level only in early progenitors of UBCs. Using multiplex immunofluorescence (Immuno-SABER), we are investigating the co-expression of 9 transcription factors and 4 receptor-markers during UBC development in wildtype mice on one single brain section. This study will help us gain insight into how protein expression and localization changes during UBC development. With this knowledge, we are better equipped to model Group 4 medulloblastoma in the future, addressing a critical gap.

**50** **Jing Chen**, Yifeng Zheng, Bahardokht Tolou-Dabbaghian, Melanie Motsch, Norbert Weidner, Radhika Puttagunta

### The modulatory effects of activity-based interventions on spinal cord injury-induced neuropathic pain: exploring sex differences

Neuropathic pain is a debilitating condition often experienced by individuals with spinal cord injury (SCI). It is characterized by sensory abnormalities and is notoriously difficult to treat. Activity-based interventions (ABI) have emerged as a promising approach for ameliorating SCI-induced neuropathic pain (SCI-NP). Growing evidence suggests males and females may differ in their perception and experience of SCI-NP. Additionally, the potential influence of sex on the modulatory effects of ABI remains unclear. To address this gap, we conducted a moderate T11 contusion SCI model (50 kDyn) in adult male and female C57BL/6 mice, followed by an ABI regimen of 3-week treadmill training (2 x 15 min/day, 3 x/week). At 7 days post-injury (dpi), both male and female injured mice developed mechanical allodynia when tested with small-diameter von Frey filaments but exhibited hypo-responsiveness to noxious mechanical stimuli. Moreover, there was a significant decrease in the response latency to heat stimuli, indicating the presence of thermal hyperalgesia. At 7 days post-ABI, animals displayed a significant reduction in the response rate to light mechanical stimuli, and this analgesic effect persisted throughout ABI. However, thermal sensitivity, as assessed by the response latency to heat stimuli, was not affected by ABI. Importantly, our data revealed no distinction in the presentation of SCI-NP nor any significant difference in the alleviation of ABI between male and female SCI mice at several testing time points (7, 14, 21, and 28 dpi). Thus, these findings together indicate that ABI partially relieves SCI-NP and modulates pain states without sex-based differences.

**51** **Bahardokht Tolou-Dabbaghian**, Jing Chen, Jarred Griffin, Melanie Motsch, Norbert Weidner, Radhika Puttagunta

### The role of the α2-δ2 subunit of the voltage-gated calcium channel in nociceptors in spinal cord injury-induced neuropathic pain in mice

Following experimental spinal cord injury (SCI), below injury-level mechanical allodynia is associated with increased sprouting of calcitonin gene-related peptide (CGRP+) fibers into laminae III-IV. We examined the role of this sprouting in the development of mechanical allodynia through prophylactic pregabalin (PGB) treatment, a commonly prescribed drug for SCI patients following the development of neuropathic pain. Male and female C57BL/6J mice were treated with PGB (46 mg/kg, i.p., 2x/day, for 7 days) immediately after a T11 moderate contusion. Prophylactic PGB administration prevented the development of mechanical allodynia and sprouting of CGRP+ fibers into laminae III-IV in the lumbar spinal cord, which was sustained for up to two weeks following PGB discontinuation. To investigate the role of the α2-δ2 subunit of voltage-gated calcium channel (VGCC), a target of PGB, we have utilized SNS-Cacna2d2-/+ mice in which the subunit (Cacna2d2) is partially knocked out in nociceptors. Strikingly, SNS-Cacna2d2-/+ mice did not develop thermal (Hargraves) or mechanical allodynia (von Frey filaments and place escape/avoidance paradigm) post-SCI. Furthermore, hindpaw stimulation using a typically non-noxious filament prior to perfusion led to dorsal horn activation (cFos), with significantly lower activation in PGB treated as well as partial knockout mice. The highest neuronal activation level was observed in lamina III-IV of the dorsal horn. Through 3D imaging of nociceptor-labeled transgenic mice (SNS-tdTomato), we are studying below-level nociceptor termination patterns in response to SCI. These findings highlight the crucial role of nociceptors as well as their VGCCs α2-δ2 subunit in the development of neuropathic pain following SCI.

**52** **Sarah Hörner**, Nathalie Couturier, Daniele Gueiber, Roman Bruch, Mathias Hafner, Rüdiger Rudolf

### Human iPSC and 3D-bioprinting technologies for the development of neuromuscular tricultures including glia cells

Neuromuscular junctions (NMJs) are tripartite synapses in the peripheral nervous system formed by motor neurons, skeletal muscle fibers, and terminal Schwann cells. So far, Schwann cells have not been represented in NMJ cell models primarily due to technical limitations. We have established protocols to differentiate Schwann cells from human induced pluripotent stem cells (hiPSC) in a robust manner by tuning of BMP signaling activity during the differentiation, further maturation of Schwann cells in medium which is specifically composed to be compatible with neuromuscular tricultures, and to set up tricultures of hiPSC-derived Schwann cells and hiPSC-derived motoneurons in combination with murine C2C12 muscle cells or hiPSC-derived muscle cells. In 2D tricultures, we demonstrate colocalization of all cell types at sites positive for post-synaptic muscle acetylcholine receptor, and effects of cocultured cell types on myotube growth and receptor plaques. Furthermore, 3D-bioprinting and culturing methods are explored to selectively integrate hiPSC-derived Schwann cells into complete 3D neuromuscular cultures.

**53*** **Nathalie Couturier**, Sarah Janice Hörner, Mathias Hafner, Rüdiger Rudolf

### Towards a human iPSC-derived model to address neuromuscular development and disorder

Skeletal muscle mediates voluntary movements thanks to cholinergic synapses, neuromuscular junctions (NMJs). NMJ formation, maintenance, and functioning rely on an efficient crosstalk between Schwann cells, motoneurons,

sympathetic neurons, and myofibers. Defects in any of these cellular components might lead to neuromuscular disorders. To address cell-type specific contributions to neuromuscular disorders, we have worked on engineered hiPSC-derived NMJ models. Therefore, we previously optimized and developed protocols for differentiation and coculture of hiPSC-derived motoneurons and Schwann cells. Here, we demonstrate efficient differentiation of muscle cells and their coculture with motoneurons, both derived from wildtype and mutant hiPSC, the latter carrying a SOD1 D90A mutation involved in the neuromuscular disorder, amyotrophic lateral sclerosis. Upon stimulation of muscle cells with acetylcholine, both wildtype and SOD1 D90A mutant cells showed consistent Ca2+ transients and contraction, that could be suppressed by a-bungarotoxin, an antagonist of nicotinic acetylcholine receptors (nAChR) at NMJs. However, Ca2+ transients were reduced in SOD1 D90A mutant cells. Upon coculture with isogenic motoneurons, wildtype muscle cells displayed stabilized nAChR clusters and a reduction of endocytic nAChR vesicles. Conversely, in SOD1 D90A mutant muscle cells the number of endocytic nAChR vesicles was low in the absence of motoneurons and it was only slightly reduced upon their addition. In summary, this work continued the construction of an all-human NMJ model and its application to aspects related to amyotrophic lateral sclerosis. Future work will include further hiPSC-derived components to address developmental and biomedical neuromuscular aspects.

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**54** **Julia Dyckow**, Celine Geywitz, Torben Ruhwedel, Hannah Kapell, Wiebke Möbius, Klaus-Armin Nave, Lucas Schirmer

### Investigating the function of Piezo proteins in the oligodendrocyte lineage

Proper myelin wrapping along axons is essential to a fast saltatory conduction of action potentials. In the central nervous system (CNS), myelin is built by oligodendrocytes (OLs) and shows pathological abnormalities not only in demyelinating diseases such as multiple sclerosis (MS), but also in neurodevelopmental disorders. Piezo proteins are mechanosensitive ion channels which convert mechanical impulses into electrical signals. So far, studies have focused on their role in pain and touch sensation in the peripheral nervous system. This study aims at understanding the role of Piezo2 in the CNS during development and aging. We investigated dynamics in expression profiles over time of Piezo1 and Piezo2 in the OL lineage. Besides, we performed rotarod behavioral assay in two different Piezo2 loss of function mouse lines, discovering motor deficits in later time points. Electron microscopy of Cnp-Piezo2 depleted optic nerves revealed changes in g-ratios and axon diameters pointing towards disturbed myelin wrapping. By using retinal flat mounts, we stained for retinal ganglion cells and found decreased numbers in knockout mice at later developmental time points. Our findings suggest that Piezo2 is important for proper myelination of axons and myelin-axon signaling. Therefore, this study will ultimately help decipher Piezo2 channel function during homeostatic and disease conditions such as MS.

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**55** **Rangeet Manna**, Duncan Archibald Allan MacLaren, Magdalene Isabell Schlesiger

### Lateral entorhinal spatial coding in a conditioned place preference task

The formation and processing of episodic memory relies on the hippocampo-entorhinal system. The lateral entorhinal cortex (LEC) provides a major cortical projection to the hippocampus. It has been shown in behavioural experiments in rats and mice that lesions of the LEC impair the ability to form memories that require the association of object, spatial and contextual information. The neuronal mechanisms that underly these computations are yet little understood. Early studies using *in vivo* electrophysiological recordings in behaving rats found that LEC neurons lack sophisticated spatial firing patterns as typically observed in the hippocampus, but are preferentially concerned with coding for particular objects within the environment. These initial studies were performed in simplistic experimental settings such as foraging in empty open-field environments. An increasing number of studies, however, indicate that processing in the system substantially changes in more complex environmental settings. The spatial tuning of LEC neurons, for example, increases substantially when objects are put into the open-field environment. Of note, this transformation in LEC coding seems to be associated with engaging or rewarding conditions that are also known to activate the midbrain DA system. Here we use *in vivo* electrophysiological recordings in a conditioned place preference (CPP) paradigm to test the hypothesis that the activation of DA neurons in the ventral tegmental area (VTA), which strongly project to LEC, drives reward-context associations by increasing the precision of spatial coding in LEC.

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**56** **Kalaivani Manibarathi**, Tam Pham, Emma Katharina Fürtsch, Sophie Schäfer, Katrin Bratl, Maike Nagel, Klaus Dittmann, Rebecca Schüle

### RNA therapies for ultrarare diseases: development of a mutation-specific ASO therapy for POLR3A-associated spastic ataxia

**Objective:** We aim to devise a mutation-specific RNA therapy for *POLR3A* c.1909+22G>A, using antisense oligonucleotides (ASOs), in disease specific human induced cortical neuronal model systems (hiCNs) *in vitro*.

**Background:** Spastic ataxias (SA) are neurodegenerative disorders that share overlapping cellular and molecular pathomechanisms of hereditary spastic paraplegia and cerebellar ataxia. In our recent study, we have identified POLR3A as an rare cause of SA. Specifically, we observed a recurrent mutation at c.1909+22G>A in both autosomal recessive and sporadic cases in a compound heterozygous state. This mutation leads to an intronic inclusion, resulting in the

production of a leaky aberrant transcript. The observed intronic variant is a promising target for a mutation-specific splice-modulating antisense oligonucleotide therapy.
**Methods:** To investigate the molecular pathomechanisms of *POLR3A* c.1909+22G>A and establish cellular readouts for ASO treatment, we employed the following methods 1) Establishment of human induced cortical neuronal (hiCN) model systems *in vitro* for downstream analyses 2) Validation of the RPC1 (*POLR3A*) DNA repair function in patients and healthy fibroblasts using γH2AX irradiation assay 3) Chromatin immunoprecipitation and sequencing (ChIPSeq) to examine the effects on *POLR3A* transcriptome in the established hiCNs.
**Results:** Here we reprogrammed and differentiated fibroblasts of three unrelated male *POLR3A* c.1909+22G>A patients and age and sex matched healthy individuals to hiPSC and hiCN models that are further characterised. RPC1 was recently established for its function in repairing double strand breaks, which was analysed through γh2AX irradiation assay, shows a significant two-fold higher residual damage in patient fibroblasts than controls, underlining a novel pathomechanism for SA. To identify the RPC1 transcribed genes in patient and control hiCNs, ChIPseq was carried out, which identified a novel set of small RNA candidates that are affected by the *POLR3A* loss of function in hiCNs.
**Conclusion:** From the current study, we have validated one of the novel molecular pathomechanisms of *POLR3A* c.1909+22G>A mutation in repairing DNA damage using fibroblasts; Further we also established a set of small RNAs that are transcribed by *POLR3A* and are vulnerable to a *POLR3A* deficiency in hiCN model systems. These cellular readouts will be used to evaluate the efficiency of a splice-modulating ASO *in vitro*.

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**57** **Francesco Giannone**, Arian Hach, Magda Chrószcz, Marion Friske, Marcus Meinhardt, Rainer Spanagel, Wolfgang H. Sommer, Anita C. Hansson

### Generalized habitual tendencies in alcohol dependent rats

Habitual responses and ultimately compulsive behavior are thought to be at the core of addiction including alcohol use disorder (AUD). Little is known whether the habituation concerns exclusively the response towards alcohol or generalizes to other daily activities. Here, we address this question in a well-established animal model of AUD – the post-dependent rat model – by testing habitual responses towards a sweet palatable reward in two striatal learning paradigms: spatial navigation and reward conditioning. For the spatial navigation task, alcohol-dependent and control rats were tested on a sequential decision-making test after short and prolonged T-Maze training, for the reward conditioning task, rats were trained under a random interval schedule for a short and prolonged period and tested in a satiety devaluation test at each time point. Moreover, two additional experiments were conducted to assess the role of the dorsomedial striatum (DMS) in the observed AUD-related habitization via bidirectional chemogenetic manipulation. Our results provide evidence that a history of alcohol dependence produces a bias towards habitual responding that generalizes to a natural reward in rats. Similarly, a habitual bias was induced in non-dependent rats after DMS inhibition, while DMS activation in dependent rats led to restored goal-directed control, thus confirming the critical role of this region in maintaining goal-directed behavior and suggesting it's diminished control in AUD.

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**58** **Armin Drusko**, Julian Reichert, Prof. Dr. Jonas Tesarz

### Computational modeling of aberrant pain perception within a Bayesian framework

Fibromyalgia syndrome (FMS) is characterized by severe widespread pain and commonly accompanied by psychological comorbidities, such as major depressive disorder (MDD). While the pathophysiology remains poorly understood, the symptoms could be potentially explained by an aberrant central processing of sensory information. This processing bias was previously suggested for symptoms in MDD and experimentally shown in patients with psychosis. Considering the high comorbidity of MDD and FMS, similar mechanisms of aberrant cognitive processing might yield in the perception of non-noxious or low-pain stimuli as more painful in FMS. To test the hypothesis of erroneous pain perceptions in FMS, the sensory processing of electrical stimuli, administered during a conditioned perceptions task, was investigated in patients with FMS, patients with MDD and healthy controls (HCs). Subsequent computational modeling was utilized to quantify the weighting between pain expectation (prior) and sensory stimulation during pain perception. Additionally, a potential association of strong prior weighting with occurrences of victimization experiences (VEs) and clinical symptoms was investigated. Patients with FMS were expected to have a strong prior weighting during pain perception, associated with a higher prevalence of VEs and clinical symptoms. Although the results show a higher occurrence of VEs in FMS and MDD, there was no evident difference in prior-to-sensory-evidence weighting between the study groups. Thus, a strong prior in FMS could not be demonstrated in this work. Improving the experimental paradigm and testing alternative models of perception might help facilitate the understanding of potential aberrant pain perceptions in FMS in future work

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**59** **Cedric Stahl**, Christian Thiel

### Towards understanding the impact of ALG5 impairment on protein N-glycosylation

Glycosylation is an important modification of proteins and lipids by sugar structures. Depending on the attachment of sugar structures to the protein, glycosylation is further divided into N-linked and O-linked glycosylation, addition of

phosphorylated glycans, glycosaminoglycans, glycosylphosphatidylinositol (GPI) anchors and C-mannosylation. N-linked glycosylation displays the most common form of glycan attachment. Synthesis of oligosaccharides for the N-glycosylation pathway takes place in the endoplasmic reticulum (ER), whilst alteration/modification occurs in the Golgi apparatus. The sugar moieties affect processes like protein folding, transport and enzyme activity. Defects in protein glycosylation processes are termed congenital disorders of glycosylation (CDG). Dolichylphosphate beta-glucosyltransferase (ALG5) is an enzyme located in the ER membrane and is essential for N-glycosylation as it generates Dol-P-Glucose, the substrate for the ALG6, ALG8 and ALG10 glucosyltransferases. To this date, the role of ALG5 for protein glycosylation is insufficiently studied and only one patient with a monoallelic variant in ALG5 has been described. The patient presents nephropathy characterized by the development of small bilateral kidney cysts as well as renal interstitial fibrosis causing a late-onset progressive loss of kidney function. In this project we aim to investigate organ specific ALG5 expression patterns and utilize CRISPR/Cas9 methods as well as site-directed mutagenesis and overexpression experiments to investigate the impact of biallelic ALG5 impairment on protein N-glycosylation.

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**60** **Giulia Di Muzio**, Hsin-Jui Lu, Franciscus van der Hoeven, Brittney Armstrong, Lorenzo Corazzi, Yassin Harim, Li-Chin Wang and Pei-Chi Wei

### Cycling plasticity of neuronal progenitor cells during neuronal development

Radial glial cells (RGCs) are the common progenitors of neuronal cells in the brain. In mice, within ten days, embryonic RGCs undergo innumerable cell divisions to generate over 70 million neurons in the brain. Although embryonic RGC division is tightly controlled, whether this process is exclusively intrinsically regulated or can be modulated by extrinsic factors *in vivo* is, surprisingly, poorly understood. We propose that RG cells intrinsically sense their pool size. Therefore, we suggest that a shortage of embryonic RGs signals the remaining cells to increase their proliferation rate to support the neurogenesis. To test this hypothesis, we created a NestinCre-mediated diphtheria toxin subunit A expression mouse model (Nestin-Cre+::ROSA-LSL-DTA+), where 30-50% of embryonic RG cells will die at E11.5-12.5. In this model, the leftover progenitor population is forced to reconstruct the shrunken progenitor pool. According to our hypothesis, in the Nestin-Cre+::ROSA-LSL-DTA+ embryos we were able to detect a decrease in the cell cycle length of the surviving progenitor cells. Moreover, histology and immunofluorescent stainings confirmed that the brain of the Nestin-Cre+::ROSA-LSL-DTA+ embryos are comparable to the littermate controls in both structure and lamination. We can conclude that RG cells are plastic in reconstituting the depleted progenitor pool. On the other hand, because of that, RG cells experience increased replication stress that might lead to an accumulation of DNA damage, causing genome instability. In this view, the final goal of this study is to investigate the relationship between RG proliferation plasticity and the acquisition of genomic mutations during neurogenesis.

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**61** **Isabel Loss**, Rüstem Yilmaz, Rosanna Parlato, Carsten Sticht, Babak Loghmani, Axel Freischmidt, Johannes Wilbertz, Loic Cousin, Philipp Koch, Jochen Weishaupt

### Modelling ALS caused by KIF5A mutations in patient-derived motor neurons

Our group has previously described heterozygous ALS-causing mutations in the Kinesin Family Member 5A (KIF5A). These mutations are located in the C-terminal tail and have been predicted to affect the splicing of exon 27, altering the globular cargo-binding domain of the kinesin. Indeed, a mutation resulting in KIF5A exon 27 skipping (ΔExon27) has been shown to cause altered protein and RNA interactions. Moreover, we recently found that the conformational changes caused by ΔExon27 is inducing neurotoxicity by abolishing KIF5A autoinhibition. We obtained hiPSCs from one pre-manifest carrier of a heterozygous ΔExon27 mutation (c.3020+2T>C) and from two ALS patients of a family with a c.2993-1G>A heterozygous mutation, and differentiated them into motor neurons. We showed that these mutations alter exon 27 splicing differently, yet they both lead to the production of a common C-terminal aberrant 39 amino acid end. In addition, patient-derived motor neurons displayed a significant increase in KIF5A inclusions in comparison to control, in accordance with recent publications showing that ΔExon27 is prone to form cytoplasmic aggregates when overexpressed in different cell lines. Here, we characterized these aggregates as the starting point for the setup of a pre-clinical platform for the development of new pharmaceutical strategies. Ultimately, RNA bulk sequencing analysis of induced motor neurons revealed that the expression of mutant KIF5A lead to pathways involved in RNA processing, chromatin remodelling and neuronal projection development to be altered. Taken together, these findings will expand the mechanistic understanding of KIF5A/ALS pathology and help identifying therapeutic targets for modulating ALS pathobiological mechanisms.

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**62** **Ketrin Dimco**, Rosanna Parlato, Rüstem Yilmaz, Jochen Weishaupt

### Myorg protein quality control dysfunction in primary familial brain calcification

Primary Familial Brain Calcification (PFBC, formerly known as Fahr's disease) is a clinically and genetically heterogeneous neurological disorder, represented by progressive bilateral intra- and perivascular calcifications in different brain regions, such as basal ganglia, cerebellum, thalamus, and brain stem. The clinical penetration of PFBC is incomplete and heterogeneous. Depending on the severity of calcifications, patients can be asymptomatic or, in cases of excessive calcifications, clinical symptoms range from occasional headaches to severe movement disorders with

cerebellar and extrapyramidal syndromes, as well as cognitive and neuropsychiatric manifestations. To date, no causal therapy exists. More recently, we have discovered the first disease gene that causes autosomal-recessively inherited PFBC, known as myogenesis regulating glycosidase or MYORG. MYORG is a putative glycosidase, enriched in the endoplasmic reticulum, and involved in post-translational modifications. Strikingly, all PFBC genes identified so far are predominantly expressed in cells that form the blood-brain barrier (astrocytes, pericytes, endothelial cells). Nevertheless, the specific role(s) of distinct cell types for PFBC pathogenesis are not clear yet. We propose the use of induced astrocytes (iAs) from human embryonic stem cells (hESCs) in order to accurately study the role of MYORG in a human model and the pathological mechanisms governed by loss-of-function mutations on astrocytes and the human brain. The overall goals of this project are to delineate pathways and cell-autonomous as well as non-cell-autonomous pathomechanisms underlying PFBC by comparative transcriptomic analysis of iAs at different ages, with the ultimate goal of delineating *in vitro* models amenable to high throughput screening for therapeutic molecules. More recently, we have discovered the first disease gene that causes autosomal-recessively inherited PFBC, known as myogenesis regulating glycosidase or MYORG. MYORG is a putative glycosidase, enriched in the endoplasmic reticulum, and involved in post-translational modifications. Strikingly, all PFBC genes identified so far are predominantly expressed in cells that form the blood-brain barrier (astrocytes, pericytes, endothelial cells). Nevertheless, the specific role(s) of distinct cell types for PFBC pathogenesis are not delineated yet.

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## 63* **Alexander Dieter**, Lena Eschholz, Chantal Wissing, Maxime Maheu, Simon Wiegert

### Investigating the neuromodulation of learning and memory

Hippocampus-dependent learning and memory is modulated by neuromodulatory transmitters such as dopamine or noradrenaline. Here, we present optogenetic and photometric approaches to study the release of neuromodulators *in vivo*, and discuss future project ideas on how to implement these tools to investigate the neuromodulation of learning and memory.

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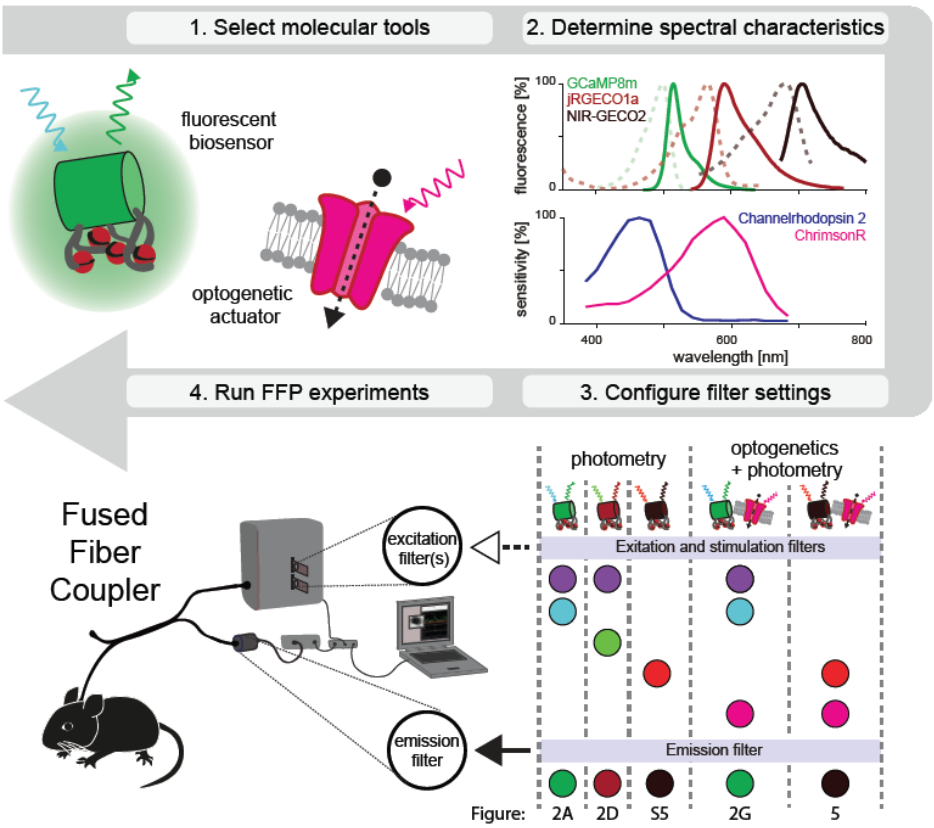
## 64* **Andrey Formozov**, **Alexander Dieter**, J. Simon Wiegert

### A flexible and versatile system for multi-color fiber photometry and optogenetic manipulation

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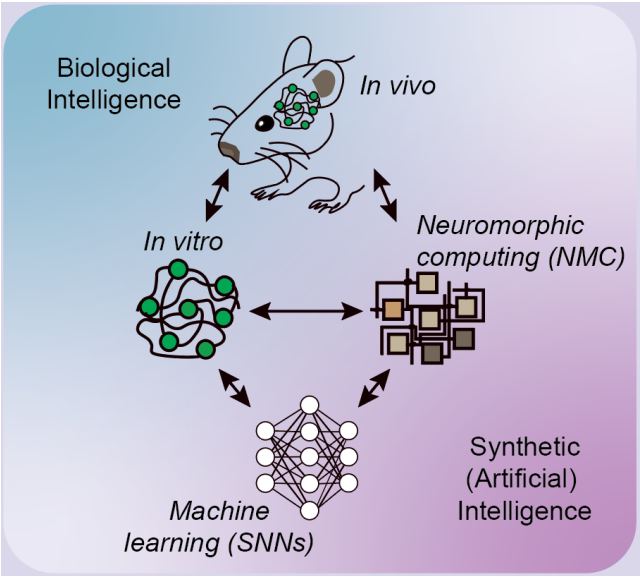
Fiber photometry is a technique of growing popularity in neuroscience research. It is widely used to infer brain activity by recording calcium dynamics in genetically defined populations of neurons. Aside from the wide variety of calcium indicators, other genetically encoded biosensors have recently been engineered to measure membrane potential, neurotransmitter release, pH, or various cellular metabolites, such as ATP or cAMP. Due to the spectral characteristics of these tools, different assemblies of optical hardware are usually needed to reveal the full potential of different biosensors. In addition, combining multiple sensors in one experiment, often requires the investment in more complex equipment, which limits the flexibility of the experimental design. Such constraints often hamper a straightforward implementation of new molecular tools, evaluation of their performance *in vivo*, and construction of new experimental paradigms – especially if the financial budget is a limiting factor. Here, we propose a novel approach for fiber photometry recordings and optogenetic manipulation. In combination with a multi-color light source and appropriate emission filters, our approach offers remarkable flexibility in experimental design and facilitates the implication of new molecular tools *in vivo* at minimal cost. The ease of assembly, operation, characterization, and customization of this platform holds the potential to foster the development of experimental strategies for multicolor fiber photometry combined with optogenetics far beyond its current state.

## 65* **Andrey Formozov**, J. Simon Wiegert

### Neurobiological computing and all-optical brain interfacing

How organisms acquire, process, and store information is the central question of neurobiology. A large body of evidence suggests that plasticity is a main element of learning and memory formation, while complex interactions in neuronal networks with plasticity are believed to explain biological intelligence and higher cognitive functions. However, direct experimental demonstration of complex emergent phenomena remains challenging. Nevertheless, significant progress in the understanding of complex phenomena was made through modeling and simulations thanks to theoretical and computational neuroscience. Neurobiology has also inspired the development of synthetic (artificial) intelligence with a scope far beyond biological questions, accompanied by a manifestation of neuromorphic engineering and computing. Importantly, it was shown computationally that biologically-plausible spiking neural networks could perform purely synthetic machine-learning tasks. Direct experimental implementation of such synthetic algorithms in living brains is still absent: full computational power of biological neuronal networks has never been practically used, and the underlying research field is only emerging. Building on the technological progress in all-optical interrogation of brain circuits and biological networks and the long-term maintenance of brain cultures, I raise the following question: Can neuromorphic-like computing be realized in real biological networks?




## 66 **Lena Eschholz**, Chantal Wissing, Maxime Maheu, Fabio Morellini, Alexander Dieter, J. Simon Wiegert

### Targeting noradrenergic neurons of the locus coeruleus: A comparison of model systems and strategies

In recent years, the Locus Coeruleus (LC) has been refined from a widely broadcasting nucleus, mainly involved in stress response and arousal, to a more modular structure with context-dependent function, involved in a plethora of physiological and pathophysiological processes. Detailed investigation of LC function has become possible thanks to new technologies. These include genetic tools such as cre driver lines and viral vectors, enabling access to molecularly identified neural populations. Here, we compare carious strategies for virus-mediated transgene expression in the catecholaminergic neurons of LC. We found substantial differences both in the efficacy and molecular specificity of reporter gene expression between the different strategies. In particular, the DBH-cre line and a strategy based on the PRS-promotor showed promising results. While cre-driver lines did not show altered behavior as assessed by anxiety tests and memory tasks, the TH-cre line was not suitable for precise LC-targeting due to low specificity and efficiency for transgene expression. Together, these results might guide the choice for an adequate targeting strategy in future research.

## 67 **Sophie Stichert**, Jürgen Haas, Sven Jarius, Brigitte Fritz, Katharina Mattes, Mirjam Korporal-Kuhnke, Brigitte Wildemann

### Impaired X-chromosomal inactivation—a key mechanism for female predisposition to MS and NMOSD?

Introduction: As in most human autoimmune diseases (AID), there is a strong female predisposition in Multiple Sclerosis (MS) (female:male ratio 3:1) and neuromyelitis optica spectrum disorder (NMOSD, ratio 9:1). X-chromosomal inactivation (XCI), a process that is mediated by a long non-coding RNA (XIST), balances the amount of gene expression between the sexes through silencing of one X-chromosome in each female cell. XCI has long been hypothesized to be involved in AID and may partly explain this gender bias. One possible mechanism could be skewed XCI, which means maternal and paternal X-chromosomes are not inactivated in equal amounts, as previously shown for autoimmune thyroid disease and scleroderma. During normal development of lymphocytes, XCI is temporarily interrupted. A permanent interruption of XCI has been suggested to be another possible mechanism for increased susceptibility to AID. Objectives/Aims: 1. To compare the XCI skewing rates in peripheral blood mononuclear cells (PBMC) of female patients with MS and NMOSD to that in healthy women of the same age. 2. To assess whether skewed XCI may trigger a more aggressive disease course in female patients with MS and NMOSD. 3. To analyze XIST localization and expression in B- and T-cells obtained from peripheral blood samples of female RRMS patients, NMOSD patients and healthy controls in order to address the question whether persistent XCI plays a role in the immunopathogenesis of the diseases. Methods: PBMCs of 115 female MS patients and 52 female NMOSD patients were collected to analyze XCI.

XCI skewing rates were determined by the PCR-based HUMARA-assay. This included DNA-isolation, enzymatic digestion, PCR and fragment-length-analysis. After magnetic enrichment of B- and T-cells, XIST RNA expression analysis was determined by following RNA isolation and reverse transcription by quantitative RT-PCR. XIST localization was analyzed with simultaneous RNA-FISH and immunofluorescence. Results: A tendency towards higher skewing degrees can be seen in female MS (mean 57,3%) and NMOSD (mean 59,9%) patients compared to healthy controls (mean 55,2%). XIST expression tended to be lower in MS and NMOSD patients compared to healthy individuals, although there was no statistical significance. Conclusion: We observed a tendency towards (a) a higher frequency of skewed XCI and (b) lower XIST expression in MS and NMOSD patients than in healthy individuals, supporting the hypothesis that impaired XCI may play a role in female predisposition to MS and NMOSD.

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**68** **Viktoria Greeck**, Cornelia Würthwein, Richard Fairless, Jürgen Haas, Brigitte Wildemann

### Reduced Treg suppressive capacity exacerbates B cell dysfunction in Multiple Sclerosis

Research strongly indicates the multi-factorial role of self-reactive B cells in driving multiple sclerosis (MS) pathophysiological processes. In MS, B cell clones expressing auto-reactive B cell receptors (BCRs) are able to escape tolerance checkpoints that maintain self-tolerance under normal physiological conditions. Incomplete elimination of self-reactive B cells may partially be mediated by dysfunctions in the suppressive capacity of regulatory T cells (Treg). Furthermore, B cell fate is to a large extent regulated by BCR stimulation-induced calcium signals and the downstream activation of distinct, calcium-dependent transcriptional programmes that either result in B cell apoptosis, or survival and expansion. We aimed to assess whether calcium responses and their downstream signalling cascades in B cells differ between healthy donors and MS patients, and whether MS patient-derived Treg differently affect B cells. Using single-cell calcium imaging and *in vitro* proliferation assays, we showed that in both healthy donors and MS patients, BCR stimulation with anti-IgM and anti-CD40 co-stimulation resulted in a significant increase in intracellular calcium and B cell proliferation, indicating that B cell responses to stimulation are unaltered in MS. Treg did not interfere with anti-IgM/anti-CD40 stimulation-induced calcium signals, but suppressed B cell proliferation in healthy donors. MS patient-derived Treg, however, reduced BCR stimulation-induced B cell proliferation to a lesser extent. Mixed co-cultures with cells derived from healthy donors and MS patients revealed that this alteration in B cell proliferative capacity was due both to a reduced Treg suppressive capacity in MS, and a reduced ability of B cells to integrate suppressive signals.

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**69*** **Matthia A. Karreman**, Nils R. Hebach, Varun Venkataramani, Chanté D. Mayer, Linh C. Nguyen, Cedric Tehranian, David Hausmann, Lukas Geckeler, Theresa Kraft, Michael Seifert, Dana Westphal, Thomas Kuner, Wolfgang Wick, Frank Winkler

### Cancer networks in brain metastases

Brain Metastases (BrM) are the most common malignancy of the brain, arising most commonly from lung, melanoma and breast cancer primaries. While the interaction of BrM with the brain microenvironment and the role of calcium signals induced by neurons, astrocytes and endothelial has been characterized, relatively little is known about tumor-tumor and tumor-neuron interactions. Here, we present melanoma BrM-intrinsic calcium network communication *in vitro* as well as *in vivo*, monitored by intravital two-photon microscopy through a cranial window in mice. Importantly, inhibiting of calcium oscillations results in reduced BrM growth *in vitro* and *in vivo*. Moreover, we discovered functional glutamatergic synapses between neurons and BrM, which can also induce calcium transients. In preclinical models of melanoma and breast cancer BrM, pharmacological and genetic inhibition of these synapses leads to a reduction of brain metastatic growth. These findings underscore the roles of network communication and neuron-tumor crosstalk in BrM pathobiology, revealing potential new therapeutic targets to combat this devastating disease.

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**70*** Anne K. Thomann, **Mike M. Schmitgen**, Kristina Szabo, Matthias P. Ebert, Wolfgang Reindl, Robert C. Wolf

### Structural correlates of extraintestinal symptoms in Crohn's disease in active and remitted patients

Crohn's disease (CD) is often accompanied with extraintestinal symptoms, which cannot be fully assigned to intestinal inflammatory processes. In this regard fatigue, anxiety, and depression are very common, and these symptoms occur more often during active phases of the disease and are possibly linked to gut-brain interactions. Here we investigated differences in gray matter volume (GMV) between active (aCD) and remitted (rCD) CD-patients and healthy controls (HC). Additionally, we tested for associations between GMV and fatigue, anxiety, and depression, as well as concentration of fecal calprotectin (fC). Ninety MRI brain-scans were acquired (aCD = 30, rCD = 23, HC = 37) and then tested for differences in GMV using the CAT12 toolbox. Fatigue was measured via the WEIMuS questionnaire and anxiety and depression via HADS-A and HADS-D, respectively. Brain-symptom-relationships were tested via Spearman correlations. The groups differed in anxiety, depression, fatigue, and fC, where aCD showed the highest burden. GMV differed between HC and patients, irrespective of disease status (PAT). HC showed greater GMV in left cerebellum, precentral gyrus, right cuneus, fusiform gyrus, gyrus rectus, and lingual gyrus. No differences in GMV were found between aCD and rCD. Fatigue was negatively correlated with GMV of precentral, fusiform, and lingual gyrus in PAT and fC was positively correlated with depressiveness. Our findings show that GMV of PAT differs from HC in distinct

brain regions that are tightly associated with fatigue. The data underlines the role of gut-brain interactions in the development of extraintestinal symptoms in CD.

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**71** **Yéléna Le Prieult**, Marie-Luise Otte

### Structural integrity of the language network in patients with borderline personality disorder with and without auditory verbal hallucinations

Borderline Personality Disorder (BPD) is a severe mental disorder, characterized by extreme sensitivity to perceived interpersonal slights, an unstable sense of self, intense and volatile emotionality and impulsive behaviors that are often self-destructive. In addition, auditory verbal hallucinations (AVH) can occur. Most of the neuroscientific research considered individuals with AVH in schizophrenia. The neural underpinnings of AVH in BPD patients are unknown. Through a cross-sectional magnetic resonance imaging (MRI) study, we studied structural correlates of the AVH in BPD patients with AVH (n=14) and without AVH (n=24) and healthy control (HC, n=25). We focused on key regions of the language network and conducted region-interest (ROI) analyses for three distinct structural markers, i.e. gray matter volume (GMV), cortical thickness and gyrification. Data processing was performed with the Statistical Parametric Mapping analysis package (SPM12) and the computaStructural integrity of the language network in patients with borderline personality disorder with and without auditory verbal hallucinationstional anatomy toolbox (CAT12). Subsequently, analyses of variance were computed using age and total intracranial volume as covariates. These analyses suggested significant differences between patients with and without AVH .i.e. i) gyrification in the right transverse temporal gyrus (p=0.026) and marginally significant in the left planum temporale (p=0.05) and for the cortical thickness in the left opercularis part of the inferior frontal gyrus (p=0.05). These preliminary findings suggest a putatively transdiagnostic neural signature of AVH involving abnormalities of brain regions related to speech generation and auditory perception. The data also support a multi-parametric neural model that considers both pre- and postnatal neurodevelopmental factors having an impact on AVH occurence in BPD.

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**72** **Marton Istvan Molnar**, J. Simon Wiegert, Andrey Formozov

### New optical approaches for the manipulation and read-out of hippocampal circuits at multiple time scales

The hippocampal formation is a bilateral medial temporal lobe structure found across all vertebrates. Among many of its physiological roles, it is also believed to be involved in the pathogenesis of several psychiatric diseases: Alzheimer's disease (AD), schizophrenia, depression, epilepsy, and autism disorder; through alterations in hippocampal network-level rhythmogenesis. Key mediators of hippocampal rhythm generation and coordination are perisoma-targeting parvalbumin-positive interneurons (PVIs). Many hippocampal interneurons are targeted by neuromodulators through their specific composition of G-protein coupled receptors (GPCRs). However, the precise dynamics of GPCR activation at interneurons via neuromodulators in the hippocampus is still not very well understood. Therefore, it would be important to fill this gap especially with the availability of the modern optogenetic toolkit, enabling exceptional spatiotemporal precision. In my research project, I will apply novel GPCR-coupled opsins to investigate the effects of neuromodulation on PVI dynamics and consequently on hippocampal network activity *in vitro* and *in vivo.*

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**73** **Maryam Najafian Jazi**, Adrian Tymorek, Ting-Yun Yen, Felix Jose Kavarayil, Moritz Stingl, Sherman Richard Chau, Benay Baskurt, Celia García Vilela and Kevin Allen

### Hippocampal firing fields anchored to a moving object predict homing direction during path-integration-based behavior

Homing based on path integration (H-PI) is a form of navigation in which an animal uses self-motion cues to keep track of its position and return to a starting point. Despite evidence for a role of the hippocampus in homing behavior, the hippocampal spatial representations associated with H-PI are largely unknown. Here we developed a homing task (AutoPI task) that required a mouse to find a randomly placed lever on an arena before returning to its home base. Recordings from the CA1 area in mice showed that hippocampal neurons remap between random foraging and AutoPI task, between trials in light and dark conditions, and between search and homing behavior. During the AutoPI task, approximately 25% of the firing fields were anchored to the lever position. The activity of 24% of the cells with a lever-anchored field predicted the homing direction of the animal on each trial. Our results demonstrate that the activity of hippocampal neurons with object-anchored firing fields can predict homing behavior.

*** Posters marked with an asterisk do not qualify for the IZN students' poster prize.**