LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

HARVARD UNIVERSITY

LMU–Harvard Young Scientists' Forum

From Molecules to Organisms XV,
Munich, July 19 – July 21, 2023

The LMU-Harvard Young Scientists' Forum (YSF) seeks to unite PhD students and Postdoctoral fellows from the Harvard University and the Ludwig-Maximilians-Universität (LMU Munich) with core faculty from the two universities to create a framework for an interdisciplinary exchange of ideas.
The YSF was initiated as a yearly event in 2009 and is held alternately in Munich and Cambridge.

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- **LMU-Harvard Young Scientists' Forum at the LMU Biocenter:** From Molecules to Organisms, July 19 – July 21, 2023
- **Under the auspices of** Prof. Dr. Francesca Biagini, Vice President for International Affairs and Diversity, LMU
- **Program Management:** Dr. Susanne Döring-Buchmann (LMU International Office), Sylvia Zehner (LMU Munich Center for Neurosciences)
- **Participating academic units:** Munich Center for Neurosciences (MCN), Graduate School for Systemic Neurosciences (GSN)
- **Academic Management:** Prof. Dr. Oliver Behrend, Prof. Dr. Benedikt Grothe (MCN/GSN)
- **Institutional Responsibility:** LMU International Office, LMU Biocenter

Conference Agenda

Tuesday, July 18

	Arrival (LMU International Office, or individually arranged)
	IZB Residence CAMPUS@HOME (address below)

Wednesday, July 19

	LMU Biocenter, Grosshadernerstr. 2, 82152 Martinsried, D00.003
09:00 – 09:15	*Walk* from IZB Residence to Biocenter
09:15 – 09:30	**Welcome address** (B.Grothe, Munich Center for Neurosciences and S.Lauterbach, LMU International Office)
09:30 – 10:30	**Lecture 1** – M.Andermann: **"Cortical reactivations predict future sensory responses"** (Intro: B.Grothe)
	Coffee break (catered; foyer D00.003)
11:00 – 13:00	**Session 1** – **"Sensory circuit processing"** Schuhknecht/Sobolev/Ribero/Alcami (Chair: B.Grothe)
	Lunch break (catered; foyer)
14:30 – 16:30	**Session 2** – **"Systems Neurology"** Feiten/Blaskovic/Hahn/Douglass (Chair: M.Pecka)
	Coffee break (catered; foyer)
17:00 – 18:00	**Lecture 2** – C.Haass: **"Is the Amyloid cascade still valid to explain Alzheimer's disease?"** (Intro: M.Pecka)
18:45 – open	Bavarian Conference Evening (Fürstenrieder Schwaige, Forst-Kasten-Allee 114, 81475 München; transfer pre-arranged at IZB Residence)

Thursday, July 20

	LMU Biocenter Martinsried, D00.003
08:45 – 09:00	*Walk* from IZB Residence to Biocenter
09:00 – 10:00	**Lecture 3** – S.Koch: **"Limited Limitations: Restoring Vision in Retinal Degeneration"** (Intro: M.Myoga)
	Coffee break (catered; foyer)
10:30 – 12:30	**Session 3** – **"Biomedical Neurosciences and Clinical Perspectives"** Besedovsky/Kenet/Lagomarsino/Martinez R./Nagappan C. (Chair: M.Myoga)
	Lunch break (catered; foyer)
14:30 – 16:30	**Session 4** – **"Neurodevelopment"** Ries/Pravata/Faravelli/Terauchi/Marahori (Chair: L.Busse)
	Coffee break (catered; foyer)
17:00 – 18:00	**Lecture 4** – H.Umemori: **"Molecular logic in synaptic circuit development and disease"** (Intro: L.Busse)
18:00 – open	*At free disposal (student representative activities)*

Friday, July 21

	LMU Biocenter Martinsried, D00.003
08:45 – 09:00	*Walk* from IZB Residence to Biocenter
09:00 – 10:00	**Lecture 5** – S.Jacob: **"A brain-computer-interface with cellular resolution for the investigation of language"** (Intro: P.Alcami)
	Coffee break (catered; foyer)
10:30 – 12:30	**Session 5** – **"Molecular and Cellular Components of Neuronal Circuit Function"** Chen/Russell/Bludau/Campbell/Bernklau (Chair: P.Alcami)
	Lunch break (catered) & **YSF poster session** (foyer) & **YSF faculty meeting** (B00.051)
	Poster – De Weerd/Essner/Evans/Heisterkamp/Held/Hohendorf/ Hoermann/Khuntia/Lin/Lutz/Meyerolbersleben/Muppirala/Popovic/ Righetti/Totiger/Vilceanu/Wang/Winhart
14:30 – 15:30	**Lecture 6** – M.Rao: **"The brain in the gut: a central regulator of digestive health and disease"** (Intro: O.Behrend)
15:30	**Closing remarks** (O.Behrend MCN-LMU; K.Blum CBS)
15:45	*Walk* from Biocenter to IZB Residence / *individually: beergarden*

Saturday, July 22

IZB Residence CAMPUS@HOME,
Am Klopferspitz 21, 82152 Martinsried
Departure (LMU International Office, or individually arranged)

Participants*

*Participating PhD students and Postdoctoral fellows have been nominated by selected faculty members of LMU and Harvard University (please note the heads of the nominees' "home laboratories" at the end of each entry).

Harvard University Delegation

- **Mark L. Andermann**, Professor, Harvard Medical School, Department of Medicine & Beth Israel Deaconess Medical Center
- **Kenneth Blum,** Executive Director, Harvard Center for Brain Science
- **Malcolm Campbell,** Postdoctoral Fellow, Department of Molecular and Cellular Biology, Laboratory of Naoshige Uchida
- **Alex Chen**, PhD student, Department of Molecular and Cellular Biology, Laboratory of Florian Engert
- **Amelia Douglass**, Postdoctoral Fellow, Beth Israel Deaconess Medical Center, Laboratory of Bradford Lowell
- **Rachel Essner**, PhD student, Harvard Medical School, Department of Medicine & Beth Israel Deaconess Medical Center, Laboratory of Mark Andermann
- **Kathryn Evans**, MD/PhD student, Harvard Medical School, Department of Medicine & Beth Israel Deaconess Medical Center, Laboratory of Mark Andermann
- **Irene Faravelli**, Postdoctoral Fellow, Harvard Stem Cell Institute, Laboratory of Paola Arlotta
- **Niko Hörmann**, Postdoctoral Fellow, Department of Molecular and Cellular Biology, Laboratory of Florian Engert
- **Hakan Kucukdereli**, Postdoctoral Fellow, Beth Israel Deaconess Medical Center, Laboratory of Mark Andermann
- **Valentina Lagomarsino**, PhD student, Harvard Medical School, Laboratory of Meenakshi Rao
- **Anoohya Muppirala**, PhD student, Harvard Medical School, Laboratory of Meenakshi Rao
- **Sivapratha Nagappan-Chettiar**, Postdoctoral Fellow, Harvard Medical School, Laboratory of Hisashi Umemori
- **Meenakshi Rao**, Professor, Harvard Medical School
- **Andy Russell,** Postdoctoral Fellow, Harvard Medical School, Laboratory of Chinfei Chen
- **Gregor Schuhknecht**, Postdoctoral Fellow, Harvard Department of Molecular and Cellular Biology, Laboratory of Florian Engert
- **Akiko Terauchi**, Postdoctoral Fellow, Harvard Medical School, Laboratory of Hisashi Umemori
- **Hisashi Umemori**, Professor, Boston Children's Hospital, Harvard Medical School

Harvard University Nominating Faculty

- **Mark L. Andermann**, Professor, Harvard Medical School, Department of Medicine & Beth Israel Deaconess Medical Center
- **Paola Arlotta**, Professor, Harvard Center for Brain Science, Stem Cell Institute
- **Chinfei Chen**, Professor, Harvard Medical School, Division of Medical Sciences
- **Florian Engert**, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology
- **Brad Lowell**, Professor, Beth Israel Deaconess Medical Center & Harvard Medical School
- **Venkatesh Murthy**, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology
- **Meenakshi Rao**, Professor, Harvard Medical School
- **Naoshige Uchida**, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology
- **Hisashi Umemori**, Professor, Boston Children's Hospital, Harvard Medical School

Ludwig-Maximilians-Universität München (LMU)
Helmholtz Zentrum München – German Research Center for Environmental Health (HMGU)
Max Planck Institute of Biological Intelligence (MPI-BI)
Max Planck Institute of Psychiatry (MPI Psych)
Technische Universität München (TUM)
Delegation

- **Pepe Alcami**, Principal Investigator, LMU, Department of Biology, Division of Neurobiology, Laboratory of Benedikt Grothe
- **Oliver Behrend**, Managing Director, LMU, Munich Center for Neurosciences (MCN), Graduate School of Systemic Neurosciences (GSN)
- **Tobias Bernklau**, Postdoctoral Fellow, TUM, Department of Neurosurgery, Laboratory of Simon Jacob
- **Luciana Besedovsky**, Professor, LMU, Institute of Medical Psychology
- **Martin Biel**, Professor, LMU, Department of Pharmacy
- **Borbola Blaskovic**, Postdoctoral Fellow, LMU, Medical Psychology, MPI of Psychiatry, Laboratory of Martha Merrow
- **Oliver Bludau**, Postdoctoral Fellow, LMU, Department of Physiological Genomics, BioMedical Center (BMC), Laboratory of Antje Grosche

- **Laura Busse**, Professor, LMU, Department Biology, Division of Neurobiology
- **Jan Deussing**, Principal Investigator, MPI of Psychiatry
- **Lis De Weerd**, PhD student, German Center for Neurodegenerative Diseases (DZNE), Laboratory of Christian Haass
- **Astrid Feiten**, Postdoctoral Fellow, LMU BioMedical Center, Metabolic Biochemistry, Laboratory of Christian Haass
- **Thomas Geyer**, Professor, LMU Department of Psychology
- **Magdalena Götz**, Professor, LMU, Department of Physiological Genomics, HMGU
- **Antje Grosche**, LMU, Department of Physiological Genomics, BioMedical Center (BMC)
- **Benedikt Grothe**, Professor, LMU, Department Biology, Division of Neurobiology, Munich Center for Neurosciences (MCN), Graduate School of Systemic Neurosciences (GSN)
- **Christian Haass**, Professor, LMU, Biomedical Center, Metabolic Biochemistry, German Center for Neurodegenerative Diseases (DZNE), SyNergy Excellence Cluster of Systems Neurology
- **Lisa Hahn**, Postdoctoral Fellow, LMU, Department of Psychiatry and Psychotherapy, MPI of Psychiatry, Laboratory of Nikolaos Koutsouleris
- **Patrick Heisterkamp**, Postdoctoral Fellow, LMU, Department Biology, Laboratory of David Keays
- **Lisa Held**, PhD student, TUM, Translational Neurotechnology, Laboratory of Simon Jacob
- **Victoria Hohendorf**, PhD student, TUM, Translational Neurotechnology, Laboratory of Simon Jacob
- **Simon Jacob**, Professor, TUM, Translational Neurotechnology
- **Selin Kenet**, Postdoctoral Fellow, TUM, Institute of Neuronal Cell Biology, Laboratory of Thomas Misgeld
- **Adyasha Khuntia**, PhD student, LMU, Department of Psychiatry and Psychotherapy, MPI of Psychiatry, Laboratory of Nikolaos Koutsouleris
- **Susanne Koch**, Professor, LMU, Department of Pharmacy, Center for Drug Research
- **Stefan Lauterbach**, Head, LMU, International Office
- **Xiaxiong Lin**, PhD student, TUM, Translational Neurotechnology, Laboratory of Simon Jacob
- **Nicolas Lutz**, Postdoctoral Fellow, LMU, Medical Psychology, Laboratory of Martha Merrow
- **Natalia Marahori,** Postdoctoral Fellow, TUM, Institute of Neuronal Cell Biology, Laboratory of Thomas Misgeld
- **Fernanda Martinez Reza**, PhD student, HMGU, Institute for Stem Cell Research, Laboratory of Magdalena Götz
- **Lucas Meyerolbersleben**, PhD student, LMU, Department Biology, Division of Neurobiology, Laboratory of Laura Busse
- **Stylianos Michalakis**, Professor, LMU, Department of Pharmacy

- **Thomas Misgeld**, Professor, TUM, Institute of Neuronal Cell Biology, German Center for Neurodegenerative Diseases (DZNE)
- **Michael Myoga**, Professor, LMU, BioMedical Center
- **Michael Pecka**, Professor, LMU, Department Biology, Division of Neurobiology
- **Luksa Popovic**, PhD student, LMU, Clinic of Psychiatry and Psychotherapy, Laboratory of Michael Wehr
- **Veronica Pravata**, Postdoctoral Fellow, LMU, BioMedical Center, MPI of Psychiatry, Laboratory of Silvia Capello
- **Ines Ribeiro**, Principal Investigator, LMU, Medical Psychology, Laboratory of Martha Merrow
- **Clemens Ries**, PhD student, MPI of Psychiatry, Graduate School of Systemic Neurosciences (GSN), Laboratory of Jan Deussing
- **Beatrice Righetti**, PhD student, TUM, Translational Neurotechnology, Laboratory of Simon Jacob
- **Andrey Sobolev**, Postdoctoral Fellow, LMU, Department Biology, Division of Neurobiology, Laboratory of Michael Pecka
- **Santosh Totiger**, PhD student, LMU, Department Biology, Division of Neurobiology, Laboratory of Pepe Alcami
- **Alexandra Vilceanu**, Postdoctoral Fellow, LMU, Department Biology, Laboratory of David Keays
- **Xuanyu Wang**, PhD student, TUM, Translational Neurotechnology, Laboratory of Simon Jacob
- **Valentin Winhart,** PhD student, LMU, Department Biology, Division of Neurobiology, Laboratory of Michael Pecka

Munich Nominating Faculty

- **Laura Busse**, Professor, LMU, Department Biology II, Division of Neurobiology
- **Silvia Capello**, LMU, Department of Physiological Genomics, BioMedical Center (BMC)
- **Jan Deussing**, Principal Investigator, MPI of Psychiatry
- **Peter Falkai**, Professor, Director, LMU, Clinic of Psychiatry and Psychotherapy
- **Magdalena Götz**, Professor, LMU, Department of Physiological Genomics, HMGU
- **Antje Grosche**, LMU, Department of Physiological Genomics, BioMedical Center (BMC)
- **Benedikt Grothe**, Professor, LMU, Department Biology, Division of Neurobiology, Munich Center for Neurosciences (MCN), Graduate School of Systemic Neurosciences (GSN)

- **Christian Haass**, Professor, LMU, Biomedical Center, Metabolic Biochemistry, German Center for Neurodegenerative Diseases (DZNE), SyNergy Excellence Cluster of Systems Neurology
- **Simon Jacob**, Professor, TUM, Translational Neurotechnology
- **David Keays**, Professor, LMU, Department Biology
- **Nikolaos Koutsouleris**, Professor, LMU Department of Psychiatry and Psychotherapy, King's College London Institute of Psychiatry, Psychology and Neuroscience, MPI of Psychiatry
- **Martha Merrow,** Professor, LMU, Medical Psychology
- **Thomas Misgeld**, Professor, TUM, Institute of Neuronal Cell Biology, German Center for Neurodegenerative Diseases (DZNE)
- **Michael Pecka**, Professor, LMU, Department Biology, Division of Neurobiology

Abstracts of lecturers and posters

Do mitochondria impact axonal action potential conduction?

Pepe **Alcami**[1,2]
[1] **LMU Department Biology, Division of Neurobiology**
[2] **MPI for Biological Intelligence, Department Behavioural Neurobiology**

We explored the impact of mitochondria on the propagation of action potentials in the small-diameter non-myelinated axons found in the vertebrate brain. Combining electron microscopy from the songbird motor pathway responsible for the production of birdsong and computational modeling, we show that by partially occupying axoplasm, mitochondria constitute a biological design constraint that delays action potential conduction, inducing a non-homogeneous propagation of action potentials along axons.

Cortical reactivations predict future sensory responses

Nguyen, N. D., Lutas, A., Fernando, J., Vergara, S., McMahon, J., Dimidschstein, J. and Mark L. **Andermann**
Harvard Medical School, Beth Israel Deaconess Medical Center

Many theories of offline memory consolidation posit that the pattern of neurons activated during a salient sensory experience will be faithfully reactivated, thereby stabilizing the entire pattern. However, sensory-evoked patterns are not stable, but instead drift across repeated experiences. To investigate potential roles of reactivations in the stabilization and/or drift of sensory representations, we imaged calcium activity of thousands of excitatory neurons in mouse lateral visual cortex. Presentation of a stimulus resulted in transient, stimulus-specific reactivations during the following minute. These reactivations depended on local circuit activity, as they were abolished by local silencing during the preceding stimulus. Contrary to prevailing theories, reactivations systemically differed from previous patterns evoked by the stimulus. Instead, they were more similar to future patterns evoked by the stimulus, thereby predicting within-session representational drift. In particular, neurons that participated more or less in early reactivations than in stimulus response patterns subsequently increased or decreased their future stimulus responses, respectively. The rate and content of these reactivations was sufficient to accurately predict future changes in stimulus responses and, surprisingly, the decreasing similarity of responses to distinct stimuli. Thus, activity patterns during sensory cortical reactivations may guide the drift in sensory responses to improve sensory discrimination.

Striatal dopamine teaching signals reflect an agent's perceived locus of control

Tobias W. **Bernklau**[1,2], Beatrice Righetti[1], Leonie S. Mehrke[1], Simon N. Jacob[1]
[1] **TUM Department of Neurosurgery, Translational Neurotechnology Laboratory, Klinikum rechts der Isar**
[2] **LMU Graduate School of Systemic Neurosciences**

Striatal dopamine drives associative learning by acting as a teaching signal. Much work has focused on simple learning paradigms, in which dopaminergic signals passively track the statistics of externally controlled outcomes. However, higher cognition requires an agent to generate internal concepts of its environment, in which sensory stimuli, actions, and outcomes become associated. Here, we perform direct dopamine measurements across the striatum and computational modeling in mice learning cue-instructed actions following implicit task rules. Rule changes prompted the animals to cut learned associations and reset outcome expectations, resulting in dissociations of cue and outcome triggered dopamine signals that depended on the adopted behavioral response strategy. As the animals rediscovered the impact of their own actions, reward predictions for the different trial events were recoupled, indicating a crystalizing mechanistic understanding of the current task. Our results suggest that dopaminergic reward prediction errors reflect an agent's perceived locus of control.

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Sleep and the immune system – a prime example of neuro-immune communication

Luciana **Besedovsky**
LMU Institute of Medical Psychology

For a long time, it was believed that the nervous system and the immune system were two separate entities that work independently of each other. Today, it is clear that the opposite is true: There is an intensive and complex bidirectional interaction between the two systems. Furthermore, the nervous and immune systems also share striking similarities, such as their ability to process information and form long-lasting memories. The interaction between sleep and the immune system is a prime example of how the nervous system and the immune system can potently affect each other. In this talk, I will provide an overview of how sleep and the immune system interact, with a specific focus on the effects of human sleep on peripheral immune functions and immunological memory. I will also outline why the effects of poor sleep on the immune system are considered relevant for a variety of different diseases, including neurodegenerative, psychiatric, and cardiovascular diseases.

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Headband EEG in a mixed psychiatric sample: Home-based objective measurement of potential transdiagnostic sleep disruption

Borbala **Blaskovich**[1,2], Esteban Bullón-Tarrasó[1], Dorothee Pöhlchen[1], Alexandros Manafis[1], Hannah Neumayer[1], Luciana Besedovsky[2], Tanja Brückl[1], BeCOME Working Group[1], Peter Simor[3,4], Florian P. Binder[1], Victor I. Spoormaker[1]
[1] **MPI of Psychiatry Department Genes and Environment**
[2] **LMU Institute of Medical Psychology**
[3] **Institute of Psychology, ELTE, Eötvös Loránd University**
[4] **Institute of Behavioral Sciences, Semmelweis University**

Study Objectives: Several stress-related mental disorders are characterized by disturbed sleep, but objective sleep biomarkers are not routinely examined in psychiatric patients. We examined the use of wearable-based sleep biomarkers in a psychiatric sample with headband electroencephalography (EEG) including pulse photoplethysmography (PPG), with an additional focus on microstructural elements as especially the shift from low to high frequencies appears relevant for several stress-related mental disorders (cortical hyperarousal).
Methods: We acquired 483 nights and could analyze 372 nights of sufficient quality from 83 healthy participants and those with a confirmed stress-related mental disorder (anxiety-affective spectrum). We analyzed the data with respect to macrostructural and microstructural characteristics according to the newly described spectral slope fitting over the whole frequency spectrum.
Results: The headbands were accepted well by patients and the data quality was sufficient for most nights. The macrostructural analyses revealed trends for significance regarding sleep continuity but not sleep depth variables. The spectral analyses yielded no between-group differences except for a group × age interaction, with the normal age-related decline in the low versus high frequency power ratio flattening in the patient group. PPG analyses showed that the mean heart rate was higher in the patient group in pre-sleep epochs, a difference that reduced during sleep and dissipated at wakefulness.
Conclusions: Wearable devices that record EEG and/or PPG could be used over multiple nights to assess relevant markers such as sleep fragmentation, cortical hyperarousal, and sympathetic drive throughout the sleep–wake cycle in patients with stress-related mental disorders.

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Müller cell-specific TSPO is beneficial for preservation of retinal function and macroglial metabolism in response to transient ischaemia

Oliver **Bludau**[1], Sophie Knoll[1], Susanne Koch[2], Patricia Hoffelner[1], Lew Kaplan[1], Michael Schumacher[3], Philippe Liere[3], Antje Grosche[1]
[1] **LMU Department of Physiological Genomics, Biomedical Center**
[2] **LMU Department of Pharmacy, Center for Drug Research**
[3] **U1195, INSERM et Universite Paris-Sud**

Translocator protein (TSPO) is an integral mitochondrial outer membrane protein predominantly expressed by non-neuronal cell types in the retina. Treatment of injured retinas with TSPO ligands has reduces microglial reactivity and improves preservation of neurons. However, the mechanism by which TSPO ligands act remains largely unknown and controversial. Among a plethora of reported functions, TSPO main role seems to be the cholesterol shuttle to the inner mitochondrial membrane, the initial site of steroidogenesis. This suggests that the observed treatment effects may be mediated by an increased production of neuroprotective steroid hormones. While knockout of TSPO in microglia was reported to be beneficial for the retina after injury, we speculate that TSPO has cell type specific functions and that neuroprotective effects of TSPO ligands are mainly mediated by Müller cells.

To investigate TSPO function in the context of transient retinal ischemia/reperfusion specifically in Müller cells we utilized cell type-specific recombination to conditionally knockout TSPO. We assessed retinal damage by quantification of neurons via immunohistochemistry and preservation of retinal function by electroretinography. Metabolic changes in Müller cells due to TSPO loss were investigated using JC-1 assay, to assess mitochondrial membrane potential, volumetric measurements in response to hypoosmolality, and fluorescence lifetime imaging of NAD(P)H, revealing changes in energy metabolism. Complementary single cell sequencing was performed to reveal transcriptional changes and potential compensatory gene regulatory mechanisms.

After ischemia we observed an increased loss of neurons in the Müller cell-specific TSPO-KO retina and an impaired retinal electrical response to light stimulation. Furthermore, TSPO-KO in Müller cells alters their physiology: (I) their mitochondrial membrane potential is less stress tolerant in homeostatic conditions and (II) Müller cells fail to compensate hypoosmotic stress after ischemia. Furthermore, (III) we observed a metabolic switch from OXPHOS to glycolysis in response to retinal damage in TSPO-KO. Preliminary transcriptomic data indicate changes consistent with increased fatty acid metabolism.

Our results show that Müller cell TSPO is a critical factor for these cells to fulfill their function in maintaining retinal homeostasis, but also to coordinate functional changes in response to damage. Furthermore, loss of Müller cell TSPO appears to be detrimental to glial mitochondrial health. These findings support the theory that TSPO acts in a cell type-specific manner, and we provide evidence that the neuroprotective effect of TSPO ligands is mediated by Müller cells.

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Dissecting the algorithmic and neural circuit basis of dopamine-driven learning in the striatum

Malcolm **Campbell**[1,2], Sara Matias[1,2], Shudi Xu[1,2], Yongsoo Ra[1,2], Mitsuko Watabe-Uchida[1,2], Naoshige Uchida[1,2]
[1] **Harvard Department of Molecular and Cellular Biology**
[2] **Harvard Center for Brain Science**

The neurotransmitter dopamine (DA) is thought to play a central role in reward-based learning. The leading theory posits that DA release acts as a reward prediction error (RPE) which incrementally updates the brain's predictions about future rewards. Recently, however, this hypothesis has come under attack, with two distinct alternatives suggested related to learning rate and retrospective inference. However, these models make similar predictions for patterns of DA release in standard classical conditioning tasks, making them difficult to separate. Additionally, these studies, as well as some supporting RPE, suffer from several caveats: (1) Rewards generate movements, which confound the interpretation of neural signals related to learning; (2) Rewards activate many learning systems in parallel, not just the DA system, limiting the ability to attribute learning to DA itself; (3) DA neurons have diverse functions that depend on their projection target, but prior studies often mixed these diverse populations when recording or stimulating DA neurons. Thus, the algorithm(s) by which DA drives reward learning and how this may be implemented in neural circuits remain unknown. The central idea of this project is to use artificial conditioning tasks in which natural rewards have been replaced with calibrated optical stimulation of dopamine axons (cDAS) in specific striatal subregions in head-fixed mice. By design, this approach (1) limits movements, (2) isolates the effect DA release itself, and (3) targets a projection-specific population of DA neurons, thus limiting caveats that hindered prior studies. Using this approach, I demonstrate that contrary to recent studies, cDAS specifically within the lateral nucleus accumbens (lNAc) causes the development of two signatures of RPE learning: a positive DA response to a paired neutral cue (odor), and a negative response to the omission of predicted stimulation. Artificial conditioning experiments were designed to further distinguish RPE from alternative algorithms; these experiments are ongoing. Regardless of the algorithm, this reduced preparation opens possibilities to dissect the neural circuit basis of DA-driven learning in vivo with unprecedented precision. As a first step, using multisite cDAS combined with antidromic optotagging of projection-specific DA neurons with Neuropixels, I demonstrate that cDAS specifically within lNAc causes the development of cue responses in DA neurons that project broadly throughout the striatum, possibly forming the basis of an actor-critic architecture of DA-driven learning.

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A feedforward inhibitory motif in the neuromodulatory connectome

Alex B. **Chen**, Marc Duque Ramirez, Xuelong Mi, Sujatha Narayan, Guoqiang Yu, Florian Engert, Misha B. Ahrens
Harvard Medical School, Graduate Program in Neuroscience
Harvard Department of Molecular and Cellular Biology
Howard Hughes Medical Institute
Virginia Tech, Department of Electrical and Computer Engineering

The precise synaptic connectivity among all neurons in a brain defines its connectome, and specific sets of connections form neural circuit motifs that implement different computations essential for behavior. In addition to synaptic signaling, neurons also communicate through the release of diffusible neuromodulators that, with their cognate receptors, form the neuromodulatory or chemo-connectome. The neuromodulatory connectome is thought to modulate fast synaptic transmission over relatively long timescales. We challenge the framework of the chemical connectome as a slow modulatory layer by uncovering a biochemical circuit, downstream of the neuromodulator norepinephrine, that implements feedforward inhibition over fast timescales during futility-induced behavioral state transition in the larval zebrafish. Norepinephrine released during futility drives a short-term elevation in motor vigor (the excitatory phase) followed by a long-term suppression of swimming (the inhibitory phase). Combining whole-brain imaging of neural activity and neuromodulator release with behavioral pharmacology, we find that norepinephrine causes adenosine triphosphate (ATP) release from astroglia sufficient for passivity. ATP does not act directly on downstream neurons but is instead first metabolized into adenosine, and the inhibition of this biochemical pathway, or of adenosine receptors, inhibits futility-induced passivity. Remarkably, while broad inhibition of noradrenergic signaling in both neurons and astroglia suppresses both the excitatory and inhibitory phases of the futility response, inhibition of the astroglial purinergic signaling pathway suppresses only the inhibitory phase, suggesting that neurons and astroglia play different roles in mediating norepinephrine's behavioral effects. In sum, our work uncovers a feedford inhibitory circuit motif implemented by the neuromodulatory, instead of anatomical, connectome and, together with other work in flies and rodents, identify an evolutionarily conserved and behaviorally relevant noradrenergic-to-purinergic signaling channel in astrocytes.

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Investigating the effects of anti-amyloid-β peptide antibody therapy on microglia

Lis **de Weerd**[1], Selina Hummel[2], Stephan Müller[1], Brigitte Nuscher[1], Astrid Feiten[1], Kai Schlepckow[1], Michael Willem[1], Stephan Lichtenthaler[1,3,4], Matthias Brendel[2], Joe Lewcock[6], Kathryn Monroe[6], Christian Haass[1,3,5]

[1] **German Center for Neurodegenerative Diseases (DZNE)**
[2] **LMU Department of Nuclear Medicine, University Hospital Munich**
[3] **SyNergy Excellence Cluster of Systems Neurology**
[4] **TUM School of Medicine, Neuroproteomics, Klinikum Rechts der Isar**
[5] **LMU Biomedical Center, Metabolic Biochemistry**
[6] **Denali Therapeutics, Inc., South San Francisco, USA**

The development of disease modifying therapies for Alzheimer's disease (AD) has recently seen successes with the first clinically significant results in phase 3 trials of monoclonal anti-amyloid β peptide (Aβ) antibody treatment. Anti-Aβ antibodies, such as Aducanumab and Lecanemab, show robust target engagement and their clinical benefit on cognition correlates with the magnitude of Aβ lowering in a dose-dependent manner. However, treatment dose is also associated with an increased risk of adverse side effects, such as amyloid-related imaging abnormalities (ARIA).
Antibody-mediated plaque clearance is in part mediated by Fc-receptor-mediated activation of microglia. In addition, in vitro evidence shows that Aβ clearance is influenced by the expression of triggering receptor expressed on myeloid cells 2 (TREM2), which is required for microglia to switch from a homeostatic to a disease-associated state. Previous work has shown that TREM2-deficient microglia are unable to respond adequately to Aβ pathology. Conversely, therapeutic boosting of TREM2 signaling with TREM2 agonizing antibodies has been shown to reduce amyloid load in several mouse models.
Future treatment paradigms for AD patients could potentially include combinatorial monoclonal antibody strategies, which could have the benefit of lower dosing and reduced risk of ARIA. Here we investigate the effects of Aducanumab treatment on pathology and microglial response. In a long-term dosing study of Aducanumab in APP-SAA triple knock-in mice, a dose-dependent reduction of Aβ by Aducanumab was accompanied by a parallel reduction of TREM2 and sTREM2 protein levels in the brain, suggesting reduced microglial activation. The microglial TREM2 response around plaques is unchanged, suggesting that TREM2 levels closely reflect Aβ levels and could be used as a potential biomarker read-out of Aducanumab treatment. This study informed the design of an ongoing combinatorial treatment study to investigate whether ATV:4D9 can synergistically enhance Aducanumab-mediated Aβ clearance, which could inform future combination treatment strategies in patients.

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Circadian control of feeding

Amelia **Douglass**[1], Hakan Kucukdereli[1], Joseph Madara[1] and Bradford Lowell[1,2]*

[1] **Harvard Medical School, Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center**
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Even when food is constantly available, feeding is temporally organized across the circadian cycle. In this case, feeding is not driven by energy deficit but instead occurs proactively to prevent negative energy balance from ever occurring. Additionally, tightly scheduled feeding is essential because mistimed eating, prevalent in modern society, can significantly affect metabolic health, rendering it a major public health challenge. Nevertheless, the neural mechanisms that control meal timing are unknown. We hypothesized that the circadian timing system orchestrates daily rhythms of food intake by engaging hypothalamic agouti-related peptide (AgRP)-expressing 'hunger' neurons to control meal timing.
To examine the role of AgRP neurons, we implemented long-term continuous in vivo fiber photometry recordings to monitor AgRP neuron activity for up to weeks. In doing so, we discovered that AgRP neuron activity has a free-running circadian rhythm that peaks during the late light phase. Critically, this rhythm is circadian because it persists in the absence of light cues and re-entrains to a shifted light-dark cycle. Notably, the AgRP neuron rhythm persists when 100% of daily nutrition is provided via constant-rate gastric infusions. Hence, it is not secondary to a feeding rhythm. Finally, in vivo optogenetic stimulation of the circadian clock, the suprachiasmatic nucleus (SCN) neurons reliably activates AgRP neurons. Ongoing studies are delineating the neural pathway between the SCN and AgRP neurons that drives circadian changes in hunger and food intake. This work will reveal the neural pathway that underlies the temporal organization of feeding and provide insight into human pathophysiologies resulting from disrupted circadian rhythms.

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Representation of visceral signals in the lateral parabrachial nucleus during feeding

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Interoception, the sensing of internal bodily state, is critical for maintaining physiological homeostasis. For example, the proper regulation of food intake requires that animals perceive satiety signals related to stretch and/or nutrients within the gastrointestinal (GI) tract. These visceral signals are carried to the brain via vagal, spinal, and hormonal pathways, which converge in the brainstem lateral parabrachial nucleus (LPBN) to drive associated changes in behavior and physiology through forebrain projections. One major function of the LPBN is to suppress appetite following a meal or in response to pain and/or illness. Previous studies have shown that stimulation of all LPBN neurons or of specific genetic subpopulations (e.g., CGRP neurons) suppresses food intake in mice. In addition, many Fos studies have suggested that several feeding/satiety related stimuli strongly activate LPBN neurons. Despite this knowledge, the in vivo dynamics of LPBN neurons during natural food consumption, and how different sources of visceral input contribute to these dynamics, remain largely unknown. Instead, previous attempts to record LPBN neurons in vivo have either focused on a limited number of stimuli or on a specific genetically defined subpopulation. Our main goal was to characterize the functional diversity of natural feeding-related responses in LPBN. To achieve this goal, we developed a novel approach for chronic, three-dimensional, two-photon calcium imaging of LPBN via a gradient-index (GRIN) lens implanted at an angle above the surface of LPBN. With this imaging preparation, we recorded LPBN responses to liquid food consumption, injection of satiety hormones or visceral illness-inducing compounds, stomach stretch, mild tail-shocks, and activation of long-range inputs to LPBN. We found that food consumption drives a wave of activity across LPBN, with activity peaking early, at the onset of consumption, in some neurons, and ~3-5 s later in other neurons. We hypothesize that sensory signals arising from distinct regions of the GI tract (e.g., mouth vs. esophagus vs. stomach) contribute to these temporal dynamics. In support of this hypothesis, we found that postingestive signals, such as stomach stretch and satiety hormones, specifically activate the late peaking LPBN neurons. Our ongoing work will relate the activity of LPBN neurons to the real-time movement of food through the GI tract during consumption. Together, these experiments reveal functional diversity in feeding-related activity in LPBN, aiding in our understanding of the role of LPBN in appetite regulation.

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Representations of the interoceptive effects of nicotine in the insular cortex

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Interoception – the sensing of internal bodily signals – is critical to addiction because the rewarding effects of addictive drugs and the aversive aspects of withdrawal are largely experienced as bodily sensations. The insular cortex (InsCtx) has been implicated in interoception because of its roles in integrating sensory, visceral, and limbic information. The InsCtx has been implicated in the maintenance of nicotine use disorders by several studies that have found smokers who have an ischemic stroke involving the InsCtx are more likely to maintain smoking cessation than smokers who have strokes involving other areas of cortex. Our ability to assess the role of interoceptive signals in the development of nicotine dependence has been limited by our ability to simultaneously monitor the effects of nicotine on the brain and the body. I have overcome this challenge by combining our lab's framework for chronic two-photon calcium imaging of hundreds of InsCtx neurons with measurements of bodily physiology. Nicotine administration causes a centrally mediated decrease in body temperature in naïve animals that decreases in magnitude and duration as animals are repeatedly exposed to nicotine. I have found that ensembles of neurons in the InsCtx show consistent responses to nicotine administration, even as animals develop tolerance to the hypothermic effects of nicotine. Because nicotine has direct effects centrally on the brain as well as peripherally on bodily physiology, I am using natural and pharmacological manipulations to describe how the ongoing InsCtx activity patterns reflect both the central and peripheral actions of nicotine. These experiments will advance our understanding of how InsCtx activity patterns change during the emergence of nicotine dependence, and how the neural representations of the interoceptive effects of nicotine change during the development of dependence.

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Multi-donor human cortical Chimeroids to study inter-individual variability to neurotoxic triggers

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Inter-individual genetic variation affects the individual response to many diseases and environmental triggers. Efforts to study the molecular mechanisms mediating the impact of human genetic variation on normal development and disease phenotypes are limited, however, by the paucity of faithful cellular human models, and the difficulty of scaling current systems to represent many individuals. Here, we present human brain "Chimeroids", a highly reproducible, multi-donor brain organoid model that allows co-development of human cerebral cortex from a panel of individual donors in a single organoid, while maintaining fidelity to endogenous tissue. By re-aggregating cells from multiple single-donor organoids at the neural stem or committed progenitor stage, we generate Chimeroids in which each donor produces all cell lineages of the cerebral cortex, even when using pluripotent stem cell lines with notable growth biases. We leveraged Chimeroids to investigate inter-individual variation in susceptibility to neurotoxic stressors that exhibit high clinical phenotypic variability: ethanol and the anti-epileptic drug valproic acid. Individual donors varied in both the penetrance of the effect on target cell types, and the molecular phenotype within each affected cell type. Our results show that human genetic background is an important mediator of neurotoxin susceptibility and introduce Chimeroids as a scalable system for high-throughput investigation of the contribution of human genetic variation to brain development and disease.

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Microglia lipid metabolism is controlled by TREM2 level rather than disease state

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Microglia, the innate immune cells of the brain, are expected to play a major role in Alzheimer's disease. Particularly, since the discovery of many genetic risk factors which are predominately expressed by microglia. Triggering receptor expressed on myeloid cells 2 (TREM2) polymorphisms constitute one such risk factor. The function of TREM2 has been intensively studied recently, however, the exact mechanism by which TREM2 contributes to disease remains unknown. We developed a TREM2 reporter mouse that expresses a fluorescent mKate2 tag in a polycistronic construct. Using controlled cortical impact, we validated that TREM2 function was not impaired. Microglia showed the expected, disease associated upregulation of activation markers. When we crossed the reporter mice with a mouse model for amyloid plaque pathology we noticed a gradual upregulation of TREM2 with increasing plaque proximity. Using FACs sorting we isolated microglia based on their mKate2 expression and subjected the different populations to radiotracing, transcriptomic and lipidomic analysis. Microglia expressing high levels of TREM2 took up more radioactively labelled glucose than cells with lower levels, independent of disease genotype. Further, the RNA signature of the individual populations matched with previously published RNAseq data sets. Co-expression network and pathways enrichment analysis identified TREM2 level dependent and independent changes. Cholesterol homeostasis and metabolic processes were the top terms in the cluster largely driven by TREM2 level. Indeed, Cholesterol was amongst the metabolites affected the most by the different TREM2 levels. Overall, increased TREM2

levels modified the lipidome to a state associated with increased phagocytic and metabolic capacity. Taken together, we present a new and much needed tool to study the involvement of TREM2 in neurodegenerative diseases. Using our new model, we show the importance of the TREM2 level in determining microglia fate, which can directly influence the disease outcome.

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Is the Amyloid cascade still valid to explain Alzheimer‘s disease?

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Strong genetic evidence supports an imbalance between production and clearance of amyloid β-protein (Aβ) in people with Alzheimer disease (AD). Microglia that are potentially involved in alternative mechanisms are actually integral to the amyloid cascade. Fluid biomarkers and brain imaging place accumulation of Aβ at the beginning of molecular and clinical changes in the disease. So why have clinical trials of anti-amyloid therapies not provided clear-cut benefits to patients with AD? Can anti-amyloid therapies robustly decrease Aβ in the human brain, and if so, could this lowering be too little, too late?
These central questions in research on AD are being urgently addressed.

Further reading:
Haass & Selkoe, PlosBiol, 2022; If amyloid drives Alzheimer disease, why have anti-amyloid therapies not yet slowed cognitive decline?
https://doi.org/10.1371/journal.pbio.3001694

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Predicting schizophrenia using the co-localization of structural imaging with specific neurotransmitter systems

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Background
Aside to common psychotic symptoms such as hallucinations, delusions and disorganized thinking, schizophrenia (SCZ) is characterized by structural alterations such as volume reductions in the temporal, frontal, and parietal lobes [1]. Only little is known about the underlying mechanisms leading to the anatomical constraints of the pathophysiology. Here, we evaluated if these alterations are linked to the distribution of specific neurotransmitter systems. Furthermore, we assessed the predictive value of these associations by building a supervised machine learning classifier for the differentiation of SCZ patients and healthy controls (HC).

Methods
Maps of grey matter volume (GMV) were derived from T1-weighted structural magnetic resonance imaging for 67 SCZ patients (mean age = 35.6 ± 12.0, 15 females) and 56 HC (mean age = 33.1 ± 11.8, 31 females). The data were collected within the scope of the MIMICSS (Multimodal Imaging in Chronic Schizophrenia Study; part of the PsyCourse study) [2] study. To test for group differences in GMV, pairwise group t-contrasts were performed in SPM12 using a one-way ANOVA with group (SCZ patient or HC) as independent variable and age, sex and TIV as covariates (family wise error corrected voxel threshold: $p < .05$). Furthermore, we examined if these structural alterations co-localize with the known non-pathological distribution of 25 specific neurotransmitter systems using the JuSpace toolbox [3]. Finally, we used the co-localization features to build a support vector classifier discriminating between groups. The model was trained in a nested cross validation structure with five folds and ten permutations at each level.

Results
Compared to HC, SCZ patients displayed significantly reduced grey matter volume in the left and right amygdala. Moreover, these alterations significantly co-localized with the distribution of serotonin and dopamine receptors (5-HT1a: mean $r = -.14$, $p < .001$; 5-HT2a: mean $r = -.07$, $p = .01$; D1: mean $r = .08$, $p < .001$), serotonin, dopamine, and acetylcholine transporters (DAT: mean $r = .10$, $p < .001$; SERT: mean $r = .07$, $p = .002$; VAChT: mean $r = .14$, $p < .001$), and FDOPA (mean $r = -.09$, $p < .001$). Whereas negative correlation coefficients point to GMV reductions in areas with high density of those neurotransmitters in health, positive correlation coefficients suggest increased GMV in areas with high neurotransmitter density. Finally, using the Fisher's z transformed correlation coefficients of GMV with 25 neurotransmitter systems as features the classifier discriminated SCZ from HC with a balanced accuracy of 70.6 %.

Conclusion
GMV volume reductions in SCZ follow the distribution of specific neurotransmitter systems, supporting the notion of the preferential vulnerability of specific neurotransmitter systems. Moreover, SCZ was clearly distinguishable from HC based on the association of structural alterations with 25 neurotransmitter systems. These findings suggest that the association with specific neurotransmitter systems might serve as a diagnostic biomarker.

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The molecular and cellular mechanisms underlying MAST1-associated Mega-Corpus Callosum Syndrome

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Mutations in the microtubule-associated serine/threonine kinase 1 (MAST1) cause a severe neurodevelopmental disorder characterized by enlargement of the corpus callosum, malformations of the cortex, and hypoplasia of the cerebellum. The molecular and cellular mechanisms underlying this disorder are currently unknown. Here, we establish new model systems to investigate this Mega-Corpus Callosum syndrome including two mouse lines and human stem cell lines based on Mega-Corpus Callosum-associated patient mutations. Through proteomic analysis of both mutant mice and stem-cell derived neurons, we show that MAST1 mutations lead to a reduction in the levels of MAST1 protein and disrupt the levels of other MAST family members, namely MAST2 and MAST3. Through quantitative proteomic/phosphoproteomic analysis we furthermore identify a set of proteins differentially phosphorylated upon MAST1 mutation and which may present novel downstream targets of MAST proteins. We utilize an in-vitro kinase assay to confirm one of these candidates as a previously unknown stubstrate of MAST1. To elucidate the cellular mechanisms of this disorder, we establish a microdevice-based organoid protocol to study the development of the corpus callosum *in-vitro*.

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Cellular and circuit mechanisms of right-hemispheric language functions in aphasia

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Damage to the left-hemispheric brain regions of the human language system can lead to detrimental long-term deficits in language production and comprehension. A large body of evidence has shown that language functions are amenable to neurological rehabilitation. This functional recovery of linguistic abilities is hypothesised to be driven by a reorganisation of the language network whereby preserved cortical structures in perilesional and right-hemispheric homotopic areas compensate for the loss of brain tissue by taking on new language relevant functions. The neuronal mechanisms underlying such reorganisation are not well understood. To obtain detailed insights into the role of the right cortical hemisphere in language recovery at the single-neuron and neuronal circuit level, we chronically implanted a patient with aphasia (6 years post-onset) with four intracortical planar microelectrode arrays (64 channels per array, 256 channels in total). Specifically, we targeted right-hemispheric homotopic areas of the language network and placed arrays in the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), supramarginal gyrus (SMG) and angular gyrus (AG). These extracellular recordings allowed us to monitor large-scale neuronal activity with millisecond and sub-millimeter resolution and capture single unit spiking activity as well as local field potentials. Neuronal data acquisition proceeded in parallel to the patient performing a variety of language-related tasks. Experimental sessions were conducted multiple times per week over the course of several months and covered three central pillars of language, namely single word comprehension, word production and word repetition. The tasks were designed to allow us to contrast language-related neuronal responses associated with processing of stimuli of different linguistic complexity, of different semantic, syntactic and phonological categories, and under different task demands. Our preliminary findings argue for a role of the right hemisphere in language functions. Specifically, we observed locking of single unit responses to different trial events that was task-specific (word repetition vs. word retrieval) and brain region-specific (prefrontal vs. parietal cortex). For example, we recorded changes in IFG and MFG unit activity prior to speech onset in both repetition and naming tasks, suggesting a role of these regions in speech planning and word retrieval. In contrast, SMG responses were more prominent after speech onset, in agreement with a role in vocalisation. An in-depth understanding of the mechanisms underlying functional reorganisation and neuronal plasticity in the human brain will promote novel therapeutic approaches for individuals with disorders of language and other higher cognitive functions.

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Characterization of the autonomic ganglia innervating the heart in zebrafish

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Homeostatic regulation is necessary to adjust internal body function to the organism's needs, such as during rest or hunting. The heart is essential in the process to adapt the animal to changing circumstances by increasing or decreasing its rate. Heart rate modulation occurs through the communication between sensory and motor ganglia of the autonomic nervous system. How they interact to change heart activity, however, is not well understood. To address the neuronal circuits regulating the heart, we are characterizing the autonomic ganglia functionally, morphologically, and transcriptionally. This allows us to investigate which populations of neurons innervate the zebrafish heart and how they connect the heart to other parts of the autonomic nervous system.

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Behavioral and neuronal signatures in delayed response and working memory tasks in freely moving mice

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In order to deal with a large variety of diverse tasks, the brain's cognitive control centers such as the prefrontal cortex (PFC) facilitate representation, memorization and interpretation of sensory stimuli and orchestrate appropriate (re)actions. Many studies investigating cognitive behaviors use task designs that are heavily reduced in an attempt to understand specific components of complex behaviors and to increase reproducibility. However, even in highly controlled experiments, variability between individuals is frequently found. Further, simplified task protocols might not be representative of the complex problems we encounter in the real world. Here, we leveraged behavioral variability to distinguish between individual strategies and explore neuronal signatures that underlie different short-term memory functions. Mice were trained to memorize spatial information in a touchscreen chamber, enabling the animals to move freely and develop distinct behavioral strategies to solve the task. Importantly, training proceeded in two steps. First, the animals were trained on a delayed response task in which they could use the location of a sample stimulus to fully predict the correct location of the subsequently presented test stimulus. Second, we introduced a working memory condition, where the animals had to memorize the sample location without being able to predict the test location and prepare an action. Mouse behavior was analyzed using DeepLabCut and Keypoint-Moseq. Individual animals could be characterized based on idiosyncratic behavioral signatures including distinctive running and turning behaviors. Faster mice with a more direct path performed better in delayed response trials, but their mean performance dropped strongly when starting on the working memory trials. In contrast, slower mice performed better in working memory trials, indicating that the two tasks have different behavioral demands and are met with distinct strategies by the animals. We hypothesized that these differences are reflected in the prefrontal neuronal representation of the memorized information. We therefore imaged large-scale mPFC activity at single-neuron resolution with GCaMP6f and Miniscopes during key training stages. Ongoing data analysis will enable us to decompose neuronal activity and possibly separate correlates of inter-individually varying behavioral strategies from conserved short-term memory coding principles, specifically, how the representation of the sample stimulus changes when behavioral demands dictate a shift from delayed responding to memorizing without the possibility of action preparation.

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A brain-computer-interface with cellular resolution for the investigation of human language and verbal communication

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Language constitutes one of the most formidable sensorimotor integration functions of the human brain. While the cortical regions in the human frontal, temporal and parietal lobe that comprise the language network have already been identified, there are vast gaps in our understanding of the neuronal mechanisms that govern how we engage in vocal communication and verbalize thoughts, intentions and emotions. I will present recent efforts in my laboratory devoted to establish a brain-computer-interface with cellular resolution for patients with language disorders (aphasia) after stroke. Using large-scale neurophysiological recordings from microelectrode arrays chronically implanted into right-hemispheric language-homotopic brain areas, we have begun to investigate how linguistic elements are encoded at the single-neuron level and how population-wide activity gives rise to temporal integration and combinatorial processes during speech production. The long-term goal of our transdisciplinary work is to explore neurotechnological approaches that leverage right-hemispheric cognitive resources for aphasia rehabilitation.

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Limited limitations: Restoring vision in retinal degeneration

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Retinitis pigmentosa (RP), a hereditary retinal degenerative disease, is characterized by progressive loss of photoreceptors and thus, vision. In human clinical trials, gene therapy has been shown to improve vision; however, this benefit has not been sustainable. It is not clear if the lack of long-term benefit is due to the advanced stage of the disease at the time of treatment. To determine the therapeutic time window, we generated an RP mouse model in which mutant rod-specific phosphodiesterase 6b (PDE6B) can be restored to WT levels in all rod photoreceptors. We then systematically mapped the treatment time window relative to disease progression. We demonstrate rescue of photoreceptor structure and visual function, even when the therapy was administered at mid-to-late disease stages, showing that the therapeutic window is broader than previously thought. On the other hand, we observed ongoing secondary remodeling of retinal pigment epithelium (RPE) and retinal blood vessels which could impair the health of the photoreceptor cells at a greater age. These findings define the potential and limitations of RP treatment and suggest possible nonphotoreceptor targets for gene therapy optimization.

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Oligodendrocyte injury in a model of autoimmune astrocytopathy

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Autoimmune neurological conditions such as neuromyelitis optica (NMO) or myelin oligodendrocyte glycoprotein antibody disease (MOGAD) are characterized by the presence of serum antibodies that target different glial antigens, defining the respective diseases. Despite their distinct cellular targets, these diseases exhibit a converging pathology of inflammatory lesions observed in the optic nerve and spinal cord. Such lesions not only display the loss of primary glial targets, but also involve consecutive injury to multiple cell types; including astrocytes, oligodendrocytes and neurons. However, the cellular mechanisms underlying this intercellular spread, particularly during the acute stages of the diseases remain poorly understood. Here performing in vivo spinal cord imaging of astrocytes and oligodendrocytes in an acute experimental model of NMO, we show that following aquaporin-4 antibody mediated fast global astrocyte loss, a slow progressing oligodendrocyte injury develops with accompanying calcium dyshomeostasis. Expression of complement-inhibitor protein CD59 on oligodendrocytes protected these cells from secondary injury after astrocyte loss, suggesting the bystander effects of soluble complement proteins that derive during complement-dependent cytotoxicity to astrocytes. These findings indicate that, despite the common initiation of complement-mediated glial injury in NMO, the subsequent stages of cell damage may diverge, potentially activating distinct cell death pathways in oligodendrocytes and astrocytes.

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BMIgap: tool for quantifying brain variations associated with obesity

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Introduction

Obesity is becoming a growing issue in public health, due to its significant association with an increased risk of medical comorbidities (Heymsfield and Wadden, 2017), thus, contributing to a rise in mortality. Additionally, numerous studies have demonstrated that individuals who are overweight or obese face a higher susceptibility to developing mental illnesses (Blasco et al. 2020; Sarwer and Polonsky 2016). But the interaction between obesity and psychiatric diseases is inadequately comprehended. In this study, we studied the interaction between structural brain variation and obesity measured by body mass index (BMI) in healthy controls (HC) and individuals with mental disorders. We developed a sMRI-based BMI predicting regression model using whole-brain grey matter volume (GMV) data and extended the concept of normative modelling to disentangle the interactions between obesity and mental-illness related brain patterns. We introduce the concept of brain BMI gap (BMIgap) as a measure of obesity-based brain deviation by calculating the difference between individualised predicted BMI and the original BMI units and apply the model to various psychiatric groups to investigate the association of the brain-based BMI trends with different psychiatric conditions. Finally, we explored whether clinically relevant variables were predictive of BMIgap for the patient groups.

Methods

We used the T1-weighted Magnetic Resonance images (MRI) of 1504 healthy individuals from four independent studies across fourteen sites: IXI dataset, the Personalised Prognostic Tools for Early Psychosis Management (PRONIA), NORMENT and the Munich schizophrenia and depression cohort (MUC). We sampled a uniform-like distributed group of 770 healthy subjects within BMI ranges of 18.5-35 kg/m2 and 15-75 years of age due to less available subjects at the extreme ends. Further the discovery model was applied to the patient cohorts: Schizophrenia (SCZ; N=146) from MUC; Recent Onset Psychosis (ROP; N=243), Recent Onset Depression (ROD; N=200), Clinical High Risk (CHR; N=213) groups from PRONIA study. We used support vector machine regression to predict individualised whole brain-based BMI. The pre-processing steps iwere implemented within a nested cross validation framework using NeuroMiner toolbox (v1.1;www.proniapredictors.eu/neurominer/). Next, we visualised these predictive brain voxels.

The model generalisability was assessed by applying the discovery model to the replication group. The BMIgap was further assessed with clinically relevant items using additional multivariate analysis.

Results

The discovery model had a coefficient of determination (R2) of 0.28, mean absolute error (MAE) of 2.75 at P<0.001 between predicted and true BMI and a mean BMIgap score of -0.01. Model performance for the replication group were: R2=0.26, MAE=2.29, BMIgap=1.73, P<0.001). The visualisation of the predictive voxels showed a more pronounced negative correlation in the temporal and frontal regions. We found a systematic positive brain deviation for all patient groups with the most pronounced deviation for the SCZ group (2.5 units), implying a systematic higher estimate than true BMI based on the MRI data.

Conclusions

The results indicate a clear interaction between the brain regions linked to psychiatric disorders and those associated with obesity. Our findings indicate that BMIgap can be a potential tool to study such brain-interactions between mental illnesses and metabolic comorbidities.

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Microbial metabolism of host androgens regulates peripheral nervous system function *in vivo*

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Irritable bowel syndrome (IBS) affects nearly 10% of the global population and is characterized by abnormal bowel movements and debilitating abdominal pain. Diminished levels of the androgen hormone, testosterone, are linked to the diagnosis and severity of IBS; and androgen signaling to the peripheral nervous system is necessary for normal colonic motor behaviors in mice. It remains unclear which neurons mediate this signaling and why it is particularly important for colonic motility. We probed androgen receptor (AR) expression in the mouse colon and found that 95% of AR+ enteric neurons are inhibitory motor neurons marked by NOS1 immunoreactivity. Microbe depleted mice have fewer colonic NOS1+ neurons, reduced levels of bioavailable androgens in the gut, and slowed gastrointestinal (GI) transit compared to mice with intact flora. Thus, we hypothesized that bacteria are necessary to generate androgens that signal to NOS1+ enteric neurons to regulate GI motility. Male mice exposed to broad-spectrum antibiotics (ABX) for 7 days to cause microbial depletion had slowed GI transit times, reduced levels of systemic androgens, and loss of AR expression in enteric neurons. Androgen supplementation was sufficient to rescue these effects. Conversely, to determine if androgens are necessary for microbial regulation of GI motility, we examined the effects of ABX on two different groups of mice with low levels of circulating androgens: pre-pubertal mice and castrated mice. Microbial depletion did not slow GI transit in prepubertal mice or in castrated adults lacking gonadal androgens, indicating that androgens are required for microbial effects. Steroid hormones are normally glucuronidated in the liver and excreted through the GI tract. Bacteria that express b-glucuronidase (GUS) enzymes can cleave the glucuronide moiety to regenerate bioactive steroids in the intestinal lumen. In ABX mice, colonic infusion of recombinant bacterial GUS was sufficient to restore systemic androgen levels and AR expression in NOS1+ neurons. We found that fecal GUS enzyme activity increases in male mice post puberty in parallel with AR immunoreactivity in NOS1 neurons, suggesting that the surge of host androgens produced during puberty may functionally shift the microbiome to regulate androgen signaling to enteric neurons. Taken together, these observations establish a novel mechanism through which microbes modulate GI motility by regulating host androgen signaling to the peripheral nervous system.

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The neuronal implementation of representational geometry in primate prefrontal cortex

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Modern neuroscience has seen the rise of a population-doctrine that represents cognitive variables using geometrical structures in activity space. Representational geometry does not, however, account for how individual neurons implement these representations. Here, leveraging the principle of sparse coding, we present a framework to dissect representational geometry into biologically interpretable components that retain links to single neurons. Applied to extracellular recordings from the primate prefrontal cortex in a working memory task with interference, the identified components revealed disentangled and sequential memory representations including the recovery of memory content after distraction, signals hidden to conventional analyses. Each component was contributed by small subpopulations of neurons with distinct electrophysiological properties and response dynamics. Modelling showed that such sparse implementations are supported by recurrently connected circuits as in prefrontal cortex. The perspective of neuronal implementation links representational geometries to their cellular constituents, providing mechanistic insights into how neural systems encode and process information.

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The effect of sleep on multielement associative structures – enhancing pattern completion

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Sleep is known to benefit the consolidation of episodic memory. However, this has been mainly shown in reductionistic experiments based on, e.g., simple two-element associations, while in real life, events often have a much more complex structure, consisting of multiple elements with either strong, weak, direct or indirect associations. To address this complexity, in the present study, we investigated how sleep affects the associative structure of complex events and the ability to retrieve an entire multielement event episode based on a single cue – a process termed 'pattern completion'. We found that post-encoding sleep, compared to a period of nocturnal wakefulness (followed by a recovery night) selectively benefits memory for weakly encoded associations and supports the formation of associations between elements that were not directly associated during encoding. These effects were accompanied by an enhancement of the ability to recall multiple elements of an event based on a single cue. Furthermore, retrieval performance was predicted by sleep spindle activity during post-encoding sleep. Our findings show that sleep shapes the associative structure of complex multielement events, thereby enhancing pattern completion. These processes can be considered highly adaptive given their role in forming and retrieving more coherent representations of our environment, which allows to make more wide-reaching predictions of the world.

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An optineurin-dependent retrograde transit filter in distal axons mediates mitochondrial quality control in synapses

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Mitochondrial homeostasis – 'mitostasis' – is an enigmatic, yet disease-prone process in neurons that maintain a large axonal and synaptic pool of mitochondria. Using an optical pulse-chase imaging approach to track individual mitochondria, we now discovered a reiterative quality control system near distal nodes of Ranvier that removed ~75% of synaptic mitochondria in mature mouse motor axons. Near these nodes, dysfunctional mitochondria were 'captured' from the retrogradely passing stream of mitochondria and then redirected to on-site hotspots of lysosomal degradation. Compared to healthy mice, a larger proportion of mitochondria was removed in presymptomatic motor neuron disease mouse models with known impairments in mitochondrial integrity. Conversely, deleting the ALS-related mitophagy-adaptor Optineurin, but not PINK1 and Parkin, reduced mitochondrial capture, implying a non-canonical mitophagy pathway. Thus, we identify a new system of mitochondrial quality control in the axonal periphery, with a cascade of perinodal checkpoints acting as sites of local mitophagy – a system which normally establishes mitochondrial mass balance but is disrupted early in degenerative axonopathies.

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Shaping a new generation of grafts with adequate myelination

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Adult humans, as well as most mammals and birds, have a very limited central nervous system regenerative capacity. Therefore, degeneration or damage of neuronal circuits can lead to an irreversible loss of neurons. Transplantation of neurons is a clinically relevant approach that could be used to replace the lost neurons for many more disease conditions if the transplanted cells integrate adequately into the host circuitry. Tracing of afferent connections of the transplanted neurons (tNs) has shown that these neurons are able to integrate in the host circuits receiving input from the appropriate regions (Falkner et al. 2016; Thomas et al. 2022; Grade et al. 2022). However, little is known about the output connectivity and whether the axons of tNs acquire myelination. Myelination can be essential for restoring adequate neuronal function after injury. For instance, it has been shown that when regenerated axons are not myelinated, they exhibit poor conduction and fail to mediate functional recovery (Bei et al. 2016; Wang et al. 2020). Therefore, it is crucial to understand whether tNs acquire adequate myelination to achieve correct and functional circuit repair.
Using immunohistochemistry and serial scanning electron microscopy, we show that fetal neurons transplanted after stab wound injury into the murine cerebral cortex scarcely myelinate at 3, 6 and 9 months post-transplantation. Single-nuclei and spatial transcriptomic analyses of the grafted site suggest that the host oligodendrocyte progenitor cells (OPCs) appear to be trapped in a pre-myelinating state. Intriguingly, albeit the inflammatory environment, postnatal OPC transplantation in the site of injury results in myelin ensheathment of host axons, but not of the tNs. Promyelinating strategies targeting specific pathways involved in OPC-neuron interaction and modulating tN activity are being undertaken to improve myelination and functional integration of the transplanted cells after stab wound injury. Understanding the mechanisms underlying myelination in replacing neurons will not only shed light onto the long-searched key players triggering myelin ensheathment after injury, but also will be of high therapeutic relevance for the future implementation of neuronal replacement strategies.

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Narrowband-gamma oscillations in mouse primary visual cortex track local luminance in natural stimuli and recruit local spiking activity with retinotopic specificity

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Throughout the brain, fine time scale coordination of neural activity is associated with the presence of fast oscillations, which have been hypothesized to serve a range of functions, including synchronization, communication, and information processing. Extensive research has focused on these brain rhythms in the mammalian visual thalamocortical system, where recent studies in mice have identified a prominent narrowband (NB)-gamma rhythm (centered at 50 - 70 Hz, with a narrow bandwidth of 5 - 7 Hz; Saleem et al., 2017). NB-gamma is elicited by full-field visual stimuli with uniform, high luminance, but it is suppressed by stimuli with high contrast. This stimulus selectivity of NB-gamma raises questions about its functional relevance in visual information processing. Specifically, the role of NB-gamma remains unclear under natural conditions, where visual input involves complex spatio-temporal distributions of luminance and contrast. Here, we show that NB-gamma tracks local luminance in natural scenes and recruits V1 spiking with retinotopic specificity. Using extracellular recordings in head-fixed mice and data from the Allen Neuropixels Visual Coding project, we show a tight correlation between the NB-gamma power in the V1 local field potential (LFP) and local luminance in static natural scenes, specifically in the region of the scene covered by the receptive fields of the recorded population. Such tracking of local luminance was unique to NB-gamma, as the power of neighboring frequency bands was instead correlated with the images' local spatial-frequency power. Importantly, high local luminance not only predicted NB-gamma power in the V1 LFP, but also recruited spiking activity of individual V1 neurons with retinotopic specificity. Furthermore, we observed a similar representation of local luminance by NB-gamma for natural movies, where bursts of NB-gamma oscillations in the V1-LFP were preceded by local increases in luminance. These findings suggest that NB-gamma can serve as a temporal organizer of local V1 spiking activity in conditions of high local luminance in naturalistic stimuli. Through contributions to the encoding of local luminance information, NB gamma might thus have a potential functional relevance for natural vision.

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Tachykinin signaling defines a functionally distinct compartment of enteric glia

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The enteric nervous system (ENS) is a dense neuroglial network within the digestive tract that regulates intestinal motility and immunity. While enteric neurons are confined to two ganglionated plexuses, enteric glia are located throughout the laminar structure of the intestine occupying niches ranging from the myenteric plexus (MP) where they encircle neuronal soma in ganglia and fibers in connectives, the smooth muscle syncytium where intramuscular glia closely associate with nerve fibers, and the mucosa where glia appose immune and epithelial cells near the gut lumen. To date, it remains unclear whether there are different types of enteric glia that are developmentally defined and have distinct roles in intestinal homeostasis. Reasoning that glia in the mucosa and those in the muscularis externa (MP and intramuscular glia) are most likely to be distinct types, we isolated each population from the small intestine of Plp1eGFP glial reporter mice and compared their transcriptional programs to each other and their neighboring cells. We discovered that Tacr3, which encodes a G-protein coupled receptor, was selectively enriched in muscularis glia. Using Tacr3IRES-Cre/+ Rosa26Ai9/+ reporter mice to genetically label Tacr3-expressing cells and their derivatives, we found that over 95% of tdTomato+ cells in the muscularis externa were S100B+ enteric glia. The majority of Tacr3+ glia were restricted to myenteric ganglia and closely associated with neuronal soma. TdTomato was rarely detected in other enteric glia and never detected in extra-intestinal glia, suggesting that TACR3 might play a role in enteric glial specification and/or subtype-specific function. To test these possibilities, we took genetic and pharmacologic approaches. First, we examined mice lacking the high affinity TACR3 ligand, neurokinin B (NKB). NKB-/- mice had normal ENS architecture at 3-weeks of age that became markedly abnormal by 16-weeks, characterized by profound glial loss in the muscularis externa. Mucosal glia, in contrast, remained completely intact. Genetic labeling of NKB-expressing cells identified a small population of cholinergic enteric neurons that arborized extensively in the muscularis externa, the likely source of NKB to Tacr3+ glia within the muscularis niche. NKB-/- mice had prolonged GI transit times, similar to wildtype mice treated with TACR3 antagonists, indicating that neuropeptide signaling to the subset of glia in the MP has both developmental and functional consequences. Together, these findings suggest that Tacr3+ muscularis glia are developmentally and functionally distinct from glia in the mucosal niche and require NKB for ENS maintenance and function.

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Distinct molecular signals for synapse and axon refinement

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During development, competition between converging active and inactive inputs results in the stabilization of active connections and the elimination of inactive ones. This elimination can occur at multiple scales: the elimination of individual synapses or the elimination of entire axons. However, the signals that detect levels of neuronal activity and determine which and how much of a connection to eliminate remain to be elucidated. Here, we address this unknown by studying the development of cortical callosal connections, the brain's largest axon bundle that facilitates information transfer between cortical hemispheres. We found that callosal connections, both synapses and axons, undergo activity and competition-dependent refinement. Inactive callosal connections are eliminated only in the presence of other active connections.

By screening for molecules that are differentially expressed/activated in active vs. inactive callosal neurons, we identified the tyrosine kinases, Pyk2 and JAK2 as being more expressed/activated in inactive neurons relative to active ones at the start of synapse elimination. Suppressing neuronal activity drives the activation of Pyk2/JAK2 in inactive neurons; however, this only occurs in the presence of other active neurons, indicating that Pyk2/JAK2 are activated in an activity and competition-dependent manner. Furthermore, we found that Pyk2/JAK2 are necessary for synapse and axon elimination during development. Thus, we propose that Pyk2 and JAK2 are elimination signals that are activated at and signal the elimination of inactive connections.

What is the purpose of two elimination signals? In addressing this question, we demonstrate distinct functions for Pyk2 and JAK2 during developmental refinement. We found that the activation of either Pyk2 or JAK2 only is sufficient to drive callosal synapse and axon elimination. We also found that Pyk2 can activate JAK2. However, Pyk2-driven axon elimination, but not synapse elimination, is suppressed by the loss of JAK2, suggesting that Pyk2 is an elimination signal for synapses while JAK2 is an elimination signal for axons. These distinct functions of Pyk2/JAK2 would allow neurons control over the elimination of individual synapses vs. the elimination of an axon. Together, this work reveals the molecular mechanisms by which the brain detects neuronal activity and determines which and how much of a connection to eliminate to establish functional neural networks. These mechanisms may advise therapeutic strategies to restore balance to neural networks in diseases that are characterized by too much or too little synapse/axon elimination.

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Integrated multiplexed profiling enables simultaneous target based and phenotypic drug discovery

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There are two major drug discovery methodologies for the identification of first-in-class drugs, namely target-based drug discovery and phenotypic drug discovery.1 Target-based screening has a rational approach where the target structure and disease mechanism are well described, thus having a longer initial stages in a drug development process.2 On the contrary, phenotypic drug screening tackles diseases without thorough information of the disease target and/or disease mechanism, hence being faster, but experiencing challenges in the hit validation and drug optimization.3A more holistic approach that combines the target/disease background knowledge with the drug phenotype is needed to characterize better compounds. In this work, we developed a multiparametric cell-based assay platform that can simultaneously profile efficacy of compounds to both disease-relevant target molecules and physiological pathways, thus combining target-based and phenotypic drug discovery. Here we focused on ERBB family kinases of receptor tyrosine kinase (RTK) family, as they play key roles in developmental processes and human disorders, including but not limited to cancer, cardiovascular disorders, as well as neurodevelopmental and mental disorders.4-7 This ERBB receptor profiling assay, enables (1) to determine the efficacy of a drug candidate and (2) to detect side effects including toxicity of a drug candidate in the early stages of drug development. Using this multiplexed approach, we were able to profile therapeutic and side effects, as well as resistance patterns of tool compounds and drugs that are either approved, in clinical trials, or have failed. In addition to known effects, we identified so far hidden activities of ERBB antagonists, and synthesized and profiled novel first-in-class ERBB4 selective drugs that have the potential for clinical trials. Therefore, this multiparametric profiling approach may guide compound screenings in the early phase of drug discovery campaigns.

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Ancestral DCHS1 influences interneuron specification through putative changes in protein glycosylation

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Identifying similarities and differences between hominids is particularly important for understanding the genetic, molecular and cellular basis of human brain specialisation. To this end, whole genome sequences from modern humans, archaic hominins, chimpanzees and the other great apes provide a basis for explaining brain evolution and ultimately human brain development.
For this reason, DNA from closely related archaic hominins such as Homo neanderthalensis, has been sequenced and several single nucleotide variants (SNVs) have been identified. Among these is a SNV that could affect brain structure and function that harbouring the DCHS1 gene, which encodes a protocadherin involved in axon guidance and dendrite arborisation during neurodevelopment (Cappello 2013, Klaus 2019).

Here, we investigate the consequences of these evolutionary changes in the DCHS1 gene at the molecular, cellular, and developmental levels.

Our analyses show that a SNV in the DCHS1 gene is predicted to result in a loss of glycosylation in the human DCHS1 protein, which could affect its stability and binding affinity to DCHS1 interactors. Interestingly, using brain organoids and scRNA-seq analyses, we found that the ancestral DCHS1 leads to alterations in the production of inhibitory striatal projection neurons, potentially influencing cell fate decisions during neurodevelopment.

Collectively, these findings suggest that evolutionary changes in the DCHS1 gene may have played a role in shaping the neurodevelopmental trajectories of Homo sapiens and Homo neanderthalensis, contributing to the distinct cognitive and behavioural differences between the two species. Further investigation into the molecular mechanisms underlying these differences could provide valuable insights into the evolutionary history of human brain development.

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The brain in the gut: a central regulator of digestive health and disease

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The gastrointestinal (GI) tract is by far the largest interface between the mammalian body and the external environment. The dietary, microbial, and other signals communicated from the intestinal lumen to the nervous system are continuous inputs that define metabolic homeostasis, behavior, and immunity. The GI tract is innervated by vagal afferent and efferent neurons, spinal afferent neurons, and sympathetic post-ganglionic neurons. These extrinsic inputs, however, are vastly exceeded by those of its own intrinsic nervous system, a complex network of neurons and glial cells organized into two interconnected plexuses that densely populate its entirely length. This enteric nervous system (ENS) operates both autonomously and in collaboration with the central nervous system to regulate virtually every aspect of gut function including the coordinated transport of luminal contents for digestion, epithelial turnover, fluid secretion, and mucosal immunity. Within laminated structure of the intestine, the nerve fibers and associated glia projecting to its innermost layer, the mucosa, are situated in one of the most unique microenvironments in the nervous system. Here, enteric circuits are in close proximity to immune cells, microbial products and epithelial cells that place them one cell breadth away from the external environment. With a focus on this mucosal compartment, we are working to define the essential functions of the ENS in GI homeostasis, the nature of bidirectional communication across neuro-epithelial circuits, and how pathogens exploit these circuits to cause disease.

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Inputs, topography and behaviors in the largest optic glomerulus of fruit flies

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The 2-dimensional array of fluctuating light intensities produced in the retina is transformed into visual features, such as motion, color, or discrete objects. In insects, visual projection neurons relay such features to several retinorecipient areas in the central brain, including synapse-dense optic glomeruli. Among these, the anterior optic tubercle is unique because it retains spatial organization that represents space and receives input from different neuron types, including LC10a, LC10bc, and LC10d. In Drosophila melanogaster, LC10a neurons sense moving objects and are essential for tracking the female during courtship, a complex social interaction involving a persistent internal state that modulates LC10a activity. LC10d and LC10bc are dispensable for female tracking, suggesting that the anterior optic tubercle might house neural circuits mediating different behaviors. Drosophila males initially avoid an unknown fly, but orient to and chase a female when courting. We found that LC10d neurons mediate avoidance in response to an unknown fly or small visual object, whereas LC10bc contribute to orienting maneuvers towards another fly before courtship is initiated. Functional imaging of neuronal responses to a barrage of visual features revealed that both LC10a and LC10d neurons detect discrete objects, with LC10d neurons exhibiting overall broader tuning properties than LC10a. Surprisingly, LC10bc neurons sense full field gradients in an orientation-selective manner. Analysis of the fly connectome (Neuprint) revealed that LC10a and LC10d neurons share several downstream neurons but establish different connections, such that LC10a-downstream circuits populate the contralateral brain hemisphere, whereas LC10d-downstream circuits remain in the ipsilateral brain hemisphere. Together these results implicate the anterior optic tubercle as a hub for processing diverse visual cues that subserve different, even opposing, behaviors.

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More than a stress mediator: A novel role of the neuropeptide CRH in oligodendrogenesis

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Neuropeptides and their receptors have been largely neglected in the physiological function of oligodendrocyte progenitor cells (OPCs). One of those neuropeptides is the corticotropin-releasing hormone (CRH), which is a key regulator of the body's stress response. Although, CRH had already been implicated in the brains reaction to ischemia its specific function in central nervous system injury remains elusive. In our study, we describe a novel neuropeptide system in OPCs, formed by CRH and its high affinity type 1 receptor (CRHR1). First, we discovered a subpopulation of CRH-expressing OPCs aggregating around stab wound injuries in the midbrain of CRH-Cre::Ai9 reporter mice. These CRH-expressing OPCs possess a high capacity for differentiation into oligodendrocytes and differ from other oligodendrocyte lineage cells in their population dynamics. De novo expression of CRH in OPCs is an immediate response to acute injury starting within the first 12 hours following injury. Furthermore, we identified CRHR1-expressing astrocytes and OPCs as targets of this CRH. By using various gain- and loss-of-function approaches involving different transgenic mouse models, we showed that: i) excessive CRH elevates the activation state of astrocytes after acute injury in a CRHR1-dependent manner and ii) the inhibition of CRH/CRHR1 signaling in both OPCs and astrocytes amplifies the generation of oligodendrocytes following acute injury. Altogether, our findings delineate a novel CRH/CRHR1 system in OPCs and astrocytes regulating oligodendrocyte generation, implying neuropeptides with a role in regenerative processes following acute brain injury. Further investigation has to show whether neuropeptide systems are also involved in developmental oligodendrogenesis or myelination.

Circuit mechanisms of dopamine teaching signals in mouse frontal cortex

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As a neurotransmitter with extensive neuromodulatory properties, dopamine plays an important role in a wide range of distinct brain functions. A large body of experimental and theoretical evidence has shown that midbrain dopamine neurons are required for high-level cognitive processes generated by the medial prefrontal cortex (mPFC). Specifically, phasic dopamine transients encode a reward prediction error (RPE), which represents the difference between predicted and actual reinforcing outcomes. The RPE is a canonical learning signal, and converging evidence suggests that the mPFC functions as a crucial recipient for dopamine neuromodulatory signals to guide learning. However, the prefrontal neuronal mechanisms that govern this process are not known. Here, we examined the role of dopaminergic transients in mPFC during abstract associative learning. Specifically, we investigated whether and how dopaminergic signatures evolve as task competency increases. We developed an auditory decision-making task with implicit (uncued) rules switches that was designed to capitalize on the hypothesized role of mPFC dopaminergic neuromodulation in cognitive processing and decision-making. Head-fixed mice learned to associate auditory cues with directed motor outputs (licks) to obtain liquid rewards. Auditory stimuli varied along the dimensions of location (left or right) and frequency (high or low). Only one feature dimension was relevant at a given time, depending on the currently applied task rule, which was changed after the animals reached expert performance levels. Dopamine concentrations in cortical areas are orders of magnitude lower than in the typically studied striatum, posing considerable experimental challenges for the investigation of prefrontal dopaminergic neurotransmission. To this end, we virally expressed the newly developed high-sensitivity fluorescent dopamine sensor GRAB DA3h in mPFC. Dopaminergic transients were measured with fiber photometry over the course of several months while the animals learned and re-learned the required tasks. Our efforts have resulted in successful dopamine recordings in the mouse mPFC with high levels of specificity and sub-second temporal resolution. Preliminary results show that the measured dopamine signals were event-locked and followed the task structure. Phasic dopamine transients evoked by the auditory cue and the obtained rewards were also modulated by the animals' performance levels and thus reflected their mechanistic understanding of the task. Together, our results will contribute detailed insights into the role of prefrontal dopaminergic neuromodulation in abstract associative learning.

Slide-tags: single-nucleus high-resolution multi-modal spatial genomics

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Recent technological innovations have enabled the high-throughput quantification of gene expression and epigenetic regulation within individual cells, transforming our understanding of how complex tissues are constructed. Missing from these measurements, however, is the ability to routinely and easily spatially localize profiled cells. We developed a novel strategy, which we call Slide-tags, in which single nuclei within an intact tissue section are 'tagged' with spatial barcode oligonucleotides derived from DNA-barcoded beads with known positions. As a proof of concept, we performed Slide-tags on the mouse hippocampus, which has a highly stereotyped architecture that enables rapid validation of spatial assays. Assay of this region by Slide-tags captured 463 nuclei per mm2, and delivered whole-transcriptome data that was indistinguishable in data quality from ordinary snRNA-seq. To demonstrate that Slide-tags can be applied to a wide variety of human tissues, we performed the assay on kidney, lymph node, tonsil, and brain. A major benefit of Slide-tags is that it is easily adaptable to virtually any single cell measurement technology. To demonstrate this, we performed multiomic measurements of open chromatin and RNA in the same cells from a mouse embryo, identifying spatial patterns of neuronal differentiation. These advances facilitate high-resolution analysis of cell-cell interactions, as well as being more powered to detect changes in gene expression across cell types in space. Slide-tags offers a universal platform for importing established single cell measurements of gene expression, epigenetic regulation, and antibody-based quantification into the spatial genomics repertoire.

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Validation of a neuronal integrator circuit in the larval zebrafish with correlated light and electron microscopy

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When larval zebrafish experience whole-field visual motion, as in the random-dot task, they swim in the direction of motion, an innate behavior enabling animals to maintain position in moving water. Intriguingly, this behavior is well-explained by the same bounded drift-diffusion model that captures human and primate behavior in analogous random-dot paradigms. We previously proposed a circuit model that implements this algorithm via a neural integrator circuit in the anterior hindbrain that accumulates noisy visual evidence and excites downstream motor circuits after overcoming competitive inhibition from surrounding cells. However, because the anatomical cell types and connectivity of the hindbrain are unknown, our circuit model remains hypothetical. I will present a two-pronged collaborative effort using correlated light and electron microscopy (CLEM) to relate functional responses of hindbrain neurons with their ultrastructure and synaptic connectivity with the goal to test and revise our proposed circuit model.
In the 'rich person's approach', we generated a multi-modal dataset containing an electron microscopy (EM) volume of the hindbrain in which we previously performed calcium imaging during visual stimulation. By first identifying functional responses of neurons and then reconstructing the same cells in EM and mapping their synaptic connectivity, we can directly test the predictions made by our circuit model.
In the complementary 'poor person's approach', we used two-photon guided GFP photoactivations of neurons of interest during functional imaging. This allowed us to reconstruct the 3D morphologies of functionally identified cells in the light microscope (LM) and to group them into distinct anatomical-functional cell classes. In parallel, we are generating a comprehensive library of hindbrain neurons reconstructed at synaptic resolution in an existing whole-brain EM volume of a different larval zebrafish. By mapping the anatomical-functional LM cell classes onto our EM reconstructions, we hope to identify the same cell classes in our EM dataset, where we can then generate circuit maps at synaptic resolution to test and revise our circuit model.
While the 'rich person's approach' is costly and time-consuming, it provides 'ground-truth' for CLEM and is critical for validating the 'poor person's approach', which relies on published methods and EM datasets that will be made openly accessible – and could thus become a useful resource for the zebrafish community. Intriguingly, both approaches have independently validated our assumption that integrator neurons are embedded in a recurrent circuit in the hindbrain, and they have falsified our hypothesis of how inter-hemispheric inhibition is implemented in the hindbrain circuitry. Taken together, our work provides an example of how CLEM can be used for testing existing hypothetical circuit models in the larval zebrafish.

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Constructing auditory space: modulation of the spatial map by auditory cues and landmarks

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Pathfinding and navigation through one's environment are crucial for survival. Extensive research over the last 50 years identified that in order to build and update the location of self in the world, both external (allocentric) and internal (idiothetic) information streams are used by the brain (reviewed in Moser, Rowland, 2015). As a consequence, a central goal of sensory and navigational neuroscience is to understand how different sensory modalities build a coherent internal spatial representation (Nyberg, Spiers, 2022). So far, researchers have mainly manipulated visual, tactile (walls, borders) and/or olfactory sensory information in pursuit of this goal (Chen, 2013; Aronov, Tank, 2014; Plitt, Giocomo, 2021; see also review by O'Keefe, Krupic, 2021). While auditory cues are highly informative for our orientation and play a crucial role in creating a contextual picture of the current scene (reviewed e.g. in Bregman 1990, Pecka et al., 2020), their contributions to the formation of idiothetic maps has been more or less overlooked (O'Keefe, Krupic, 2021). Specifically, to what extent and how auditory cues and audio-spatial associations shape the internal spatial representation is not well investigated.
To gain understanding over the construction of auditory space and its influence on the spatial representation, we performed chronic multi-electrode recordings from the hippocampal area CA1 (place cells), retrosplenial and parietal cortices (head direction cells and egocentric vector representations) in freely-behaving Gerbils. By using an audio-spatial version of the Sensory-Island Task (SIT; Ferreiro, Amaro et al., 2020; Amaro et al., 2021) in both light and darkness enabled us to manipulate spatial cues and hence to introduce a conflict between the auditory spatial reference frame and the spatial map maintained by an idiothetic path integrator. Specifically, we investigate the degree of integration of independent position estimations given auditory and idiothetic reference frames. Additionally, we explore potential neural and behavioral correlates of spatially-relevant auditory landmarks, exemplified by direction or distance tuning to the location of the sound sources. Together, this project provides insight into the logic and mechanisms of auditory-based orientation and spatial representation.
For example, in the daylight animals highly rely on visual allocentric cues for navigation, but at night they use idiothetic path integration to perform their goal-directed actions (Shettleworth et al., 2005; Etienne et al., 2004; Kobayashi et al., 2003; Hok et al., 2007). Accordingly, a current central goal of navigational neuroscience is to understand how sensory modalities influence and interact with the internal spatial representation (Nyberg, Spiers, 2022). To this end, researchers have manipulated mainly visual, tactile (walls, borders) and/or olfactory sensory information in pursuit of this goal (Chen, 2013; Aronov, Tank, 2014; Plitt, Giocomo, 2021; see also review by O'Keefe, Krupic, 2021).
Auditory cues are highly informative for our orientation in the environment and play a crucial role in creating a contextual picture of the current scene (reviewed e.g. in Bregman 1990, Pecka et al., 2020). Nonetheless, the interactions /contributions of the auditory modality with / to idiothetic maps has been more or less overlooked (O'Keefe, Krupic, 2021). Specifically, to what extent and how auditory cues and learned audio-spatial associations shape the internal spatial representation is not well investigated.
The Sensory-Island Task (SIT; Ferreiro, Amaro et al., 2020; Amaro et al., 2021; funded by DFG project GZ: PE 2251/2-1) is a well-tested experimental paradigm for probing auditory perception in freely navigating rodents. SIT readily allows testing to what extent sound sources are used as spatially-relevant cues for pathfinding and to investigate the formation of local audio-spatial associations between a particular sound with a fixed spatial location. Moreover, the SIT setup design enables foraging in absolute darkness, rendering the spatial orientation dependent on auditory cues and idiothetic signals only. Specifically, manipulating auditory cues in darkness enables us to introduce a conflict between the auditory spatial reference frame and the spatial map maintained by an idiothetic path integrator, providing unique opportunities for research on the ability of the auditory information to influence spatial representations.
One of the main neural correlates of the internal spatial representation are the hippocampal place cells (O'Keefe, Dostrovsky, 1971) uniquely mapping animal's position, and head direction cells (Taube, 2007), reflecting animal's allocentric orientation in any environment. To gain understanding over the construction of the auditory space and its influence on the spatial representation we plan to perform chronic recordings from the hippocampal area CA1 (HPC CA1, place cells) and the retrosplenial cortex (RSC, head direction cells) in freely-behaving animals in the audio-spatial SIT task. As RSC serves as a hub integrating different types of idiothetic and allocentric information including landmark information and reward location (Stacho et al., 2022), we also seek to find neural correlates of spatially-relevant auditory landmarks, exemplified by direction or distance tuning to the location of the sound source.
In addition, as spatial associations develop with learning (Miller et al., 2019), we will vary the degree of prior gained task experience to test how fast the audio-spatial associations can be established and to what extent it affects the strength of its spatial modulation. Finally, simultaneous electrophysiological recordings in the hippocampus and RSC would allow to investigate the coherence of the influence of the auditory space on both place cell and head direction systems. Together, this project provides insight into the mechanisms of auditory-based orientation and spatial representation.

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The pathway-specific signals that organize functionally distinct dopaminergic synapses

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Dopaminergic projections regulate various brain functions and are implicated in many neuropsychiatric disorders. There are two anatomically and functionally distinct dopaminergic pathways connecting the midbrain to the striatum: the nigrostriatal pathway, which controls movement and exploration, and the mesolimbic pathway, which regulates motivation and emotion. However, how these discrete dopaminergic synaptic connections are established is unknown. The aim of this study is to reveal the molecular mechanisms underlying the establishment of functionally segregated dopaminergic synaptic connections.
To identify molecules that can induce dopaminergic synaptic differentiation in nigrostriatal and mesolimbic neurons, we performed an unbiased search using dopaminergic synaptic vesicle clustering in cultured midbrain dopaminergic neurons as an assay. We found that two groups of antagonistic TGFβ family members, BMP6/BMP2 and TGFβ2, are secreted from target striatal neurons and regulate the formation of dopaminergic presynaptic terminals in the nigrostriatal and mesolimbic neurons, respectively. By using shRNA-mediated in vivo gene silencing, we found that BMP6/BMP2 is necessary for nigrostriatal, and TGF 2 is necessary for mesolimbic dopaminergic synapse formation. We then found that nigrostriatal and mesolimbic neurons preferentially express the BMP receptor and TGΦβ receptor, respectively, which supports pathway-specific dopaminergic synapse development. Furthermore, we found that downstream signal mediators of these receptors, Smad1 and Smad2, are specifically activated and required for dopaminergic synapse development and physiological function in nigrostriatal vs. mesolimbic pathways. Finally, as behavioral consequences, we found that Smad1 mutant mice show motor defects, while Smad2 mutant mice show a lack of motivation. These results uncover the molecular logic underlying the proper establishment of functionally segregated dopaminergic synaptic connections in the mammalian brain and shed light on the development of new therapy for pathway-specific symptoms by targeting specific BMPs/TGFβ and/or Smads.

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Daily and seasonal variation in singing in Canaries (*Serinus canaria*)

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Canaries are studied in the context of seasonal behavioral and neurobiological plasticity. However, whether changes occur in their singing in social environments has not been thoroughly characterized. We therefore studied changes in singing behaviour between the non-breeding and the breeding season as well as at another time-scale, days, in a fixed population of captive canaries in an aviary in Munich. Results reveal variations in singing at both time-scales. These will guide future investigations on the neurobiological underpinnings of these behavioural changes.

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Molecular logic in synaptic circuit development and disease

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We are studying synaptic circuit development in the mammalian brain. There are many circuits in the brain, each of which regulates different behavior. Such specific circuits need to be established precisely during development. Furthermore, after the initial assembly of synapses, synaptic connections are refined by neural activity to establish functional neural circuits in the brain. We are trying to understand the mechanisms and molecular logic by which specific and functional synaptic circuits are established in the brain, using both in vitro and in vivo systems. Abnormal synaptic circuit development leads to various neuropsychiatric disorders, including autism, schizophrenia, and epilepsy. Through our research, we hope to provide clues for the treatment of such neuropsychiatric disorders.

The role of MAST2 in brain development and disease

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Constructing a human brain, from progenitor cells to transhemispherically connected mature neurons, relies on a complex interplay of molecular and cellular processes. Disturbances caused by genetic mutations affecting neuronal birth, migration, or differentiation can lead to severe neurological disorders. Notably, recent studies have implicated the MAST family of microtubule-associated kinases in neurodevelopmental conditions, such as mega-corpus-callosum syndrome and developmental and epileptic encephalopathy; however, the underlying mechanisms of disease remain unknown. In this work, we describe the clinical profile associated with MAST2 mutations. Patients in our cohort exhibit classical symptoms of altered neurodevelopment including early-onset epilepsy, autism spectrum disorder and intellectual disability. We go on to describe the expression pattern of MAST2 in the developing brain and we employ tagging techniques to investigate the subcellular localization of MAST2. To further study the pathogenesis of MAST2 mutations, we have set up two mouse models: a MAST2 knock-out, as well as a mouseline recapitulating a patient mutation. Current work focuses on characterizing the behavioural, anatomical, and molecular phenotype of MAST2 mutant mice. Taken together, this study will shed light on the role MAST2 plays in brain development, as well as pathophysiological mechanisms associated with MAST2 mutations.

Mesoscale modules for the control of working memory in primate frontoparietal cortex

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Working memory tasks often reveal sustained neural activity that represents the memorized information. However, recent discoveries suggest an alternative biophysical model with temporally sparse, short-lived oscillatory activity arranged in bursts. How these oscillatory bursts relate to the functional organization of local and long-range circuits in the working memory network and the storage and processing of working memory content remains unclear. To address these questions, we recorded spiking activity and local field potentials (LFP) in the lateral prefrontal cortex (PFC) and ventral intraparietal area (VIP) of two rhesus monkeys performing a delayed-match-to-sample task with visually presented target numerosities (sets of dots) and interfering distractor numerosities. We analyzed the spatiotemporal patterns of LFP bursts across recording sites and their relationship to neuronal spiking activity. We found that the burst probability was monotonically modulated by numerosity, while individual neurons typically showed peaked tuning to number. In both brain regions, bursts of different frequencies exhibited unique patterns during different task epochs. In PFC, where precise reconstruction of the spatial layout of recording sites was possible, sensory signals triggered by sample presentation arrived at separate anterior sites, associated with either gamma (60-90Hz) or beta (15-35Hz) band oscillations. Sample memory maintenance was accompanied by gamma bursts at a more posterior site. Remarkably, following distraction, sample information was recovered in the same posterior sites, albeit with beta bursts dominating. Local and inter-regional functional connectivity differed across these prefrontal clusters, further supporting their distinct roles in working memory processing. These mesoscale modules remained spatially stable across recording days. Our findings indicate that LFP bursts in the frontoparietal cortex are not direct representations of working memory content. Instead, frequency-specific oscillatory neural activity contributes to contextual processing and dynamic organization within a distributed cortical network. Spatially separable modules in the prefrontal cortical sheet are tasked with sensory and memory coding. Our study sheds light on the complexity of working memory mechanisms and circuit organization in frontoparietal cortex, emphasizing the importance of considering mesoscale spatiotemporal dynamics in future research.

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Probing auditory perceptual thresholds in a naturalistic go/no-go paradigm for freely moving animals: re-assessing temporal sensitivity

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Recent calls for more naturalistic experiments are challenging the experimental reductionism towards more behavioral variability during data acquisition. In order to advance these goals, we have recently developed the Sensory Island Task (SIT), a flexible behavioral paradigm that combines closed-loop auditory feedback during self-motion and natural free exploratory behavior to study auditory processing.

In this paradigm, animals are trained via positive reinforcement to search for a particular area in the arena ("target island"), which triggers a change in the presented stimulus. The animal reports detection of the target stimulus by remaining within the target island for a defined time ("sit-time"). The location of the target island is randomized across trials, making the stimulus feature under investigation the only informative cue for task completion. We have successfully trained animals (Mongolian gerbils) on sound features that are either based on spectral (frequency discrimination and identification, Ferreiro et al., 2020) or temporal processing (sound localization, Amaro et al., 2021).

Here, we investigate duration discrimination in gerbils using the SIT paradigm. Previous studies of sound duration discrimination conducted in rodents have reported thresholds that were significantly elevated compared to those found for humans and other primates. This apparent discrepancy is remarkable because high temporal precision is regarded as a general hallmark of auditory processing across species. Utilizing SIT, we tested two different reference durations – 50 ms and 90 ms – for 7 gerbils. We observed that the animals not only readily learned the task, but could also discriminate sounds that differed 5 to 15 ms in duration. To facilitate comparisons across studies, we calculated the respective Weber fractions, i.e. the ratio of the just noticeable difference (threshold) to the duration of the reference stimulus. Across the tested animals, we obtained Weber fractions between 0.1 and 0.3 for the reference duration of 50 ms and between 0.1 and 0.15 for 90 ms. The precision in duration discrimination that we report on gerbils is considerably higher than previous reports in rodents and closer to that which has been shown in humans. The marked difference between these results and previous reports for rodents could potentially be attributed to a species-specific effect, as duration discrimination had not been tested in gerbils before. Specifically, the gerbils were initially tested using low frequency sounds (660 Hz), which are within the gerbil's hearing range but not of other rodents. Therefore, additional experiments were conducted with higher frequencies (10 kHz). No significant change

in the task performance or determined Weber fractions was observed in the high frequency condition.

Overall, these results indicate that SIT facilitates the readout of perceptual levels, as the detection of stimulus change is reported in a more ethologically intuitive way compared to traditional paradigms (e.g. posterior forced choice).

The LMU-Harvard Young Scientists' Forum (YSF) seeks to unite PhD students and Postdoctoral fellows from the Harvard University and the Ludwig-Maximilians-Universität (LMU Munich) with core faculty from the two universities to create a framework for an interdisciplinary exchange of ideas. The YSF was initiated as a yearly event in 2009 and is held alternately in Munich and Cambridge.

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