LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

HARVARD UNIVERSITY

LMU–Harvard Young Scientists' Forum

From Molecules to Organisms XI,
Munich, June 23 – June 27, 2019

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.

- **LMU-Harvard Young Scientists' Forum at the Center for Advanced Studies (CAS[LMU]) and the LMU Biocenter:** From Molecules to Organisms, June 23 – June 27, 2019
- **Under the auspices of** Prof. Dr. Hans van Ess, Vice President for International Affairs, LMU
- **Program Management:** Dr. Anna Jakubowska (LMU International Office), Sylvia Zehner (LMU Munich Center for Neurosciences)
- **Participating academic units:** Munich Center for Neurosciences (MCN[LMU]), Graduate School of Systemic Neurosciences (GSN[LMU]), Center for Integrated Protein Science Munich (CIPSM)
- **Academic Management:** Prof. Dr. Oliver Behrend, Prof. Dr. Benedikt Grothe (MCN[LMU]/GSN[LMU])
- **Institutional Responsibility:** LMU International Office, LMU Biocenter, Center for Advanced Studies (CAS[LMU])

Conference Agenda

Sunday, June 23

	CAS(LMU), Seestr. 13, 80802 Munich (arrival individually arranged)
18:15 – 18:30	**Welcome address** (B.Grothe MCN(LMU); L.Bouman CAS(LMU))
18:30 – 19:30	**Lecture 1** – **A.Herz:** "The many ways to read from grid cells in navigating rodents"
19:30 – 20:30	*Snacks/drinks*
20:30 – 21:00	Pre-arranged transfer to **IZB Residence CAMPUS@HOME** (address below)

Monday, June 24

	LMU Biocenter, Grosshadernerstr. 2, 82152 Martinsried, D00.003
09:00 – 09:15	Walk from IZB Residence to Biocenter
09:15 – 09:30	**Welcome address** (J.Schleiss; Deputy Head LMU International Office)
09:30 – 10:30	**Lecture 2** – **T.Misgeld:** "Cytoskeletal dynamics as a regulator of neuronal remodeling" (Intro: L.Busse)
	Coffee break (catered; foyer D00.003)
11:00 – 13:00	**Session 1** – "Remodelling and plasticity of neural circuits" **M.Frank / T.Czopka / M.Caiati / J.Reggiani** (Chair: L.Busse)
	Lunch break (catered; foyer)
14:30 – 16:30	**Session 2** – "Sensory circuits: development and neural coding" **J.Pujol-Marti / J.Zak / D.Amaro / A.Grama** (Chair: M.Pecka)
	Coffee break (catered; foyer)
17:00 – 18:00	**Lecture 3** – **T.Hensch:** "Balancing brain plasticity/stability" (Intro: L.Kunz)
18:00 – open	*At free disposal (student representative activities)*

Tuesday, June 25

	LMU Biocenter Martinsried, D00.003
08:45 – 09:00	Walk from IZB Residence to Biocenter
09:00 – 10:00	**Lecture 4** – **C.Leibold:** "Computing with hippocampal sequences" (Intro: S.Katzner)
	Coffee break (catered; foyer)
10:30 – 12:30	**Session 3** – "Modulation of neural processing and behaviour" **L.Busse / R.Santos / K.McGuire / K.Herrera** (Chair: S.Katzner)
	Lunch break (catered; foyer) & **YSF faculty meeting** (D00.013)

14:30 – 16:30	**Session 4** – "Navigation and sensory-motor control" **P.zu Eulenburg / D.Fetterhoff / M.Pröll / K.Liu** (Chair: A.Sirota)
	Coffee break (catered; foyer)
17:00 – 18:00	**Lecture 5** – **V.Murthy:** "Odor-guided navigation in terrestrial animals" (Intro: A.Sirota)
18:00 – open	Bavarian Conference Evening (**Fürstenrieder Schwaige, Forst-Kasten-Allee 114, 81475 München**; transfer pre-arranged at IZB Residence)

Wednesday, June 26

	LMU Biocenter Martinsried, D00.003
08:45 – 09:00	Walk from IZB Residence to Biocenter
09:00 – 10:00	**Lecture 6** – **L.Goodrich:** "Sounding out diversity in the developing auditory system" (Intro: B.Grothe)
	Coffee break (catered; foyer)
10:30 – 12:30	**Session 5** – "Neurodevelopment and regeneration" **F.Auer / A.O'Neill / S.Kröger / V.Splith** (Chair: S.Michalakis)
	Lunch break (catered) & **YSF poster session** (foyer)
	Y.Bauer / A.Chen / O.Durak / L.Kaplan / S.Özugur / L.Pilz / L.Rast / R.Rühl / M.Schifferer / T.Weili / W.Yan / T.Yang
14:30 – 15:30	**Lecture 7** – **A.Ertürk:** "Molecular and cellular profiling of intact organs" (Intro: M.Biel)
15:30	**Closing remarks** (O.Behrend MCN[LMU]; K.Blum CBS)
15:45	Walk from Biocenter to IZB Residence / individually: beergarden

Thursday, June 27

	IZB Residence CAMPUS@HOME, **Am Klopferspitz 21, 82152 Martinsried**
09:00 – 19:00	**Excursion**, Petersberg and Kufstein castle

Friday, June 28

Departure, Individually arranged

Participants*

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

Harvard University Delegation

- **Kenneth Blum**, Executive Director, Harvard Center for Brain Science
- **Maddalena Caiati**, Research Associate, Department of Molecular and Cellular Biology, Laboratory of Takao Hensch
- **Alex Chen**, PhD student, Department of Molecular and Cellular Biology, Laboratory of Florian Engert
- **Omer Durak**, Postdoctoral Fellow, Department of Stem Cell and Regenerative Biology, Laboratory of Jeffrey Macklis
- **Michelle Frank**, PhD student, Harvard Medical School, Department of Neurobiology, Laboratory of Lisa V. Goodrich
- **Lisa V. Goodrich**, Professor, Harvard Medical School, Department of Neurobiology
- **Abhinav Satish Grama**, Postdoctoral Fellow, Department of Molecular and Cellular Biology, Laboratory of David Cox, Harvard Medical School, Department of Neurobiology, Laboratory of Richard Born
- **Takao Hensch**, Professor, Center for Brain Science, Department of Molecular and Cellular Biology, Harvard Medical School
- **Kristian Herrera**, PhD student, Department of Molecular and Cellular Biology, Laboratory of Florian Engert
- **Yuanyuan Liu**, PI, Harvard Medical School, Boston Children's Hospital, Laboratory of Zhigang He
- **Kelly McGuire**, PhD student, Harvard Medical School, Department of Medicine & Beth Israel Deaconess Medical Center, Laboratory of Mark L. Andermann
- **Venkatesh Murthy**, Professor, Harvard Center for Brain Science
- **Luke Rast**, PhD student, Harvard Medical School, Department of Neurobiology, Laboratory of Jan Drugowitsch
- **Jasmine Reggiani**, PhD student, Harvard Medical School, Department of Medicine, Laboratory of Mark L. Andermann & Laboratory of Chinfei Chen
- **Wenjun Yan**, Postdoctoral Fellow, Department of Molecular and Cellular Biology, Laboratory of Joshua Sanes
- **Joseph Zak**, Postdoctoral Fellow, Harvard Center for Brain Science, Laboratory of Venkatesh Murthy

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Harvard University Nominating Faculty

- **Mark L. Andermann**, Professor, Harvard Medical School, Department of Medicine & Beth Israel Deaconess Medical Center
- **Richard Born**, Professor, Harvard Medical School, Department of Neurobiology
- **Chinfei Chen**, Professor, Harvard Medical School, Division of Medical Sciences
- **David Cox**, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology
- **Jan Drugowitsch**, Professor, Harvard Medical School, Department of Neurobiology
- **Florian Engert**, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology
- **Lisa V. Goodrich**, Professor, Harvard Medical School, Department of Neurobiology
- **Zhigang He**, Professor, Harvard Medical School, Boston Children's Hospital
- **Takao Hensch**, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology, Harvard Medical School
- **Jeffrey Macklis**, Professor, Harvard Center for Brain Science, Department of Stem Cell and Regenerative Biology
- **Venkatesh Murthy**, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology
- **Joshua Sanes**, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology

Ludwig-Maximilians-Universität München (LMU)
Helmholtz Zentrum München – German Research Center for Environmental Health (HMGU)
Max Planck Institute of Neurobiology (MPIN)
Technische Universität München (TUM)
Delegation

- **Diana Amaro**, PhD student, LMU, Department Biology II, Division of Neurobiology, Laboratory of Benedikt Grothe & Laboratory of Michael Pecka
- **Franziska Auer**, PhD student, TUM, Institute of Neuronal Cell Biology, Laboratory of Tim Czopka
- **Yannik Bauer**, PhD student, LMU, Department Biology II, Division of Neurobiology, Laboratory of Laura Busse

- **Oliver Behrend**, Managing Director, LMU, Munich Center for Neurosciences (MCN[LMU]), Graduate School of Systemic Neurosciences (GSN[LMU])
- **Martin Biel**, Professor, LMU, Department of Pharmacy, Center for Integrated Protein Science Munich (CIPSM)
- **Alexander Borst**, Professor, MPIN, Department of Systems and Computational Neurobiology
- **Lena Bouman**, Academic Coordinator (Natural Sciences and Medicine), LMU, Center for Advanced Studies (CAS[LMU])
- **Laura Busse**, Professor, LMU, Department Biology II, Division of Neurobiology
- **Tim Czopka**, PI, TUM, Institute of Neuronal Cell Biology
- **Ali Ertürk**, PI, LMU, Institute for Stroke and Dementia Research (ISD)
- **Dustin Fetterhoff**, Postdoctoral Fellow, LMU Bernstein Center for Computational Neuroscience (BCCN), Laboratory of Christian Leibold
- **Leanne Godinho**, PI, TUM, Institute of Neuronal Cell Biology
- **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 II, Division of Neurobiology, Munich Center for Neurosciences (MCN[LMU]), Graduate School of Systemic Neurosciences (GSN[LMU])
- **Ilona Grunwald Kadow**, Professor, TUM, School of Life Sciences Weihenstephan (WZW)
- **Andreas V. M. Herz**, Professor, LMU, Department Biology II, Bernstein Center for Computational Neuroscience (BCCN)
- **Anna Jakubowska**, Project Manager, LMU, International Office
- **Lew Kaplan**, PhD student, LMU, Department of Physiological Genomics, Laboratory of Antje Grosche
- **Steffen Katzner**, PI, LMU, Department Biology II, Division of Neurobiology
- **Stephan Kröger**, Professor, LMU, Department of Physiological Genomics
- **Lars Kunz**, PI, LMU, Department Biology II, Division of Neurobiology, Laboratory of Benedikt Grothe
- **Christian Leibold**, Professor, LMU, Bernstein Center for Computational Neuroscience (BCCN)
- **Hernán López-Schier**, PI, HMGU, Research Unit Sensory Biology and Organogenesis
- **Stylianos Michalakis**, PI, LMU, Department of Pharmacy, Center for Integrated Protein Science Munich (CIPSM)
- **Thomas Misgeld**, Professor, TUM, Institute of Neuronal Cell Biology, German Center for Neurodegenerative Diseases (DZNE)
- **Suzan Özugur**, PhD student, LMU, Department Biology II, Division of Neurobiology, Laboratory of Hans Straka
- **Adam C. O'Neill**, Postdoctoral Fellow, HMGU, Institute for Stem Cell Research, Laboratory of Magdalena Götz

- **Michael Pecka**, PI, LMU, Department Biology II, Division of Neurobiology
- **Luisa K. Pilz**, Postdoctoral Fellow, LMU, Institute of Medical Psychology, Laboratory of Till Roenneberg
- **Michaela Pröll**, PhD student, LMU, Bernstein Center for Computational Neuroscience (BCCN), Laboratory of Andreas Herz
- **Jesus Pujol-Marti**, Postdoctoral Fellow, MPIN, Laboratory of Alexander Borst
- **Till Roenneberg**, Professor, LMU, Institute of Medical Psychology
- **Ria Maxine Rühl**, Postdoctoral Fellow, LMU, Department of Neurology, Laboratory of Peter zu Eulenburg
- **Ricardo Santos**, Postdoctoral Fellow, LMU, Department Biology II, Laboratory of Anton Sirota
- **Martina Schifferer**, AI, German Center for Neurodegenerative Diseases (DZNE), Munich Cluster for Systems Neurology (SyNergy), Laboratory of Thomas Misgeld
- **Jean Schleiss**, Deputy Head, LMU, International Office
- **Anton Sirota**, Professor, LMU, Department Biology II, Division of Neurobiology, Bernstein Center for Computational Neuroscience (BCCN)
- **Victoria Splith**, PhD student, LMU, Center for Integrated Protein Science Munich (CIPSM), Laboratory of Stylianos Michalakis
- **Hans Straka**, Professor, LMU, Department Biology II, Division of Neurobiology
- **Tian Weili**, PhD student, HMGU, Research Unit Sensory Biology and Organogenesis, LMU Graduate School of Systemic Neurosciences (GSN[LMU]), Laboratory of Hernán López-Schier
- **Taoxi Yang**, PhD student, LMU, Institute of Medical Psychology and Human Science Center, Laboratory of Ernst Pöppel
- **Peter zu Eulenburg**, Professor, LMU, Department of Neurology, German Center for Vertigo and Balance Disorders (DSGZ)

LMU Munich Nominating Faculty

- **Alexander Borst**, Professor, MPIN, Department of Systems and Computational Neurobiology
- **Laura Busse**, Professor, LMU, Department Biology II, Division of Neurobiology
- **Tim Czopka**, PI, TUM, Institute of Neuronal Cell Biology
- **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 II, Division of Neurobiology, Munich Center for Neurosciences (MCN[LMU]), Graduate School of Systemic Neurosciences (GSN[LMU])
- **Andreas V. M. Herz**, Professor, LMU, Department Biology II, Bernstein Center for Computational Neuroscience (BCCN)

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- **Peter zu Eulenburg**, Professor, LMU, Department of Neurology, German Center for Vertigo and Balance Disorders (DSGZ)

Abstracts of lectures and posters

Neuronal encoding of behaviorally relevant sound source locations in primary auditory cortex

Diana Amaro and Michael Pecka
LMU Department Biology II, Division of Neurobiology

Sounds are a constant presence in our lives and help us navigate in complex sensory environments, e.g. crossing a busy road. The formation of meaningful auditory streams in a given behavioral scenario relies on our brain's capacity to extract the situationally relevant properties from sounds, such as the spatial location of their sources – a process known as auditory scene analysis (ASA). Despite its crucial importance for auditory perception, the neuronal mechanisms of ASA are still poorly understood since in most studies, animals are in a passive environment (in which sounds have no particular behavioral relevance) and are head-fixed (i.e. in an egocentric reference frame). In opposition, natural ASA is characterized by the selective listening to the sound source of relevance while moving, resulting in a continuous change of the position of this source relative to one's head. These ethological circumstances suggest that an allocentric-based neuronal code representing the relevant sound source would be advantageous. To investigate to what extent such a neuronal representation exists in the auditory cortex, we developed a goal-directed auditory localization task in which Mongolian gerbils freely move and are trained to forage in an arena for an auditory target. The target corresponds to sound coming from a particular sound source and is associated to an area in the arena, which is differently located across trials. The animals are continuously tracked during the trial and through a feedback-loop system, depending on their position, either the target or another sound source is active. With this task, we introduce behavioral relevance to different sound sources in an environment in which animals have to constantly change their position with respect to these sources. During task performance, we record neuronal activity in primary auditory cortex via multiple tetrodes connected to a wireless-transmitting headstage. During offline analysis, we calculated the head angle relative to the active source and correlated these angles with the recorded neuronal responses to construct spatial tuning functions. We find that tuning varies across neuronal population: as expected, some neurons are similarly tuned to both target and non-target sound sources, i.e. are not affected by the difference in their behavioral relevance. Interestingly, however, some neurons show differential tuning to the behaviorally relevant source. Since the only difference between the sound sources is their position in space, their distinct neuronal representations requires allocentric information already at the level of the primary auditory cortex. Thus, our novel behavioral paradigm allows the identification of a neuronal processing regime that facilitates the localization of relevant sound sources during ASA.

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Investigating mechanisms underlying formation and remodeling of axonal myelination patterns *in vivo*

Franziska Auer[1,3], Stavros Vagionitis[1], Roberta Marisca[1,3], Tim Czopka[1,2,3]
[1] **TUM Institute of Neuronal Cell Biology**
[2] **SyNergy Excellence Cluster of Systems Neurology**
[3] **LMU Graduate School of Systemic Neurosciences**

Myelination of axons is crucial for proper nervous system function by enabling fast saltatory nerve conduction. One important factor is the distance between the nodes of Ranvier and in consequence the length of the myelin sheaths. Although various factors have been identified that can affect myelin sheath length, only little is known about the mechanisms that control where myelin sheaths and nodes of Ranvier are positioned along an axon.

To investigate the formation of axon-myelin patterns we generated transgenic reagents to visualize axons, myelin, and nodes of Ranvier using live cell imaging in zebrafish. We identified that distinct types of neurons get myelinated with different dynamics. While some neurons were fully myelinated within a few days, others maintained large unmyelinated stretches over long periods of time. When we followed the growth dynamics of individual sheaths, we found that all sheaths showed the same growth pattern characterized by an initial phase of rapid and variable growth, which ceased within three days after their respective initiation. This growth cessation was independent whether a myelin sheath met a neighboring sheath or not. We also observed that the majority of nascent sheaths showed asymmetric lateral growth, again without the presence of neighboring sheaths that could prevent further extension in one direction. We found that some axons had collateral branches, and these axonal branch points were always the sites where sheaths stopped to form a node of Ranvier. However, the vast majority of nodes did not have axon collaterals, indicating the existence of another signal that could act as a barrier to prevent sheath growth. We tested different transgenic markers whose localization is restricted to nodes of Ranvier along myelinated axons, but which remain diffuse along unmyelinated stretches of the same axon. One of these markers (Neurofascin-XFP) also displayed inhomogeneous localization and clustered fluorescence along unmyelinated axon stretches. The position of these clusters remained stable over several days in the absence of any myelination. When we correlated cluster position prior to ensheathment with the eventual node of Ranvier position, we found that the majority of nodes already had detectable Nfasca clusters at the same position. Together, our data suggest that different axonal cues control myelin sheath length and the positioning of nodes of Ranvier along axons.

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Processing of visual feedforward and feedback signals in mouse dLGN

Yannik Bauer
LMU Department Biology II, Division of Neurobiology

Little is known about how the representation of visual information changes between the retina and the dorsolateral geniculate nucleus (dLGN) of the thalamus, the main relay station between the retina and cortex. In the mouse, the dLGN receives its main driving inputs from the retina, whose 30+ retinal ganglion cell (RGC) types serve as the output for all further visual processing in the brain. However, it is currently unknown, firstly, which RGCs project to the dLGN and how their inputs get recombined there, and, secondly, how cortico-thalamic (CT) feedback contributes to dLGN signal transformations. To address the first question about retinal inputs to the dLGN, we functionally characterized responses of retrogradely labelled dLGN-projecting RGCs via ex vivo two-photon Ca^{2+}-imaging of the retina, and, in a separate experiment, also performed *in vivo* multi-electrode recordings of dLGN neurons to the same set of visual stimuli. We found that many of the previously identified functional RGC types innervate the dLGN, which maintained a high degree of functional diversity. We assessed functional connectivity between RGC types and dLGN neurons with a feedforward model and found that the responses of dLGN neurons could be predicted as a linear combination of inputs from on average five RGC types, with only two of those having the strongest functional impact. To address the second question of the causal role of feedback on dLGN function in general, and on our model predictions in particular, we are currently extending the dLGN recording experiments with direct optogenetic inactivation of layer 6 CT pyramidal neurons. For this purpose, we conditionally express anion-conducting Channelrhodopsins (SwiChR++ or GtACR-2) and test how dLGN responses are affected by CT feedback suppression. On this basis, we will be able to assess, amongst others, whether feedback suppression will make dLGN responses more linear, and whether our model will then be able to reconstruct cell responses more accurately with fewer inputs. In summary, having found a limited functional convergence of various retinal inputs onto the dLGN, which may create emergent response features, our next goal is to see how these signals get shaped further by cortical feedback.

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Effects of cortico-thalamic feedback on responses in mouse dLGN

Laura Busse
LMU Department Biology II, Division of Neurobiology

Feed-forward sensory processing is a fundamental model of how the brain mediates visual perception. Using a largely feed-forward architecture, artificial neural networks can now carry out robust and dynamic operations as to rival human perception.

So why then, in the brain is feedback such a prominent and ubiquitous motif? As a model for feedback effects on sensory processing, the cortico-thalamic (CT) circuit has, for over half a century, sparked much interest. Despite these efforts, however, howCT feedback influences the representation of visual information remains poorly understood.

Here, we revisited the fundamental question of cortical feedback's role in thalamic visual processing. We performed a series of experiments using optogenetic tools for circuit manipulations in awake mice.

We found that CT feedback during spontaneous activity enhanced firing rates and reduced bursting, and, during processing of natural movie clips, reduced sparseness of dLGN responses. Hence, CT feedback seems crucial for promoting tonic firing mode in dLGN, potentially allowing a more linear transmission of incoming visual information.

Furthermore, our results indicate that CT feedback shapes spatial processing. Measuring tuning for stimulus size, we found that dLGN RFs in conditions with intact CT feedback were smaller and showed stronger surround suppression. Finally, we demonstrate that these effects on spatial integration might, at least partially, be mediated by neurons in the visual part of TRN, via which CT feedback can exert suppressive effects.

Together, our findings suggest that a function of CT feedback is to enhance responses to local visual signals and shape contextual modulations.

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Bcl-xL gene imprinting regulates neuron-specific microglia crosstalk and cortical plasticity

Magdalena Caiati
Harvard Department of Molecular and Cellular Biology

Beyond its well-established function in cell death, the apoptotic pathway may regulate neuronal synaptic transmission and plasticity under physiological conditions. Moreover, it has been implicated in the regulation of the immune complement cascade at the synaptic level. Whether and how active caspases might play a role in synapse development and cell-specific neuro-immune crosstalk (in the absence of ongoing cell-death) is unknown. Here, we examined Bcl-xL, an anti-apoptotic factor expressed widely in the post-mitotic neocortex, which is imprinted throughout the mouse brain – exhibiting a robust paternal expression bias. In the visual cortex, we find this parent-of-origin allelic expression of Bcl-xL impacts synapse maturation, plasticity and microglia-neuronal coupling. Using *in vitro* patch-clamp recordings combined with biocytin filling and post hoc neuronal 3D-reconstrution, we observed that paternal (but not maternal) Bcl-xL deletion halted the maturation of AMPA-mediated excitatory synaptic transmission. It also prevented long-term potentiation (LTP) and blocked the visual experience-dependent pruning of dendritic spines specifically in Satb2+ callosally projecting pyramidal neurons. These phenotypes were rescued by inhibitors of caspase 3. Consistent with this, the highly quantitative single molecule FISH method unveiled monoallelic *Bcl-xL* expression specifically in Satb2+ neurons. In contrast, we found that *Bcl-xL* expression was biallelic in microglia, the resident immune cells of the brain. Accordingly, both maternal and paternal deletion affected microglia, as revealed by flow cytometric, morphological and gene expression analyses. Altogether, our study reveals a surprising parent-of-origin and cell-type specific role for Bcl-xL in cortical maturation and experience-dependent plasticity. More broadly, our data provide new insights into the involvement of the apoptotic pathway in microglia-neuronal coupling with cell-specific implications for the imprinted regulation of proper cortical development.

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Principles underlying luminostasis, a previously unknown behavior in larval zebrafish

Alex Chen
Harvard Department of Molecular and Cellular Biology

We report the discovery and characterization of a previously unappreciated luminance set-point seeking behavior, which we term luminostasis, in larval zebrafish. Luminance preference depends on a set point, centrally computed as the mean luminance of the left and right visual hemifields. A constrained computational model suggests that previously reported spatial photaxis behaviors emerge from luminostasis. Whole brain imaging provides candidate brain regions involved in the behavior. Luminostasis interacts with other visuomotor behaviors.

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Mechanisms of axon-oligodendrocyte communication *in vivo*

Tim Czopka
TUM Institute of Neuronal Cell Biology

A major challenge for understanding our central nervous system (CNS) is to elucidate the mechanisms by which the myriads of neurons and glial cells that constitute our brain and spinal cord coordinate and influence each other to form and maintain a functional organ. The intricate interaction between axons and surrounding oligodendrocytes represents a unique example for regulation of nervous system function by intercellular communication.

Oligodendrocytes ensheath (myelinate) axons by iteratively ‚wrapping' theTUM axon. Myelination is absolutely critical for proper nervous system function: it regulates transmission speed between nerve cells, ensures long-term axonal health, and is even involved in forms of learning and memory. Defective myelination impairs CNS function in multiple disorders ranging from diseases and pathologies of the developing and adult nervous system to neurodegenerative and psychiatric disorders. For example, degeneration of myelin is a major cause for sensory and motor dysfunction in diseases such as Multiple Sclerosis.

My group investigates principles of how axons and oligodendrocytes communicate to control myelinated axon structure, how it can plastically remodel after damage, and how oligodendrocyte precursor cells serve as a source for long-term developmental changes as well as regenerative remodelling of myelinated axons. To do this, we apply a combination of high resolution microscopy methods and genetic manipulations using zebrafish as an *in vivo* model organism. Here, I will present an overview of the state of current research and our approach to address open questions in the field.

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Ctip1 function in generation of associative circuitry, growth cone machinery, and ASD-related behavior

Omer Durak, Yasuhiro Itoh, Ji-Yoon Kim, Prakruti Nanda, and Jeffrey D. Macklis
Harvard Center for Brain Science, Department of Stem Cell and Regenerative Biology

Autism spectrum disorders (ASD) are a complex, multigenic set of neurodevelopmental disorders that manifest in social deficits, communication difficulties, stereotyped behaviors, and cognitive delays. The large number of genes linked to ASD contributes to the variability of symptoms among ASD patients. Recent studies identify that patients with microdeletions or missense mutations of the transcriptional regulator *BCL11A/CTIP1* display ASD and intellectual disability and behavioral deficits associated with ASD, such as impaired social interaction and cognition, repetitive behavior, and anxiety. These patients also have hypoplasia of the corpus callosum (CC), microcephaly, and developmental delay. Our lab recently identified *Ctip1* as a critical regulator of both precision of areal connectivity and subtype development of callosal projection neurons (CPN) in mice, with deletion of mouse *Ctip1* resulting in abnormal cortical areal and projection neuron subtype development, the same associated hypoplasia of the CC, and thinner cortex thus microcephaly. CPN are the broad population of interhemispheric commissural pyramidal neurons whose axons connect the two cerebral hemispheres via CC, the largest axonal tract in the mammalian brain. CPN play key roles in high-level associative, integrative, cognitive, behavioral, sensory, and motor functions, based on precise, area-specific CPN subtype connectivity and diversity. This precise connectivity by CPN is central for core associative functions, and both bilateral and other cortico-cortical integration of sensori-motor, perceptual, and cognitive information. How these circuits develop with precision and diversity is not well-understood.

A central question in neuroscience is how function-specific circuitry, such as associative circuitry, is established during development, then maintained and modified for remarkably diverse neuronal connections. This question has remained inaccessible in multiple aspects, including the molecular composition of subtype-specific axon growth cones (GCs) *in vivo*. GCs of diverse projection neurons navigate complex extracellular environments to reach distant, subtype-specific targets (e.g. CPN contralateral hemisphere targeting). For rapid and spatially precise response to extracellular cues, GC competence for autonomous behavior without feedback from the nucleus is necessary. Indeed, recent studies strongly indicate that subcellular localization of specific molecular machinery to GCs might underlie precise GC behaviors during circuit formation. Because most of this current knowledge of GC biology was identified *in vitro*, often with heterogeneous neuron populations, access to subtype-specific GCs in their native environment during normal and perturbed development will substantially elucidate molecular bases of cortical circuit formation, of diverse CPN circuitry. Our laboratory has recently developed experimental and analytical approaches to directly access the molecular machinery (transcriptome and proteome) of purified GCs from fluorescently labeled subtype- and stage specific GCs of cortical projections neurons directly from mouse brain (Poulopoulos*, Murphy* et al., Nature, 2019).

We are currently investigating *Ctip1* function in development of areally- and functionally-specific CPN subtypes, and hypothesize that dysfunction of *Ctip1* might contribute to disorders of CPN connectivity and diversity such as ASD. We have applied these new approaches to study the subcellularly distinct and dynamic transcriptomes of GCs of *Ctip1* null/het CPN (vs. WT) to identify potential molecular abnormalities causing aberrant CPN-specific associative circuitry. Further, we are investigating whether disruption of these *Ctip1* functions in cortex cause the abnormal social interaction, cognitive, and other behaviors associated with ASD. This work connects insights from an ASD risk gene to cortical circuits and behavior.

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Molecular and cellular profiling of intact organs

Ali Ertürk
LMU Institute for Stroke and Dementia Research (ISD)

My lab creates technologies to combine nanotechnology, bio-engineering and artificial intelligence (AI). We aim to help to cure most of the devastating diseases including dementia, stroke, diabetics, and cancer in our lifetime. In particular, we have been developing DISCO transparency technologies to obtain a holistic view of the whole organism at single cell resolutions. Using this unbiased imaging approach, we recently constructed the first neuronal connectome of an intact adult mouse and discovered short vascular connections between the skull and brain (Cai, Ertürk, Nature Neuroscience, 2019). We also combined our transparency technologies with deep learning to analyze cancer metastasis and drug targeting and single cell level in whole mouse bodies (Pan, Ertürk, available at BioRxiv). We recently developed a new tool to analyze whole mouse brain vasculature at the microcapillary level using tissue transparency and deep learning (Todorov, Ertürk, available at BioRxiv). Finally, we introduced SHANEL method utilizing a new tissue permeabilization approach to clear and label stiff human organs. We used SHANEL to generate the first intact transparent adult human brain and kidney and perform 3D histology using antibodies and dyes in centimeters depth. Thereby, we revealed structural details of sclera, iris and suspensory ligament in the human eye, and the vessels and glomeruli in the human kidney (Zhao, Ertürk, available at BioRxiv).

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Hippocampal coding of spatial and image information during virtual reality navigation

Dustin Fetterhoff and Christian Leibold
LMU Bernstein Center for Computational Neuroscience

Virtual reality is useful to study spatial navigation because it enables environmental manipulations that would be unfeasible in real world setups. In this study, male Mongolian gerbils (Meriones unguiculatus) were exposed to two different virtual hallways that could be identified based on both turning direction and sequence of images on the walls of straight hallways. Specifically, maze A had two right turns and images of zebra skin, stars and targets, while maze B had two left turns and images of moons, pyramids and leaves. All turns were made at 45 degree angles with plain white walls and images in the next hallways were not visible until turns were completed. Milk reward was automatically given at the end of the maze. One objective of this study was to identify single-unit and population activity of place cells during navigation of a maze with a well-known sequence of images compared to one which had images shuffled between two different image sequences. By shuffling between image sequences, identification of neuronal activity corresponding to spatial location versus image selectivity will be possible.

After learning how to navigate mazes with well-known sequences, a micro-drive with eight individually movable tetrodes was implanted above the right hippocampal CA1 and CA3 regions. Over a period of two weeks, tetrodes were lowered to the hippocampal principal cell layer where single units and local field potential recordings were made before, during and after virtual maze navigation. On testing days, gerbils first ran 20 laps with the well-known images, while the last 20 laps contained the initial image from one maze type but the final two images from the opposite maze type (i.e., mixed maze A contained zebra skin, pyramid and leaf; mixed maze B contained moon, stars and targets.). The turning direction was always consistent with the first image perceived at the start of each lap.

Behavioral results showed that gerbils learned how to navigate virtual mazes. For analysis purposes, mazes were divided into three hallway and two corner segments. Analysis of electrophysiological data collected when images were shuffled between mazes showed that hippocampal principal cells fired specifically to either spatial location, turning direction or to specific images, while some cells only fired during the initial maze but not after shuffling. Single unit remapping analysis showed that more neurons tended to fire based on turning direction, an effect that was more pronounced in the first beginning and middle segments of the maze. In the last segment, image cues more strongly contributed to place cell firing patterns coinciding with the end of the maze and milk reward. Population vector correlations were low between the initially, learned unshuffled mazes. After shuffling images, population vector correlations were strongest between mazes with the same turning direction during the first unchanged segment and both turns, while the middle and especially the last segments showed a mixture of correlation strength between image and turning direction. Although population vector correlation during the intertrial intervals does not show much selectivity, a linear decoder was able to predict the previously experienced maze under specific conditions. The hippocampus is strongly influenced by spatial cues, but we found an additional response to images linked to rewards at the end of mazes.

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Molecular heterogeneity in a peripheral auditory feedback circuit

Michelle M. Frank, Austen A. Sitko, and Lisa V. Goodrich
Harvard Medical School, Department of Neurobiology

Sensory systems rely on intricately connected networks of feedforward and feedback circuitry to encode sensory information and guide behaviors. In the auditory system, incoming sound information is transduced by hair cells in the cochlea and transmitted into the brain by spiral ganglion neurons (SGNs). Early auditory computations occur largely in the brainstem, where specialized circuits in the superior olivary complex (SOC) aggregate sensory information from both ears to mediate sound localization. The SOC also houses a group of auditory feedback cells that project back into the cochlea to target both hair cells and SGNs. These olivocochlear efferent neurons (OCNs) are known to play numerous roles in the auditory system, including protecting the cochlea from acoustic injury and aiding in speech-in-noise detection. Mammalian OCNs are typically classified into two or three major categories based on their anatomical projections. Little is known, however, about the molecular or genetic factors that distinguish these major subsets of OCNs from each other or from other brainstem neurons. As such, no markers exist to identify or manipulate subsets of OCNs, and virtually nothing is known about any heterogeneity within these major OCN subtypes. To address this gap, we've used a high-throughput, single-cell sequencing approach to profile the transcriptome of individual neurons in the SOC, including OCNs. Our analysis has identified several populations of SOC neurons, including two major clusters of OCNs. We've discovered several new markers for each of these OCN clusters, offering new insights into these key regulators of cochlear function.

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Sounding out diversity in the developing auditory system

Lisa V. Goodrich
Harvard Medical School, Department of Neurobiology

Animals are able to detect and discriminate among a wide variety of sounds in their environment, even against a noisy backdrop. This ability originates in the cochlea, where spiral ganglion neurons (SGNs) receive input from sensory hair cells and transmit signals to the central nervous system. A number of functional and anatomical differences among SGNs have been described over the years that contribute to the sense of hearing. For instance, some SGNs exhibit low spontaneous firing rates and are thus recruited at higher sound intensity levels, thereby extending the dynamic range of the cochlea and improving hearing in noisy environments. However, until recently, the nature and origins of SGN heterogeneity has been unclear. We used single cell RNA-sequencing to perform an unbiased analysis of SGN diversity in the mouse. We found four molecularly distinct SGN subtypes: the Type II SGNs, which innervate outer hair cells, and three types of Type I SGNs, which innervate inner hair cells. The SGN subtypes appear to correspond to those originally identified using physiological and anatomical criteria, but also express genes suggestive of additional functional variation. Currently, we are focused on understanding how SGN heterogeneity arises during development. Emerging results suggest that the specification and subsequent diversification of SGNs relies on a combination of a pan-SGN Gata3 network and an activity-dependent pathway that stimulates subtype-specific features of differentiation.

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Structure of the visual surround in a patch of primary visual cortex

Abhinav Satish Grama
Harvard Center for Brain Science, Department of Molecular and Cellular Biology

V1 neurons show contextual modulation of responses to stimuli presented in their classical receptive fields (RFs) based on what is present in the surround. Termed extra-classical receptive field effects, the most popular is surround suppression or end-stopping where stimuli extending beyond the classical RF suppress the activity of the neuron. How this modulation is mediated is still largely an unanswered question with likely candidates being feedback from neighboring V1 neurons or feedback from V2 and higher visual areas which survey a larger fraction of the visual scene. In our study we try to address the source of feedback from the visual surround by using optical tools we developed to simultaneously image local V1 activity and either local V1 synapses or feedback synapses from V2 (area LM in rodents).

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Balancing brain plasticity/stability

Takao Hensch
Harvard Center for Brain Science, Department of Molecular and Cellular Biology

Behavior is shaped largely by early life experience — windows of both great opportunity and vulnerability. Maturation of specific inhibitory circuits is pivotal for defining these trajectories. Their manipulation can potently shift critical period timing regardless of age, as seen in neuro-developmental disorders. Closure of critical periods in turn reflects not just a passive loss of plasticity factors, but rather an active molecular process. Lifting these “brakes” reopens the rewiring of circuits later in life, which may also render them unstable in mental illness. Proper understanding of this balance promises novel strategies for the safe therapeutic recovery of brain function in adulthood.

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The neural mechanisms of salt avoidance in a freshwater fish

Kristian Herrera
Harvard Department of Molecular and Cellular Biology

In the present study, we use the larval zebrafish as a model to examine the capabilities of fish to sense and encode the ionic content of their environment. As a freshwater fish, zebrafish cannot tolerate high salt environments. Therefore, we predicted that zebrafish possess neural mechanisms that enable the avoidance and navigation of salt gradient. We find determine that zebrafish can avoid and thus detect salt. In particular, they respond to temporal increases in salt by increasing their reorientation probability. We then use calcium imaging techniques to describe the systems responsible for absolute and relative salt detection. We find that the lateral line and olfactory systems largely encode absolute salinity concentrations by detecting small cations. Meanwhile, changes in salinity are represented in the hindbrain by populations of neurons with different dynamics. Most notably, inhibitory neurons with time constants up to a minute long allow the fish to dynamically adjust their estimate of baseline salinity.

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The many ways to read from grid cells in navigating rodents

Andreas V.M. Herz
LMU Department Biology II, Bernstein Center for Computational Neuroscience

How do we know our way from A to B and can even take short cuts on routes that we never travelled before? Over the last fifty years, valuable insight into this question about the biological nature of “cognitive maps“ (Edward Tolman) has been gained from studies in rodents. Pioneered by John O’Keefe and colleagues, various classes of neurons with different spatial tuning properties have been identified. One type is particularly fascinating – grid cells in the medial entorhinal cortex, which were discovered by the group of Edvard and May-Britt Moser just 15 years ago. The firing fields of these cells form hexagonal lattices that span the explored environment. Lattice scales follow a geometric series so that discrete grid-cell modules emerge. The detailed grid layout reflects the environment‘s shape, contextual information and goal locations but overall, the spatial coding properties of grid cells are surprisingly robust. Starting out with a brief review of the experimental literature, this talk will highlight the link between neurophysiology and mathematical theory. In particular, I will show that the fascinating grid-cell arrangement leads to (at least) three complementary codes for spatial location that may operate simultaneously. Perhaps surprisingly, grid codes with nested modules vastly outperform traditional place-like representations. For goal-directed navigation, one of these grid-cell representations can be flexibly transformed into egocentric goal coordinates so that an animal can readily plan its movements. Furthermore, the versatility of grid codes has proven itself through the discovery of grid codes in the brain for non-spatial variables, such as the frequency of an acoustic stimulus. All these results demonstrate that multi-scale grid codes provide a powerful substrate for spatial cognition and widen our view on population coding and collective computation in biological systems.

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Does the retinal photoreceptor composition influence Müller cell heterogeneity?

Lew Kaplan[1], Peter Fuchs[2], Ursula Schlötzer-Schrehardt[3], Maria Thereza Perez[4], Christian Grimm[5], Magdalena Götz[1], Stefanie Hauck[6], Antje Grosche[1]

[1] **LMU Department of Physiological Genomics**
[2] **University of Vienna, Department of Biochemistry and Cell Biology, Max F. Perutz Laboratories**
[3] **Friedrich-Alexander-Universität Erlangen-Nürnberg, Department of Ophthalmology**
[4] **Lund University, Division of Ophthalmology**
[5] **University of Zurich, Department of Ophthalmology**
[6] **MGU Research Unit Protein Science**

Purpose: Being key for accurate vision, the human macula is exceptionally prone to neurodegenerative processes. We aim to elucidate whether a functional heterogeneity of Müller cells, the major macroglia of the retina, may explain part of this macular susceptibility. To clarify the genetic basis of this heterogeneity, we generated and analyzed proteomic data from cone- and rod-rich systems from human and mice.

Methods: Müller cells, microglia, vascular cells and retinal neurons from all cone R91W;Nrl-/- and R91W control mice as well as from human macular and peripheral samples were isolated by immunomagnetic separation and searched for differential protein expression by use of tandem mass spectrometry. Müller cell specificity of proteins of interest was additionally tested by evaluating their expression in retinal scRNAseq datasets (1, 2), while particularly promising candidates were subjected to immunofluorescence staining in several mouse models followed by microscopy for validation. Screens for putative interaction partners were performed via immunoprecipitation and subsequent mass spectrometric analysis.

Results: We found significant differences in protein expression between predominantly cone- and rod-associated Müller cells in human as well as in the murine model, strengthening our hypothesis of functional Müller cell heterogeneity in the human retina. Indeed some proteins showed a Müller cell specific expression pattern in both the scRNAseq and our own proteomic data making these candidates especially promising for further research.
We identified Epiplakin (*Eppk1*) as a Müller cell specific and differentially expressed protein and for the first time showed through immunofluorescent imaging how it is localized along the entire length of the stem processes of murine Müller cells. Superresolution STED microscopy revealed, that *Eppk1* seems to dot-like colocalize with *Gfap* in an ischemia induced gliosis model indicating a possible role in this pathology. Lack of intermediate filaments *Gfap* and vimentin (*Vim*) lead to a delocalization of Eppk1 to Müller cell somata pointing at a close interaction of *Eppk1* with Müller cell intermediate filaments. Via the IP approach, we identified *Slmap* as an additional novel interaction partner of *Eppk1* that was also specifically expressed along Müller cell stem processes confirming a close interaction with *Eppk1* and the intermediate filament system.

Conclusion: Here we could show that the consistently different expression profile of some genes in human and murine Müller glia yields first interesting candidates that may coin functionally distinct Müller cell subpopulations. In future experiments the physiological relevance of these candidates needs to be validated in the cone-only mouse model and human donor tissue. Ultimately, our studies will help to improve the understanding of why the human macula is so sensitive to disease-associated changes and probably will open avenues for the development of novel strategies to treat macular degeneration.

(1) Macosko et al. Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets. Cell. 2015, 161:1202-1214

(2) Peng et al. Molecular Classification and Comparative Taxonomics of Foveal and Peripheral Cells in Primate Retina. Cell. 2019, 176:1222-1237

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Synaptogenesis in the CNS – learning lessons from the neuromuscular junction

Stephan Kröger
LMU Department of Physiological Genomics

The neuromuscular junction (NMJ) is the best-characterized synapse in the entire nervous system and the only synapse, where the major players responsible for its formation have been identified and characterized. Numerous lines of evidence have shown that agrin and its receptor complex consisting of the agrin-binding low-density lipoprotein receptor-related protein 4 (Lrp4) and the muscle-specific tyrosine kinase MuSK are the key determinants during formation, maintenance and regeneration of this particular synapse. Binding of agrin to Lrp4 activates the tyrosine kinase MuSK and induces an intracellular signaling cascade, which leads to the formation of all pre- and postsynaptic specializations. The agrin transcript is subject to alternative splicing at two sites named "y" and "z" in the C-terminus and this splicing regulates agrin's binding to Lrp4 and its synaptogenic activity. In addition, alternative first exon usage results in the synthesis of either a soluble basal lamina-associated or a transmembrane form of agrin (TM-agrin). Agrin is widely expressed in many tissues, including the CNS, but its function outside the NMJ is unknown. To analyze the role of agrin during CNS synaptogenesis, we overexpressed different isoforms of full-length TM-agrin in embryonic and adult cortical neurons from wildtype as well as from Lrp4 and MuSK knockout animals. Based on these experiments I will provide evidence that

- TM-agrin overexpression increased the density of excitatory synapses in neurons from wildtype and MuSK-deficient- but not in neurons from Lrp4-deficient mice, suggesting that Lrp4 was required for the TM-agrin-mediated increase in excitatory synapses.
- The increase in excitatory synapses depended on a particular "y"-site C-terminal splice variant of TM-agrin but not on direct Lrp4 binding.
- TM-agrin overexpression reduced the number of inhibitory synapses independent of MuSK and Lrp4 expression.
- Phosphorylation of a highly conserved serine residue in the intracellular domain of TM-agrin was required for the reduction of inhibitory synapse density.
- The increase in excitatory and the decrease of inhibitory synapses were at least in part due to an effect of TM-agrin on the expression levels of pre- and postsynaptic proteins.

Collectively, these results demonstrate a differential effect of TM-agrin on excitatory and inhibitory synapses, show that different domains within TM-agrin affect synaptogenesis at excitatory and inhibitory synapses and establish selective roles for agrin, MuSK and Lrp4 during synapse formation in the CNS. Thus, synapse formation at the NMJ and in the CNS is more similar than previously anticipated and might share molecular determinants.

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Computing with hippocampal sequences

Christian Leibold
LMU Department Biology II, Bernstein Center for Computational Neuroscience

Hippocampal place cell populations are activated in sequences on multiple time scales during active behavior, resting and sleep states, suggesting that these sequences are the genuine dynamical motifs of the hippocampal circuit. Recently, prewired hippocampal place cell sequences have even been reported to correlate to future behaviors, but so far there is no explanation of what could be the computational benefits of such a mapping between intrinsic dynamical structure and external sensory inputs. I will propose a computational model in which a set of predefined internal sequences are used as a dynamical reservoir to construct a spatial map of a large unknown maze based on only a small number of salient landmarks. The model is based on a new variant of temporal difference learning and implements a simultaneous localization and mapping algorithm. As a result sequences during intermittent replay periods can be decoded as spatial trajectories and improve navigation performance, which supports the functional interpretation of replay to consolidate memories of motor actions.

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Deciphering corticospinal circuits in sensorimotor control

Yuanyuan Kevin Liu
Harvard Medical School, Boston Children's Hospital

The corticospinal circuits directly connect the cortex with the spinal cord via the corticospinal tract (CST) and are the neural basis by which our mind controls our body. As yet, the design principles for such top-down control remain elusive.

With a viral based high-efficient intersectional tool, we dissected the role of CST in controlling distinct spinal circuits. In motor control, we discovered that spatially defined corticospinal neurons (CSNs) function in specific phases of a multistep, goal-directed food-reaching task (Wang & Liu et al., Cell, 2017). On the other hand, we identified an unexpected sensory role of the CST, which was originally known as a dedicated motor circuit. Our findings showed that somatosensory CSNs are activated by tactile stimulation and the direct output from the somatosensory cortex to the spinal deep dorsal horn mediates powerful facilitation of tactile sensory processing. This reveals a spino-cortico-spinal feed-forward sensitization loop that is crucial for controlling both normal and pathological touch sensations (Liu, et al., Nature, 2018). My future work will explore the roles of supraspinal circuits in regulating multiple somatosensations, both in physiological states and under pathological conditions (pain). These studies will help to design targeted inventions to treat pain and traumatic brain and spinal cord injuries.

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Tracking large-scale neuronal populations in lateral visual cortex across cue-outcome association learning

Kelly McGuire[1,2], RN Ramesh[1,2], CR Burgess[2,3], AU Sugden[1,2], JD Zaremba[1,2], ML Andermann[1,2]
[1] **Harvard Medical School, Department of Medicine**
[2] **Beth Israel Deaconess Medical Center, Boston**
[3] **University of Michigan, Ann Arbor**

Rodent and primate lesion studies and human neuroimaging studies suggest that lateral visual association cortex is critical for linking stimuli with predicted outcomes. Previously, our lab has shown that pharmacological silencing of postrhinal cortex and surrounding regions of lateral visual association cortex in mice performing a Go-NoGo orientation discrimination task dramatically impairs their ability to selectively respond to presentation of a stimulus associated with reward. In particular, mice continue to perform the task, but now respond equivalently to all three stimuli-including an unrewarded and a punished stimulus-suggesting an impairment of stimulus-outcome associations. While substantial progress has been made in understanding the effects of learning on visual circuits, very few studies have tracked cortical neurons throughout the course of sensory learning (e.g., Peters et al. 2014). We used two-photon calcium imaging to track visual responses of the same large set of hundreds of neurons in behaving mice across dozens of sessions spanning the entire training process. We aligned responses of the same neurons over months of imaging (714-2285 neurons per mouse across 5 mice; 12-53 imaging days per mouse, median 30) starting in naïve mice, during gradual learning of a three-orientation discrimination task, and following a change in cue-outcome contingencies. Preliminary analyses suggest that distinct ensembles of neurons respond stably to specific visual stimuli throughout the course of training, while other ensembles change their response properties over the course of learning. Using large-scale population analyses, including dimensionality reduction techniques (e.g. tensor component analysis), we are beginning to elucidate the distinct computations of ensembles of neurons in lateral visual association cortex in an unbiased manner across stages of association learning.

Disclosures: KL McGuire: None. RN Ramesh: None. CR Burgess: None. AU Sugden: None. JD Zaremba: None. ML Andermann: None.

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Cytoskeletal dynamics as a regulator of neuronal remodeling

Thomas Misgeld
TUM Institute of Neuronal Cell Biology, German Center for Neurodegenerative Diseases DZNE

Cells use the cytoskeleton to maintain shape, but also to adapt and remodel in response to environmental requirements. A special form of such adaptation is neuronal remodeling, which many nerve cells undergo during development to revise transient wiring patterns and establish mature circuits suitable to adult life. The neuromuscular system in rodents has served as a prime example to study the driving forces and executive pathways of such remodeling, and my lab – building on Jeff Lichtman's pioneering work – has used the mouse neuromuscular junction to understand the role of axonal cell biology in synapse remodelling and axon removal. In this talk, I will discuss results from my lab that establish microtubule dynamics as an important mediator of motor axonal fate, and emerging data that support the notion that post-translational microtubule modifications and microtubule-based transport act as encoders and interpreters of these subcellular remodeling events during axonal remodeling and homeostasis.

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Odor-guided navigation in terrestrial animals

Venkatesh Murthy
Harvard Center for Brain Science, Department of Molecular and Cellular Biology

Many animals use olfaction to guide their search for food and mates, and to avoid danger. Terrestrial animals are known for tracking odor trails on the ground, but additional information is also available in airborne odor cues. The relative importance of information conveyed by surface-bound and airborne cues, what controls switches between the two types of cues, and how animals integrate them for effective navigation, are poorly understood. An additional important factor for terrestrial animals is the discrete nature of odor sampling by antennal movement or sniffing, which is under voluntary control. We have designed an experimental system for continuous trail tracking in ants and mice. By video recording behaving animals at high resolution and altering the geometric properties of the trail, we are beginning to uncover the algorithmic strategies used by animals to track odor trails. In complementary studies, we are investigating if and how mice use airborne cues to navigate to odor sources.

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Relation between neuronal spike discharge and oxygen level in amphibians

Suzan Özugur[1,2], Myra N. Chávez[3], Jörg Nickelsen[3], Lars Kunz[1] and Hans Straka[1]
[1] **Department Biology II, Ludwig-Maximilians-University Munich, Germany**
[2] **Graduate School of Systemic Neurosciences, Ludwig-Maximilians-University Munich, Germany**
[3] **Department Biology I, Ludwig-Maximilians-University Munich, Germany**

Neuronal activity in the brain depends to a large extent on ATP generation and thus on the availability of oxygen. This makes the latter molecule a highly relevant readout for studying the interrelation between neuronal metabolism and computation. In order to evaluate the dependency of neuronal activity from oxygen availability, we employed semi-intact preparations of *Xenopus laevis* tadpoles with functional central and peripheral nervous systems. Trochlear motor nerve spike discharge served as physiological correlate for neuronal activity, while oxygen concentrations in the bath chamber and the brain, were concurrently monitored using a Clark-type oxygen microsensor during superfusion of Ringer solution with various levels of oxygen. The oxygen concentration was accurately set to a desired value by aeration with carbogen (95% O2, 5% CO_2) or nitrogen. In air-saturated Ringer solutions (280 µM O_2), the IVth ventricle was devoid of oxygen due to consumption in the adjacent brain tissue. At oxygen bath concentrations > 300 µM, spontaneous burst discharge of the trochlear nerve caused a transient drop of the oxygen level within the IVth ventricle, indicating a neuronal activity-related increase in the demand for oxygen. In contrast, decreasing the bath concentration of oxygen below ~40 µM completely ceased the trochlear motor nerve activity. Aiming at a spatially more accurate and faster means for the modulation of the oxygen level in the brain, we exploited the natural capability of algae to produce oxygen upon illumination. Injection of the green algae *Chlamydomonas reinhardtii* or the cyanobacteria *Synechocystis sp.* into the vascular system of *Xenopus* tadpoles prior to the generation of the semi-intact preparation distributed these single celled organisms throughout the entire brain. While the hypoxic condition within the IVth ventricle persisted in such preparations in darkness, illumination with visible light increased the oxygen level up to ~80 µM. In addition, the abolished trochlear motor nerve activity in oxygen-depleted bath solutions restarted upon illumination, suggesting that algal oxygen production is sufficient to restore the energy equivalents required for maintained neuronal activity. Accordingly, introduction of algae and illumination represents a promising method to augment the oxygen level in any diffusion-limited *in vitro* neuronal preparation devoid of a functional circulation and potentially also under *in vivo* conditions.

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Neurodevelopmental disease – from human genetics to novel mechanisms

Adam C. O'Neill[1,2], Saskia Freytag[3], Sirui Zhang[4], Alex Jäck[1,2], Giulia Antognolli[1,2], Miriam Esgleas[1,2], Kalina Draganova[1,2], Sven Falk[1,2], Zefeng Wang[4], Stefanie Hauck[5], Melanie Bahlo[3], Stephen P Robertson6 and Magdalena Götz[1,2,7]
[1] **HMGU Institute for Stem Cell Research**
[2] **LMU Physiological Genomics**
[3] **Population Health and Immunity Division, The Walter and Eliza Hall Institute of Medical Research, 1G Royale Parade, 3052, Parkville, Australia**
[4] **CAS-MPG Partner Institute of Computational Biology, Shanghai**
[5] **HMGU Research Unit Protein Science**
[6] **University of Otago New Zealand Department of Women's & Children's Health, Dunedin School of Medicine**
[7] **LMU Excellence Cluster of Systems Neurology**

Malformations of cortical development encompass a diverse set of developmental disorders. Periventricular heterotopia (PH) is one such condition whereby populations of neurons fail to migrate to the cerebral cortex and instead adopt heterotopic positions along their sites of origin – adjacent to the lateral ventricles. Although seven loci are currently implicated in its cause these genes explain only 25% of sporadic instances. By analyzing the coding sequence of the genome (the exome) in 202 undiganosed individuals with PH we further identified an additional gene – *MAP1B* – to be causally implicated, however, 98% of cases still remain to be assigned a genetic diagnosis. In this study we integrate human brain transcriptomic data and show that 15% (34/219) of the candidate PH loci identified in the 202 undiagnosed patients with PH converge onto shared expression signatures with genes already implicated in the disease. These genes are also enriched for factors involved in mRNA splicing via the spliceosome. *In vivo* modeling for at least one of these factors – PRPF6 – phenotypically recapitulates aspects of PH in the developing mouse brain and outlines impaired neuronal differentiation and increased apoptosis as a novel mechanism in its cause. Furthermore, we show that PRPF6 interacts with a number of other candidate PH genes prioritized in the transcriptomic analysis suggesting dysregulation of a common complex. Finally, we outline the results of a wide-scale screen for novel centrosome components in human neural progenitor cells whereby we surprisingly identify PRPF6 and other components of this complex. We hypothesize that PH is caused by specific dysregulation of axillary centrosome components and that this association could be cell type specific.

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Circadian phase delays with industrialisation but changes with age independently of state of industrialisation

Luisa K. Pilz[1,2,3], Nicóli B. Xavier[2,3], Rosa Levandovski[4], Maria Paz Hidalgo[2,3], Till Roenneberg[1]
[1] **LMU Institute of Medical Psychology**
[2] **Laboratório de Cronobiologia e Sono, HCPA/UFRGS. Porto Alegre, RS – Brazil**
[3] **PPG em Psiquiatria e Ciências do Comportamento, UFRGS. Porto Alegre, RS – Brazil**
[4] **PPG Avaliação e Produção de Tecnologias para o SUS, GHC; PPG Saúde Coletiva, UFRGS Porto Alegre, RS – Brazil**

Introduction: Quilombolas communities live in all states of industrialisation, from rural where they are exposed to sunlight during the day and to real darkness at night, to urban where they work indoors and have access to artificial light. These qualities make them a unique population for studying light-dependencies of behaviour and the historical transition in rest-activity behaviour between pre-electric and modern era. We have shown that rural Quilombolas with no or only recent access to electricity sleep earlier and longer than those who have had electricity for several years and are more urbanised. Data from the large MCTQ database shows that chronotype progressively delays until the end of adolescence, and then advances until the end of life. Here we aimed to investigate if circadian phase also delays with age in Quilombolas communities.

Methods: We assessed rest-activity- and sleep-patterns in Quilombolas' daily context using wrist actimetry and the Munich ChronoType Questionnaire (MCTQ).
208 subjects (age range 16-92; median 45 yrs [30 – 57], 60% women) who completed the questionnaire were included. We used midpoint of sleep on free days (MSF) as a phase marker. Subjects were categorised into the following groups: 29 subjects were from a communities without electricity (no-E), 171 subjects were from rural communities that had had electricity for 15 to about 20 years (Rural 15-20 yrs, n = 71) or 30 years or more (Rural ≥ 30 yrs, n = 101) and 8 subjects were from a urban community (Urban).
Data from 14 days of actimetry recordings were used to compute the acrophase (peak of cosine curve fitted to activity rhythm) of 84 subjects (age range 16-78; median 40 yrs [25 – 59], 55% women). 28 subjects of each of the first three groups were included (no-E, Rural 14-20 yrs, Rural ≥ 30 yrs).
We regressed both phase markers (MSF and acrophase) on age, sex and group (backwards linear regression). Homoscedasticity was verified using Breusch-Pagan test. VIF of all factors was lower than 4 and tolerance higher than 0.20. Analyses were run using R. Unstandardized ß coefficients and adjusted R^2 are reported.

Results: Age (ß = -0.03, $p < 0.01$) and group (reference *no-E; Rural 15-20 yrs:* ß = 0.93, $p < 0.001$, *Rural ≥ 30 yrs:* ß = 2.18, $p < 0.001$, *Urban:* ß = 3.37, $p < 0.001$) were significantly associated to sleep phase (MSF as assessed by the MCTQ, $R^2 = 0.33$, $p < 0.001$). Similarly, age (ß = -0.03, $p < 0.001$) and group (reference *no-E; Rural 15-20 yrs:* ß 1.37, $p < 0.001$, *Rural* ≥ 30 yrs: ß = 1.79, $p < 0.001$) were significantly associated to activity phase (acrophase measured by actimetry, $R^2 = 0.32$, $p < 0.001$).

Conclusions: Our results suggest that both stage of industrialisation and age are associated to circadian phase in Quilombolas (including in a community without electricity). These results add to the evidence opposing the notion that adolescents are later chronotypes due to attitude/ behaviour and support the promotion of strategies to minimize their circadian misalignment.

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Grid-cell activity on linear tracks indicates purely translational remapping of 2D firing patterns at movement turning points

Michaela Pröll, Stefan Häusler, Andreas V.M. Herz
LMU Bernstein Center for Computational Neuroscience

Grid cells in rodent medial entorhinal cortex are thought to play a critical role for spatial navigation. When the animal is freely moving in an open arena the firing fields of each grid cell tend to form a hexagonal lattice spanning the environment. For movements along a linear track the cells seem to respond differently. They show multiple firing fields that are not periodically arranged and whose shape and position change when the running direction is reversed. In addition, peak firing rates vary widely from field to field. Measured along one running direction only, firing fields are, however, compatible with a slice through a two-dimensional (2D) hexagonal pattern. It is an open question, whether this is also true if leftward and rightward runs are jointly considered. By analyzing data from 15 male Long–Evans rats, we show that a single hexagonal firing pattern explains the linear-track data if translational shifts of the pattern are allowed at the movement turning points. A rotation or scaling of the grid is not required. The agreement is further improved if the peak firing rates of the underlying 2D grid fields can vary from field to field, as suggested by recent studies. These findings have direct consequences for experiments using linear tracks in virtual reality.

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Emergence of shared and distinct properties between direction-selective T4/T5 neuron subclasses

Jesus Pujol-Marti
MPI of Neurobiology, Department of Systems and Computational Neurobiology

How neurons acquire a diverse repertoire of structural and physiological properties in order to establish functional neural circuits remains unclear. To address this question, we study the development of motion-sensitive T4/T5 neurons of the fly visual system. We focus both on the molecular programs that define T4/T5 neurons and on the programs that generate diversity within the T4/T5 neuronal population.

All T4/T5 neurons share properties essential for sensing motion, such as dendrites arborizing within a specific synaptic layer, which is thought to support precise synaptic connectivity. We have recently found that the transcription factors SoxN and Sox102F are required in all maturing T4/T5 neurons in order to restrict their dendrites and axons into single synaptic layers. When this process fails, some postsynaptic partners of T4/T5 neurons also exhibit aberrant morphologies. Altogether, these defects impair the proper functioning of the fly motion sensing circuits.

Moreover, T4 and T5 neurons exist in four subclasses, each responding exclusively to motion in one of the four cardinal directions. Differences between T4/T5 neuron subclasses in directional tuning correlate with differences in dendritic orientation and in the spatial organization of synapses they receive from an identical set of input neurons. Our working hypothesis is that the direction in which a T4/T5 dendrite grows during development determines the arrangement of its synaptic inputs and thus its direction selectivity. We currently use single cell RNA-sequencing to transcriptionally profile the different T4/T5 neuron subtypes during development and to identify the molecular programs underlying their differences in dendritic growth.

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Efficient coding by optimal control of resource allocation

Luke Rast, Jan Drugowitsch
Harvard Medical School, Department of Neurobiology

The efficient coding hypothesis proposes that neural representations are well adapted to the requirements of both task demands and the environments that they operate in. It is commonly approached by determining the parameters of neural codes, such as tuning curve widths or their distribution across the stimulus range, that maximize information transmission or task performance while obeying constraints on overall neural activity. Despite having been applied to multiple code types, performance objectives, and constraints, our understanding of the general features of efficient codes remains limited, as, in most cases, results are either restricted to specific parameterizations of the neural code (e.g., densely tuned, independent Poisson populations) or only yield numerical solutions. Here we examine the problem in more generality by abstracting away neural population activity, and instead investigating efficient coding directly in Fisher information space. Constraints and specific task-dependent loss functions that might depend on the neural encoding then enter the problem only through corresponding Fisher information modulations. Expressing the underlying variational optimization as an optimal control problem, we derive a family of solutions under very expressive constraints and loss functions. This generalizes previous efficient coding results and, due to its sole dependency on Fisher information, highlights coding invariants, for example allowing for tradeoffs between tuning sharpness and neural correlations. These invariants imply that rather than relying on individual features of population activity, we should instead assess collective features, such as encoded Fisher information, to assess coding efficiency. Furthermore, assuming specific constraints, we can invert the problem and reverse-engineer the task-dependent objective that makes an experimentally observed code efficient. Given its flexibility across loss functions and constraints, and its agnosticism to parameterizations of the underlying code, the result lays the groundwork for identifying efficiency principles that are in play in observed neural activity.

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Serotonin-dependent selective modulation of retinal ganglion cell axonal boutons

Jasmine Reggiani
Harvard Medical School, Department of Medicine

The processing of environmental stimuli to generate behavior can be strongly modulated by an animal's internal states, such as hunger, arousal, or fear. Internal states, through the action of neuromodulators, can affect sensory processing as early as the thalamus, which sends information to the cortex. Serotonin stands out among neuromodulators for its known presynaptic and postsynaptic effects at the retinogeniculate synapse, where afferent fibers from the eye transfer information to thalamocortical cells of the dorsolateral geniculate nucleus of the thalamus (dLGN). At the postsynaptic side, serotonin slightly depolarizes thalamocortical cells which is thought to favor linear transmission of visual information. At the presynaptic side, serotonin has been shown to suppress release of glutamate from retinal ganglion cell (RGC) by binding to htr1b receptors. Our preliminary data show that many, but not all RGC axon boutons express htr1b, suggesting heterogeneity in serotonergic modulation of retinal axon boutons. It remains unknown whether, in an awake behaving animal, this modulation could provide state-dependent selectivity in which visual features are preferentially processed by central visual circuits. We investigate, at the synaptic and circuit level, whether serotonin can selectively and differentially gate the flow of information at the presynaptic side of retinothalamic channels tuned to specific visual features, and whether this gating is dependent on the internal state of the animal.

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Responses of human navigation-related cortical regions to naturalistic vestibular stimulation

Ria Maxine Rühl[1,2], L. Ophey[1,2], Theresa Raiser[2], Peter zu Eulenburg[1,2,3]
[1] **LMU Department of Neurology**
[2] **LMU German Center for Vertigo and Balance Disorders**
[3] **LMU Graduate School of Systemic Neurosciences**

Introduction: Navigation is a highly dynamic process using multimodal cues from different sensory networks, including the visual, the vestibular, the auditory, and the proprioceptive system. Recent studies propose a common cortical navigation network including the retrosplenial region, the hippocampus, the posterior parietal cortex, the posterior parahippocampal cortex and the dorsolateral prefrontal cortex as well as the thalamus (1). This network seems to resemble the foundation for a continuum of interactions between allocentric and egocentric spatial representations. Vestibular signals supposedly feed into this network at all times with regards to the processing of egocentric spatial information and heading direction (2, 3). However, in how far navigation areas permanently interact with the vestibular network is still an ongoing debate. In this study, we aimed at investigating the involvement of navigation related areas in pure vestibular stimulation to study the overlap between the vestibular and the navigation network.

Methods: We examined 156 healthy subjects (78 F; mean age 27 years, main group n=80, internal replication group n=76) with galvanic vestibular stimulation (GVS) after local postauricular anaesthesia in 3T fMRI (64-channel coil, TR 700ms, 56 interleaved slices, MB 6, 1 mm in-plane resolution, slice thickness 2.5 mm). Data analysis was performed using SPM12. Results were considered significant at FDR $p<0.001$.

Results: GVS activated the cortical homologues to known non-human primate vestibular representations. This network included the cerebellar nodule, the uvula, and area OP2 as core equivalent to PIVC, as well as MST, area PFcm (VPS), area PF (area 7). Area VIP, areas 2v and 3aV were identified in the human IPS, area 6 in the human lateral premotor region, and the periarcuate cortex may be homologous to activations in the human SMA. Human area CSv was found to be the VC region. Of the previously described hubs and nodes central to navigation, here vestibular stimulation activated solely the ventral thalamus as a common denominator.

Discussion: The role of the vestibular system in navigation appears to be highly context dependent. Outside of an environment which requires active navigation, the vestibular and the navigation network only show a very limited overlap. Our results also imply that vestibular-driven ego-motion perception does not generally feed into the navigation network.

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Probing cholinergic modulation of hippocampal rhythms underlying memory encoding and consolidation

Ricardo Santos[1,2], Ziyan Huang[1,2], Anton Sirota[1,2]
[1] **LMU Department Biology II**
[2] **LMU Bernstein Center for Computational Neuroscience**

Acetylcholine (ACh) is an essential neuromodulator that effectively gates neuronal circuits engaged in high order cognitive operations. During active behavior, an important mechanism underlying the cognitive roles of ACh relies on the modulation of theta rhythm generators in the hippocampal formation, which are critical for the encoding of spatial and contextual information. In contrast, low cholinergic tone during sleep favors the occurrence of hippocampal sharp-wave/ripple complexes (SWRs), leading to memory consolidation.

Though most cholinergic effects on neuronal circuits have been considered as a function of brain state, this simplified view leaves behind the mechanism that gives rise to non-stationary dynamics of both behavior and neuronal network activity, as well as their interactions. To account for such dynamics, it is essential to characterize the correlation between these variables and ACh on a fast time-scale.

Here we have designed an optical setup using a novel genetically encoded ACh sensor allowing fast, selective and spatially resolved measurement of ACh release in hippocampus dorsal CA1 (dCA1). These measurements were combined with multichannel electrophysiology and quantitative 3D behavioral analysis. The latter enabled disambiguation of the coupling between hippocampal network activity and ACh across behavioral states that would otherwise overlap on a coarser time-scale.

Experiments under multiple behavioral paradigms, including open-field exploration, social interaction and punishment show that phasic ACh and theta recorded from dCA1 and can be dissociated by the emotional valence of experiences. This uncoupling contrasts with the positive correlation between ACh and theta found across brain states and highlights the relevance of probing fast cholinergic signals. Furthermore, we found a rich phasic dynamics of ACh during NREM sleep that has not been described before. Contradicting previous assumptions, these data suggest a bi-directional interaction between phasic cholinergic dynamics and SWRs that is time-scale dependent. Cholinergic modulation of the fine temporal structure of SWRs may have important implications for memory consolidation.

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Application of correlative light and electron microscopy to neurobiology

Natalia Marahori[1,2], Aleks Mezydlo[1,2], Nicolas Snaidero[1,2], Stavros Vagionitis[1,2], **Martina Schifferer**[1,2], Tim Czopka[1,2], Mikael Simons[1,2], Martin Kerschensteiner[1,2], Thomas Misgeld[1,2]
[1] **SyNergy Excellence Cluster of Systems Neurology**
[2] **DZNE German Center of Neurodegenerative Diseases**

Overcoming the resolution required for the identification of synaptic contacts, Electron Microscopy (EM) was decisive for progress in connectomics. EM provides further ultrastructural insights into cellular and subcellular interactions and morphologies in neurobiology. The lack of temporal resolution, small field of view as well as limited genetic tagging or immunolabeling options restrict the informative value of ultrastructural data. Correlative light and electron microscopy (CLEM) combines the best of both worlds by assigning detailed morphological context to dynamic information and molecular identities. Depending on the nature of the event of interest, correlation involves a combination of exogenous labeling (Near infrared branding = NIRB, nanobody labeling) and endogenous markers (autofluorescence, anatomical landmarks). We adapted and developed CLEM workflows for several neurobiological model systems including mouse NMJ, cortex, corpus callosum and zebrafish spinal cord. By combining longitudinal 2P- or confocal imaging with transmission EM (TEM) and volume SEM methods we gained insight into myelin or mitochondria morphologies of specific neurobiological processes.

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Functional interaction between TET3 and MECP2 – Novel insights into epigenetic mechanisms in neuronal differentiation

Victoria Splith, Anna Geserich, Franziska Traube, Gilles Gasparoni, Karl Nordström, Constanze Scheel, Dilara Özdemir, Jörn Walter, Thomas Carell, Stylianos Michalakis
LMU Center for Integrated Protein Science Munich

Active DNA demethylation involves the oxidation of genomic 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and further to 5-formyl- and 5-carboxycytosine (5fC and 5caC). This oxidation process is catalyzed by the alpha-ketoglutarate and Fe (II)-dependent ten-eleven translocation (TET) protein family of dioxygenases comprising TET1, TET2 and TET3. TET3 is the most abundant TET enzyme in the central nervous system. It is thought to act in cooperation with other proteins like transcription factors and chromatin remodelers to modify the DNA and thereby influence transcription. However, the exact mechanisms how TET enzymes are regulated and guided to the DNA for catalytic activity remain elusive.

We performed affinity proteomics in human iPSC-derived neurons and found several novel TET3 interaction partners, which are known to play an important role in transcriptional regulation and developmental processes. Of all found interactors, the Methyl-CpG Binding Protein 2 (MECP2) was chosen for further validation. MECP2 is a known 5mC and 5hmC binding protein and highly abundant in the brain. We found that MECP2 regulates TET3 activity thereby influencing global 5hmC. Genomic deletion of either MECP2 or TET3 by CRISPR-Cas9 led to similar changes in the methylome and transcriptome of human iPSC derived neurons pointing to the synergistic action of both proteins during neuronal development.

In conclusion, we identified a novel functional interaction between TET3 and MECP2, which influences neuronal differentiation.

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Systemic loss of Sarm1 is glioprotective after neurotrauma

Tian Weili
HMGU Research Unit Sensory Biology and Organogenesis

Protecting the nervous system from chronic effects of physical and chemical stress is a pressing clinical challenge that has sparked intense efforts to identify molecular inhibitors of axon destruction. Yet, one caveat of such strategy is the extent of unintended deleterious effects of blocking axon degeneration systemically. Here we use genetics and pharmacology in zebrafish to show that elimination of the obligate pro-degenerative protein Sarm1 is compatible with neural homeostasis and function, and is glioprotective. We find that severed axons lacking Sarm1 subsist independently of Schwann-cell support. Regenerating axons in Sarm1 mutants do not reseal with non-degradable axon segments and regain connectivity with peripheral synaptic targets to enable sensorimotor recovery, revealing that neural-circuit repair is not contingent upon expeditious clearance of damaged axons. Unexpectedly, we found that Sarm1 deficiency increases Schwann-cell resistance to toxicity by diverse chemotherapeutic agents after nerve injury. Our findings increase our understanding of the cellular environment that enables Schwann-cell reprogramming upon nerve damage. They also have clinical implications because they anticipate that pharmacological interventions targeting Sarm1 are promising strategies to reduce chronic consequences of neurotrauma.

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Cell atlas of mouse and primate retina

Wenjun Yan[1], Yi-Rong Peng[1], Tavé van Zyl[2], Qiangge Zhang[3], Guoping Feng[3], Joshua Sanes[1]
[1] **Harvard Department of Molecular & Cellular Biology, Center for Brain Science**
[2] **Harvard Medical School, Glaucoma Service, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary**
[3] **MIT McGovern Institute for Brain Research and Department of Brain & Cognitive Sciences**

The retina has been studied intensively in a variety of model organisms, leading to a growing understanding of the cells and circuits that underlie the initial steps in vision. Among mammals, however, only primates have a central specialized retinal region called the fovea, embedded in a slightly larger macula. The fovea underlies most high acuity and much chromatic vision, and is most vulnerable in age-related macular degeneration and other macular diseases. As a first step in understanding the molecular and cellular bases of structural and functional foveal specializations, we built on initial studies of the mouse retina (Macosko et al., Cell, 2015; Shekar et al., Cell, 2016; and unpublished) to analyze the fovea and peripheral retina of three primate species: macaque, marmoset and human. (>165k single cell transcriptomes from macaque (Peng, Shekhar et al., Cell, 2019), >75k from 5 human donors, and >45k from marmoset). Most but not all cell types are conserved between fovea and periphery. There are, however, differences in proportions and in gene expression between corresponding foveal and peripheral types; these presumably underlie foveal specializations. Finally, we used these data sets to compare retinal cell types among the three primates and between primates and mice. We found that photoreceptor and bipolar types were largely conserved across species, but found species-specific differences among horizontal, amacrine and retinal ganglion cell types. Together these results reveal foveal specializations, shed light on retinal evolution, and set the stage for studies of human retinal disease.

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Temporal twilight zone and beyond: timing mechanisms in consciously delayed actions

Taoxi Yang
LMU Institute of Medical Psychology and Human Science Center

Precise timing is essential for many kinds of human behavior, both for actions and reactions. In the reaction mode, tasks have to be completed as fast as possible; in the action mode, tasks have to be initiated at an appropriate time requiring an anticipatory temporal component. Temporal mechanisms for actions with such an anticipatory component are not yet sufficiently understood; in particular, it is not known whether on the operational level for delayed movements distinct time windows are used, or whether anticipatory control is characterized by continuous temporal processing. With a modified reaction time paradigm, we asked subjects to act with predefined time delays between 400 and 5000 milliseconds; after each individual trial a numerical feedback was provided which allowed correction of the response time for each next trial. Visual stimuli (in experiment 1) and auditory stimuli (in experiment 2) were used. In the statistical analyses piecewise linear models and exponential decay models for the response variability of different delay times were compared. These analyses favored piecewise linear models; a decreasing variability with increasing delay of voluntary controlled actions was observed up to approximately one second, followed by close to constant variability beyond this delay. We suggest that precise temporal control of voluntary actions is reached only after a "temporal twilight zone" of around one second which apparently marks a temporal border between two different timing mechanisms.

Key words: temporal processing, delayed responses, reaction time, motor control, anticipatory control, oscillations

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In vivo odor tuning and antagonism in individual olfactory sensory neurons

Joseph Zak
Harvard Center for Brain Science, Department of Molecular and Cellular Biology

An odor landscape is a complex blend of discrete molecules that each activate unique, yet highly overlapping, populations of olfactory receptor neurons (ORNs). Despite a rich diversity of ORN subtypes (~1200 in mouse and ~400 in humans), the overlapping nature of odor inputs may lead to saturation of neural responses, which could be mitigated by normalizing mechanisms at the early stages of stimulus encoding. A potential mechanism to accomplish normalization is competitive antagonism at the level of odor receptor-ligand. Theoretical work demonstrates that if ORN activation occurs through a multistep pathway where ligand binding and G-protein activation are decoupled, antagonistic interactions between odor molecules in a mixture may be readily observed. These antagonistic interactions may thereby provide a mechanism to normalize input to the olfactory system without the need for recurrent circuitry or lateral interactions between glomeruli.

Prior experimental studies have described non-linear interactions resulting from odor mixtures; however, it remains unknown whether antagonism is a central feature of how odor information is encoded by receptor neurons. We have begun to investigate odor mixture interactions, with a focus on antagonism, in live, freely breathing mice. We used multiphoton microscopy to visualize odor responses of ORNs axons in the glomerular layer of the olfactory bulb. We frequently observed antagonistic interactions that were predicted by our model. We could not, however, rule out the possibility that these interactions arise through lateral inhibition in the glomerular layer. To exclude this possibility, we have developed a method that allows for direct optical access to receptor neuron cell bodies within the olfactory epithelium. The ability to study mixture interactions in ORNs in their native environment offers new avenues for linking odor encoding in the periphery to olfactory perception in a tractable animal model.

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To space and back: persisting structural changes to the human brain after long-duration space travel

Peter zu Eulenburg[1], Angelique Van Ombergen[2,11], Steven Jillings[2,11], Ben Jeurissen[3], Elena Tomilovskaya[4], Alena Rumshiskaya[5], Liudmila Litvinova[5], Inna Nosikova[4], Ekaterina Pechenkova[6], Inessa B. Kozlovskaya[4], Stefan Sunaert[7], Paul M. Parizel[8], Valentin Sinitsyn[9], Steven Laureys[10], Jan Sijbers[3], Floris L. Wuyts[2]
[1] **LMU Department of Neurology**
[2] **University of Antwerp, Department of Physics**
[3] **Imec/Vision Lab, University of Antwerp**
[4] **Russian Academy of Sciences SSC RF – Institute of Biomedical Problems**
[5] **Radiology Department, Federal Center of Treatment and Rehabilitation**
[6] **Research Institute of Neuropsychology of Speech and Writing**
[7] **University of Leuven, Department of Imaging & Pathology, Translational MRI**
[8] **Radiology Department, Antwerp University Hospital & University of Antwerp**
[9] **Faculty of Fundamental Medicine, Lomonosov Moscow State University**
[10] **University and University Hospital of Liège, Coma Science Group, GIGA research, Neurology Department**
[11] **University of Antwerp, Department of Translational Neurosciences – ENT**

The impact of spaceflight and microgravity on the human central nervous system and its structure and function relationship has been investigated in only a handful of studies. Using prospectively collected neuroimaging data from European and Russian space travelers, our lab initially aimed to investigate the structural changes of long-term microgravity exposure with respect to cortical representations of vestibular cognition and navigation. Doing voxel- and surface-based morphometry with additional region-of-interest testing on 12 cosmonauts and 4 astronauts pre- and postflight after a stay of on average 191 days on the International Space Station (ISS) and half a year after return to Earth our research though quickly turned into a different direction.

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For scientific enquiries, please contact:
Oliver Behrend, Managing Director
Munich Center for Neurosciences – Brain & Mind (MCN[LMU])
o.behrend@lmu.de

For administrative enquiries, please contact:
Anna Jakubowska, Project Manager
International Cooperation LMUexcellent, LMU International Office
anna.jakubowska@lmu.de

MCN LMU MUNICH CENTER FOR NEUROSCIENCES

Graduate School of Systemic Neurosciences
LMU Munich

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