LMU-Harvard Young Scientists' Forum – ONLINE
From Molecules to Organisms XIII
Munich, July 12 – July 14, 2021

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. After 11 consecutive events in as many years, the YSF had to be cancelled on short notice in 2020 in light of the Corona-Pandemic.

For the first time in 2021 the YSF is held as a purely virtual conference to accommodate ongoing health concerns.

Content

<u>Agenda</u> 13th Harvard-LMU Young Scientists' Forum, July 12-14, 2021

Oral presentations via *zoom*
https://lmu-munich.zoom.us/j/91223628249?pwd=bjBFMnROMzFMNmJhbnZEMWFjQ25XUT09

Monday, July 12, all time slots indicated in CET (= EST + 6h)

- 15:00-15:10   Welcome address (S.Lauterbach, LMU, International Office)

- 15:10-15:50   **Lecture 1** – D.Paquet, LMU "**Developing a new generation of human brain disease models using CRISPR editing and iPS cells**" (Chair: M.Götz, LMU, HGMU)
- 15:50-16:00   Break

- 16:00-18:00   **Session 1** - "**Neural circuits, learning, and behaviour**"
D.Crombie (Busse lab); L.Groschner (Borst lab); S.A.Kim (Sabatini lab); A.K.Pradhan (Rammes lab); H.Twarkowski (Sahay lab); W.Xiao (Kreiman lab) (Chair: A.Sirota, LMU)
- 18:00-18:10   Break

- 18:10-19:00   **Lecture 2** - S.R.Datta, HRVD "**Dopamine links learning and variability during naturalistic behavior**" (Chair: A.Sirota, LMU)

Tuesday, July 13

- 15:00-15:50   **Lecture 3** – I.Kadow, TUM "**Influence of state on brain activity, perception and behavior in Drosophila**" (Chair: H.Lopez-Schier, HGMU)
- 15:50-16:00   *Break*

- 16:00-18:00   **YSF poster session via *spatial.chat*** https://spatial.chat/s/ysf2021

(1)A.Berners-Lee (Murthy lab); (2)R.Bögle (Dieterich lab); (3)E.Bonke (Koerte lab); (4)S.Folkerts (Dieterich lab); (5)A.F.Gonzales-Suarez (Lopez-Schier lab); (6)S.Jayakumar (Murthy lab); (7)N.Kadmon-Harpaz (Ölveczky lab); (8)V.Kirsch (Dieterich lab); (9)U.Klibaite (Ölveczky lab); (10)D.Lavrentovich (de Bivort lab); (11)J.Marshall (Ölveczky lab); (12)P.Masset (Murthy lab); (13)M.McAssey (Dieterich lab); (14)A.Nabel (Grothe lab); (15)M.Peter (Macklis lab); (16)J.Rhee (Cox lab); (17)V.Schwarz (Ninkovic lab); (18)T.Schwarzmeier (Merrow lab); (19)A.Sobolev (Sirota lab); (20)V.Susoy (Samuel lab); (21)T.Wiegand (Koerte lab); (22)C.Winter (He lab)

- 18:00-18:10   *Break*

- 18:10-19:00   *Lecture 4* - M.Watabe-Uchida, HRVD "**Balancing separate dopamine systems in behavioral choice**" (Chair: M.Pecka, LMU)

Wednesday, July 14

- 15:00-15:50   *Lecture 5* - J.Ninkovic, LMU "**Phase-separated TDP-43 regulates the activation states of microglia after traumatic brain injury**" (Chair: H.Straka, LMU)
- 15:50-16:00   Break

- 16:00-18:00   *Session 2* - "**Neural development, plasticity and repair**"
A.Engmann (Macklis lab); J.Froberg (Macklis lab); C.Gordy (Straka lab); Q.Jiang (Chen lab); S.Kenet (Misgeld lab); C.Li (Kreiman lab) (Chair: G.Rammes, TUM)
- 18:00-18:10   *Break*

- 18:10-19:00   *Lecture 6* - J.Sanes, HRVD "**What can we learn from a molecular atlas of cell types**?" (Chair: B.Grothe, LMU)

- 19:00   Closing remarks (B.Grothe, MCN-LMU / K.Blum, CBS-HRVD)

Participants*

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

Harvard University – Delegation

- Kenneth Blum, Executive Director, Harvard Center for Brain Science
- Alice Berners-Lee, Postdoctoral Fellow, Laboratory of Venkatesh Murthy
- Sandeep Datta, Professor, Harvard Medical School, Department of Neurobiology
- Anne Engmann, Postdoctoral Fellow, Harvard Center for Brain Science, Laboratory of Jeffrey Macklis
- John Froberg, Postdoctoral Fellow, Harvard Center for Brain Science, Laboratory of Jeffrey Macklis
- Qiufen Jiang, Postdoctoral Fellow, Harvard Medical School, Laboratory of Chinfei Chen
- Siddarth Jayakumar, Postdoctoral Fellow, Harvard Center for Brain Science, Laboratory of Venkatesh Murthy
- Naama Kadmon Harpaz, Postdoctoral Fellow, Harvard Department of Organismic and Evolutionary Biology, Laboratory of Bence Ölveczky
- Seul Ah Kim, PhD student, Harvard Medical School, Laboratory of Bernardo Sabatini
- Ugne Klibaite, Postdoctoral Fellow, Harvard Department of Organismic and Evolutionary Biology, Laboratory of Bence Ölveczky
- Danylo Lavrentovich, PhD student, Harvard Center for Brain Science, Laboratory of Ben de Bivort
- Chenguang Li, PhD student, Harvard Graduate Program in Biophysics, Laboratory of Gabriel Kreiman
- Jesse Marshall, Postdoctoral Fellow, Harvard Department of Organismic and Evolutionary Biology, Laboratory of Bence Ölveczky
- Paul Masset, Postdoctoral Fellow, Harvard Center for Brain Science, Laboratory of Venkatesh Murthy
- Manuel Peter, Postdoctoral Fellow, Harvard Center for Brain Science, Laboratory of Jeffrey Macklis
- Juliana Rhee, PhD student, Harvard Department of Molecular and Cellular Biology, Laboratory of David Cox
- Joshua Sanes, Professor, Harvard Center for Brain Science, Department of Molecular and Cellular Biology

- Vadislav Susoy, Postdoctoral Fellow, Harvard Department of Physics & Center for Brain Science, Laboratory of Aravithan Samuel
- Hannah Twarkowski, Postdoctoral Fellow, Harvard Harvard Brain Science Initiative, Laboratory of Amar Sahay
- Mitsuko Watabe-Uchida, Research Fellow, Harvard Center for Brain Science
- Carl-Frederik Westin, Professor,
- Carla Winter, PhD student, Harvard Medical School, Laboratory of Zhigang He
- Will Xiao, PhD student, Harvard Medical School, Laboratory of Gabriel Kreiman

Harvard University – Nominating Faculty
- Kenneth Blum, Executive Director, Harvard Center for Brain Science
- Chinfei Chen, Professor, Harvard Medical School, Division of Medical Sciences
- David Cox, Professor, Harvard Department of Molecular and Cellular Biology
- Sandeep Datta, Professor, Harvard Medical School, Department of Neurobiology
- Ben de Bivort, Professor, Harvard Center for Brain Science, Department of Organismic and Evolutionary Biology
- Zhigang He, Professor, Harvard Medical School, Department of Neurology
- Gabriel Kreiman, Professor, Harvard Medical School, Department of Opthalmology
- Jeff 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
- Bence Ölveczky, Professor, Harvard Department of Organismic and Evolutionary Biology
- Bernardo Sabatini, Professor, Harvard Medical School, Department of Neurobiology
- Amar Sahay, Assoc. Professor, Harvard Brain Science Initiative, Center for Regenerative Medicine
- Aravinthan Samuel, Professor, Harvard Department of Physics & Center for Brain Science
- 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

- Oliver Behrend, Managing Director, LMU, Munich Center for Neurosciences (MCN), Graduate School of Systemic Neurosciences (GSN)
- Rainer Bögle, Postdoctoral Fellow, LMU, Department of Neurology, University Hospital, Laboratory of Marianne Dieterich
- Michaela Bonfert, Senior Postdoctoral Fellow, LMU, Department of Child and Adolescent Psychiatry, Laboratory of Inga Koerte
- Elena Bonke, PhD student, LMU, Department of Child and Adolescent Psychiatry, Laboratory of Inga Koerte
- Davide Crombie, PhD student, LMU, Department Biology II, Division of Neurobiology, Laboratory of Laura Busse
- Sarah Folkerts, Postdoctoral Fellow, LMU, Department of Neurology, University Hospital, Laboratory of Marianne Dieterich
- Magdalena Götz, Professor, LMU, Department of Physiological Genomics, HMGU
- Andres Felipe Gonzales Suarez, PhD student, HMGU, Laboratory of Hernan Lopez-Schier
- Clayton Gordon, PhD student, LMU, Department Biology II, Division of Neurobiology, Laboratory of Hans Straka
- Lukas Groschner, Project Leader, MPIN, Laboratory of Alexander Borst
- Benedikt Grothe, Professor, LMU, Department Biology II, Division of Neurobiology, Munich Center for Neurosciences (MCN), Graduate School of Systemic Neurosciences (GSN)
- Ilona Grunwald Kadow, Professor, TUM, Neuronal Control of Metabolism, School of Life Sciences
- Anna Jakubowska, Project Manager, LMU International Office
- Leonard Jung, PhD student, LMU, Department of Child and Adolescent Psychiatry, Laboratory of Inga Koerte
- Selin Kenet, PhD student, TUM Faculty of Medicine, Laboratory of Thomas Misgeld
- Valerie Kirsch, Postdoctoral Fellow, LMU, Department of Neurology, University Hospital, Laboratory of Marianne Dieterich
- Stefan Lauterbach, Head of LMU International Office
- Hernán López-Schier, PI, HMGU, Research Unit Sensory Biology and Organogenesis

- Michaela McAssey, PhD student, LMU, Department of Neurology, Laboratory of Marianne Dieterich
- Alisha Nabel, LMU, Department of Biology II, Division of Neurobiology, Laboratory of Benedikt Grothe
- Jovica Ninkovic, Professor, LMU, Biomedical Center, Department for Cell Biology, Neurogenesis and Regeneration
- Dominik Paquet, Professor, LMU, University Hospital, Institute for Stroke and Dementia Research (ISD)
- Michael Pecka, Principal Investigator, LMU, Department Biology II, Division of Neurobiology
- Arpit Kumar Pradhan, Scientific Fellow, TUM Klinik für Anaesthesiologie, Klinikum rechts der Isar, Laboratory of Gerhard Rammes
- Maria Robles, Professor, LMU, Institute of Medical Psychology, Laboratory of Martha Merrow
- Veronika Schwarz, PhD student, LMU, Department for Cell Biology, Laboratory of Jovica Ninkovic
- Tanja Schwarzmeier, PhD student, LMU, Institute of Medical Psychology Laboratory of Martha Merrow
- Anton Sirota, Professor, LMU, Department Biology II, Division of Neurobiology, Bernstein Center for Computational Neuroscience (BCCN)
- Andrey Sobolev, Postdoctoral Fellow, LMU, Department Biology II, Laboratory of Anton Sirota
- Tim Wiegand, PhD student, LMU, Department of Child and Adolescent Psychiatry, Laboratory of Inga Koerte

LMU Munich – Nominating Faculty
- Alexander Borst, Professor, MPIN, Department of Systems and Computational Neurobiology
- Laura Busse, Professor, LMU, Department Biology II, Division of Neurobiology
- Marianne Dieterich, Professor, LMU, Department of Neurology, University Hospital
- Benedikt Grothe, Professor, LMU, Department Biology II, Division of Neurobiology, Munich Center for Neurosciences (MCN), Graduate School of Systemic Neurosciences (GSN)
- Inga Koerte, Professor, LMU, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy
- Hernán López-Schier, PI, HMGU, Research Unit Sensory Biology and Organogenesis
- Martha Merrow, Professor, LMU, Institute of Medical Psychology
- Thomas Misgeld, Professor, TUM, Faculty of Medicine, Institute of Neuronal Cell Biology, Munich Center for Neurosciences (MCN), Graduate School of Systemic Neurosciences (GSN)

- Jovica Ninkovic, Professor, LMU, Biomedical Center, Department Cell Biology, Neurogenesis and Regeneration
- Gerhard Rammes, Professor, TUM Klinik für Anaesthesiologie, Klinikum rechts der Isar
- Anton Sirota, Professor, LMU, Department Biology II, Division of Neurobiology, Bernstein Center for Computational Neuroscience (BCCN)
- Hans Straka, Professor, LMU, Department Biology II, Division of Neurobiology

Abstracts – Faculty Lectures, Short Talks and Posters

(in alphabetical order of 1st authors)

TBD
(poster #01)

Alice Berners-Lee
Harvard Department of Molecular and Cellular Biology

Withdrawn.

Does the Anna Karenina principle apply to vestibular migraine (VM) and Meniere's disease (MD)?
(poster #02)

Rainer Boegle[1,2], Emilie[1,2], Johannes Gerb[1,2], Sandra Becker-Bense[1,2], Marianne Dieterich[1,2,3], Valerie Kirsch[1,2,4],

[1]LMU, Department of Neurology, University Hospital
[2]LMU, German Center for Vertigo and Balance Disorders-IFB, University Hospital
[3]Munich Cluster for Systems Neurology (SyNergy)
[4]LMU, Graduate School of Systemic Neuroscience (GSN)

Introduction:

It is unclear how Meniere's disease (MD) and vestibular migraine (VM), which often appear in clinically similar attacks, differ from healthy controls (HC) in functional connectivity, especially during the interictal phase. The central functional connectivity feature of VM and MD might be "disorganization" relative to HC, due to unpredictable attacks that cannot be compensated for. This "Anna Karenina principle" states that all HCs are very alike while all patients are very dissimilar from each other and the HCs. Here we examined the distribution parameters of functional connectivity between HC, VM and MD to elucidate the state of disorganization in the interictal phase.

Methods:

50 HCs and 93 patients (42 VM, 51 MD) underwent fMRI while resting in a 3T MRI (Siemens). Resting-state fMRI connectivity measures were extracted via dual regression and normalized in mean and standard deviation relative to HCs. Robust distribution parameters for all voxels in the grey matter were compared between groups.

Results:

Distribution parameters were compact for HCs, while those of VM and MD patient groups were significantly more dispersed, i.e., disorganized (Fig 1). In figure 1 the bulk of values for the HCs were marked by black outline and superimposed onto the values for the MD and VM groups.

Conclusion:

Resting-state functional connectivity measures imply disorganized interactions between patients relative to HCs, even in the interictal phase. VM and MD patients are very different in functional connectivity, suggesting that the Anna Karenina principle might apply to these patients.

Figure 1:
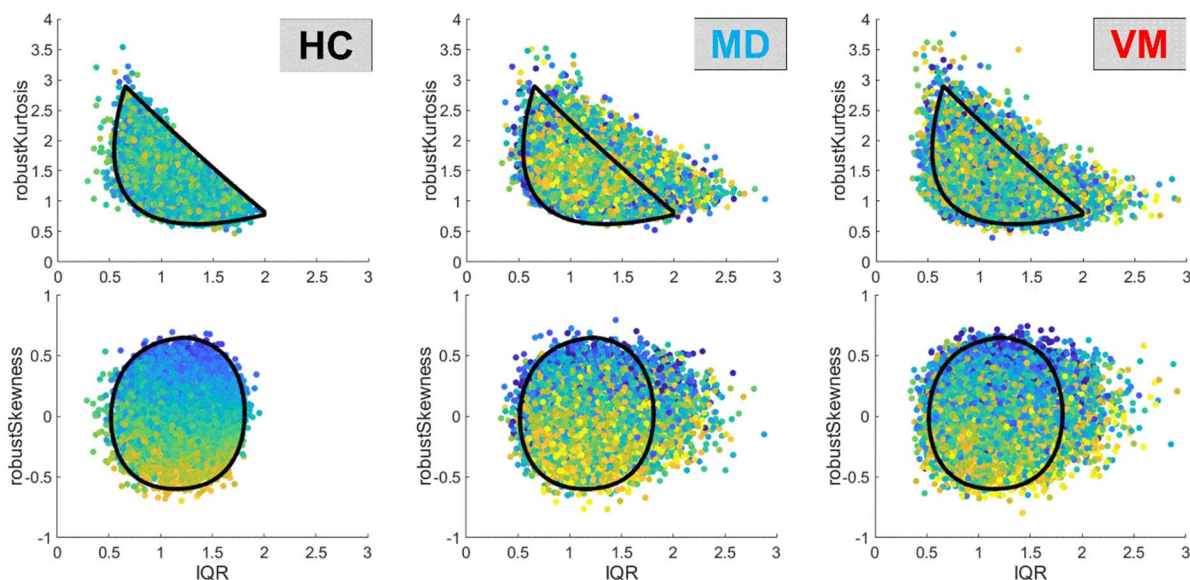
Distribution parameters per voxel. Color of dots indicates the robust skewness from -1 to 1 (blue to yellow). Values for healthy controls (HC) were marked with a black line and superimposed on Meniere disease (MD) and vestibular migraine (VM) group data.

References:
1) Dieterich et.al. J Neurol (2016);
2) Liu & Xu, Behav Neurol (2016);
3) Tabet & Saliba, J Clin Med Res (2017)

Prevalence of signs of minor neurological dysfunction and its association with higher cognitive functions in youth athletes
(poster #03)

E.M. Bonke[1,2,3,] M. Bonfert[4], S. Hillmann[4,5], S.B. Sandmo[6,7], T.L.T. Wiegand[1,3], E. Yhang[8], F. Dégeilh[1], M. Gaubert[1], D. Kaufmann[1,3,9], B. Schwarz-Moertl[1], A. Clauwaert[10], C. Seer[10], J. Seitz-Holland[1,3], A. De Luca[11], J. Gooijers[10], A. Leemans 11, A.P. Lin 3,12,13, O. Pasternak 3,12, S.P. Swinnen 10, Y. Tripodis 8,14, U. Tacke 15, F. Heinen 4, I.K. Koerte 1,2,3,16

[1]cBRAIN, Department of Child and Adolescent Psychiatry, Psychosomatic and Psychotherapy, Ludwig-Maximilians-Universität, Munich, Germany;
[2]Graduate School of Systemic Neurosciences, Ludwig-Maximilians-Universität, Munich, Germany;
[3]Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;
[4]Department of Pediatric Neurology and Developmental Medicine, Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany;
[5]University Hospital rechts der Isar, Technical University of Munich, Munich, Germany;
[6]Oslo Sports Trauma Research Center, Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway;
[7]Department of Neurology, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway;
[8]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA;
[9]Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Augsburg, Augsburg, Germany;
[10]Movement Control and Neuroplasticity Research Group, Department of Movement Sciences, KU Leuven, Leuven (3000), Belgium;
[11]Image Sciences Institute, University Medical Center Utrecht, Utrecht, the Netherlands;
[12]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;
[13]Center for Clinical Spectroscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;
[14]Alzheimer's Disease and CTE Centers, Boston University School of Medicine, Boston, MA, USA;
[15]University Children's Hospital (UKBB), Basel, Switzerland;
[16]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA;

The presence of coherent clusters of neurological signs is age-dependent yielding to approximately 45% in preschool and 25% in school-aged children. Studies systematically reporting on the prevalence of signs of minor neurological dysfunction (MND) in otherwise healthy adolescents are missing. Fine motor function plays a crucial role within the concept of MND. Preliminary evidence associates deficits in the fine motor domain to lower performance in tests of higher cognitive functions in school-aged children. Whether this association persists into adolescence has not yet been investigated.

The aim of this work is to assess the prevalence of signs of MND in youth athletes, and to characterise potential differences in higher cognitive functions in youth athletes with signs of MND compared to peers without.

Data from this study has not yet been published. Please visit my poster presentation if you are interested in more details

Modulation of dLGN activity predicted by pupil size dynamics across multiple timescales (short talk session #1)

Davide Crombie
LMU, Department Biology II, Division of Neurobiology

The way in which sensory systems encode information, even at early processing stages, is modulated according to the internal state of the animal. Internal states, such as arousal, are often characterized by relating neural measures to a single "level" of arousal, defined using a behavioral variable such as locomotion or pupil size. However, recent evidence suggests that internal states result from a combination of factors, including fluctuations in neuromodulatory tone and sequences of active behaviors, which occur over a wide range of temporal scales. Here, we exploit the multi-scale dynamics of the pupil size signal to show that spiking activity in the mouse dLGN, the primary visual thalamic nucleus, is modulated across a broad range of behaviorally relevant time scales. This modulation involves a change in the firing mode of the dLGN, with tonic spiking preferentially occurring during pupil dilations, and burst spiking prevalent during contractions. This modulation does not dependent on pupil size itself, or on overt active behavior such as locomotion, indicating that the internal state of the dLGN is not fully captured by assigning a single arousal level based on either one of these variables. Furthermore, the persistence of these dLGN firing mode modulations during periods of patterned stimulus viewing has implications for how sensory information is passed on to the cortex, suggestive of highly flexible encoding of visual information throughout wakefulness.

Dopamine links learning and variability during naturalistic behavior (faculty lecture #2)

Sandeep Robert Datta
Harvard Medical School, Department of Neurobiology

TBD

Toward a new understanding of CNS circuit (re)generation: Subcellular analysis of corticospinal growth cone molecular machinery in development vs. regeneration (short talk session #2)

Anne Engmann & Jeffrey Macklis
Harvard Center for Brain Science, Department of Stem Cell and Regenerative Biology

During development, subcerebral projection neurons (including their best-known subset– corticospinal neurons) grow axons over remarkably long distances to the midbrain, brainstem, and spinal cord, generating exquisitely precise functional circuitry indispensable for voluntary and fine motor execution. The same neurons, however, fail to regenerate following injury or degeneration, resulting in irreversible impairment of motor function, severely impacting the health and quality of life of affected people. Despite current knowledge about mechanisms that hinder regeneration, including inhibitory extrinsic cues and failure to activate intrinsic growth machinery, no causal treatment currently exists for traumatic injuries to the CNS.

Neurons are uniquely polarized cells with extreme spatial expanse. In development and regeneration, growth cones (GCs) are the subcellular units effecting axonal growth, guidance, and circuit assembly. New experimental and analytic approaches recently developed in our lab provide access to the RNA and protein molecular machinery of subtype- and stage-specific GCs isolated directly from the mouse brain. Combination of neuronal subtype-specific labeling, biophysical fractionation, and newly developed fluorescent small particle sorting enables the purification of GCs of interest to study their local transcriptomic and proteomic machinery. We are currently investigating the molecular machinery of corticospinal GCs across a range of developmental stages, generating deep insight into the local subcellular molecular changes that enable precise navigation of GCs all the way from the cortex caudally to the spinal cord, then subtype-specific synapse formation. Additionally, we are expanding this work to regenerative corticospinal GCs following spinal cord injury, aiming to identify similarities and differences between the local molecular controls of developing (growth-permissive) and regenerating (growth-abortive) GCs.

Cognitive function in vestibular disorders
(poster #04)

Sarah Folkerts
LMU, Department of Neurology, University Hospital

Bilateral vestibulopathy (BVP) is a chronic loss of function of the vestibular organs of both inner ears. The most common symptoms are postural and gait instability which usually worsens in the dark or on uneven ground. In addition to impaired balance and vestibular reflexes, there is emerging evidence that a chronic loss of vestibular input also has a detrimental effect on higher cognitive functions. Evidence so far has consistently shown visuospatial orientation and memory to be affected in individuals with BVP. In addition, there are suggestions that other cognitive domains such as executive function, attention and memory suffer as the result of the loss of vestibular input. The aim of this study is to further explore domains of higher cognitive function that might be affected by chronic vestibular loss with a focus on memory deficits. 22 BVP patients and 21 age-matched healthy controls are assessed on their memory function using a visual learning task, a list learning task, the DMS-48. In addition, all participants complete a Stroop task to assess executive function and processing speed. For the BVP patients, the results are correlated with the degree of vestibular dysfunction.

Subcellular translational regulation in cortical projection neuron subtypes: development of ultra-low input ribosome profiling
(short talk session #2)

John Froberg, Jeffrey D. Macklis
Harvard Center for Brain Science, Department of Stem Cell and Regenerative Biology

Global comparisons of the sets of mRNAs actively translated into proteins (the "translatome") in distinct cortical subtypes, and in distinct subcellular compartments of the same subtype, might provide critical insight into molecular mechanisms underlying cortical circuit formation and synapse maintenance and function, as well as pathological processes caused by mutations in RNA binding proteins in several neurodevelopmental and neurodegenerative disorders. However, such comparisons are challenging with current approaches, due to the relatively large amounts of material standardly required for ribosome profiling. Here, we present an optimized approach for ribosome profiling using as few as 17K neurons. This approach yields high-quality, reproducible libraries, exhibiting several known quality control features: 1) strong enrichments for coding sequences versus UTRs and non-coding sequences; 2) narrow fragment length distributions over coding sequences that are also different from length distributions over non-coding sequences; 3) P-sites mainly in-frame to annotated coding sequences; and 4) sufficient coverage to estimate abundance for thousands of mRNAs. Comparison between interhemispheric callosal projection neurons (CPN) and subcerebral projection neurons (SCPN; including their best known subset– corticospinal neurons) in developing mouse cortex identifies hundreds of mRNAs regulated by translation in cortical neurons, and that transcriptional changes between subtypes are frequently counteracted by opposing translational changes. Finally, we analyze upstream ORF (uORF) translation in both subtypes, and find that uORFs containing mRNAs are enriched among genes involved in axon guidance and synapse assembly. Together, we present a simple but comprehensive discovery approach and resource for subcellular, ultra-low input ribosome profiling experiments in cortical subtypes (likely generalizable to any cell type).

Elucidating negr1 at single cell resolution
(poster #05)

Andres Felipe Gonzales Suarez
HMGU, Research Unit Sensory Biology and Organogenesis

On poster only.

One-eared frogs: insight into brainstem plasticity
(short talk session #2)

Clayton Gordy[1, 2] and Hans Straka[1]
[1]LMU, Department Biology II,
[2]LMU, Graduate School of Systemic Neurosciences

Bilateral vestibular endorgans provide sensory information about position and motion in space. This information is transformed by brainstem sensorimotor circuits to drive gaze- and posture-stabilizing reflexes, and to update circuits responsible for navigation and orientation. Vestibular endorgans have a mirror-symmetric bilateral arrangement, which assigns each individual endorgan a distinctive directional sensitivity. The assembly of vestibular circuits during ontogeny is influenced by sensory input; however, the extent to which bilateral activity plays an instructive role is unclear. To explore this, one-eared Xenopus laevis tadpoles were generated by embryonic removal of an otic placode. Sensorimotor circuits in these tadpoles were therefore challenged to develop while lacking full bilateral complements of peripheral sensory domains required for motion detection. The functional outcome of this condition was evaluated by assessment of vestibular-evoked eye motion during sinusoidal rotation. Despite the lack of one ear, tadpoles were able to produce vestibular-evoked eye movements, although with spatio-temporal characteristics different to controls. During unidirectional motion, an asymmetric directional sensitivity was observed with surprisingly more robust responses originating from motion toward the extirpated side compared to those elicited by motion toward the intact side. This outcome indicates that sensory input from the singular ear is processed differentially within the brainstem. Electrophysiological recordings suggest that this plasticity may be localized at the level of the extraocular motor nuclei, and presents as a likely mechanism used by one-eared frogs to evoke vestibular-driven ocular movements. Such neurodevelopmental plasticity highlights mechanisms available in response to altered sensory conditions.

The biophysics of multiplication by a single neuron
(short talk session #1)

Lukas Groschner
MPIN Department of Systems and Computational Neurobiology

Nonlinear, multiplication-like operations carried out by individual neurons greatly enhance the computational power of a neural system. However, our understanding of the biophysical nature of such arithmetic is still lacking. I study this problem in the Drosophila motion vision circuit by recording the membrane potentials of direction-selective T4 neurons and their presynaptic partners in response to visual stimuli. Electrophysiological measurements and conductance-based model simulations reveal the presence of a passive supralinear synaptic interaction in T4. I will explain this multiplication-like nonlinearity in terms of the underlying ionic conductances and relate it to the animals' ability to perceive visual motion.

Influence of state on brain activity, perception and behavior in Drosophila (faculty lecture #3)

Ilona Grunwald Kadow
TUM School of Life Sciences Weihenstephan (WZW)

Behavior is not only a response to external stimulation but also to the current state of the body which provides essential information when an animal interprets the world around it. I will present two studies from my lab which address the question of how signals from the body influence sensory perception and behavior. In the first study, using fast whole brain imaging in Drosophila melanogaster, we show that walking including turning and straight runs induces a global state change in the brain. Imaging of specific sets of neurons across the brain reveals that both excitatory and inhibitory neurons are active during walking inconsistent with a global reduction of inhibition on neural activity. All classes of modulatory neurons respond during walk with some neurons being inhibited. Flies being forced to walk present highly similar brain activation patterns as flies moving spontaneously arguing against higher motor centers as main origin of a whole brain state change during ongoing behavior. Together, our data suggest that walk itself and walk-related feedback signals induce wide-spread activity in the brain allowing integration of behavioral state into most or all brain processes. The second study I will discuss deals with the role of the mushroom body, the fly's higher cognitive center and its role in integrating physiological state-dependent information into feeding decisions.

Neural basis of odour trail tracking in rodents
(poster #06)

Siddharth Jayakumar, Alexander Mathis, Venkatesh N. Murthy
Harvard Department of Molecular and Cellular Biology

Active sensing, where sensing is under voluntary control, is extensively used for scanning the environment to extract features of interest from relevant stimuli. A great example of active sensing is repeated visual saccades made for scene recognition. However, active sensing is not exclusive to vision, and in rodents sniffing and whisking are key to active olfactory and tactile sensory processing. Odour-guided navigation is important for rodents as they rely heavily on olfactory cues for finding food, mates and avoiding predators. Navigating odour trails involves bilateral comparison from the two nostrils across multiple sniffs, followed by subsequent motor actions. The neural basis for such flexible yet precise behaviour remains poorly understood. Olfactory processing begins when odour molecules act on olfactory receptors (OR) that are expressed on specific olfactory sensory neurons (OSN) in the nasal epithelium. The OSNs converge based on the similarity in ORs on to glomeruli in the olfactory bulb. Projection neurons from the bulb relay the information onto higher brain regions that include the olfactory cortical areas - the anterior olfactory nucleus (AON) and the piriform cortex. The AON has privileged access to information coming from both nostrils and sends feedback projections to the bulb. This circuit architecture suggests that the AON is a key hub, relevant for olfactory guided behaviours, where bilateral odour concentrations are continuously estimated and integrated for correct motor outputs.

Here we use an open-loop treadmill with dynamic odour trails that continuously challenge the mice to navigate with high precision to get rewards. We use DeepLabCut to estimate positions of the snout and other body parts with high accuracy. Mice learn this behavior quickly (>70% rewards collected after 3 days). We observed that while mice predominantly cast while tracking, there exist other modes of following a trail that have not been previously characterized such as trailing and biased searching based on previously encounters with the trail. We corroborated previous work showing that naris occlusion biases, but does not abolish, trail tracking behavior. To begin to address the neural basis of how odor cues are integrated in the brain to modulate motor output, we chose to study the AON as well as the antero-lateral motor cortex (ALM), a hub for motor planning. We find that the targeted chemogenetic perturbation of activity either the AON or the ALM led to altered trail tracking, which we are currently characterizing in greater detail.

Synaptic convergence of retinal inputs coding different information in the visual thalamus (short talk session #2)

Qiufen Jiang[1], Elizabeth Y. Litvina[1,2], Guanhua Shu[1], Takuma Sonoda[1] and Chinfei Chen[1]
[1]Harvard Medical School, Department of Neurology, F.M. Kirby Neurobiology Center,
 Children's Hospital Boston
[2]National Institute of Neurological Disorders and Stroke, Bethesda, MD 20824, USA

In the mouse visual system, multiple types of retinal ganglion cells (RGCs) each encode different features of the visual space. How this information is parsed in their downstream target, the visual thalamus, is a topic of great interest. Here, we examined retinogeniculate connectivity in specific mouse lines labelling distinct groups of RGCs tuned to on-off direction selectivity in different directions.

Our electrophysiological and optogenetic studies reveal that the different types of RGCs provide primary retinal drive for only a small fraction of the thalamocortical (TC) neurons that they functionally innervate in the visual thalamus. The majority of the retinal inputs are weak and converge together with inputs from other RGC types onto common TC neurons. However, subtypes of RGCs coding the same information, but in different directions, are less frequent to converge with each other. Taken together, these results indicate that convergence of distinct information lines in the visual thalamus follows specific logics of organization.

Learning multiple actions – stability and flexibility in neural activity and motor output (poster #07)

Naama Kadmon Harpaz[1], Steffen B. E. Wolff[2], Kristopher T. Jensen[3], Bence P. Ölveczky[1]

[1]Harvard Department of Organismic and Evolutionary Biology
[2]Department of Pharmacology, University of Maryland School of Medicine, Baltimore MD USA
[3]Computational and Biological Learning Lab, Department of Engineering, University of Cambridge, Cambridge UK

One of the intriguing features of our nervous system is its ability to acquire new actions, gradually broadening our pool of motor expertise. From learning to use utensils, through tying our shoelaces, to fluently writing the alphabet, mastering multiple skills relies on the acquisition of new task-specific motor sequences, without overriding previously learned ones. Through practice, these learned skills are stabilized and remain so thereafter, even if not practiced for months and years. Such stable performance implies that the neural representation of the learned motor sequence is robust and resistant to interference. Yet how the brain can maintain a stable motor memory while also flexibly adapt to learning new skills is far from understood.

Here, we utilize a novel experimental setup that allows training and careful monitoring of freely behaving rats in their home-cages, along with recent advances in tracking single neuron activity over long time periods, to probe the dynamics of neural circuits during the acquisition of multiple motor sequences. The motor cortex and the basal ganglia, specifically the striatum – the main input nucleus that receives projections from the motor cortex, have been implicated in the learning and execution of motor sequences. We therefore track the neural activity of single units within these regions while rats train on complex forelimb motor sequences. First, we examined the activity underlying a single motor sequence following months of training and stabilization of the motor output. Our results show that the activity of single units in both motor cortex and dorsolateral striatum (DLS) are highly stable with only little change over weeks and months, that may be explained by an observed slow drift of the behavior. These results suggest that the neural circuits maintain a highly stable representation of the learned motor output over long time periods. To reveal whether and how the network changes when learning an additional motor sequence, we next trained rats on multiple lever-tap sequences using a continual learning paradigm, in which they first learn and train on one motor sequence, then switch to learning a new sequence. Our preliminary findings show that the motor output of the first learned sequence remains stable for long time periods and can be quickly recalled after learning the second sequence, suggesting that the underlying motor memory is robust to interference. Tracking precise kinematics simultaneously with recording the activity of many single units in both the motor cortex and the striatum throughout the entire learning period will provide an unprecedented understanding of how neural circuits flexibly adapt to acquire new actions, while keeping a stable performance and representation of previously learned behaviors.

In vivo imaging of oligodendrocyte injury in an NMO mouse model
(short talk session #2)

Selin Kenet
TUM Institute of Neuronal Cell Biology
LMU Graduate School of Systemic Neurosciences

Neuromyelitis optica (NMO) is an autoimmune disease predominantly affecting spinal cord and optic nerve. The majority of NMO patients have serum antibodies (IgG) against the water channel protein aquaporin 4 (AQP4), which in the CNS is expressed on astrocytic end-feet and ependymal cells. Despite this primary astrocytic target, demyelination is also prominent in AQP4-IgG+ NMO, and is regarded as secondary to astrocyte loss. However, the in vivo mechanisms by which targeting an astrocytic antigen can drive injury of other cell types, such as oligodendrocytes, remain unresolved. We investigated early signs of oligodendrocyte damage in a mouse model of acute NMO-related pathology induced by spinal application of patient-derived AQP4-IgG and human complement followed by in vivo imaging. Morphological assessment and calcium imaging of genetically labeled astrocytes and oligodendrocytes revealed the relative time-course of glial cell injury: Within an hour of AQP4-IgG application, intracellular calcium levels in astrocytes increased globally and membrane rupture swiftly followed as confirmed by uptake of a cell-impermeable nuclear dye and subsequent cellular fragmentation. Concurrent to the global astrocytic calcium rise, oligodendrocyte processes also showed calcium overload, which however reached the soma comparatively later. In contrast to the pervasive and swift lytic cell death of astrocytes, only some oligodendrocytes were lost at later time points. While dye exclusion experiments negated overt membrane rupture, expression of human MAC-inhibitor protein CD59 on oligodendrocytes still protected these cells from secondary damage after AQP4-IgG–mediated astrocyte injury.

These results imply that oligodendrocyte pathology in NMO is not driven by the loss of astrocytes per se, but rather evolves from MAC-dependent 'bystander' targeting of oligodendrocytes as suggested by prior in vitro and fixed tissue observations. At the same time, our dynamic observations suggest that despite the similar starting point of injury, the executive phase of cell injury might differ and could result in activation of distinct cell death pathways in the two major glial target cells of NMO.

Opposing neurotransmitters co-packaged in individual synaptic vesicles (short talk session #1)

Seul Ah Kim
Harvard Medical School, Department of Neurobiology

Survival of an animal depends on its capacity to 1) make associations of sensory cues with outcomes encountered in previous experiences and 2) to use these associations to predict what may happen in the future. Neurons in the lateral habenula (LHb) encode the error in the prediction of punishments and the observed outcome, thereby influencing downstream dopamine activity in the ventral tegmental area and substantia nigra.

Interestingly, a subclass of entopeduncular nucleus (EP) neurons that project to the lateral habenula (LHb) releases both excitatory and inhibitory neurotransmitters, glutamate and GABA, respectively. However, it is unclear if these opposing neurotransmitters are packaged into the same or segregated pools of synaptic vesicles. Here, we demonstrate a novel method combining electrophysiology, spatially-patterned optogenetics, and computational modeling designed to analyze the mechanism of glutamate/GABA co-release. We find that the properties of postsynaptic currents elicited in LHb neurons by optogenetic activation of EP terminals are only consistent with co-packaging of glutamate and GABA into individual vesicles. Furthermore, serotonin, which acts presynaptically to weaken EP to LHb synapses, does so by altering the release probability of vesicles containing both transmitters. Our approach is broadly applicable to the study of multi-transmitter neurons throughout the brain and our results constrain mechanisms of neuromodulation in LHb.

Intravenous delayed Gadolinium-enhanced MR imaging of the endolymphatic space: A methodical comparative study
(poster #08)

Valerie Kirsch[1-3], Rainer Boegle[1-3], Johannes Gerb[1-2], Marianne Dieterich[1-4]
[1]LMU, Department of Neurology, University Hospital
[2]LMU, German Center for Vertigo and Balance Disorders-IFB, University Hospital
[3]LMU, Graduate School of Systemic Neuroscience (GSN)
[4]Munich Cluster for Systems Neurology (SyNergy)

Introduction: Verification of endolymphatic hydrops (ELH) via intravenous delayed Gadolinium (Gd) enhanced magnetic resonance imaging of the inner ear (iMRI) is developing into a standard clinical tool to investigate vestibulo-cochlear syndromes [1].

Methods: 108 participants, 75 patients with Meniere's disease (MD; 55.2±14.9 years) and 33 vestibular healthy controls (HC; 46.4±15.6 years) were included to examine how (i) MR acquisition protocols influence the signal within endolymphatic space (ELS); (ii) ELS quantification methods correlate to each other and clinical data; and finally, (iii) ELS extent influences MR-signals.

Results: Within 0.1 to 0.2 mmol/kg Gd dosage and 4h $\pm$ 30 min time delay, semi-quantitative (SQ) and 2D- or 3D-quantifications of the ELS were independent of signal intensity (SI) and signal-to-noise ratio (SNR) (FWE corrected, $p < 0.05$, Figure 1). Used methods correlated strongly (0.3-0.8) and were highly reproducible across raters, thresholds. 3D-quantifications showed least variability. Asymmetry indices and normalized ELH were most useful for predicting quantitative clinical data. ELH size influenced SI, but not SNR. SI could not predict the presence of ELH.

Conclusion: 1) Gd dosage of 0.1-0.2 mmol/kg after 4h±30 min time delay suffices for ELS quantification. 2) A clinical SQ grading classification including a standardized level of evaluation reconstructed to anatomical fixpoints is needed. 3) ELS 3D-quantification methods are best suited for correlations with clinical variables, should include both ears and ELS values reported relative or normalized to size [2]. 4) ELH leads to mild SI increases. However, these signal changes cannot be used to predict the presence of ELH.
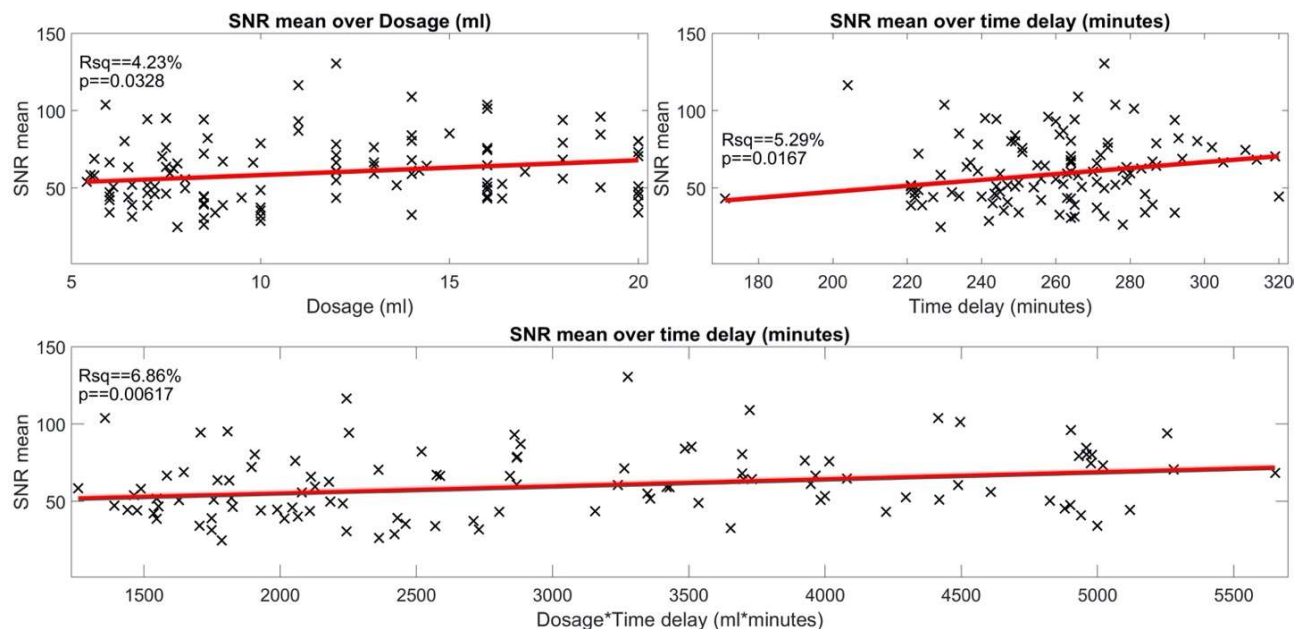
Figure 1: Influence of gadolinium (Gd) dosage and Gd time delay on the signal-to-noise ratio (SNR).

References: [1] Brandt T & Dieterich, Nature Reviews Neurology, 2017; [2] Oh SY et al., Frontiers in Neurology, 2021

Phenotyping ASD in rats through kinematics, social interactions and problem-solving tasks (poster #09)

Ugne Klibaite
Harvard Department of Organismic and Evolutionary Biology

On poster only.

Loci of individuality in the *Drosophila* olfactory circuit
(poster #10)

Danylo Lavrentovich
Harvard Department of Organismic and Evolutionary Biology

Individuality is a fundamental aspect of behavior that is observed even in isogenic flies reared in the same environment. Broad individual-to-individual behavioral distributions are observed in odor preference, exploratory handedness bias, and other sensory and motor modalities. Behavioral variation may confer evolutionary benefit as a "bet hedging" strategy against fluctuating environments. While some neural circuit elements have been identified as controlling the extent of variability in some behaviors, the exact circuit mechanisms underlying individual differences in sensorimotor behaviors are largely unknown.

Olfaction is a powerful model for studying neural loci of individuality, as the relevant circuit elements are well characterized and generally stereotyped across individuals. By combining behavioral and neural activity recordings within the same individuals, we have recently identified loci of individuality within the antennal lobe. To measure behavior, we tracked individual flies in linear chambers in which each half was perfused with one of two odors, MCH or OCT. Individual odor preference scores were calculated as the fraction of time the fly spent in one half of the chamber. To measure neural activity, we performed two-photon imaging of ORN (Orco-gal4) or PN (gh146-gal4) calcium dynamics across glomeruli of individual flies in response to a panel of odors. A linear model of glomerular activations on odor preferences revealed that idiosyncratic PN, but not ORN, dynamics from a subset of glomeruli were predictive of OCT-MCH odor preference.

While we have found that idiosyncratic activity in a subset of PNs constitutes a locus of behavioral individuality, how these idiosyncratic dynamics arise remains unknown. Local inhibitory neurons (LNs) are one likely source of neural variation, as LN wiring patterns differ widely across individuals (Chou et al, 2010), and silencing LNs decreases behavioral variation (Honegger, Smith, et al, 2019). Here we test the hypothesis that morphological variation in LNs across individuals drives individual variation observed in PN activity using an in silico circuit model of the AL that resolves ORNs, PNs, and LNs.

We utilize behavioral and neural activity recordings and mathematical modeling to identify loci of individuality in the fly olfactory circuit. This work contributes to our understanding of the mechanistic underpinnings of variation in odor preference and decision-making even within seemingly stereotyped neural circuits.

Active learning in *C. elegans* using optogenetics
(short talk session #2)

Chenguang Li
Harvard Graduate Program in Biophysics

Active learning is a field of machine learning where an algorithm decides where in a state space to query for new information. Ideally this reduces the amount of labelled data required for learning by querying regions with the most information content. Behavioral experiments in biology are often limited by the amount of labelled data available. We show that in the nematode C. elegans, we can use an active learning algorithm to learn neuronal roles in certain behaviors using a closed-loop system. The system consists of an optogenetically modified animal, a camera that tracks behaviors linked to a computer, and a computer-controlled light that will activate our optogenetically modified neurons. We aim to reduce the amount of perturbations to the animal required to learn how a neuron can function in natural behavior. Our setup thus combines active learning and an animal's nervous system in a way that allows us to learn about an animal and behavior control while minimizing optogenetic interference.

Continuous 3D kinematic tracking across the rodent behavioral repertoire (poster #11)

Jesse D. Marshall[1], Diego E. Aldarondo[2], Timothy W. Dunn[3], William L. Wang[1],
Gordon J. Berman[4], and Bence P. Ölveczky[1]
Harvard Center for Brain Science, Department of Organismic and Evolutionary Biology
[2]Program in Neuroscience, Harvard University, Cambridge MA 02138, USA
[3]Department of Statistical Science, Duke University, Durham NC 27710, USA
[4]Department of Biology, Emory University, Atlanta GA 30322, USA

Mammals are generalists, capable of flexibly re-using the same behaviors across a range of environmental contexts. However, existing experimental paradigms in mammals currently lack the behavioral diversity and kinematic resolution needed to examine which features of movement the brain encodes and how this encoding varies across contexts. To extend the range of behaviors and contexts that can be studied, we developed a new behavioral monitoring system, CAPTURE, that combines motion capture and deep learning to track the 3D movements of twenty points on a freely-behaving rat's trunk and appendages, continuously over weeks-long timescales in naturalistic environments. CAPTURE has sub-millimeter and millisecond-timescale spatial and temporal resolution, and exhibits substantial gains in precision over existing 2D convolutional network approaches to behavioral tracking. We developed a comprehensive behavioral analysis platform alongside CAPTURE that allowed us to detect known and novel behaviors, behavioral sequences, and states in our continuous kinematic recordings. Continuous neural and CAPTURE recordings in the dorsolateral striatum revealed significant tuning to kinematic and behavioral variables. However across behavioral states, these tuning properties changed, in a manner that improved the within-state but not across-state behavioral decodability. This suggests that striatal representations undergo state-specific remodeling in order to facilitate motor coding, and reinforces the need to interpret the neural correlates of behavior in a context-specific manner.

The neural code implicitly controls the geometry of probabilistic inference in early olfactory processing.
(poster #12)

Paul Masset[1,2] Venkatesh N Murthy[1,2] and Cengiz Pehlevan[2,3]
Harvard Center for Brain Science, Department of Molecular and Cellular Biology
[2]Harvard Center for Brain Science
[3]Harvard School of Engineering and Applied Sciences, Harvard University, Cambridge, USA

The sampling hypothesis proposes that the variability in the activity of single neurons is a signature of probabilistic computation. Rather than simply converging on a solution, the activity of single neurons samples the space of possible solutions proportionally to their probability given the data. However, sampling algorithms suffer from slow convergence in high dimensions and their precise implementation in neural circuits remains an open question. Work in machine learning and statistics has shown that the geometry of the inference can be leveraged to accelerate the sampling process. However, these algorithms include structured noise which would imply a strong electrical coupling at fast timescales that is independent of the synaptic connectivity across individual neurons. Here, we propose that decoupling the variables of interest from single neuron representations allows populations of electrically uncoupled neurons to encode a geometry of interest in order to speed up sampling. We map this process onto the circuitry of early olfactory processing. We propose a model separating the computation into excitatory units (mitral/tufted cells) which transform the sensory input and project a compressed representation of the outcome of the inference to cortical areas, and inhibitory units (granule cells) which implement the sampling.

Handedness dependent differences in EEG alpha power during visually induced self-motion perception
(poster #13)

Michaela McAssey[1-4], James Dowsett[1-2], Valerie Kirsch[1-3], Thomas Brandt[2-4], Marianne Dieterich[1-5]
[1]LMU Department of Neurology
[2]LMU German Center for Vertigo and Balance Disorders
[3]LMU Graduate School of Systemic Neuroscience (GSN)
[4]LMU RTG 2175, Perception in context and its Neural Basis
[5]LMU Munich Cluster of Systems Neurology (SyNergy)

Visually induced self-motion perception (vection) involves the integration of visual and vestibular information. Previous studies combining imaging techniques with vestibular stimulation suggest a vestibular thalamo-cortical dominance in the right hemisphere in right handers and the left hemisphere in left handers. In this study, we investigated if the behavioural characteristics and neural correlates of vection differ between left and right handed individuals. 64-channel EEG was recorded while 25 right handers and 25 left handers were exposed to vection-compatible roll motion and a matched, vection-incompatible control condition. Behavioural characteristics, i.e. vection presence, onset latency, duration and subjective strength, were also measured. The results showed no differences in the behavioural characteristics of vection between left and right handers. The vection-compatible roll motion resulted in a significant decrease in alpha power, relative to the vection-incompatible control condition. The topography of this decrease was handedness-dependent, with left handers showing a left lateralized centro-parietal decrease and right handers showing a bilateral midline centro-parietal decrease. Further analysis, time-locked to vection onset, revealed a comparable decrease in alpha power around vection onset and an increase in alpha power during ongoing vection, for both left and right handers. Similar analyses revealed no effects in theta and beta bands. In conclusion, left and right handed individuals exhibit vection-related alpha power decreases at different topographical regions, potentially related to an influence of handedness-dependent vestibular dominance in the visual-vestibular interaction that facilitates visually-induced self-motion perception. Despite this difference in where vection-related activity is observed, left and right handers show comparable behavioural characteristics and underlying alpha band changes during vection.

Development of specific functional axon and myelin morphology
(poster #14)

Alisha Nabel
LMU, Department Biology II, Division of Neurobiology

On poster only.

Phase-separated TDP-43 regulates the activation states of microglia after traumatic brain injury
(faculty lecture #5)

Jovica Ninkovic
LMU, Biomedical Center, Department Cell Biology, Neurogenesis and Regeneration

Inactivation of pathology-activated microglia is crucial to prevent chronic neuroinflammation and tissue scarring. We identified an injury-induced microglial state at the transition between activation and homeostasis in injured zebrafish brains, which was characterized by accumulation of lipid droplets and phase-separated TDP-43 condensates. Granulin-mediated clearance of both lipid droplets and TDP-43 condensates was necessary and sufficient to promote this microglial transition and the return to homeostatic function. Clearance of phase-separated TDP-43 condensates promoted both the return of activated microglia back to homeostasis and scarless regeneration. Importantly, the activated state of microglia also correlated with the accumulation of lipid droplets, TDP-43 condensates and stress granules in patients with ischemic stroke, thus supporting the existence of a similar regulatory mechanism in humans. Together, our results identified a drug-targetable mechanism required for the inactivation of microglia, which is necessary to avoid chronic neuroinflammation and has high potential for new therapeutic applications in humans.

Developing a new generation of human brain disease models using CRISPR editing and iPS cells
(faculty lecture #1)

Dominik Paquet
LMU Institute for Stroke and Dementia Research, University Hospital

Molecular human brain research heavily depends on model systems recapitulating key aspects of brain physiology and disease pathology. Most current knowledge about mechanisms organising brain function and dysfunction comes from primary or immortalized cell cultures, as well as rodent models, especially mice. However, these models have drawbacks, including species differences and incomplete phenotypes, impeding research on impactful neurodegenerative and neurovascular disorders. Furthermore, it is also conceivable that shortcomings of current models contribute to failures of model-tested drugs in clinical trials. Human models derived from induced pluripotent stem cells (iPSCs) have great potential to complement existing disease models, as they allow directly studying affected *human* cell types, have the genetic configuration of patients, and display crucial cell biological features also found in human brain. In addition, recent developments in genome editing using the CRISPR/Cas system have revolutionized the way we can study our genome and reveal the impact of genetic alterations on disease formation. In principle, the combination of genome editing with iPSC technology allows studying most genetic alterations in most cell types of our body, yielding a highly versatile system for disease research.

Current work in my lab focusses on advancing these technologies to establish and apply a new generation of iPSC-based disease models for human neurodegenerative and neurovascular brain diseases, with 3 major aims:

(1) We have improved CRISPR editing in many ways to increase specificity, efficiency and reliability of genome editing in iPSCs. In our most recent work, we describe the widespread occurrence of deleterious on-target effects (OnTEs) after CRISPR editing in iPSCs and show how these can negatively affect formation of disease phenotypes. We developed simple and broadly accessible technologies to detect these OnTEs, which will help the field to identify and remove erroneous cell lines from research projects, and thus lead to more faithful disease modelling in iPSC-based models.

(2) We are optimizing iPSC differentiation protocols to generate highly pure, homogeneous and well-characterized cultures of major disease-relevant human brain cell types, including cortical neurons, astrocytes, oligodendrocytes, microglia, endothelial cells, smooth muscle cells and pericytes. Based on these cells, we are developing 3D co-culture and tissue engineering technology of these brain cells, to generate self-organizing brain-like tissues with typical cell biological features.

(3) combining these two approaches we generate genetic models of neurodegenerative and neurovascular disease by introducing disease-causing mutations/risk SNPs etc. with our efficient CRISPR platform, to accelerate naturally occurring disease processes and promote pathology.

In my talk, I will present our recent progress in these research areas. We expect that our models will form the basis for studies elucidating novel, potentially human-specific pathomechanisms and provide a human framework for translational and screening approaches.

Subcellular molecular machinery of purified subtype-specific human cortical neuron growth cone
(poster #15)

Manuel Peter
Harvard Center for Brain Science, Department of Stem Cell and Regenerative Biology

During development, distinct areas of the brain and subtypes of neurons form highly specific connections to construct functional circuitry. Growth cones (GC), located at the axon terminal tips, must respond to substrate-bound and diffusible signals in a subtype- and context-specific fashion to construct functional cortical and subcortical connectivity. Recent studies strongly indicate that the subcellular localization of molecular machinery specific to GCs likely underlies the precise behavior of those GCs during circuit "wiring", and it is becoming increasingly clear that intracellular, local GC biology critically controls circuits formation, their appropriate synapse formation, and function.

Until recently, the molecular states of GCs during development were experimentally not accessible. Our laboratory has developed novel experimental and analytical approaches that enable high-throughput, high-depth transcriptomic, and proteomic investigation of purified GCs. We combine specific labeling, biophysical fractionation, and newly developed small particle sorting to purify GCs, and their parental somata from fluorescently labeled stage- and subtype-specific cortical projection neurons. The application of this quantitative "subcellular" RNA-proteome mapping" approach already identified hundreds of RNAs/proteins specifically enriched in GCs and virtually absent in their parental somata, in callosal projection neurons. (A. Poulopoulos, A.J. Murphy & J.D. Macklis, Nature 2019).

Due to the lack of material, human aspects of growth cone biology remain largely unstudied. Here, we use in vitro brain organoids, to model some elements of circuit development, during human brain development. We differentiated human pluripotent stem cells into region- specific brain organoids and fused them to recapitulate some aspects of cortical and subcortical connectivity. (Y. Xiang & IH. Park, Cell Stem Cell 2019; J. Andersen & S.P. Pasca, Cell 2020).

Fused organoids developed strong reciprocal axonal connections with growth cones at their axon terminals, enabling isolation and purification of fluorescently labeled subtype-specific human GCs. In parallel, retrograde tracing in fused brain organoids allows efficient isolation of parental somata, allowing us to directly investigate human GC molecular machinery, and their parental somata to better understand how human GCs control circuit formation in the human brain

Impact of translocator protein activation on Aβ-induced synaptotoxic effects - focus on learning and memory-related processes
(short talk session #1)

Arpit Kumar Pradhan
TUM Klinikum rechts der Isar

Accumulation of β-amyloid peptide is a characteristic pathophysiological feature of Alzheimer's (AD). Depression has been considered as a common antecedent of AD and may be an early manifestation of dementia before the cognitive decline becomes apparent. Pharmacologically targeting these overlapping cellular mechanisms would allow for a novel therapeutic strategy. The translocator protein (18 kDa) (TSPO) also known as peripheral benzodiazepine receptor controls the translocation of cholesterol from the outer to the inner mitochondrial membrane and is therefore essential in neurosteroidogenesis. XBD173 which has high selective affinity for TSPO exerts rapid anxiolytic effects and doesn't have any tolerance or withdrawal effects. Since TSPO activation promotes the synthesis of active neurosteroids, we hypothesized that the application of XBD173 restores the Aβ-induced deficits on LTP.

The different species of Aβ such as Aβ1-42, Aβ1-40, 3NTyr10-Aß, and AßpE3 antagonize LTP induction and exert potent synaptotoxicity. Application of XBD173 restores the Aß-induced deficits on LTP. Similarly incubation of hippocampal slices with Aβ1-42 results in a significant decrease in the total spine density as well as individual spine density which is bettered by the application of the TSPO ligand XBD173. Our current findings from the behavioural experiments suggest that chronic application of XBD173 alleviates the cognitive response in Alzheimer's modelled mice while the acute treatment with XBD 173 is not sufficient to improve cognitive performance. The difference in the performance of the tasks is based on the individual perceiving of the tasks. One of the interesting aspects from the amyloid plaques staining suggests that there is a decrease in the plaque load in the XBD treated animals which hints towards either a clearance mechanism of the plaques or a neuroprotection mechanism which prevents the formation of plaques at the first place.

TBD
(poster #16)

Juliana Rhee
Harvard Department of Molecular and Cellular Biology

Withdrawn.

What can we learn from a molecular atlas of cell types
(faculty lecture #6)

Joshua R. Sanes
Harvard Center for Brain Science

Classification of neurons, long viewed as a fairly boring enterprise, has emerged as a major bottleneck in analysis of neural circuits. High throughput single cell RNA-seq has provided a new way to improve the situation. We initially applied this method to mouse retina, showing that its five neuronal classes (photoreceptors, three groups of interneurons, and retinal ganglion cells) can be divided into 130 discrete types. We then applied the method to other species including human, macaque, zebrafish and chick. With the atlases in hand, we are now using them to gain insights into several issues that I will address, relating to development, disease, injury and disease.

The interplay between innate immunity and scar formation in response to brain injury (poster #17)

Veronika Schwarz
LMU, Biomedical Center, Department for Cell Biology, Neurogenesis and Regeneration

Withdrawn.

The circadian clock and G-protein-coupled receptor signaling: RGS16 and how it controls chronotype
(poster #18)

Tanja Schwarzmeier
LMU Institute of Medical Psychology

The circadian clock is a reaction and an adaptation to the 24h rhythm of the world. It gates different physiological functions from behaviour to the level of single cells. One possible measurable output is Chronotype, which describes the phase of entrainment of the individual to the 24h rhythm of the environment. G-protein-coupled receptors (GPCRs) are a class of receptors that play a major role in relaying signals from the outside world to the organism. They are involved in many different pathways and functions, but little is yet known of the interplay between GPCRs and the circadian clock.

RGS16 is a regulator of G-protein signaling which negatively regulates GPCR signaling by increasing the GTPase activity of G-proteins. Several studies have linked RGS16 with Chronotype: It has been shown as a top hit in GWAS studies looking and the genetics of Chronotype and has been shown to be critical for cAMP rhythmicity in the Suprachiasmatic Nucleus (SCN), the so-called central pacemaker of the brain and the body. The circadian clock as well as GPCRs are considered ubiquitous in the mammal body, so we hypothesize that the function of RGS16 in interacting with the clock is not restricted to the SCN, but is also important in non-SCN cells. Therefore, my work is focused on the influence of RGS16 on circadian properties such as freerunning period, temperature compensation and phase of entrainment, as well as the influence of cycling RGS16 levels on cAMP levels, which in turn feed back to the clock. In my experiments, a knockdown of RGS16 in U2OS cells lead to an alteration in the circadian properties, and RGS16 levels impacted the cAMP response after GPCR stimulation. Therefore, RGS16 seems to have an impact on the circadian clock in peripheral cells in addition to the previously reported SCN.

Weighted multimodal spatial representation in the gerbil hippocampus
(poster #19)

Andrey Sobolev
Department Biology II, Division of Neurobiology, Bernstein Center for Computational Neuroscience

Estimation of an actual location in space involves simultaneous assessment of information coming from different sensory systems. Multiple behavior studies in humans and animals have demonstrated that independent estimations given by different sensory modalities are combined in an optimal manner. Moreover, while integration of coherent estimations increases response precision, it is reasonable to abandon a less reliable estimation if it is highly conflicting with others. The way it is implemented on the level of neuronal ensembles is still not fully understood. We asked if position estimation performed by the hippocampal place cells follows these principles. Using the freely-moving 3D virtual reality for rodents we introduced a conflict between the visual and the physical boundary-defined reference frames involved in position estimation while recording the hippocampal activity. On the population level, hippocampal neurons showed mixed representation of both reference frames, balanced between visual and physical environmental geometry depending on the proximity to the boundary and saliency of the visual stimulus. On the single neuron level, most of the place cells were integrating sensory inputs and represented position using a weighted combination of sensory estimations, consistent with optimal position encoding. The activity of place fields in small / large conflicts followed the integration / abandonment of sensory estimations predicted by behavior studies for other sensory systems. Integration of the conflicting sensory information led to recalibration of the hippocampal map, producing a new, morphed spatial representation, indicating a continuous plastic bi-directional coupling of hippocampal-entorhinal networks. Ultimately, the detected individual variabilities between animals show that the strengths of the integrated multisensory inputs are not only proportional to the input certainty, but also dependent on the individual sensory preferences.

Circuit-wide functional organization of a natural multistep behavior – *C. elegans* mating (poster #20)

Vadislav Susoy
Harvard Department of Physics & Center for Brain Science

Natural goal-directed behaviors often involve complex sequences of many stimulus-triggered behavioral components. Understanding how brain circuits organize such multistep behaviors requires mapping the interactions between an animal, its environment, and its nervous system. We use continuous brain-wide neuronal imaging to study the full performance of mating by the C. elegans male. Posterior brain of the male C. elegans is fully mapped and is responsible for every sensory, motor, and decision-making step during mating behavior. With our imaging technology, we are able to record the activity of nearly every neuron in the brain of freely-moving male C. elegans from beginning to end of mating. With these recordings, we are not only able to crack numerous microcircuits and computations that are ethnologically relevant for mating, but also to probe the brain-wide organization of the entire sensorimotor behavior. We show that as each mating unfolds in its own sequence of component behaviors, the brain operates similarly between instances of each component, but distinctly between different components. When the full sensory and behavioral context is taken into account, unique roles emerge for virtually every neuron. Functional correlations between neurons in the brain are not fixed but change with behavioral dynamics. Because one wiring diagram supports many patterns of functional correlations, the relationship between the connectome and brain-wide activity is not one-to-one. From the contribution of individual neurons to circuits, our study shows how diverse brain-wide dynamics emerge from the complex interactions in a natural context.

Dentate gyrus-CA3 feed-forward inhibition dictates evolution of hippocampal-cortical ensembles underlying memory consolidation
(short talk session #1)

Hannah Twarkowski
Harvard Brain Science Initiative, Center for Regenerative Medicine

Considerable body of work suggests that memories are re-organized in hippocampal-cortical networks over time as they are transformed from a recent to remote state, a process known as memory consolidation. Here, we investigate the role of feed-forward inhibition (FFI) in the dentate gyrus-CA3 circuit in dictating the evolution of hippocampal-cortical ensembles underlying memory consolidation. Using viral genetics to enhance dentate granule cell recruitment of parvalbumin interneurons in CA3, longitudinal in vivo calcium imaging in hippocampal CA1 and anterior cingulate cortex and a contextual fear memory task, we demonstrate that FFI facilitates the formation and maintenance of context-specific neuronal ensembles in CA1. Precise CA1 ensembles, in turn, promoted context specificity of neuronal ensembles in the anterior cingulate cortex at remote timepoints. These findings begin to illuminate how FFI in DG-CA3 maybe harnessed to improve memory consolidation and suggests a memory indexing role for hippocampal CA1 in stabilization of cortical representations.

Balancing separate dopamine-striatum systems for behavioral choice (faculty lecture #4)

Mitsuko Watabe-Uchida
Harvard Center for Brain Science

Animals adaptively learn to repeat rewarding actions and refrain from dangerous actions. Although our understanding of reward learning and threat learning has advanced tremendously in recent years, these are mostly studied independently of one another. However, in the natural world, it is critical to consider both potential reward and threat. What is the brain mechanism for balancing reward and threat? While fear conditioning has been by far the best studied paradigm for threat learning, this fails to take into account the tradeoffs between reward and threat that animals encounter in their natural environment. Further, although most studies have used painful stimuli such as electric shocks for threat learning, it is critical to predict potential threat without experiencing serious outcomes such as pain from injury and death. In this talk, I will introduce our series of studies using different behavioral paradigms where mice must navigate potential threats to obtain water rewards. I will focus on the tail of the striatum (TS, or sensory striatum), which we found receive input from a unique subpopulation of dopamine neurons that encodes threat (but not reward) prediction errors. Thus, there are at least two major evaluation axes by dopamine, one is along value and the other is along threat. This marks a departure from classical reinforcement learning models, which treat reward and punishment as a single dimension. Finally, from our preliminary data, I will share our working hypothesis that animals integrate reward and threat using multi-layered, competing cortico-striatal loops in the brain.

Neurochemical abnormalities in adolescent soccer players
(poster #21)

Tim L. T. Wiegand[1,2]; Elena M. Bonke[1,2,3]; Euky Yhang[4]; Malo Gaubert[1]; Johanna Seitz-Holland[1,2]; David Kaufmann[1,2,5]; Stian B. Sandmo[6,7]; Jolien Gooijers[8]; Alberto De Luca[9]; Alexander Leemans[9]; Stephan P. Swinnen[8]; Florian Heinen[10]; Yorghos Tripodis[4,11]; Ofer Pasternak[2,12]; Alexander P. Lin[2,12,13]; Inga K. Koerte[1,2,14]

[1]cBRAIN, Department of Child and Adolescent Psychiatry, Psychosomatic and Psychotherapy, Ludwig-Maximilians-Universität, Munich, Germany;
[2]Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;
[3]Graduate School of Systemic Neurosciences, Ludwig-Maximilians-Universität, Munich, Germany;
[4]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA;
[5]Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Augsburg, Augsburg, Germany;
[6]Oslo Sports Trauma Research Center, Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway;
[7]Department of Neurology, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway;
[8]Movement Control and Neuroplasticity Research Group, Department of Movement Sciences, KU Leuven, Leuven (3000), Belgium;
[9]Image Sciences Institute, University Medical Center Utrecht, Utrecht, the Netherlands;
[10]Department of Pediatric Neurology and Developmental Medicine, Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany;
[11]Alzheimer's Disease and CTE Centers, Boston University School of Medicine, Boston, MA, USA;
[12]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;
[13]Center for Clinical Spectroscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;
[14]Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

Soccer is played by more than 265 million people worldwide. In soccer, heading leads to repetitive head impacts that usually do not cause acute symptoms but, cumulatively, may have adverse effects on the maturing brain. First studies using magnetic resonance spectroscopy have found neurochemical alterations indicative of inflammation and neural damage in former professional soccer players around the age of 50 years. However, it is unclear if alterations are also already present in adolescent soccer players.

If you want to find out more on this yet unpublished data, please visit my poster presentation.

Anatomical and molecular profiling of adult mammalian descending projection neurons (poster #22)

Carla Winter
Harvard Medical School, Department of Neurology

TBD

What you see is what IT gets: responses in primate visual cortex during natural viewing (short talk session #1)

Will Xiao
Harvard Medical School, Childrens Hospital

How does the brain support our ability to see? Studies of primate vision have typically focused on controlled viewing conditions exemplified by the rapid serial visual presentation (RSVP) task, where the subject must hold fixation while images are quickly flashed on and off in randomized order. In contrast, during natural viewing, eyes move frequently, guided by subject-initiated saccades, resulting in a sequence of related sensory input. Thus, natural viewing departs from traditional assumptions of independent and unpredictable visual inputs, leaving it an open question how visual neurons respond in real life.

We recorded responses of interior temporal (IT) cortex neurons in macaque monkeys freely viewing natural images. The IT cortex is a high-level visual area essential for visual object recognition. We first examined responses of face-selective neurons and found that face neurons responded according to whether individual fixations were near a face, meticulously distinguishing single fixations. Second, we considered repeated fixations on very close-by locations, termed 'return fixations.' Responses were more similar during return fixations, and again distinguished each individual fixation. Third, computation models could partially explain neuronal responses from an image crop centered on each fixation.

Nevertheless, IT neurons were not passive filters of the instantaneous input, but rather anticipated the future. The content (face or non face) of an upcoming fixation could be decoded from responses before fixation onset, even after controlling for receptive field size and comparing to matched retinal image responses during RSVP.
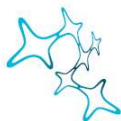
These results shed light on how the IT cortex does (and does not) contribute to our daily visual percept: a stable world despite frequent saccades.

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

For technical enquiries, please contact: Sven Schörnich, IT Administrator, LMU, Department of
Biology, Division of Neurobiology
schoernich@biologie.uni-muenchen.de