LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

HARVARD UNIVERSITY

LMU - Harvard Young Scientists' Forum

July 23 – 26, 2018

Center for Brain Science

Harvard University, Cambridge, MA

CENTER FOR BRAIN SCIENCE

2018 YSF LMU-Harvard Schedule

July 23 – 26, 2018

All talks will be held in the Biolabs Lecture Hall, 16 Divinity Ave, Room 1080, Cambridge, MA

Monday 23 July

8:45AM Continental breakfast at Biolabs central lobby, near room 1080
9:15AM Opening Remarks
9:30AM Young Scientist Session 1 – *Computation and Cognition I*
Session Chair: Kenneth Blum
YS1: Daniel Berger, Lichtman lab
YS2: Johannes Bill, Drugowitsch/Gershman labs
YS3: Martin Stemmler, Herz lab
11:00AM Break
11:30AM Faculty Seminar 1: Sam Gershman (Harvard University)
12:30PM Lunch (Boxed lunch pick up near BL1080. Seating at Northwest Building, 2nd Flr Landing)
2:00PM Young Scientist Session 2 – *Computation and Cognition II*
Session Chair: Antje Grosche
YS4: Nicholas Del Grosso, Sirota lab
YS5: Ariane Boehm, Kadow lab
YS6: Till Hartmann, Born lab
3:30PM Break
4:00PM Faculty Seminar 2: Laura Busse (LMU)
6:00PM Blue Ribbon BBQ in Northwest Courtyard (Rain location: Northwest Café)

Tuesday 24 July

9:00AM Continental breakfast at Biolabs central lobby, near room 1080
9:30AM Faculty Seminar 3: Joshua Sanes (Harvard University)
10:30AM Break
11:00AM Young Scientist Session 3 – *Visual Circuits: development, activity and modulation*
Session Chair: Venkatesh Murthy
YS7: Antje Grosche, LMU, short faculty presentation
YS8: Martin Biel, LMU, short faculty presentation
YS9: Irene Whitney, Sanes lab
YS10: Yirong Peng, Sanes lab
1:00PM Lunch (Boxed lunch pick up near BL1080. Seating at Northwest Building, 2nd Flr Landing)
2:30PM Faculty Seminar 4: Benedikt Grothe (LMU)
3:45PM Poster Session: Northwest Building, 2nd Flr Landing
6:00PM Dinner on your own in Cambridge (with Harvard hosts)

Tuesday Poster Presenters:

Rainer Boegle
Gregory Born
Abhinov Grama
Aleksander Janjic
Robert Johnson
Valerie Kirsch
Nuné Martiros
Michael Pecka
Martina Pigoni
Katrin Vogt
Jenelle Wallace
Jiarui Wang
Xueying (Snow) Wang

Wednesday 25 July

9:30AM	Continental breakfast at Biolabs central lobby, near room 1080
10:00AM	Faculty Seminar 5: Dragana Rogulja (Harvard University)
11:00AM	Break
11:15AM	Young Scientist Session 4 – *From Cells to Systems Control* *Session Chair:* Oliver Behrend YS11: Armin Bahl, Engert lab YS12: Christophe Dupré, Engert lab YS13: Steffen Wolff, Ölveczky lab
12:45PM	Lunch (Boxed lunch pick up near BL1080. Seating at Northwest Building, 2nd Flr Landing)
2:00PM	Young Scientist Session 5 – *Systems Connectivity and Rhythms* *Session Chair:* Martin Biel YS14: Valerie Kirsch, Dieterich lab YS15: Franziska Brüning, Robles/Mann labs YS16: Giulia Zerbini, Merrow lab
3:30PM	Break
4:00PM	Faculty Seminar 6: Martha Merrow (LMU)
5:15PM	Closing Remarks
5:30PM	Dinner on your own in Cambridge (with Harvard hosts)

Thursday 26 July – Optional Excursion Day

Provided: towel, sunscreen. Please be prepared for cooler weather while on the ocean and warmer weather at the beach. Recommend a sunhat and sunglasses. You will be able to leave your things on the bus during each stop.

8:30AM	Continental breakfast at Northwest Building, outside room 140
9:00AM	Depart via bus from the Northwest Building, 52 Oxford St. Meet in lobby on Everett St.
10:15AM	Wingaersheek Beach, Gloucester, MA
12:30PM	Depart via bus
1:00PM	Arrive at 7 Seas Whale Watch: 63 Rogers St, Gloucester
6:00PM	Approximate. Depart via bus
6:30PM	Woodman's Restaurant Clambake and Lobster Dinner, 121 Main St, Essex, MA
9:30PM	Depart Woodman's via bus
10:15PM	Arrive at Northwest Building

LMU - Harvard Young Scientists' Forum

Abstracts

Armin **Bahl**[1] & Florian Engert[1]

[1]Department of Molecular and Cellular Biology, Harvard University

Neuronal mechanisms of evidence accumulation and perceptual decision making in the larval zebrafish

Sensory evidence accumulation is a crucial part of any perceptual decision making process. Even though behavioral performance in psychophysical experiments can be well explained by abstract mathematical models of integration and thresholding, it remains elusive how such mechanisms are implemented on the level of neuronal networks. Comprehensive understanding of these underlying processes requires explorations of brain-wide circuit dynamics during individual trials. This is difficult to achieve in mammals where analysis is usually restricted to local circuits, allowing observations of only a very small fraction of the overall networks at any given time. Here we approach this problem by adapting a classical assay based on noisy random dot motion kinematograms, usually used in primate studies, to larval zebrafish. We characterized the delay and accuracy of individual swimming decisions and found that larvae can reliably integrate and remember such motion stimuli over many seconds and that their behavior follows precisely the classical diffusion-to-bound model. We then performed unbiased two-photon functional imaging experiments of the whole brain, identifying key circuit elements involved in the integration process. In particular, we found several neuronal clusters in the anterior hindbrain. One cluster represented the integrated sensory evidence, reminiscent of the diffusive variable in the model, while a second cluster represented sensory uncertainty. We propose that these two units together implement, in a biophysically plausible manner, the thresholding operation such that a third cluster, a motor command unit, is only activated when integrated evidence exceeds uncertainty. Analyzing these structures on the level of individual cells and trials allowed us to build a realistic neural network model, which not only quantitatively reproduced our experimental imaging data, but also the behavior of freely swimming fish.

Daniel R. **Berger**[1],

[1]Jeff Lichtman Lab, Harvard University

Microglia-Neuron Interactions in Neocortex

Serial section electron microscopy provides cellular details on a very fine scale and can be combined with light microscopy to identify cell types by using fluorescent markers (correlated light and electron microscopy, CLEM). My colleagues and I have used this technique to study neurons and glial cells of different types in the brain, as well as their interactions.

Microglia are glial cells resident in the mammalian brain which are thought to have mainly functions equivalent to macrophages, scanning the brain tissue for injury and infections. Recently they have also been implied in synaptic pruning and apoptosis during development, taking up debris of pruned synapses and decaying cells.

In our large-scale 3D electron microscopy studies of mouse cortex we discovered that microglia also interact with neuronal dendrites in the healthy adult brain, forming many tip-to-tip touches with dendritic filopodia. This finding has recently also been reported by other groups, and may point to a role of microglia in spine formation and synaptic plasticity.

Martin **Biel**[1, 2, 3]

[1]LMU, Department of Pharmacy, Center for Drug Research
[2]Center for Integrated Protein Science Munich
[3]LMU, Graduate School of Systemic Neurosciences

Gene therapy of human CNGA3-linked achromatopsia

Achromatopsia is a clinically well-defined inherited retinal disorder characterized by day blindness, poor visual acuity, photophobia, nystagmus, and lack the ability to discriminate colours. About 95 % of the patients carry loss-of-functions mutations in either the CNGA3 or the CNGB3 subunit of the cone photoreceptor cyclic nucleotide-gated cation (CNG) channel. Previously, we have established a murine model for CNGA3-linked achromatopsia. Importantly, in this preclinical model we were able to restore impaired cone-mediated vision using AAV (adeno-associated virus) -mediated gene supplementation. Based on this work we have designed AAV8.CNGA3, a recombinant AAV vector for gene supplementation therapy of human CNGA3-linked achromatopsia (ACHM2). The vector expresses human CNGA3 under control of a short human arrestin 3 promoter and was packaged with AAV8 capsid. A first-in-man dose escalation clinical trial with nine ACHM2 patients (NCT02610582) was conducted focusing on safety and efficacy of a single subretinal injection of AAV8.CNGA3. In my seminar, I will summarize major results of the study.

Johannes **Bill**[1], Sam Gershman[1], Jan Drugowitsch[1]

[1]Harvard University

Bayesian approaches to perception of structured motion

In everyday environments, the perceived motion of objects is highly structured. For instance, while driving a car, most of the visual scene will jointly move in the opposite direction; an antelope in a herd can approximately be located from the herd's movement even when it is temporarily occluded by a bush; on a smaller scale, body parts are connected by joints, thereby limiting their degrees of freedom. For humans and animals, incorporating knowledge of motion structure is vital for forming meaningful percepts -- especially in the presence of unreliable or incomplete sensory information.

In my talk, I will discuss potential cognitive and neural mechanisms that could recruit motion structure for understanding complex scenes.

Using Multiple-Object-Tracking tasks as an example, I will identify the computational requirements for combining percepts of individual moving objects with knowledge of relations among them. Particularly, I will introduce a simple, yet flexible representation of structured motion that accommodates a variety of organizational features in natural scenes, such as motion-hierarchies, clustered motion or independent movement. This representation promotes Bayesian solutions to tracking multiple objects in the face of uncertainty. At the end of my talk, I will speculate on how structured motion-augmented perception could be implemented by recurrent spiking neural networks.

Ariane **Boehm**[1, 2]

[1]TUM School of Life Sciences Weihenstephan, Neural Circuits and Metabolism
[2]LMU, Graduate School of Systemic Neurosciences

Reproductive state-dependent importance of transient sensory modulation in long-term behavior and decision making

Internal states (e.g. hunger or reproductive state) influence chemosensory decision making behavior, which usually shows itself by attraction or aversion towards a certain odor. Transient sensory modulation can focus an animal's attention to relevant sensory stimuli that facilitate remembering relevant vs. irrelevant stimuli. We are investigating the role of such a neuromodulation and the formation of memory with respect to reproductive state in the female fruit fly,Drosophila melanogaster.

Previous work has shown that mating changes the sensitivity of chemosensory neurons with the help of specific neuromodulators. This short-term neuromodulation leads to a long-term change in female behavior. Drosophila's genetic toolset allows us to test the hypothesis that this transient sensory enhancement facilitates the formation of a long-lasting memory.

Using a quantitative olfactory choice assay, we silenced different parts of the fly's memory center (i.e. the mushroom body). Screening 59 lines revealed a possible neuronal pathway and its modulatory switch between virgin and mated state. This data suggests that dopaminergic neurons, which are innervating the mushroom body, control virgin vs. mated female behavior by receiving differential sensory inputs before and after mating, respectively.

We suggest that transient sensory modulation induced by mating changes the synaptic weights in the mushroom body for a prolonged period. A certain experience happening throughout mating (e.g. courtship) is most likely part of this behavioral change. Hence, according to the reproductive state of an animal, a decision for or against a chemosensory cue can be adapted by neuronal modulation.

Sara B. Noya[1]*, Franziska **Brüning**[2, 3]*, Jan D. Rudolph[4], Jürgen Cox[4], Steven A. Brown[1], Matthias Mann[2#] and Maria S. Robles[3#]

[1]UZH, Institute of Pharmacology and Toxicology, Zurich
[2]MPI of Biochemistry, Department of Proteomics and Signal Transduction
[3]LMU, Institute of Medical Psychology
[4]MPI of Biochemistry
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Rest-activity cycles drive dynamics of phosphorylation in cortical synapses

The circadian clock drives daily changes of physiology, including sleep-wake cycles, by regulating gene expression, protein abundance and function. Although phosphorylation dynamics time cellular processes in peripheral organs, little is known about how phosphorylation cycles modulate brain and synaptic activity. Here we applied quantitative phosphoproteomics to mouse forebrain synaptoneurosomes isolated through the day and quantified with high accuracy more than 7,900 phosphopeptides. Nearly 30% of the phosphopeptides from almost 50% of the synaptosome proteins, including numerous kinases, displayed large amplitude daily changes of abundance, with main peaks at rest-activity-rest transitions. Our data suggest global temporal control of synaptic function via phosphorylation, including synaptic transmission, cytoskeleton reorganization and excitatory/inhibitory balance. Astonishingly, sleep deprivation abolishes 96% of all phosphorylation cycles in the mouse synaptosomes, indicating that rest-activity cycles rather than the circadian clock are the main driver of phosphorylation-dependent protein function at synapses.

Laura **Busse**[1, 2]

[1]LMU, Department of Biology II, Division of Neurobiology
[2]LMU, Graduate School of Systemic Neurosciences

Mouse dLGN receives input from a diverse population of retinal ganglion cells with limited functional convergence

In the mouse, the parallel output of more than 30 functional types of retinal ganglion cells (RGCs) serves as the basis for all further visual processing. 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. Here, we functionally characterized responses of retrogradely labelled dLGN-projecting RGCs and 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. Using a linear model to assess functional connectivity between RGC types and dLGN neurons, we found that the responses of dLGN neurons could be predicted as a linear combination of inputs from on average five RGC types, but only two of those had thestrongest functional impact. Thus, mouse dLGN receives input from a diverse population of RGCs with limited functional convergence.

Nicholas **Del Grosso**[1, 2]

[1]LMU, Department Biology II, Division of Neurobiology
[2]LMU, Graduate School of Systemic Neurosciences

Testing CAVE virtual reality systems for use in animal behavior research

Virtual reality (VR) experimental behavior setups enable cognitive neuroscientists to study the integration of visual depth cues and self-motion cues into a single percept of three-dimensional space. Rodents can navigate a virtual environment when locomotion is simulated by running on a spherical treadmill; however, two-dimensional navigation is markedly reduced when their ability to turn freely is restricted. Besides making movement more difficult, this reduced exploration may also stem from sensory conflict between the visual and vestibular systems, as head translation produces no change in the visual perspective of the virtual environment. In humans, vestibulo-visual conflict reduces the subject's immersion in the virtual environment and produces sensations of nausea. Updating the virtual environment via the subject's head movements solves both the vestibulo-visual and sensorimotor conflict issues, however, and last year, we showed that these freely-moving rats demonstrate immersion in virtual environments by displaying height aversion to virtual cliffs, exploration preference of virtual objects, and spontaneously modify their locomotion trajectories near virtual walls. These experiments help bridge the classic behavior and virtual reality literature by showing that rats display similar behaviors to virtual environment features without training, opening up opportunities for more research using virtual environments for a wide range of species.

Christophe **Dupre**[1], Florian Engert[1], and Jeff Lichtman[1]

[1]Department of Molecular and Cellular Biology, Harvard University

Scalability in a Simple Nervous System

Closely related species can vary in size by orders of magnitude, without exhibiting major differences in behavior. For instance, a mouse can perform the same tasks as pretty much any other rodent, even though its brain is about a hundred times smaller than its South American cousin the capybara. How can a nervous system change in size while keeping its functions intact?

To answer this question, one needs to compare the brain of related species at a highly detailed level. Unfortunately, the complexity of the rodent brain makes this task very difficult and as an alternative I propose to use the freshwater invertebrate Hydra because its nervous system is made of a simple nerve net whose size can change up to an order of magnitude depending on controllable environmental parameters.

I will first analyze the structure of the Hydra nervous system to determine whether it is made of building blocks that can be added and removed as the animal changes in size. I will then compare the structure of two specimens of different size to determine whether any adaptation occurred. By uncovering the mechanisms underlying brain scalability this work will help understand fundamental principles of brain function.

Samuel **Gershman**[1]

[1]Department of Psychology and Center for Brain Science, Harvard University

Believing in Dopamine

The temporal difference reinforcement learning model has successfully accounted for many aspects of phasic dopamine activity, but a number of major discrepancies have been discovered. Some of these discrepancies can be traced back to the choice of stimulus representation used by early models. In the real world, stimuli often provide ambiguous information about the underlying state, in which case the optimal representation is a conditional distribution over states given the observed stimuli --- the belief state. I will present several experimental studies and computational analyses of the dopamine system that provide support for this model. These findings demonstrate the importance of representational assumptions for understanding learning algorithms in the brain.

Benedikt **Grothe**[1,2]

[1]LMU, Department Biology II, Division of Neurobiology
[2]LMU, Graduate School of Systemic Neurosciences

Dynamics and adaptation of the auditory brainstem

Antje **Grosche**[1, 2]

[1]LMU, Department of Physiological Genomics
[2]LMU, Graduate School of Systemic Neurosciences

The glial element - how Müller cells respond to changes in the retinal network

Müller cells are the dominant macroglial cells in all vertebrate retinae. They have a characteristic radial morphology spanning the entire retina. Myriads of fine processes enable their intimate contact with virtually every retinal neuron, blood vessels, the vitreous, and the subretinal space. Based on this central morphological position, Müller cells fulfill a plethora of supportive and modulatory functions. Since more than decade my research aimed to shed light on their complex functions including the maintenance of the retinal ion and volume homeostasis, their contribution to neurotransmission or their fascinating function as living optical fibers. Currently, our research focusses on investigations of changes in the intimate cross talk between Müller glia and retinal neurons in the healthy and diseased retina. To this end, we developed tools to specifically analyse the transcriptome and proteome of Müller cells in comparison to retinal microglia, vascular cells and neurons. With this tool at hand, we collected comprehensive data sets of Müller cell expression profiles from murine mouse models of retinal degeneration (e.g. diabetic retinopathy) and from human donor retina, now seeking for candidate genes and mechanisms that coin Müller cell functional phenotypes that impact on neuronal function under varying conditions. We aim to identify key molecular regulators of Müller cell function especially in the degenerating retina. Currently, we validate putative candidate gens, such as the glucocorticoid receptor Nr3c1, for their potential to modify the functional phenotype of Müller cells.

Given that neuronal function is highly dependent on Müller cell support which however is partially diminished in gliotic Müller cells, we consider the restoration of correct Müller cell function in the diseased retina as promising therapeutic approach especially in multifactorial retinal diseases such as diabetic retinopathy or age-related macular degeneration.

Till S. **Hartmann**[1], Sruti Raja[2], Stephen G. Lomber[3], Richard T. Born[2]

[1] Postdoc, Department of Neurobiology, Harvard Medical School
[2] Department of Neurobiology, Harvard Medical School
[3] Department of Physiology and Pharmacology, The University of Western Ontario

Cortical feedback strongly influences brain rhythms in primary visual cortex

Gamma-band oscillations (30-80 Hz) in the local field potential (LFP) are a fascinating phenomenon whose functional interpretation is controversial. While some investigators have made the case for a computational role in sensory coding (Buzsáki and Chrobak, 1995; Fries, 2009), others have argued that they are simply an epiphenomenon produced by local interactions between excitation and inhibition (Ray and Maunsell, 2015). Several groups have adduced evidence that gamma oscillations are a unique signature of feedforward processing, whereas slower rhythms, like alpha (5-15 Hz), are a marker of feedback signals (van Kerkoerle *et al.*, 2014; Bastos *et al.*, 2015). Regardless of their function, gamma rhythms are believed to be generated locally through strong excitation-inhibition interactions, even though they may become synchronized across relatively large regions of cortex (Tiesinga and Sejnowski, 2009; Buzsáki and Wang, 2012). We examined the influence of cortico-cortical feedback on the LFP and on multi-unit activity (MUA) by reversibly inactivating areas V2 and V3 while recording visually evoked activity in primary visual cortex (V1) of alert macaque monkeys. We were able to produce profound effects on the LFP and rhythmicity of the MUA recorded in V1. During control conditions, the MUA and the LFP exhibited strong gamma oscillations; these were completely abolished during feedback inactivation, even though spike rates were not significantly changed. The results indicate that gamma is not a simple signature of feed forward processing. Our experiments reveal a strong influence of cortico-cortical feedback on rhythms previously believed to be of purely local origin.

Valerie **Kirsch**[1, 2, 3], Rainer Boegle[2], Thomas Brandt[2, 3, 4], Marianne Dieterich[1, 2, 3, 5]

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

Connectivity Mapping in the Human Vestibular System

Introduction: The vestibular system differs from other sensory systems (Goldberg et al., 2012). Lacking a primary cortex in the narrower sense, current evidence points towards a multisensory bilateral temporo-parietal-insular vestibular network with a handedness-dependent hemispheric lateralization of its core region (Brandt and Dieterich, 1999; Guldin and Grüsser, 1998; Lopez and Blanke, 2011). This widespread cortical allocation of its processing areas is mirrored by its dependency on multisensory inputs (Angelaki and Cullen, 2008; Carriot et al., 2015) that converge at multiple levels from the brainstem to the cortex whilst serving sensorimotor reflexes, control up to cognitive functions (Chen et al., 2011a, 2011b; Dieterich and Brandt, 2015). However, much poorly understood, especially in humans. This project aimed to map in-vivo structural and functional connectivity patterns in the human vestibular system using a quantifiable non-invasive multimodal imaging approach.

Methods: Diffusion tensor (DTI) structural and resting-state functional (fMRI) connectivity magnetic resonance imaging data of 60 healthy volunteers, 30 right-handed (RH; 17 females; aged 20-67 years, mean age 26,7 ± 8,3 years) and 30 age- and gender matched left-handed (LH; 14 females; aged 20-65 years, mean age 26,1 ± 8,6 years) was used (i) to investigate interconnections of the bilateral central vestibular network from human brainstem to cortex (Kirsch et al., 2016), (ii) to quantify the found thalamus-dependent vestibular brainstem pathways (Dieterich et al., 2017) and (iii) to reveal handedness-dependent functional organizational patterns within the bilateral vestibular cortical network (Kirsch et al., 2018a, 2018b). The data was analyzed with the FMRIB's Diffusion Toolbox and MELODIC as part of the FSL package (Oxford, UK) and in-house scripts written in MATLAB (Natick, MA, USA). Used ROIs included vestibular reference coordinates of two meta-analyses of vestibular neuroimaging experiments attempting to pinpoint the vestibular cortex (Baier et al., 2016; Lopez et al., 2012; Zu Eulenburg et al., 2012).

Results: In vivo investigation of vestibular connectivity by means of combined structural and functional connectivity mapping was found to be congruent (Kirsch et al., 2016). Crossing and non-crossing vestibular brainstem fibers provide a rope ladder system for the central vestibular network between the vestibular nuclei and the vestibular cortical core region, the parieto-insular vestibular cortex (PIVC) at four levels: three in the brainstem and one in the cortex (Dieterich et al., 2017; Kirsch et al., 2016). Vestibular pathways project through both the posterolateral and the paramedian thalamus (Baier et al., 2016; Dieterich et al., 2017; Kirsch et al., 2016). A part of the ipsilateral projections directly reach the inferior part of the insula, thus bypassing the thalamic relay station (Kirsch et al., 2016; Kirsch et al., 2018a). There is a dominance of the right vestibular meso-diencephalic circuitry in right-handers that builds up from crossing to crossing that corresponds to the right-hemispheric lateralization of the vestibular cortical network (Dieterich et al., 2017). In addition, non-binary functional parcellation of the vestibular cortical network revealed not only a handedness-dependent lateralized central region concentrated in the right

hemisphere in right-handers and left hemisphere in left-handers, but also surrounding inter-hemisphere symmetric multisensory vestibular areas that seem to be functionally influenced by their neighboring sensory systems (e.g., temporo- parietal intersection by the visual system) (Kirsch et al., 2018b).

Discussion: The “otherness” of the vestibular system seems manifold and is therefore not easy to pinpoint at first sight. The reason may be that the nature of the vestibular system is indeed manifold or multimodal or “non-binary” in many respects when considering the multisensory nature of stimuli (Angelaki and Cullen, 2008; Carriot et al., 2015; Goldberg et al., 2012) and their bilateral (Dieterich and Brandt, 2015), multi-level (Kirsch et al., 2016), hierarchical (Chen et al., 2010) computation that converge (Carriot et al., 2013; Chen et al., 2011a) not in a vestibular primary cortex but in multiple spatially distributed (Brandt and Dieterich, 1999; Guldin et al., 1992; Lopez and Blanke, 2011) and spatially tuned (Chen et al., 2011b; Kirsch et al., 2018a, 2018b) cortical areas. Within this vestibular cortical network, one may speculate that the separation of a symmetrically from an asymmetrically organized vestibular system reflects a phylogenetic evolution of various multisensory vestibular functions (Brandt and Dieterich, 2018, 2015). A symmetrically organized phylogenetically “older” system seems to have been further developed by an additional asymmetric lateralized “younger” system chiefly localized in the parieto-insular region.

Supported by the Graduate School of Systemic Neuroscience (GSN^{LMU}, DFG), the German Foundation for Neurology (Deutsche Stiftung Neurologie, DSN), the Hertie Foundation and the BMBF (German Center for Vertigo and Balance Disorders-IFB^{LMU}).

Martha **Merrow**[1, 2], Bala Koritala[4], Maria Olmedo[1], Mirjam Geibel[1], Franz-Ulrich Hartl[3], Prasad Kasturi[3], Matthias Mann[3] and Charo Robles[1]

[1]LMU, Institute of Medical Psychology
[2]LMU, Graduate School of Systemic Neurosciences
[3]MPI of Biochemistry, Department Cellular Biochemistry
[4]Ruthgers University, Philadelphia

Zeitgebers of the circadian clock alter the progress of protein aggregation

The proteostasis network is thought to be central to neurodegenerative pathologies, which are characterised by a variety of protein aggregation states. Genetic screens have identified (proteostatic) suppressors of aggregation, some of which are regulated by the circadian clock and its zeitgebers. Indeed, higher amplitude zeitgeber cycles, to which a circadian clock would synchronise more robustly, led to improved outcomes in both animal experiments and dementia patients. We hypothesised that zeitgeber cycles would have an impact on the process of protein aggregation through the regulation of suppressors. In a *C. elegans* model of Polyglutamine (PolyQ) Disease, animals held in constant conditions were compared with those in 24h temperature cycles. Animals in the cycling environment show an increased lifespan, an overall increase in chaperone expression, and a decrease in aggregation. Proteomic analysis of the aggregates showed that their composition was altered by the structured temporal environment. This work demonstrates the principle that zeitgeber cycles, as typically used by circadian clocks for their entrainment, can be manipulated to modulate protein aggregation disease progression in a model system. Our results may explain improvement in cognition following two years of daily bright light cycles versus dim light cycle conditions in elderly patients with cognitive impairment.

Yi-rong **Peng**[1], Karthik Shekhar[2], Wenjun Yan[1], Dustin Hermann[1], Aviv Regev[2,4], Michael TH Do[3], Joshua R Sanes[1]

[1]Center for Brain Science and Department of Molecular Biology, Harvard University, Cambridge MA
[2]Broad Institute of Harvard and MIT, Cambridge MA
[3]F.M. Kirby Neurobiology Center, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115
[4]HHMI

Molecular specification of cells in the primate fovea and peripheral retina

The retina, like other parts of the central nervous system, uses complex neuronal networks to perform sophisticated computations. Its genetic accessibility has made the mouse retina a valuable model for analyzing the structure and function of neural circuits. As a model for primate vision, however, it suffers from a severe drawback. High acuity vision in primates is mediated largely by a specialized, central region of the retina called the fovea. Although the fovea comprises <1% of the retina, loss of foveal function leads to blindness. However, among mammals, only primates have a fovea. Although the same cell classes (horizontal, bipolar, amacrine, and retinal ganglion cells [RGCs], photoreceptors, and Müller glia) are found in fovea and peripheral retina, structural and functional differences abound. For example, cones and rods are the dominant photoreceptors in the fovea and periphery, respectively; and the ratio of photoreceptors to RGCs is many-fold higher in periphery than fovea. Yet, little is known about genes expressed by foveal cell types, and few markers of specific types have been identified. Here, as a step toward generating a primate retinal cell atlas, we used a high-throughput single-cell RNA sequencing (scRNAseq) platform (10X Genomics) to profile 77,368 foveal and 56,264 peripheral cells from the retina of the macaque monkey, macaca fascicularis. Bioinformatic analysis of the data allowed us to identify ~70 foveal and ~80 peripheral cell types. We used in situ hybridization and immunohistochemistry to validate selectively expressed genes, and combined molecular with biolistic or viral labeling to characterize morphological features of cell types defined molecularly. We not only observed nearly 1:1 molecular correspondence between foveal and peripheral retinal cell types, but also found the differences in type-specific frequencies and gene expressions between the two regions. We also showed that some of the foveal specializations in macaque are conserved in marmoset and human and identified cell type selective expression of genes conferring susceptibility to macular degeneration or glaucoma. These results provide a foundation for analyzing gene expression patterns in primate retina that underlie visual function and dysfunction.

Alex Vaccaro[1], Dragana **Rogulja[1]**

[1]Neurobiology Department, Harvard Medical School

Why is sleep essential for survival?

Sleep is a widespread and conserved behavior. It controls cognition so it has been widely assumed that death which follows sleep deprivation stems from some form of impaired brain function. But this does not seem to be the case, as sleep deprived brains appear mostly normal. We discovered accumulation of reactive oxygen species in guts of sleep deprived flies and mice. This accumulation leads to oxidative stress and eventually death. If we prevent it, flies can live with little to no sleep.

Joshua R. **Sanes**[1,2]

[1]Center for Brain Science, Harvard
[2]Department of Molecular and Cellular Biology, Harvard

Wiring up the retina

The retina is emerging as a leading model system for elucidating mechanisms that govern neural circuit assembly and function. Visual information is passed from retinal photoreceptors to interneurons to retinal ganglion cells (RGCs) and then on to the rest of the brain. Each of >30 RGC types responds to specific visual features, and the features to which each type responds depend on which of the >70 types of interneurons synapse on it. As an example, I will focus on RGCs that respond selectively to motion in a single direction, summarizing genetic, morphological and physiological studies that have led to identification of some molecules and mechanisms that underlie assembly of the circuit that generates their direction-selectivity.

Martin **Stemmler**[1, 2]

[1]LMU, Department of Biology II, Division of Neurobiology
[2]Bernstein Center for Computational Neuroscience Munich

The case for and against attractor networks underlying grid-cell based spatial navigation

Grid cells in medial entorhinal cortex (mEC) are organized into distinct modules; within each module, the spatial firing fields of grid cells form a common hexagonal lattice with a fixed spacing between fields, a fixed orientation, and a fixed shear [1,2]. Within one module, the firing fields measured for any particular grid cell reflects a rigid translation of this common lattice. Theoretical models propose that these features result from a single attractor state of network activity [3-5]; as the animal moves through space, the attractor state simultaneously moves through mEC.

Yet the firing fields are far from uniform, as the peak firing rate within each field varies considerably [6,7]. We show that these variations obey a long-range spatial structure: a slowly varying envelope across space modulates the firing rates from firing field to firing field. Interestingly, such behavior is uncommon in attractor networks, which typically exhibit stable hexagonal patterns. Only in a narrow parameter regime can an Eckhaus instability with long-range spatial variation in field amplitudes occur, just before the activity pattern in the network changes from hexagons to stripes [8]. Evidence suggests that the spatial variation in firing fields in grid cells is not of this type, which argues against the theory that grid cells' activity arises through dynamical self-organization in a continuous attractor network.

References

[1] Hafting T, Fyhn M, Molden S, Moser MB, Moser EI: Microstructure of a spatial map in the entorhinal cortex. Nature 2005, 436:801-806.

[2] Stensola T, Stensola H, Moser M-B, Moser EI: Shearing-induced asymmetry in entorhinal grid cells. Nature 2015, 518:207-212.

[3] McNaughton BL, Battaglia FP, Jensen O, Moser EI, Moser M-B: Path integration and the neural basis of the'cognitive map'. Nature Reviews Neuroscience 2006, 7:663.

[4] Fuhs MC, Touretzky DS: A Spin Glass Model of Path Integration in Rat Medial Entorhinal Cortex. The Journal of Neuroscience 2006, 26:4266-4276.

[5] Burak Y, Fiete IR: Accurate path integration in continuous attractor network models of grid cells. PLoS Comput Biol 2009, 5:e1000291.

[6] Dunn B, Wennberg D, Huang Z, Roudi Y: Grid cells show field-to-field variability and this explains the aperiodic response of inhibitory interneurons. arXiv preprint arXiv:1701.04893 2017.

[7] Ismakov R, Barak O, Jeffery K, Derdikman D: Grid cells encode local positional information. Current Biology 2017.

[8] Cross MC, Hohenberg PC: Pattern formation outside of equilibrium. Reviews of modern physics 1993, 65:851.

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Molecular Specification of Retinal Ganglion Cells in the Mouse Retina

All information the brain receives pertaining to the visual world is delivered by retinal ganglion cells (RGCs), the sole output neurons of the retina. ~30 distinct types of RGCs have been identified based on morphological and physiological characterizations; however, no comprehensive classification of types exists based on molecular expression. Furthermore, how and when the molecular differentiation of these types occurs during development remains unknown. Using high-throughput single-cell sequencing and novel computational methods, we have profiled the transcriptomes of nearly 45,000 adult RGCs, identifying 45 unique molecular types. Additionally, we've profiled RGCs from four developmental time points to determine a differentiation timeline of each type.

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Distinct roles for cortico- and thalamo-striatal projections in motor skill learning and execution

Our daily lives are full of activities requiring complex sequences of movements, whether it is tying our shoes or playing the piano. Our ability to perform these actions depends on a distributed motor network. While many components of this network have been identified, less is known about their specific roles and how they interact during learning and execution of motor skills. We are addressing these questions by training rats in a timed lever-pressing task that produces complex and highly stereotyped movement sequences. We probe the contributions of individual brain regions and their inter-connections by recording and manipulating their activities. In my talk, I will show that the dorsolateral striatum is at the center of the distributed motor network with distinct roles of its cortical and thalamic inputs in motor skill acquisition and execution. Our results suggest a circuit level model in which motor cortex guides plasticity during learning at thalamo-striatal synapses, which in turn play a crucial role during skill execution.

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The circadian clock, sleep and performance triangulate to problems for adolescents and their education

Sleep is essential for health and performance and its timing and consolidation are regulated by the circadian clock. Sleep timing (chronotype) is highly individual and varies with age, sex, genetic background, and light exposure. During adolescence, developmental changes lead to later chronotypes. Nevertheless, most schools have early starting times. As a result, the student population is chronically sleep-deprived and thus they attend school at a sub-optimal (too early) time of day. This suggests that those with a later chronotype are handicapped with respect to education and future career opportunities.

We performed a series of studies to better understand the role of chronotype, sleep, and time of day in relation to school performance. We collected data about chronotype (with the Munich ChronoType Questionnaire), school attendance (late arrivals, dismissals from class, sick leaves), and school performance (grades) at a Dutch high school.

We found that the effect of chronotype was stronger in the early morning, while it vanished in the early afternoon. We also showed that the effect of chronotype on grades was stronger for scientific subjects, suggesting that chronotype and time of day might influence only specific cognitive abilities (fluid intelligence) that are important for scientific subjects. In addition, we found that late chronotypes were more often absent from class, which, in turn, was associated with lower grades.

The findings of these studies have important applications for school policies and suggestions to improve school schedules are proposed.

LMU - Harvard Young Scientists' Forum

Posters

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On the influence of magnetic vestibular stimulation (MVS) on resting-state functional magnetic resonance imaging (RS-fMRI) results

It is well known that strong magnetic fields (>1 tesla) cause dizziness. Until recently, it was assumed that this effect would not produce a persistent modulation of brain states measured with functional magnetic resonance (fMRI) imaging. This assumption was based on the observation that the reported experience of dizziness was only temporary while subjects moved through the magnetic field of the MRI, e.g. upon entering or exiting the bore of the MRI but did not persist when remaining stationary in the magnetic field (Schenck 1992; Glover et al. 2007; Mian et al. 2015).

However, it was recently shown that nystagmus eye-movements persist, as long as subjects remained in the field of the MRI. This nystagmus has gone unnoticed in the past as it can only be revealed if visual fixation is suppressed, e.g. by measuring eye-movements in absolute darkness in the MRI. The vestibular labyrinth of the inner ear was determined as the origin of this magnetic vestibular stimulation (MVS) in the magnetic field of the MRI, as patients with bilateral vestibular failure did not show a nystagmus. A Lorentz-force model was proposed as an explanation for the dependency of the measured nystagmus on the orientation of the subject's head relative to the magnetic field direction. It was speculated that MVS should lead to a modulation of fMRI results, as nystagmus implies a state of vestibular imbalance (Marcelli et al. 2009; Roberts et al. 2011; Glover et al. 2014; Ward et al. 2014; Otero-Millan et al. 2017).

We have recently shown that such modulation can indeed be revealed in the fluctuations of fMRI resting-state network of healthy subjects at magnetic field strengths of 1.5 tesla and 3.0 tesla (Boegle et al. 2016, 2017). These modulations were in accordance with the proposed Lorentz-force model for MVS, and the associated brain areas closely matched those previously reported in studies comparing patients with peripheral vestibular failure to healthy controls (Göttlich et al. 2014; Helmchen et al. 2014; Klingner et al. 2014; Boegle et al. 2016, 2017).

Here we will present preliminary results of our investigations of freely online available fMRI resting-state datasets (e.g. the 1000 functional connectomes project (Biswal et al. 2010)) in relation to our own data with MVS associated modulations. As MVS is based on a Lorentz-force model, it should also change its influence for different field directions, i.e., show opposing effects for different MRI vendors, as Siemens

and GE manufacture their MRI magnets with the south pole at the foot end while Phillips manufactures their magnets with the south pole at the head end of the MR machine, i.e., opposite field directions leading to opposing nystagmus eye-movement directions. This gives us opportunity to study the effect of MVS field direction on resting-state networks, while we previously investigated the effects of field strength (Boegle et al. 2016, 2017).

Our preliminary analysis of data from the 1000 functional connectome datasets with multiple vendors and multiple field directions (i.e. opposing MVS modulations), suggests that MVS modulations mostly average out over this large-scale analysis. When field direction is used as an additional explanatory variable, MVS associated variance can be revealed. These modulations were similar to those found in our previously published MVS dataset. We suggest that large-scale analysis of resting-state fMRI should use data from various MRI magnet setups to average out the effects of MVS modulation. We note that MVS is a small to mediocre effect at 3.0 tesla and mainly of interest to researchers interested in the vestibular system, but MVS might become more significant at higher field strengths and large-scale studies with only one field direction and therefore only one MVS bias direction that is the same across the dataset.

Further research into MVS and resting-state fMRI modulations is necessary to find ways of removing the MVS modulation from occurring, as this would be an even better approach to removing any MVS-related bias than via averaging different opposing MVS-biases, i.e. removing the MVS bias from the data at the data acquisition stage should be the long-term goal.

References

Biswal BB et al, 2010. Toward discovery science of human brain function. Proc Natl Acad Sci. 107:4734–4739.

Boegle R, Ertl M, Stephan T, Dieterich M. 2017. Magnetic vestibular stimulation influences resting-state fluctuations and induces visual-vestibular biases. J Neurol. 264:999–1001.

Boegle R, Stephan T, Ertl M, Glasauer S, Dieterich M. 2016. Magnetic vestibular stimulation modulates default mode network fluctuations. Neuroimage. 127:409–421.

Glover PM, Cavin I, Qian W, Bowtell R, Gowland P a. 2007. Magnetic-field-induced vertigo: A theoretical and experimental investigation. Bioelectromagnetics. 28:349–361.

Glover PM, Li Y, Antunes A, Mian OS, Day BL. 2014. A dynamic model of the eye nystagmus response to high magnetic fields. Phys Med Biol. 59:631–645.

Göttlich M, Jandl NM, Wojak JF, Sprenger A, Der Gablentz J Von, Münte TF, Krämer UM, Helmchen C. 2014. Altered resting-state functional connectivity in patients with chronic bilateral vestibular failure. NeuroImage Clin. 4:488–499.

Helmchen C, Ye Z, Sprenger A, Münte TF. 2014. Changes in resting-state fMRI in vestibular neuritis. Brain Struct Funct. 1–12.
Klingner CM, Volk GF, Brodoehl S, Witte OW, Guntinas-Lichius O. 2014. Disrupted functional connectivity of the default mode network due to acute vestibular deficit. NeuroImage Clin. 6:109–114.

Marcelli V, Esposito F, Aragri A, Furia T, Riccardi P, Tosetti M, Biagi L, Marciano E, Di Salle F. 2009. Spatio-temporal pattern of vestibular information processing after brief caloric stimulation. Eur J Radiol. 70:312–316.

Mian OS, Glover PM, Day BL. 2015. Reconciling Magnetically Induced Vertigo and Nystagmus. Front Neurol. 6:1–4.

Otero-Millan J, Zee DS, Schubert MC, Roberts DC, Ward BK. 2017. Three-dimensional eye movement recordings during magnetic vestibular stimulation. J Neurol. 264:7–12.

Roberts DC, Marcelli V, Gillen JS, Carey JP, Della Santina CC, Zee DS. 2011. MRI magnetic field stimulates rotational sensors of the brain. Curr Biol. 21:1635–1640.

Schenck JF. 1992. Health and physiological effects of human exposure to whole-body four-tesla magnetic fields during MRI. Ann N Y Acad Sci. 649:285–301.

Ward BK, Roberts DC, Della Santina CC, Carey JP, Zee DS. 2014. Magnetic vestibular stimulation in subjects with unilateral labyrinthine disorders. Front Neurol. 5:28.

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Visual response properties of mouse TRN are consistent with its potential role for feedback-mediated surround suppression

Neurons in the dorsolateral geniculate nucleus (dLGN) of the thalamus are suppressed by stimuli extending beyond the classical receptive field into the surround. Surround suppression increases between the retinal ganglion cells and dLGN, where it has been hypothesized that corticothalamic (CT) feedback from layer 6 (L6) contributes to this enhancement (Andolina et al., 2012). Because L6 CT neurons are excitatory they can inhibit thalamic relay cells only indirectly via local geniculate interneurons or inhibitory neurons in the thalamic reticular nucleus (TRN). We hypothesized that if neurons in TRN were responsible for mediating feedback-induced surround suppression in dLGN, they should have large receptive fields (RF) and be suppressed if CT feedback is disrupted.

We tested this hypothesis by head-fixing C57BL/6 mice on a floating Styrofoam ball and recording extracellular single-unit activity using high-density silicon probes in the visual part of TRN (perigeniculate nucleus, PGN). For post-mortem confirmation of our recording site, we injected a retrograde AAV into dLGN leading in connected PGN neurons to the expression of green fluorescent protein. We presented full-field drifting gratings to identify visually responsive neurons and mapped their RFs with sparse noise stimuli. We measured surround suppression by showing drifting gratings of varying sizes.

We observed that activity in PGN was strongly modulated by behavioral state; thus, we restricted our analysis to trials, in which the animal was sitting. Numerous PGN neurons showed visually evoked responses at the temporal frequency of the drifting grating. Overall, PGN neurons had large RFs (mean = 19.6 deg^2), substantially exceeding the size of those in dLGN (mean = 3.3 deg^2, $p < 10^{-4}$). PGN RFs exhibited a rough topographic mapping, where units that resided more ventrally in the PGN tended to have lower RF centers. Examining responses to varying stimulus sizes revealed that PGN neurons exhibited a broad range of suppression strengths, including some weak ones.

Next, we tested how PGN responses are affected by CT feedback. In visual cortex (V1) of PV-Cre mice we used a viral approach to conditionally express Channelrhodopsin-2 in parvalbumin positive interneurons. Activating these neurons allowed us to suppress V1 activity and hence disrupt CT feedback to PGN. Suppression of CT feedback led to a substantial reduction of PGN responses (31.7 Hz vs. 10.9 Hz, $p = 0.02$).

We conclude that PGN, given its large RFs and its suppression during disruptions of CT feedback, might play an important role for feedback-mediated surround suppression in dLGN.

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Sensitive and powerful single-cell RNA sequencing using mcSCRB-seq

Single-cell RNA sequencing (scRNA-seq) has emerged as a central method to characterize cellular identities and processes. However, as there is no optimal, onesize- fits all protocol, various inherent strengths and trade-offs exist. Among flexible, plate-based methods, “Single-Cell RNA-Barcoding and Sequencing” (SCRB-seq) is one of the most powerful and cost-efficient, as it combines good sensitivity, the use of unique molecular identifiers (UMIs) to remove amplification bias, and early barcoding of cells to reduce costs. Here, we systematically optimize the sensitivity and efficiency of SCRB-seq and develop “molecular crowding SCRB-seq” (mcSCRB-seq), one of the most powerful and cost-efficient plate-based methods to date.

Based on benchmarking data generated from mouse ES cells, we show that mcSCRBseq considerably increases sensitivity and decreases amplification bias due to the addition of polyethylene glycol and Terra polymerase respectively. Specifically, molecular crowding through the use of polyethylene glycol yielded 7,898 versus 5,542 detected genes (downsampled to one million reads per sample, p = 7 x 10-7, Welch Two Sample t-test) and amplification using Terra yielded twice as much library complexity (UMIs). Furthermore, mcSCRB-seq shows no indication of bias for GC content and transcript lengths, and it has low levels of cross-talk between cell-barcodes, which has been seen especially in droplet-based RNA-seq approaches. Compared to the previous SCRB-seq protocol, mcSCRB-seq increases the power to quantify gene expression two-fold, and optimized reagents and workflows reduce costs by a factor of three. Together, this makes mcSCRB-seq six-fold more cost-efficient than SCRB-seq.

Qualitatively, we validated our new protocol by sequencing peripheral blood mononuclear cells, a complex mixture of different cell types. We show that mcSCRBseq can be used to identify the different subpopulations and marker gene expression correctly and distinctively detect the five major cell types present in the population. mcSCRB-seq is also well suited to identify differential expression among similar cell types, which was confirmed by preparing libraries from locomotor and shaker neurons from Crotalus atrox.

Taken together, mcSCRB-seq is not only the most sensitive protocol when benchmarked using ERCCs, it is also the most cost-efficient and flexible plate-based protocol currently available. As no specialized equipment or reagents are required, mcSCRB-seq could be a valuable methodological addition to many laboratories.

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Revealing multiple timescales of structure in larval zebrafish behavior

Predictive models of an animal's behavior quantify and characterize the output space of its nervous system. This space is huge for wild animals and is often constrained in laboratory environments to limit its complexity and the volume of data needed to evaluate its structure. The study of natural behavior is further complicated by the challenge of temporally segmenting behavioral sequences into constituent elements. Zebrafish larvae are well suited for study because their behavior is naturally discrete, i.e. they swim in punctuated bouts. We reveal patterns in larval zebrafish behavior by monitoring individual larvae swimming freely in a large arena containing abundant unicellular food resources. We collected 40 hours of high-resolution video with a tracking camera programmed to move above the fish, recording its postural dynamics and interaction with prey objects. We categorized swim action types and constructed a probabilistic model – a marked point process – to predict how these actions are deployed given the internal hunger-state of the fish, its behavioral history, and the current environmental input. The distribution of swim actions is left-right symmetric at the population level and we exploit this symmetry to simplify behavioral classification and construct more robust models. We find that hunger increases the likelihood of transitioning from exploratory to hunting behavior and promotes shorter intervals between consecutive exploratory actions. We construct symmetric neural networks to interpret how statistics of these natural scenes influence action selection. Our probabilistic modeling approach has enabled us to compare the predictive power of different features (e.g. external factors like prey locations to internal factors like previous action) and sample from multi-timescale models to generate realistic behavior of a virtual fish in simulated environments. Our work reveals previously unknown patterns in larval zebrafish behavior and can serve to generate hypotheses about possible neural implementations of these behavioral algorithms.

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Connectivity Mapping in the Human Vestibular System

Introduction: The vestibular system differs from other sensory systems (Goldberg et al., 2012). Lacking a primary cortex in the narrower sense, current evidence points towards a multisensory bilateral temporo-parietal-insular vestibular network with a handedness-dependent hemispheric lateralization of its core region (Brandt and Dieterich, 1999; Guldin and Grüsser, 1998; Lopez and Blanke, 2011). This widespread cortical allocation of its processing areas is mirrored by its dependency on multisensory inputs (Angelaki and Cullen, 2008; Carriot et al., 2015) that converge at multiple levels from the brainstem to the cortex whilst serving sensorimotor reflexes, control up to cognitive functions (Chen et al., 2011a, 2011b; Dieterich and Brandt, 2015). However, much poorly understood, especially in humans. This project aimed to map in-vivo structural and functional connectivity patterns in the human vestibular system using a quantifiable non-invasive multimodal imaging approach.

Methods: Diffusion tensor (DTI) structural and resting-state functional (fMRI) connectivity magnetic resonance imaging data of 60 healthy volunteers, 30 right-handed (RH; 17 females; aged 20-67 years, mean age 26,7 ± 8,3 years) and 30 age- and gender matched left-handed (LH; 14 females; aged 20-65 years, mean age 26,1 ± 8,6 years) was used (i) to investigate interconnections of the bilateral central vestibular network from human brainstem to cortex (Kirsch et al., 2016), (ii) to quantify the found thalamus-dependent vestibular brainstem pathways (Dieterich et al., 2017) and (iii) to reveal handedness-dependent functional organizational patterns within the bilateral vestibular cortical network (Kirsch et al., 2018a, 2018b). The data was analyzed with the FMRIB's Diffusion Toolbox and MELODIC as part of the FSL package (Oxford, UK) and in-house scripts written in MATLAB (Natick, MA, USA). Used ROIs included vestibular reference coordinates of two meta-analyses of vestibular neuroimaging experiments attempting to pinpoint the vestibular cortex (Baier et al., 2016; Lopez et al., 2012; Zu Eulenburg et al., 2012).

Results: In vivo investigation of vestibular connectivity by means of combined structural and functional connectivity mapping was found to be congruent (Kirsch et al., 2016). Crossing and non-crossing vestibular brainstem fibers provide a rope ladder system for the central vestibular network between the vestibular nuclei and the vestibular cortical core region, the parieto-insular vestibular cortex (PIVC) at four levels: three in the brainstem and one in the cortex (Dieterich et al., 2017; Kirsch et al., 2016). Vestibular pathways project through both the posterolateral and the paramedian thalamus (Baier et al., 2016; Dieterich et al., 2017; Kirsch et al., 2016). A part of the ipsilateral projections directly reach the inferior part of the insula, thus bypassing the thalamic relay station (Kirsch et al., 2016; Kirsch et al., 2018a). There is a dominance of the right vestibular meso-diencephalic circuitry in right-handers that builds up from crossing to crossing that corresponds to the right-hemispheric lateralization of the vestibular cortical network (Dieterich et al., 2017). In addition, non-binary functional parcellation of the vestibular cortical network revealed not only a handedness-dependent lateralized central region concentrated in the right

hemisphere in right-handers and left hemisphere in left-handers, but also surrounding inter-hemisphere symmetric multisensory vestibular areas that seem to be functionally influenced by their neighboring sensory systems (e.g., temporo- parietal intersection by the visual system) (Kirsch et al., 2018b).

Discussion: The “otherness” of the vestibular system seems manifold and is therefore not easy to pinpoint at first sight. The reason may be that the nature of the vestibular system is indeed manifold or multimodal or “non-binary” in many respects when considering the multisensory nature of stimuli (Angelaki and Cullen, 2008; Carriot et al., 2015; Goldberg et al., 2012) and their bilateral (Dieterich and Brandt, 2015), multi-level (Kirsch et al., 2016), hierarchical (Chen et al., 2010) computation that converge (Carriot et al., 2013; Chen et al., 2011a) not in a vestibular primary cortex but in multiple spatially distributed (Brandt and Dieterich, 1999; Guldin et al., 1992; Lopez and Blanke, 2011) and spatially tuned (Chen et al., 2011b; Kirsch et al., 2018a, 2018b) cortical areas. Within this vestibular cortical network, one may speculate that the separation of a symmetrically from an asymmetrically organized vestibular system reflects a phylogenetic evolution of various multisensory vestibular functions (Brandt and Dieterich, 2018, 2015). A symmetrically organized phylogenetically “older” system seems to have been further developed by an additional asymmetric lateralized “younger” system chiefly localized in the parieto-insular region.

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Representation of chunked action sequences in the dorsolateral striatum

Understanding neural representations of behavioral routines is critical for understanding complex behavior in health and disease. We demonstrate here that accentuated activity of striatal projection neurons (SPNs) at the beginning and end of such behavioral repertoires is a supraordinate representation specifically marking previously rewarded behavioral sequences independent of the individual movements making up the behavior. We recorded spike activity in the striatum and primary motor cortex as individual rats learned specific rewarded lever-press sequences, each one unique to a given rat. Motor cortical neurons mainly responded in relation to specific movements, regardless of their sequence of occurrence. By contrast, striatal SPN populations in each rat fired preferentially at the initiation and termination of its acquired sequence. Critically, the SPNs did not exhibit this bracketing signal when the same rats performed unreinforced sequences containing the same sub-movements that were present in their acquired sequence. Thus, the SPN activity was specifically related to a given repetitively reinforced movement sequence. This striatal beginning-and-end activity did not appear to be dependent on motor cortical inputs. However, strikingly, simultaneously recorded fast-spiking striatal interneurons (FSIs) showed equally selective but inverse firing patterns: they fired in-between the initiation and termination of the acquired sequences. These findings suggest that the striatum contains networks of neurons representing acquired sequences of behavior at a level of abstraction higher than that of the individual movements making up the sequence. We propose that such SPN-FSI networks of the striatum could underlie the acquisition of chunked behavioral units.

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Adaptation to spatial statistics focally improves sound source separability by optimizing population coding efficiency

Concepts of auditory spatial processing have long been dominated by ideas of hard-wired neuronal mapping of absolute positions in space. Recently, however, findings of stimulus-history dependent adaptation of spatial sensitivity in dynamic environments challenged these concepts. We re-examined the nature of the spatial code in gerbil brainstem neurons. We find that naturalistic paradigms with dynamically changing sound sources induce pronounced dynamic-range adaptation (DRA). Yet surprisingly, average spatial tuning functions of individual adapted neurons carry little information due to high inter-trial variability. However, when considering single-trial population averages, DRA maximizes both source separability and coding efficiency specifically for the most probable source locations. Intrinsic energy imaging and modeling demonstrate that efficiency maximization is mediated by slow-acting negative feedback. Finally, human listeners tested with the same stimuli confirm a location-specific improvement in spatial resolution. Thus, the auditory spatial code is geared for efficient source separability within the concurrent sound environment.

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Physiological substrates of BACE1: safety issues or biomarkers?

The beta-secretase BACE1 is the enzyme responsible for amyloid beta generation and is a major drug target in Alzheimer's disease. However, therapeutic BACE1 inhibition may cause unwanted side effects due to the loss of cleavage of additional BACE1 substrates besides APP. Different proteomic studies have identified more than 40 membrane proteins as potential BACE1 substrate candidates, but most of them have not yet been validated nor functionally characterized.

Here, we validate seizure protein 6 (SEZ6) as an exclusive BACE1 substrate both in primary neurons and in the brain of BACE1-deficient mice. In order to investigate the function of SEZ6 and the consequences of loss of SEZ6 cleavage by BACE1, we developed a novel proteomic technique to determine the surface proteome of primary neurons. Using this method, we found that SEZ6 specifically controls neuronal surface levels of a subgroup of glutamate receptors with key functions in neurotransmission. Mechanistic analyses suggest that SEZ6 is required for glutamate receptor transport along the secretory pathway and may influence synaptic transmission. Additionally, we demonstrate that the BACE1-generated soluble ectodomain of SEZ6 (sSEZ6) is strongly reduced in the CSF of BACE1-deficient mice. Importantly, sSEZ6 is reduced also in the CSF of BACE-inhibited monkeys in a dose dependent manner.

Taken together our results prove that SEZ6 is a major substrate of BACE1, both *in vitro* and *in vivo*. Moreover, we discover a novel function of SEZ6 as glutamate receptor regulator and we investigate the possibility to use sSEZ6 as a potential companion diagnostic to monitor BACE1 activity in patients treated with BACE inhibitors.

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How do we get hangry?
The neural circuit underlying hunger modulation of olfactory preference in the Drosophila larva

Finding the right food is essential. Olfactory information can help us to evaluate food quality even before ingestion. This is especially important for the Drosophila larva, which just exists to eat, grow, pupate and then become a fly. We have a detailed map of the neural circuit underlying olfactory sensing due to EM reconstruction of all neurons in the antennal lobe, the first odor processing center in the larval brain. However, the function of several anatomically described interneurons and projection neurons is yet unknown. Interestingly, using the wide array of genetic tools in the fly larva to manipulate some of these neurons has no effect on innate odor preference. However, by starving the larva we see a switch in odor response and requirement of some of the interneurons. Also, a serotonergic neuron gets recruited to adapt the olfactory response behavior under the stressful condition. We found several neurons in the antennal lobe that can be modulated by serotonin release. However, the wiring diagram does not predict a direct interaction between the serotonergic neuron and these downstream partners. Thus, to fully understand the function and capacity of neural circuits in the brain we need to investigate how different internal states shape neuronal processing and even though EM reconstruction of neural circuit is extremely helpful, the modulation probably also happens beyond synaptic connectivity.

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Development and refinement of functional properties of adult-born neurons

New neurons appear only in a few regions of the adult mammalian brain and become integrated into existing circuits. Despite extensive studies on adult neurogenesis, little is known about the functional development of individual neurons in their native environment in vivo and whether its regulation involves mechanisms similar or distinct from those operating in other brain regions during early postnatal development. We recently examined the functional life history of visualized adult-born granule cells (abGCs) in the olfactory bulb of mice using multiphoton imaging (Neuron 96:883-896). We found that abGCs can become responsive to odorants as soon as they arrive in the olfactory bulb. Tracking identified abGCs chronically over several weeks revealed that the robust and broadly-tuned responses of newly arrived abGCs gradually become weaker and more selective over a period of about 3 weeks. To address the cellular and molecular mechanisms involved in the functional refinement of abGCs, we have begun to examine the role of microglia. The ablation of microglia, which have been shown to play a role in synaptic refinement during development in other brain regions, reduces the odor responses of developing, but not preexisting GCs and alters their odor selectivity. In ongoing work, we investigate the role of microglia, and their interplay with abGCs, in complex olfactory behaviors.

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Mesoscopic functional interactions in the human cortex

Functional interactions between brain regions play a central role in cognitive computations. Evaluating such functional interactions in the human brain has been challenging due to the difficulties inherent to interrogating human brain activity at adequate spatiotemporal resolutions and with sufficient signal-to-noise ratio. Here we investigated pairwise interactions at a mesoscopic scale by quantifying the degree of coherence in intracranial field potential recordings from 4432 electrodes in 51 patients with pharmacologically intractable epilepsy over the course of 6360 hours. After correcting for artifacts and removing seizure events, we defined putative interactions by computing the coherence in different frequency bands between electrode pairs within each patient. We observed functional interactions that are consistent with known anatomical connectivity in the human brain, with macaque anatomical connections, and with neurophysiological interactions documented in macaque monkeys. These interactions showed strong stability across days. The interactions were also were also consistent across subjects. These results provide the first mesoscopic functional interactome of the human brain and constitute an important database to study modulations by state, by cognitive function, as well as by impairments due to neurological disorder.

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Building a high-throughput pipeline for large-scale connectomics using a MultiSEM

Mapping the wiring diagrams of neural networks at the level of individual synapses will uncover the organization and logic of brain circuitry, thus providing a clear anatomical framework for generating data-driven, biologically constrained computational models. We have developed an ultra-fast pipeline to carry out large volume (~1 mm^3) circuit reconstruction using the multi-beam scanning electron microscopy (MultiSEM) manufactured by Carl Zeiss Microscopy. Collecting a volume of 1 mm^3 digitized dataset of biological tissue at 4 nm x-y resolution would require ~6 years using the world's fastest single-beam SEM. In contrast, the MultiSEM - with 61 parallel beams - allows one to image the tissue sample at millimeter scale with fine-grained cellular ultrastructure within a few months. Our pipeline provides automation and parallelization at multiple steps to minimize human labor, maximize workflow throughput, and ensure high-quality data. Methods engineered for optimizing the pipeline include an automated sectioning apparatus (ATUM), a fast wafer mapping strategy, and novel distributed computational algorithms to stitch, align and segment the image data.

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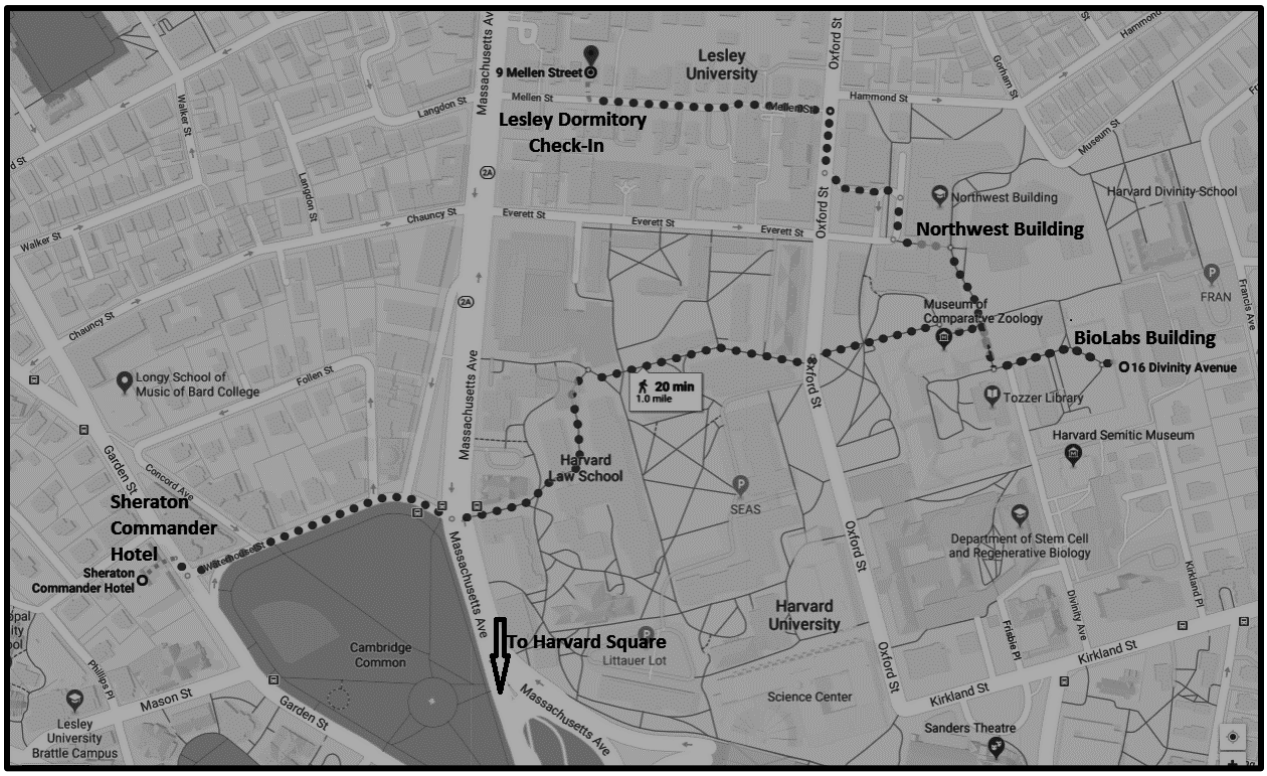
Directions and Locations

BioLabs Building – 16 Divinity Ave, Cambridge MA
Northwest Building – 52 Oxford St, Cambridge MA, Main Office: Room 249, 617-495-9765
Lesley Dormitories Check in – 9 Mellen St, Cambridge, MA
Sheraton Commander Hotel – 16 Garden St, Cambridge, MA



<u>Directions to Harvard Square from Logan Airport</u>

A taxi cab is $40 - $60 USD. Uber and Lyft car service operate from Logan airport as well. Please remember to get a receipt. If you'd like to try public transportation:

The bus and subway are free when originating from the airport. Get on the Silver Line bus outside from the Baggage Claim. The bus arrives once every 10 minutes. Take the last bus stop for South Station. Staying inside the station, go one level down to the Red Line train, *inbound* towards *Alewife*. The train runs every few minutes. Exit the train at the Harvard Square stop, taking the escalator or stairs that are about half-way down the platform. Leave the turnstyles and exit to the right. Go up the stairs and take a right at the top. Walk along Massachusetts Ave.

<u>Sheraton Commander</u>: turn left on Garden St and the hotel will be on the left at the end of the park

<u>Lesley Dormitories Summer Housing Office</u>: Walk north along Massachusetts Ave until you get to Mellen St. You will need to cross to the other side of the street to turn right onto Mellen St. 9 Mellen St.