BARRELS XXXV

Thursday, November 10th, and Friday, November 11th, 2022

Hilton La Jolla Torrey Pines
10950 North Torrey Pines Road
La Jolla, CA 92037

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BARRELS XXXV – 2022

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BARRELS XXXV Program
10-11 November 2022
The 35th Annual Barrels Society Meeting

Hilton La Jolla Torrey Pines
10950 North Torrey Pines Road
La Jolla, CA 92037

Thursday, November 10th

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A Canonical Computation?

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BARRELS XXXV Program
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Thursday, November 10th

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9:10 – 10:00 Keynote 1: ***Lauren Orefice***, Harvard University
Understanding somatosensory circuit alterations in autism spectrum disorder

10:00 – 10:15 ***Giuseppe Cataldo,*** P. Feinstein, H. P. Ziegler, J.C. Brumberg
Queens College, CUNY
Prrxl1 knockout mouse a model for chronic pain

It's been contended that models of chronic pain do not accurately represent the conditions in humans because they involve invasive procedures of relatively short durations. Here we introduce, the Prrxl1 knockout (KO) mouse as a model of chronic pain. In this KO, somatotopic patterning is normal in spinal trigeminal nucleus (SpV) as well as the spinal caudalis nucleus (SpVc). It is absent along the entire trigeminal lemniscal pathway from principal sensory nucleus (PrV) to cortex. Von Frey filaments revealed a previously observed pattern of hypoalgesia in the spinal division which contrasts markedly with our novel finding of hyperalgesia in its cranial (trigeminal) division where Prrxl1 animals showed an increased facial withdrawal frequency compared to controls. In addition, many aspects of quality of life are disrupted in this animal. The mice exhibit prolonged and intensive bouts of grooming of the head and face as well as an avoidance of rough-textured surfaces suggestive of allodynia. On lab chow, Prrxl1 KOs show a significant reduction in both amount and efficiency of feeding behavior and a persistently reduced baseline body weight. However, given soft food, it eats significantly larger amounts than controls. Taken together, feeding behavior displayed by Prrxl1 KOs we believe is also indicative of pain. These conditions appear to be present in the animal immediately after weaning, and continue throughout its lifetime, so that the condition may be described as chronic.

10:15 – 10:30 ***Anda M. Chirila***, Genelle Rankin, Shih-Yi Tseng, Alan J. Emanuel, Christopher D. Harvey, David D. Ginty
Harvard Medical School
The encoding of touch in the spinal cord dorsal horn

The encoding of touch in the spinal cord dorsal horn (DH) and its influence on tactile representations in the brain are poorly understood. Using a range of mechanical stimuli applied to the skin, large scale in vivo

electrophysiological recordings, and genetic manipulations, here we show that neurons in the mouse spinal cord DH receive convergent inputs from both low- and high-threshold mechanoreceptor subtypes and exhibit one of six functionally distinct mechanical response profiles. Genetic disruption of DH feedforward or feedback inhibitory motifs, comprised of interneurons with distinct mechanical response profiles, revealed an extensively interconnected DH network that enables dynamic, flexible tuning of postsynaptic dorsal column (PSDC) output neurons and dictates how neurons in primary somatosensory cortex respond to touch. Thus, mechanoreceptor subtype convergence and nonlinear transformations at the earliest stage of the somatosensory hierarchy shape how touch of the skin is represented in the brain. Supported by NIH and HHMI.

10:30 – 10:50 Coffee Break

10:50 – 11:05 ***Michael Mykins***, Benjamin Bridges, Logan Reid Dunn, Alexandra Hart McBryar, Sarah Perez, Trinity Rose Shultz, Billy You Bun Lau, and Keerthi Krishnan
University of Tennessee
Age dependent tactile sensory phenotypes in Rett syndrome

Rett syndrome (RTT) is a sensory processing disorder, which ultimately gives rise to motor and communication deficits in females throughout life. RTT is caused by mutations in the X-linked gene Methyl CpG-Binding Protein 2 (MECP2). In-depth studies of sensory perception in the female Mecp2-heterozygous mouse model for RTT (Het) over adolescent and adult ages is essential to determine the underlying neurobiological mechanisms over time. We observe adult Het perform inefficiently at a sensory relevant pup retrieval task. Thus, we characterized tactile sensory perception via the S1BF using novel object recognition and texture discrimination tasks, in adolescent and adult Het using systematic DataVyu analysis. Adolescent Het show typical perineuronal nets in the S1BF, mild tactile sensory deficits, and efficient pup retrieval. In contrast, adult Het show increased perineuronal net expression, significant tactile sensory deficits, and inefficient pup retrieval. Using DeepLabCut, we generated pose and found trajectory kinematics are dynamic across trials of pup retrieval. Principal component analysis of kinematics revealed two groups: Het that behave like WT, and Het that regress over trials compared to WT. Thus, we have identified behavioral metrics and cellular substrates to study regression at a specific time in the female Het mouse model. This is significant because it is difficult to model behavioral regression in preclinical animal studies for RTT. NIH R15

11:05 – 11:20 ***Stuart Wilson***
University of Sheffield
Modelling pattern formation in the barrel cortex

The barrel cortex is a model system for developmental neurobiology for many reasons, not least because of the beautiful pattern formed by the barrels on the cortical surface, and several other spatial patterns seen at sub-barrel resolution. I have been trying to understand the dynamical processes that give rise to these patterns and have developed some simulations revealing how barrel and sub-barrel patterns can emerge from only local interactions between cells. I will briefly present a published model of barrel formation, showing how gene expression gradients can constrain reaction-diffusion dynamics to produce the overall barrel pattern. Then I will show how the same basic principles, when evaluated at a different spatial scale, can also account for the emergence of the retinal-tectal map. Next I will present an analysis of the relationships between sub-

barrel patterns, which suggests that they emerge from similar self-organising principles, under constraints imposed by the shapes of the barrel boundaries. Finally I will identify some limitations of an existing model of sub-barrel pattern formation, and show how these can be overcome by considering variations in barrel shape, rather than size, as the key symmetry-breaking factor. Through this work I hope to convince (or at least to reassure!) the audience that the barrel cortex is an ideal system for investigating the impact of developmental dynamics on cortical information processing. Funding: www.jsfm.org; 220020516.

11:20 – 11:50 ***Carl Petersen***, EPFL
Neuronal circuits for goal-directed sensorimotor learning

11:50 – 12:05 ***Robert Sachdev***, Keisuke Sehara, Marcel Staab, Ronny Bergmann, Nora-Laurine Bahr, Sina Dominiak, Jens Kremkow, and Matthew Larkum
Humboldt University
Coordination of whisking with eye movement and an examination of what moves when mice move a whisker to touch

A key function of the brain is to move the body through a rich, complex environment. When rodents engage their environment, they move their whiskers as they extract tactile information. Our work shows that head fixed mice navigating a plus maze position their whiskers asymmetrically with the positioning of whiskers signifying the upcoming turn direction. In addition to whisking, mice also moved their eyes conjugately in the direction of the upcoming turn. Not only do mice move their eyes, but they coordinated saccadic eye movement with the asymmetric positioning of the whiskers. Next, we show that mice trained in a go-cue whisking to touch task -- touching a sensor with a whisker on one side of the face -- specifically controlled the movement of the single whisker they use to touch. Importantly, mice controlled the setpoint, amplitude and even the frequency of movement of individual whiskers bilaterally, independently. Note that in the course of this behavior, mice moved their whiskers bilaterally on every trial, and they moved their nose from side to side while applying forces on their head post. Additionally, even though mice achieved the goal of the task how they did so, how they coordinated movement of the nose and forces on head post with whisking was stereotyped and specific for each mouse. Taken together our work shows that even though mice can exhibit fine degree of control of single whisker movement, whisking is often coordinated with other facial behaviors.

12:05 – 1:30 Lunch

1:30 – 2:00 ***Tommaso Fellin***, Italian Institute of Technology
Contribution of multiple sensory modalities to texture discrimination

2:00 – 2:15 ***Dieter Jaeger*** and Yunmiao Wang, Emory University
Wide-field voltage imaging using JEDI-1P to reveal detailed sensory and motor cortical task dynamics in behaving mice

Population imaging of cortex-wide activities has shed light on the cortical dynamics and functional networks of motor control. To date, the majority of wide-field imaging studies utilize calcium indicators. The relatively slow

kinetics of calcium sensors have left the investigation of fast cortex-wide dynamics at the time scale of limb kinematics an uncharted area. In order to better understand cortical activities of motor control with higher temporal resolution, we performed wide-field voltage imaging at 200 Hz with a novel genetically encoded voltage sensor, JEDI-1P. First, we demonstrated that JEDI-1P reliably follows responses of air-puff stimulation of up to 60 Hz in somatosensory cortex. We then imaged mice performing a wheel running task, a water-reaching task cued for either right or left forelimb reach, and a left/right delayed lick decision making task. Imaging data showed rich and fast temporal signals with multiple components in all sensorimotor and frontal cortical areas. Pending detailed analyses of this rich dataset on fast cortical dynamics with voltage imaging is expected to provide further insights on how sensorimotor information is processed for modulating locomotion and controlling dexterous movement. Funding: NINDS BRAIN Initiative R01 NS111470-02

2:15 – 2:30 ***Ajit Ray***, Carnegie Mellon University
Dendrite-specific thalamocortical plasticity in L5 pyramidal neurons during sensory learning

Synaptic changes underlie the cellular basis of learning. Unlike electrophysiological measurements, neuroanatomical methods to assess synaptic plasticity can provide critical spatial information that inform and constrain plasticity models. The numbers and diversity of synaptic connections make imaging approaches like electron and super-resolution microscopy fiscally and technically intensive, and high-throughput studies impossible. Using genetically encoded fluorescence-based reagents for pre- and postsynaptic labeling and a digital confocal image analysis pipeline, we monitored changes in higher order thalamocortical (POm) synapses onto L5 Pyr neurons in mouse barrel cortex during a whisker-dependent learning task. We observed rapid increases in thalamocortical synaptic size, both pre- and post-synaptically. These changes were compartment- and input-specific, occurring on L5 Pyr proximal dendrites but not apical tufts. POm synapses on proximal dendrites were clustered together indicating further structural reorganization. Both axonal and dendritic changes were transient, returning to baseline as animals became expert in the task. Anatomical measurements were predictive and corroborated by synaptic recordings. The compartmental selectivity observed reveals the importance of factoring in synaptic location while building models of circuit reorganization. Our approach has broad utility in studying synaptic plasticity across experimental paradigms in a high-throughput manner.

2:30 – 3:00 ***Brice Bathellier***, Pasteur Institute
Cortical representations across sensory modalities and states

3:00 – 3:20 Coffee Break

3:20 – 3:35 Kim, H.H., Dash, S., Martinetti, L.E., Jones, C., Autio, D.M., Keller, T., Rachor, A., Ackermann, J., Bonekamp, K.E., and ***Crandall, S.R.***
Michigan State University
Identification of an inhibitory circuit that mediates motor integration in the somatosensory cortex

According to the corollary discharge theory, motor centers send signals informing sensory areas of ongoing motor actions, suppressing the expected sensory input. However, the mechanism underlying such suppression within the somatosensory cortex is unclear. Using optogenetics, we find that input from the whisker primary motor cortex (wM1) activates layer 6(L6) parvalbumin(PV)-expressing inhibitory cells whose axons arborize locally within deep layers more strongly than any other interneuron population in whisker somatosensory cortex. The greater responsiveness of these PV interneurons was not due to unique intrinsic properties or local circuit interactions but was produced by synaptic mechanisms. Notably, vM1 axons made stronger excitatory connections onto these PV cells than other neurons. Recordings in behaving mice also reveal that some excitatory neurons are suppressed before whisking, whereas some L6 PV interneurons increase their activity. Our results provide a synaptic circuit mechanism for motor-related corollary discharge in the somatosensory cortex that may help tactile sensation and whisker-dependent behaviors. Funding NIH Grant R01-NS117636, R00-NS096108, F31-NS124244

3:35 – 4:05 An Wu and ***Takaki Komiyama***, University of California, San Diego
Motor cortex circuits for learned movements

Motor cortex (M1) circuits are highly plastic, enabling adaptive control and learning of body movements. I will discuss our latest project in which we are investigating the roles of M1 ensemble activity in the control of learned forelimb movements. This is done by population calcium imaging combined with holographic two-photon optogenetic stimulation of neural ensembles. The results indicate that stimulation of ~20 movement-related neurons in M1 is sufficient to generate a learned movement. Further, the pre-stimulation state of M1 network activity had a profound impact on the stimulation effect — the stimulation is particularly effective at generating the learned M1 activity pattern and movement when the network activity is in a proper state that resembles the pre-movement state during voluntary execution of the learned movement. Together we propose that execution of learned movements requires that the M1 network enter an appropriate preparatory state, which prepares the dynamical system to generate an appropriate spatiotemporal activity in response to inputs to generate the learned movement.

4:05 – 4:20 ***Angelina Lam***, Behzad Zareian, and Edward Zagha
University of California, Riverside
Dorsolateral striatum, not motor cortex, is a bottleneck for responding to task-relevant stimuli in a learned whisker detection task in mice

A learned sensory-motor behavior engages multiple brain regions, including the neocortex and the basal ganglia. How a target stimulus is selected by these regions remains poorly understood. Here, we performed electrophysiological recordings and pharmacological inactivations of motor cortex and dorsolateral striatum to determine the representations within and functions of each region during performance in a selective whisker detection task in male and female mice. From the recording experiments, peak pre-response activity and significant choice probability emerged in the motor cortex before the dorsolateral striatum, suggesting a sensory-to-motor transformation in which the striatum is downstream of motor cortex. We performed pharmacological inactivation studies to determine the necessity of these brain regions for this task. We found that suppressing the dorsolateral striatum, but not motor cortex, severely disrupts responding to task-relevant stimuli, without disrupting the ability to respond. Together these data support the dorsolateral striatum, and not motor cortex, as an essential node in the sensory-to-motor transformation of this whisker detection task. This work was supported by the National Institutes of Health Grant R01NS107599 (to E.Z.).

4:20 – 4:35 ***Aman Maharjan***, Jason M. Guest, Jean-Alban Rathelot, Peter L. Strick, and Marcel Oberlaender
Max Planck Institute for Neurobiology of Behavior
New Definition of Cortical Motor Areas at Single Muscle Resolution

How are circuits for motor control organized in the cortex remains unclear? Here, we address this question by using retrograde transneuronal transport of rabies virus to identify the cortical areas with disynaptic access to the motoneurons that innervate a single whisker muscle. For comparison, we also examine which cortical areas have disynaptic access to the motoneurons that innervate a single forepaw muscle, extensor digitorum communis (EDC). We find that five major cortical regions in both the contra- and ipsilateral hemispheres contribute to the control of whisker motoneurons: primary motor (M1) and sensory cortex (S1), secondary motor (M2) and sensory cortex (S2), and anterior insular cortex (AI). However, the distributions of the neurons within these major cortical areas differ between hemispheres. The whisker-related part of S1, the barrel cortex, and a medial-caudal part of M1 are unilateral – i.e., they have access exclusively to whisker motoneurons on the contralateral side. The remaining parts of M1 and S1, as well as M2, S2, and AI are bilateral – i.e., they have access to whisker motoneurons on both the contra- and ipsilateral sides. The distribution for forepaw and whisker muscles are disjoint in S1, partially overlap in M1, and entirely overlap in M2 and S2. Thus, multiple functionally distinct cortical areas contribute to the control of a single muscle. Our data and approach set the stage to quantitatively disentangle the network that orchestrates movements.

4:35 – 4:50 ***Saikat Ray***, Itay Yona, Liora Las, Nachum Ulanovsky
Weizmann Institute of Science
Neural codes for natural social behaviours in a bat colony

Highly-social animals live in complex communities, and interact with each other at times, locations and manner of their choosing. However, neurophysiological investigations of social responses are rarely conducted in rich multi-animal settings that allow such natural behaviours. I will describe how the brain behaves in natural social settings, by investigating dorsal hippocampal CA1 neurons in a colony of male and female bats living 24/7 in a laboratory based “bat cave”. The freely flying and interacting bats exhibited three distinct and interleaved behavioural phases: (i) Flight phase – where a large fraction of “classical” place cells exhibited social modulation and identity coding. (ii) Social Interaction phase – where a subset of hippocampal neurons encoded specific social interactions (e.g. allogrooming or aggression). (iii) Sedentary phase – where we utilized generalized additive models (GAM, a nonlinear extension of GLM) and explainable machine learning methodologies (like Shapley values) – and found that hippocampal neurons simultaneously encoded the positions of both self and others. This information was represented either allocentrically or egocentrically. Some of these neurons exhibited sparse coding, and represented only a few behavioral dimensions, while other neurons encoded many dimensions. Overall, we found that hippocampal dorsal CA1 neurons combine complex social and spatial information to form a multidimensional representation of the natural world.

4:50 – 5:05 ***Marcel Oberlaender***, Max Planck Institute for Neurobiology of Behavior
Barrel Cortex In Silico

The standard approach to probe the neural basis of sensation and perception is by recording or imaging the activity of neurons during behavior. While such experiments identify neural correlates of sensation and action

in various areas of cortex, it remains generally unclear how the underlying circuits implement these correlates, and how their output to subcortical areas triggers a behavioral response. Mechanistic answers to both of these questions may only be established when the individual activity measurements can be integrated into a coherent model of all task-related circuits. During the past decade, my lab has used the whisker system for building such a model in the context of how a tactile-mediated percept is encoded by the interplay between cellular and circuit mechanisms. For this purpose, we established anatomically and functionally realistic models of the thalamocortical whisker system, and used the models for multi-scale simulations that mimic whisker-evoked signal flow. We demonstrated that the simulations allow us to disentangle in silico – and then test in vivo – cellular and circuit mechanisms that contribute to tactile-based sensation and perception. To share these models, the underlying data, and simulation routines with the scientific community, we developed a publically available, web-based interface. At this meeting, I will introduce this online resource, and discuss how it will facilitate future investigations on barrel cortex structure and function.

5:30 – 9:00 Posters session over dinner

Friday, November 11th

9:00-9:30 ***Garrett Stanley***, Georgia Tech
Windows of Opportunity in the Thalamocortical Circuit 2.0:
A Canonical Computation?

9:30-9:45 Hang Hu, Rachel Hostetler and ***Ariel Agmon***
West Virginia University
Ripplets - ultrafast network oscillations induced in thalamorecipient cortical layers by thalamocortical activation

Oscillations of extracellular voltage, reflecting synchronous rhythmic activity in large populations of neurons, are a ubiquitous feature in the mammalian brain and are thought to subserve critical, if not fully understood cognitive functions. Oscillations at different frequency bands are hallmarks of specific brain or behavioral states. At the higher end of the scale, ultrafast (400-600 Hz) oscillations in the somatosensory cortex, in response to peripheral stimulation, were observed in human and a handful of animal studies; however, their synaptic basis and functional significance remain largely unexplored. Here we report that brief optogenetic activation of thalamocortical axons ex-vivo elicited precisely reproducible, ~410 Hz local field potential wavelets ("ripplets") in middle layers of mouse somatosensory (barrel) cortex. Fast-spiking (FS) inhibitory interneurons were exquisitely synchronized with each other and fired spike bursts in anti-phase with ripplets, while excitatory neurons fired only 1-2 spikes per stimulus. Both subtypes received shared excitatory inputs at ripplet frequency, and bursts in layer 5 FS cells required intact connection with layer 4, suggesting that layer 4 excitatory cells were driving FS bursts in both layers. Ripplets may be a ubiquitous cortical response to exceptionally salient sensory stimuli, and could provide increased bandwidth for encoding and transmitting sensory information. Supported by NIH grant NS116604 to AA.

9:45-10:00 ***A. Bast****, J. M. Guest*, C. P. De Kock, R. T. Narayanan, R. Fruengel, M. Royo, M. Oberlaender; *equally contributing
Max Planck Institute for Neurobiology of Behavior
Thalamus drives coupling of information streams in cortical dendrites

Perception is causally linked to a calcium-dependent spiking mechanism that is built into the distal dendrites of layer 5 pyramidal tract neurons - the major output cell type of the cerebral cortex. It is yet unclear which circuits activate this cellular mechanism upon sensory stimulation. Here we found that the same thalamocortical axons that relay sensory signals to layer 4 also densely target the dendritic domain by which pyramidal tract neurons initiate calcium spikes. Distal dendritic inputs, which normally appear greatly attenuated at the cell body, thereby generate bursts of action potentials in cortical output upon stimulus onset. Our findings indicate that thalamus drives an active dendritic mechanism to couple sensory signals with top-down information streams into cortical output. Thus, in addition to being the central hub for sensory signals, thalamus is also likely to ensure that the signals it relays to cortex are perceived by the animal.

10:00-10:15 Tobias M Leva*, ***Clarissa J Whitmire****, Charlene Memler, James FA Poulet
Max Delbrück Center
Distinct cellular encoding of temperature in the thalamus

Temperature is a fundamental sensory system and key component of somatosensory perception. Unlike almost all other sensory modalities, however, the location and cellular encoding of temperature in the thalamus is unclear. Thalamic neurons could be tightly tuned to warm or cool acting as a labelled line-like pathway or single neurons could encode both warm and cool in a more mixed encoding scheme. To address this, we used high density multielectrode probes (Neuropixels, IMEC) to map cellular activity across multiple somatosensory thalamic nuclei during thermal stimulation of the mouse forepaw. Guided by retrograde labelling from the cortical representation of temperature, we targeted 4 thalamic regions: rostral and caudal ventral posterolateral nuclei (rVPL, cVPL) and posterior medial and triangular nuclei (Pom, PoT). Closely reflecting functional cortical data, we observed that the tuning of a thalamic neuron is correlated to its rostro-caudal location. Cool only neurons were positioned more rostrally, while cool and warm cells were more caudal. Intriguingly, we found that the dynamics of warm and cool encoding are distinct, even in the same neurons, with cool responses being temporally precise with a rapid onset and faster decay, and evoked responses to warm being temporally delayed and more sustained. Taken together, we provide a comprehensive map of thermal encoding in the thalamus that suggest distinct, but overlapping, encoding of warm and cool.

10:15-10:30 ***Luca Mazzucato***, Lia Papadopoulos, Mike Wehr, Su Jo, David McCormick
University of Oregon
Neural mechanism of optimal performance

To thrive in dynamic environments, animals and humans alike must be capable of rapidly and flexibly adapting behavioral responses to changing contexts. Varying internal states such as arousal and attention affect task performance, and optimal performance can be achieved at intermediate arousal, yielding the famous inverted-U law of psychophysics. A major challenge is understanding how cortical circuits can achieve this flexible information processing and whether we can harness these insights to design flexible and efficient artificial agents. In this talk, I will show that mice during auditory and visual decision-making tasks express an array of discrete strategies including optimal strategy, suboptimal ones, and disengaged ones. The optimal strategy occurs at intermediate arousal, measured by pupil size. Using a biologically plausible model of sensory cortex, where arousal is modeled as a top-down modulation of its baseline currents, the inverted-U law can be shown to rely on a phase transition from a metastable phase to a single-attractor phase. From this insight I will introduce a new theory of baseline control in recurrent networks, where optimal task performance can be achieved without any fine tuning of the recurrent couplings. Funding: R01-NS118461, R01-DA055439.

10:30-10:50 Coffee Break

10:50-11:05 ***Krista Marrero***, Krithiga Aruljothi, Behzad Zareian, Zhaoran Zhang, Edward Zagha
University of California, Riverside
Transition in Multiple Temporal Strategies Across Learning for a Selective Detection Task in Mice

Goal-directed behavior paradigms designed within temporal constructs inevitably involve significant contributions of temporal processes, even if the investigation is not temporal in nature; temporal processes include behavior aspects such as anticipation, expectation, timing, waiting, and withholding. And yet, amongst

the vast variety of object-based task paradigms, characterizations of temporal aspects are often neglected. Here, we longitudinally analyzed mice from naïve to expert performance in a somatosensory selective detection task. In addition to tracking standard measures via signal detection theory, we also characterized learning of temporal components. We find that mice transition from general sampling strategies to waiting and timing strategies across training. During this transition, mice learn to wait as they anticipate an expected stimulus presentation and to time their response after a stimulus presentation. By establishing and implementing standardized measures, we show that the development of waiting and timing in task co-occurs with the learning of object detection and discrimination. We also found that males learn to wait and time in tandem but that females demonstrate a temporal intermediate: they improve waiting after they improve timing behavior. Our results emphasize multiple aspects of learning in an object-based task, highlighting the value of spatiotemporal analyses in behavior. NIH NINDS: A01043-29089-44

11:05-11:10 Introduction of second keynote speaker

11:10-12:00 Keynote 2: ***Karel Svoboda***, Allen Institute for Neural Dynamics
Multi-regional neural circuits underlying goal-directed movement

12:00-12:15 ***Deepa L. Ramamurthy***, Andrew Chen & Daniel E. Feldman
University of California, Berkeley
Neural correlates of history-based selective attention in mouse primary somatosensory cortex

Selective attention prioritizes processing of a specific stimulus location or sensory feature to guide ongoing behavior. We developed a task to study selective attention to the whiskers, in order to probe the neural mechanisms for attention. In this task, mice use stimulus-reward associations on recent trials to improve detection of stimuli on the same whisker in subsequent trials, with rapid trial-by-trial dynamics consistent with the hallmark effects of attentional selection. This behavioral effect exhibits a distinct somatotopic gradient, suggesting a substrate in a topographic area like primary somatosensory cortex (S1). We tested for neural correlates of attention in L2/3 PYR cells in S1, using 2-photon calcium imaging. PYR cell activity showed robust history-based cueing consistent with whisker-specific selective attention. Prior hits to a whisker boosted PYR cell responses (dF/F) to subsequent deflection of that same whisker, but not other whiskers. This effect required stimulus-reward conjunction i.e. it did not occur following miss trials to the same whisker. History-based boosting of whisker-evoked PYR cell activity was somatotopically structured with a radius of 1.5 barrel columns. Prior hits also triggered spatially broad ramping of baseline PYR activity that may reflect expectation of an upcoming stimulus. Thus, mice flexibly allocate attention localized to specific whiskers, with corresponding modulation of the S1 neural code. Grants: F32 NS114327 & R37 NS092367

12:15-12:30 ***Michael Sokoletsky***, David Ungarish, Yonatan Katz, and Ilan Lampl
Weizmann Institute of Science
Isolated correlates of somatosensory perception in the mouse posterior cortex

To uncover the neural correlates of stimulus perception, experimenters commonly use tasks in which subjects are repeatedly presented with a weak stimulus and instructed to report, via movement, if they perceived the

stimulus. The difference in neural activity between reported stimulus (hit) and unreported stimulus (miss) trials is then seen as potentially perception-related. However, recent studies found that activity related to the report spreads throughout the brain, calling into question to what extent such tasks conflate perception-related activity with report-related activity. To isolate perception-related activity, we developed a paradigm in which the same mice were trained on both a regular go/no-go whisker stimulus detection task and a reversed contingencies version, in which they reported the absence of a whisker stimulus. By comparing no-report trials across the two tasks, we located perception-related activity within a posterior network of cortical regions contralateral to the stimulus. In addition, we found this activity was on average an order of magnitude lower than report-related activity and began after the low-level stimulus response. In summary, our study revealed the mouse cortical areas associated with the perception of a sensory stimulus independently of a perceptual report.

12:30-1:45 Lunch

1:45-2:00 ***Zhaoran Zhang*** and Edward Zagha
University of California, Riverside
Frontal Cortex Gates Distractor Stimulus Encoding in Sensory Cortex

Frontal cortex suppresses behavioral responses to distractor stimuli. One possible mechanism by which this occurs is by modulating sensory responses in sensory cortex. However, it is currently unknown how frontal cortex modulations of sensory cortex contribute to distractor response suppression. We trained mice to respond to target stimuli in one whisker field and ignore distractor stimuli in the opposite whisker field. During expert task performance, optogenetic inhibition of frontal cortex increased behavioral responses to distractor stimuli. During expert task performance, within sensory cortex we observed expanded propagation of target stimulus responses and contracted propagation of distractor stimulus responses. In contrast to current models of frontal cortex function, frontal cortex did not substantially modulate the response amplitude of preferred stimuli. Rather, frontal cortex specifically suppressed the propagation of distractor stimulus responses, thereby preventing target-preferring neurons from being activated by distractor stimuli. Single unit analyses revealed that wMC decorrelates target and distractor stimulus encoding in target-preferring S1 neurons, which likely improves selective target stimulus detection by downstream readers. Moreover, we observed proactive top-down modulation from frontal to sensory cortex, through the preferential activation of GABAergic neurons. Overall, our study provides important mechanistic details about how frontal cortex gates sensory propagation in sensory cortex to prevent behavioral responses to distractor stimuli. Funding: This research project was supported by NIH/NINDS R01 Grant NS107599 and Whitehall Foundation Grant 2017-05-71.

2:00-2:15 Jim McBurney-Lin Greta Vargova, Machhindra Garad, Edward Zagha, ***Hongdian Yang***
University of California, Riverside
The locus coeruleus drives behavioral switching in a tactile reversal detection task

Behavioral flexibility refers to the ability to adjust behavioral strategies in response to changing environmental contingencies. A major hypothesis in the field posits that the activity of neurons in the locus coeruleus (LC) plays an important role in mediating behavioral flexibility. To test this hypothesis, we developed a novel tactile-based rule-shift detection task where mice responded to left and right whisker deflections in a context-

dependent manner and exhibited varying degrees of switching behavior. Recording spiking activity from optogenetically-tagged neurons in the LC at millisecond precision during task performance revealed a prominent graded correlation between baseline LC activity and behavioral flexibility, where higher baseline activity following a rule change was associated with faster behavioral switching to the new rule. Increasing baseline LC activity with optogenetic activation accelerated task switching and improved task performance. Overall, our study provides important evidence to reveal the link between LC activity and behavioral flexibility. EZ was supported by NIH grant R01NS107599. HY was supported by UCR startup, Klingenstein-Simons Fellowship Awards in Neuroscience, and NIH grants (R01NS107355, R01NS112200).

2:15-2:45 ***Scott Pluta***, Purdue University
Two complimentary codes in the superior colliculus underlie tactile localization

2:45-3:00 **D. G. Lee**, C. McLachlan, A. E. Carey, G. House, G. Lagani, D. LaMay, R. Nogueira, S. Fusi, J. L. Chen
Boston University
Perirhinal cortex acquires a predictive map of the task environment through error learning and associative learning

Through learning, the brain models relationships between stimuli, events, and outcomes. These must be flexible to accommodate unreliable stimuli and novel associations. Perirhinal cortex (Prh) is a region interconnected with sensory cortex and hippocampus which encodes both complex sensory features and their associations. We investigated how Prh participates in goal-directed learning of abstract tactile representations. Mice were trained across multiple learning stages to classify sequential whisker stimuli during a tactile working memory task. Chemogenetic inactivation of Prh in mice trained using automated home-cage training systems confirmed Prh involvement in task learning. To understand how these representations evolve in Prh, we performed chronic two-photon imaging of layer 2/3 neurons over each training session and decoded population activity using support vector machines. With behavioral learning, population decoder performance decreased to task-relevant stimulus features and increased to task-relevant ones. This suggests that Prh learns a model of task-relevant stimuli and signals the difference between what was expected and experienced. Stable reward associations also appeared during early learning, expanding temporally from reward outcome to reward prediction signals. These generalized to incorporate novel stimulus-reward associations. Our results suggest that Prh forms an internal model of learned task behavior by combining error learning and associative learning.

3:00-3:15 Billy Lau, Michael Mykins, Logan Dunn, and ***Keerthy Krishnan***
University of Tennessee
Role of primary somatosensory cortex in innate maternal behaviors

Rodent maternal behavior is comprised of discrete units of behaviors, whose genesis and maintenance are differentially expressed throughout the early lifetime of the young. Both active behaviors such as pup licking and retrieval, as well as passive behaviors such as nursing provide substantial somatosensory input to the mother, primarily in the regions of the snout and the trunk. From lesion studies in the 1980s, it is clear that somatosensation plays an essential role in this process. However, many gaps exist in the underlying circuits, cellular and molecular mechanisms governing sensory perception, sensorimotor integration and long term

memory essential for reliable recall of this critical behavior. Our laboratory is interested in determining the molecular and cellular mechanisms, focusing on epigenetic regulator MECP2 and specialized extracellular matrix structures called perineuronal nets, which are thought to hold long-term memory in sensory cortices. We will present ongoing work that reveals essential roles of these proteins in regulating tactile sensory perception in wild-type adult female mice, highlighting the critical roles that primary somatosensory cortex plays in complex social behaviors.

3:15-3:35 Coffee Break

3:35-3:50 ***Ian Oldenburg***, Rutgers University
Holographic Optogenetic Dissection of Cortical Microcircuits

Both Sensory perception and motor action require the coordinated activity of hundreds or thousands of interrelated and intermixed cortical neurons. However, as these neurons are intermingled, it is incredibly difficult to assess the causal contributions of individual neurons and the interactions of groups of neurons using current technologies. We use and develop multiphoton optogenetic tools to be able to write ever more realistic patterns of activity into the cortex and use these tools to selectively activate small groups of neurons to understand the role of recurrent activity in the visual cortex. We find that neither tuning or location rules of cortical connectivity alone can predict the interactions between cells. Instead, these two dimensions interact in unpredicted ways. Furthermore, we extend our optogenetic toolbox, with new strategies and constructs to allow us to probe the neural code in an ever more precise manner. R00 EY029758

3:50-4:05 Daniel L. Gonzales, Hammad F. Khan, H.V.S Keri, Lyle Muller, Scott R. Pluta, ***Krishna Jayant***
Purdue University
Mapping the cellular and sub-cellular circuit motifs underlying touch-evoked travelling waves from the cortical surface in awake behaving mice

Traveling waves in mammalian cortex mediate vital aspects of animal cognition, such as stimuli perception and working memory. Theoretical results suggest that these low-frequency oscillations preserve timing across long-range neural circuits; thus, revealing the circuit mechanisms for traveling waves is critical to our understanding for how distributed computations maintain millisecond precision. We introduce high-density micro-scale transparent ECoG electrodes and map (electrically and optically via 2P imaging) travelling waves across the barrel cortex in awake mice under active and passive whisker touch. We observe that TWs across the barrel cortex are enabled by a sparse ensemble structure in L2/3 and that a late reverberatory wave appears 100's of ms post touch. Strikingly, we show that the origins of this late wave is tied to L5 apical dendritic spikes. We present a computational model to validate sparseness as a function of the travelling wave and discuss future work. Funding: This work was supported by the following institutes and grants to K.J. NIH R21EB029740 Trailblazer Award; HFSP RGY0069; ORAU Ralph E. Powe Junior Faculty Enhancement Award, and the Purdue Institute for Integrative Neuroscience. This material is based upon work supported by the Air Force Office of Scientific Research under award number FA9550-22-1-0078.

4:05-4:35 ***Anna Schroeder***, M. Belén Pardi, Joram Keijser, Tamas Dalmay, Erin M. Schuman, Henning Sprekeler, Johannes J. Letzkus
University of Freiburg
Inhibitory top-down projections from zona incerta control neocortical memory

Top-down projections convey a family of signals encoding previous experiences and current aims to sensory neocortex, where they converge with bottom-up information from the environment to enable perception and memory. Whereas top-down control has been attributed to excitatory pathways, the existence, connectivity and information content of inhibitory top-down projections remains elusive. Here we combine synaptic 2-photon calcium imaging, circuit mapping, cortex-dependent learning and chemogenetics to identify GABAergic afferents from the subthalamic zona incerta as a major source of top-down input to neocortex. Incertocortical transmission undergoes robust plasticity during learning that improves information transfer and controls behavioral memory. Unlike excitatory pathways, incertocortical afferents form a disinhibitory circuit which encodes learned top-down relevance in a bidirectional manner where the rapid appearance of negative responses serves as the main driver of changes in stimulus representation. Our results therefore reveal the distinctive contribution of long-range (dis)inhibitory afferents to the computational flexibility of neocortical circuits. This work was supported by the Max Planck Society, the German Research Foundation (LE 3804/3-1, LE 347 3804/4-1, LE 3804/7-1 to J.J.L.), a Marie Skłodowska-Curie Fellowship (840701 to A.S.), an EMBO Long-Term Fellowship (ALTF 882-2018 to A.S.), and an Alexander von Humboldt Fellowship (to A.S.).

4:35-4:50 ***Felipe Yáñez***, Messore, F., Qi, G., Sakmann, B., Feldmeyer, D. & Oberlaender, M.
Max Planck Institute for Neurobiology of Behavior
Robust cell-type prediction of cortical GABAergic interneurons

Cortical GABAergic interneurons (INs) are a rich and diverse class of neurons. At the single-cell level, attributes such as morphology, intrinsic physiology, connectivity patterns, and gene expression profiles exhibit complex patterns of variation, making them difficult to characterize. Here, we systematically assess the degree and character of the variability of morphoelectric and molecular properties across the entire cortical depth of the rat barrel cortex. First, we acquire a sample of 306 INs and quantitatively test its representativeness against the absolute number of INs in the rat barrel cortex. For each neuron, we compute a comprehensive list of descriptive features. Then, we assign neurons into morphoelectric types using standardized multimodal clustering methods and evaluating the robustness of cluster assignments. Throughout the entire barrel cortex, we determine the absolute number and density distribution of the three most predominant molecular marker classes. We compare the relative abundances across the cortical depth of molecularly defined IN types, with those determined by morphoelectric properties. Thus, this methodology allows us to (i) develop empirical models that reveal the degree to which particular features (such as somatic depth location) are predictive of an IN's type, and (ii) perform cross-species analyzes that provide quantitative insight into the relationships between types in the mouse motor, mouse visual, and rat barrel cortices.

4:50-5:05 ***Atika Syeda***, Renee Tung, Will Long, Marius Pachitariu, Carsen Stringer
Janelia Research Campus
Interpretable behavioral features have conserved neural representations across mice

Recent studies in mice have shown that ongoing behaviors drive a large fraction of neural activity across the brain. However, the principal components (PCs) of behavioral video recordings used in these studies are hard

to interpret what specific behaviors are encoded in the neural activity and comparisons across mice remain difficult. To address this, we developed new models of behavior for predicting the activity of ~50,000 simultaneously recorded neurons. We used simultaneous multi-camera video recordings to show that orofacial behaviors alone predict neural activity as well as behavioral features from the entire body. We thus tracked 15 distinct keypoints on the mouse face using a novel neural network model that was as accurate as state-of-the-art pose estimation tools DeepLabCut and SLEAP, while the inference speed was several times faster, making it a powerful tool for closed-loop behavioral experiments. Pose relationships derived from the keypoints predicted a much higher proportion of neural activity than the PCs. We retrained the neural network on keypoints of multiple mice recorded from arbitrary camera angles to develop a universal mouse model that predicted neural activity as well as a model fit to a single mouse. Investigating latent states from the model identified behaviors and their neural representations shared across mice. Hence, we developed a robust modeling framework for neural activity based on orofacial behaviors shared across mice.

5:05-5:35 ***Michael Brecht***, BCCN / Humboldt University
The biology of grasping in elephants

ADJOURN

BARRELS XXXV POSTER ABSTRACTS

Krithiga Aruljothi, Emaan Kaur, Edward Zagha
University of California Riverside
Emergence of focal distractor attenuation of sensory-motor propagation for a selective detection task in mice during learning

An essential feature of goal-directed behavior is the ability to selectively attend to various stimuli during decision-making. Previous studies have observed an established attenuation of distractor sensory to motor signal propagation in distractor aligned cortices for a selective detection task in mice. Expert behavior exhibits many components for ignoring distractors, but the emergence of an attenuating filter through learning remains unknown. This study focuses on investigating the process from naïve through expert stages of impulse control for mice learning a go/no-go whisker-based selective detection task utilizing a transgenic pan-neuronal GCaMP mouse line for widefield Ca2+ imaging. One hypothesis is that in naïve mice, both target and distractor sensory signals propagate to the frontal cortex effectively and through learning, the distractor sensory to motor signal propagation is suppressed while the target signal propagation is unaffected. An alternate hypothesis would be that in naïve mice, neither target nor distractor sensory signals propagate to the frontal cortex, but through learning, target sensory signal propagates effectively to the frontal cortex while distractor sensory signal fails to propagate. This study also explores how task-relevant and task-irrelevant neural representations of movement in the cortex change through learning and what role whisker motor cortex (wMC) plays in sensory-motor processes through learning.

John Martin Barrett, Megan E Martin, Gordon M G Shepherd
Northwestern University
Manipulation-specific cortical activity as mice handle food

Food-handling offers unique opportunities to investigate how cortical activity relates to forelimb movements in a natural, ethologically essential, kinematically rich form of manual dexterity. To this end, we recorded 1000 fps video and cortical spiking activity while mice handled food. Decomposing active manipulation ('oromanual') events into characteristic submovements enabled event-aligned analysis of cortical activity. Activity in forelimb M1 was modulated during food-handling: higher during oromanual events and lower during holding intervals. Optogenetic silencing & stimulation of forelimb M1 neurons partially affected food-handling movements, exerting suppressive and activating effects, respectively. We extended the analysis to forelimb S1 and lateral M1, finding oromanual-related activity in all three areas, with distinct timing and phasic/tonic temporal profiles. Non-negative matrix factorization analysis attributed this to area-specific composition of activity classes. Forelimb position could be predicted from activity in all three regions, indicating that cortical activity in these areas contains much information about forelimb movements during food-handling. These results establish that cortical activity during food-handling is manipulation-specific and distributed across multiple sensorimotor areas, exhibiting area- & submovement-specific relationships with the kinematic features of this natural form of manual dexterity. Funding: NIH grants R01NS061963, R21NS11.

K. E. Bonekamp, H.-H. Kim, C. Jones, L. E. Martinetti, S. Dash, D. M. Autio, T. Keller, A. Rachor, J. Ackermann, S. R. Crandall
Department of Physiology, Michigan State Univeristy, East Lansing, MI

Identification of an inhibitory circuit that mediates motor integration in the somatosensory cortex

According to the corollary discharge theory, motor centers send signals informing sensory areas of ongoing motor actions, suppressing the expected sensory input. However, the mechanism underlying such suppression within the cortex is unclear. Using optogenetics, we find that input from the whisker primary motor cortex (wM1) activates layer 6 (L6) parvalbumin (PV)-expressing inhibitory cells whose axons arborize locally within deep layers mores strongly than any other interneuron population in whisker somatosensory cortex. The greater responsiveness of these PV interneurons was not due to unique intrinsic properties or local circuit interactions but was produced by synaptic mechanisms. Notably, wM1 axons made stronger excitatory connections onto these PV cells than other neurons. Recordings in behaving mice also reveal that some excitatory neurons are suppressed before whisking, whereas some PV interneurons increase their activity. Our results provide a synaptic circuit mechanism for motor-related corollary discharge in cortex that may help tactile sensation and whisker-dependent behaviors. Funding: NIH Grant RO1-NS117636, NIH Grant K99/R00-NS096108, NIH Grant F31-NS124244, Michigan State Startup

Zoe Dobler[1,2], Supriya Mula[2], Carlos Portera-Cailliau[2,3]
[1]UCLA Interdepartmental PhD Program in Neuroscience, [2]Dept. of Neurology, David Geffen School of Medicine at UCLA, [3]Dept. of Neurobiology, David Geffen School of Medicine at UCLA
The remarkably dynamic identity of adapting and facilitating neurons in mouse somatosensory cortex

To construct a stable and coherent experience of the external world, sensory circuits must adapt their activity to the statistics of the surrounding environment and filter out irrelevant stimuli. This is achieved in part via stimulus-evoked sensory adaption (SA), characterized by a progressive decrease in neuronal activity in response to repetitive sensory stimulation. While SA has been extensively studied at the level of individual neurons on timescales of tens of milliseconds to a few seconds, little is known about SA over longer timescales or at the population level. Here, we investigate population-level SA in the barrel field of the mouse somatosensory cortex (S1BF), which processes whisker inputs, using in vivo 2-photon calcium imaging (GCaMP6s) of layer 2/3 excitatory neurons in awake adult Slc17-Cre x Ai162 mice. The activity profiles of stimulus-responsive (SR) neurons varied widely across a population: in addition to previously described adapting neurons that decreased their firing with repetitive stimulation, we also found facilitating neurons which increased their activity, and still others that were neither adapting nor facilitating. Within each of these populations, individual responses to different whisker deflections were strikingly heterogeneous and stochastic. We also discovered that adaptation to one stimulus does not always generalize to different stimuli. Indeed, when we exposed mice to 10 whisker stimuli at one frequency followed by a second bout at an alternate frequency, we found that adapting neurons (but not facilitating neurons) exhibited significantly increased response peak amplitudes after switching to a higher frequency. Finally, we investigated the stability of population SA dynamics by recording the same neurons during bouts of 20repetitive whisker stimulations across 8-9 days. Remarkably, most SR neurons did not maintain the same dynamics across days. Not only were the proportions of adapting or facilitating neurons dynamic over days, but the activity profile of individual neurons (adapting vs. facilitating) could change drastically from one day to the next. These results indicate that 1) Population-level SA is encoded heterogeneously in S1BF and does not universally generalize; 2) Adapting neurons are most sensitive to shifts in stimulus parameters; and 3) Exposure to the same repetitive stimulus over days shifts the balance between adaptation and facilitation at the population level.

Goz[1] R. U.; Schneider[2] N. A.; Arnold[2] M. P.; Williamson[2] R. S.; Hooks[1] B. M

Departments of Neurobiology1 and Otolaryngology2, University of Pittsburgh School of Medicine
Cortical and thalamic input to pairs of parvalbumin positive interneurons and pyramidal excitatory neurons is correlated

In mammalian cortex, feedforward excitatory connections invariably recruit feedforward inhibition. This is often carried by fast-spiking (parvalbumin, PV+) interneurons, which potentially connect densely to local pyramidal (Pyr) neurons. Whether this inhibition generically inhibits all local excitatory cells or is targeted to specific subnetworks is unknown. Here, we test how feedforward inhibition is recruited by cortical and thalamic afferents by using 2-channel circuit mapping to excite (S1 and PO) inputs to PV+ interneurons and pyramidal neurons of mouse motor cortex. We find that connected pairs of PV+ interneurons and excitatory pyramidal neurons receive correlated cortical and thalamic inputs. This suggest that excitatory inputs to M1 target inhibitory networks in a specific pattern which permits recruitment of feedforward inhibition to specific subnetworks within the cortical column. We then develop methods for in vivo circuit mapping to study changes in the connection strength of cortical and thalamic inputs to PV+ and Pyr neurons. This will enable a temporal understanding of how synaptic connectivity changes in cortical circuits during learning and disease. This work was supported by a CDMRP PRMRP Discovery Award PR201842 (RUG and BMH), a NARSAD Young Investigator Award (BMH), and NIH NINDS R01 NS103993 (BMH).

Chiaki Itami1,2, Naofumi Uesaka3, Jui-Yen Huang2, Hui-Chen Lu2, Kenji Sakimura4, Masanobu Kano3,5, Fumitaka Kimura6,7
1Saitama Med Univ, Saitama, Japan, 2Indiana Univ, Bloomington, IN, 3Univ of Tokyo, Tokyo, Japan, 4Niigata Univ, Niigata, Japan, 5Int. Res. Center for Neurointelligence (WPI-IRCN), Japan, 6Osaka Univ. , Suita, Japan, 7Jikei Univ. of Health Care and Sciences, Osaka, Japan
Endocannabinoid-dependent formation of columnar axonal projection in the mouse cerebral cortex

Columnar structure is one of the most fundamental morphological features of the cerebral cortex and is thought to be the basis of information processing in higher animals. Yet, how such a topographically precise structure is formed is largely unknown. Formation of columnar projection of layer 4 (L4) axons is preceded by thalamocortical formation, in which type 1 cannabinoid receptors (CB1R) play an important role in shaping barrel-specific targeted projection by operating spike timing-dependent plasticity (STDP) during development (Itami, et al, 2016, Kimura et al. 2019). Right after the formation of thalamocortical projections, CB1Rs start to function at L4 axon terminals (Itami et al., 2012), which coincides with the timing of columnar shaping of L4 axons. Here we show that the endocannabinoid 2-arachidonoylglycerol (2-AG) plays a crucial role in columnar shaping. We found that L4 axon projections were less organized until P12, and then became columnar after CB1Rs became functional. By contrast, the columnar organization of L4 axons was collapsed in mice genetically lacking diacylglycerol lipase α (DGLα), the major enzyme for 2-AG synthesis. Intraperitoneally administered CB1R agonists shortened axon length, whereas knockout of CB1R in L4 neurons impaired columnar projection of their axons. Our results suggest that endocannabinoid signaling is crucial for shaping columnar axonal projection in the cerebral cortex. JSPS KAKENHI grant JP26430022 (CI), JP20K06911 (FK)

Alishah Lakhani, Pete Wenner
Homeostatic plasticity in the developing barrel cortex following unilateral whisker deprivation

Homeostatic plasticity represents a set of compensatory mechanisms that ensure the maintenance of activity levels following different kinds of perturbations. Whisker deprivation can trigger both synaptic compensations

and intrinsic compensations of membrane excitability. While different methods of whisker deprivation produce distinct responses, unilateral whisker deprivation for 7-14 days in P30 mice has been shown to trigger homeostatic plasticity in the barrel cortex, expressed as an increase in whisker-evoked responses in L4 and L2/3 excitatory neurons. To characterize the homeostatic capacity at an earlier stage of development, I have begun unilateral trimming whisker trimming every other day from postnatal day 14-28. I record whisker-evoked spiking using a 3x3 array of piezoelectric stimulators to stimulate the PW and surrounding whiskers at multiple velocities. I then examine spiking activity in the L4 and L2/3 cortex using a 32-channel NeuroNexus probe. Preliminary results suggest that the whisker-deprived mice show a homeostatic increase in whisker-evoked firing in L4 compared to non-deprived control mice. I will record at multiple time points within this deprivation period to observe how homeostatic plasticity mechanisms alter excitability over development. Autism mouse models have been associated with impaired homeostatic mechanisms. Therefore, I will examine the possibility that homeostatic responses to whisker deprivation are altered in autism.

Liu Y, Délez L, Crochet S and Petersen CCH
Laboratory of Sensory Processing, Brain Mind Institute, EPFL, Switzerland
Quantification of axonal projections from neurons located in layers 2/3, 5 and 6 of mouse barrel cortex

Mice are nocturnal animals that rely heavily on their whiskers to sense the outside world. Whisker sensory information arriving from the ventral posterior medial nucleus of the thalamus is processed in the primary whisker somatosensory cortex (also known as the barrel cortex, S1-bfd). Projection neurons in S1-bfd in turn signal to various downstream brain areas including motor cortex, secondary sensory cortex, striatum, superior colliculus, thalamus, pons and brain stem. Different classes of S1-bfd neurons innervate different targets, but the precise organisation and quantification of axonal innervation remains to be determined. Here, we use adenoassociated viral (AAV) vectors to express fluorescent proteins in genetically-defined neuronal classes in S1-bfd. We injected Cre-dependent AAVs into various Cre-driver mice in order to express GFP and/or tdTomato in layer 2/3 (Rasgrf2-dCre), layer 5 (Sim1-Cre, Tlx3-Cre and Rbp4-Cre) and layer 6 (Ntsr1-Cre). After several weeks of expression, the fixed brains were immunostained and cleared through a variant of iDISCO (Renier et al., Cell 2014). Volumetric brain images were acquired by a MesoSPIM light sheet microscope (Voigt et al., Nat. Methods 2019). Voxels containing axons were segmented using TrailMap, a trained 3D convolutional network (Friedmann et al., PNAS 2020). Finally, images were aligned to the Allen mouse brain atlas (Wang et al., Cell 2020), and axonal length was quantified according to the annotated parcellations.

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1 Neuroscience Program, Michigan State University, East Lansing, MI
2 Department of Physiology, Michigan State University, East Lansing, MI
Motor control of layer 6 corticothalamic circuits in the somatosensory cortex

In the mouse whisker system, projections from the primary motor cortex (M1) to the somatosensory cortex (vS1) are thought to facilitate active sensation and sensorimotor integration by conveying motor-related signals. vM1 axons concentrate in layer 1 (L1) of S1, but also branch off in deep layers where they have excitatory effects, including in L6 corticothalamic (CT) neurons. L6 CT cells are uniquely situated where they can influence the sensory throughput of the thalamus and cortical responsiveness. Previous work has identified three general classes of L6 CT cells based on their thalamic axonal projections: (1) only to the ventral posterior medial nucleus (VPm), (2) both the VPm and the posterior medial nucleus (POm), and (3) only the POm. However, the afferent connectivity of M1 and the mechanisms by which it controls L6 CT circuits are

largely unknown. Here, we combined retrograde tracing with in vitro recordings and optogenetic control of M1 to study its synaptic effects on different L6 CT cells. We find differences in intrinsic membrane properties of different CT cells, and that CT cells segregate into sublayers, consistent with previous anatomical work. Optical stimulation of M1 axons/terminals evoked the strongest synaptic currents in VPM/POm projecting CT cells than the other classes. These results start to reveal mechanistically how inputs from M1 can influence the excitability of distinct L6 CT cells and perhaps the activity in specific thalamocortical circuits.

F Messore (1), F Yañez (1), JM Guest(2), M Oberlaender (1)
(1) Max Planck Institute for Neurobiology of Behavior – Caesar
(2) Max Planck Florida Institute for Neuroscience
Primary thalamic input governs the embedding of neurons in feedforward and feedback inhibitory circuits

Thalamus functions as the main relay nucleus of all incoming sensory and motor information to the cerebral cortex. How is organized in layer 4 and the upper layers, and the interplay between excitation and inhibition in these layers has been extensively characterized. Owing to their difficult access, and limits of current imaging techniques, the organization principles of synaptic inhibition in the deeper layers remain to be fully understood. Hence, we investigated how the thalamus targets and activates identified inhibitory and excitatory neurons. We find a clear distinction between a subset of inhibitory neurons whose response precedes and those who succeeds the excitatory response. Nevertheless, we do not see a clear distinction between these populations in term of their classical cellular properties, as can be seen for the upper layers. This lack of correlation denotes the possible difference in either their thalamic input or circuit configurations. Our findings indicate that the segregation between those INs that precede and those that succeed excitation seems to be general feature of synaptic inhibition across layers. Nevertheless, in the deeper layers both inhibitory circuits are highly heterogeneous in term of their classical cellular properties and points to the possibility that in the deeper layers, the TC input onto inhibitory neuron could be more associated with a laminar organization than to a particular cellular type.

Marco Nigro, Lucas Silva Tortorelli, Hongdian Yang
University of California Riverside
The role of locus coeruleus-prefrontal cortex pathway to mediate flexible behavior

Cognitive flexibility, the ability to adjust behavioral strategies in response to changing environmental contingencies, requires adaptive processing of internal states and contextual cues to guide goal-oriented behavior and depends on prefrontal cortex (PFC) functions. However, the neurophysiological underpinning of how the PFC supports cognitive flexibility is not well understood. To address this question, we first recorded spiking activity from PFC neurons in mice performing the attentional set-shifting task. These recordings revealed largely distinct subgroups of neurons encoding different flexibility-related variables, namely task context, trial outcome, and decision. Importantly, we found that task context and trial outcome modulated decision signals in a task stage-dependent manner. Next, we showed that noradrenergic (NA) input arising from the locus coeruleus (LC) is important for cognitive flexibility as inhibiting NA input to the PFC impaired switching behavior. Recordings from the LC revealed that LC neurons were differently modulated during decision-related processes. Together, our data show that the PFC encodes key flexibility-related variables and suggests that LC-NA input supports PFC function and cognitive flexibility.

Pala A. and Stanley G. B.
Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta GA 30332, USA
Cell-type specific signatures of bilateral tactile signal integration in awake mouse somatosensory cortices

To produce a coherent sensation of the external world, the brain must integrate tactile information obtained through both sides of the body. The cellular organization and the detailed effect of bilateral tactile signal integration on cortical sensory activity are still mostly unknown. Further, it is unclear how properties of the bilateral tactile signals and whether they are produced during movements modulate integration. Here, we targeted laminar silicon probe recordings to the whisker region of somatosensory cortices in awake head-fixed mice while delivering single-whisker unilateral and bilateral sensory stimuli. We found that the amplitude of sensory responses evoked in regular-spiking neurons by bilateral stimuli was most commonly reduced without change in variability or latency when compared to responses evoked by contralateral stimuli. Then, we compared population velocity response curves measured in response to contralateral stimuli with or without associated ipsilateral stimulation. We observed both subtractive and divisive interactions, as a function of the relative timing between contralateral and ipsilateral stimuli and of the neuron responsiveness to ipsilateral stimuli. In summary, our results reveal the role of bilateral tactile signal integration in shaping the representation of tactile information with cellular resolution. Funding: NIH/NINDS BRAIN R01NS104928; NIH/NINDS R21NS112783; SNSF Postdoctoral Fellowships P2ELP3_168506 and P300PA_177861.

Ravi Pancholi, Lauren Ryan, Simon Peron
New York University Center for Neural Science
Representational stability impacts learning of a sensory cortical microstimulation task

Sensory cortical activity is dynamic. Across sensory cortex, the responses of neurons representing a particular stimulus feature change over time. However, it remains unclear whether the stability of stimulus representations in sensory cortex has an impact on perception and behavior. Optical microstimulation is an effective means of studying representational stability because it enables precise control of the stimulated population, circumvents neural processing prior to cortex, and forces animals to use the evoked activity to perform a behavioral task. We studied the perceptual impact of representational stability by using two-photon calcium imaging to track neural activity as mice learned an optical microstimulation task. Mice were required to discriminate between a high and low number of optogenetic pulses delivered to several thousand opsin-expressing pyramidal neurons in layer 2/3 of primary vibrissal somatosensory cortex. Mice learned the task at varying rates, though levels of evoked activity did not differ between animals that learned the task and those that did not. The photoresponsive population showed instability both within and across behavioral sessions that was elevated among animals that failed to learn the task. Moreover, we found that stimulus decoding from neural activity degraded more rapidly among animals that failed to learn the task. Our results show that the rate at which sensory cortical representations change constrains learning and impacts behavior.

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Interactions between vS1 and vS2 touch populations during a two-whisker behavior

In mammalian cortex, sensory information is propagated across hierarchically organized cortical areas. Primary sensory areas and higher-order areas often exhibit reciprocal connectivity, yet the functional role of

this circuitry remains unclear. In the whisker system, primary vibrissal somatosensory cortex (vS1) sends projections to secondary vibrissal somatosensory cortex (vS2) and vS2 sends strong feedback projections to vS1. Though both areas have been extensively studied, interactions between vS1 and vS2 and the effect of these interactions on the areas' touch responses remain poorly understood. Here, we use volumetric two-photon calcium imaging to map the receptive fields of vS1 and vS2 touch neurons in mice performing a two-whisker active touch behavior. We find that touch neurons in vS2 have broader receptive fields and display longer lasting responses than touch neurons in vS1. Permanently lesioning a single barrel in vS1 leads to a whisker-specific decline in vS2 touch activity. Lesioning vS2 also leads to declines in vS1 touch responses. Our work suggests that inter-areal recurrence plays an important role in generating sensory responses.

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Sensory processing deficits in a mouse genetic model of epileptic encephalopathies

ANK3 is a leading candidate gene in Bipolar disorder (BD). Decreased expression of ANK3 isoforms containing exon 1b increase BD susceptibility. The axon initial segments (AIS) of parvalbumin interneurons contain only exon 1b Ankyrin-G isoforms. Genetic deletion of exon 1b leads to a penetrant, dosage-dependent phenotype including epilepsy, sudden death, and behavior changes modeling BD. However, little is known about how sensory information is processed in these animals. Methods. The cortical responses induced by single air-puff stimulation of the whiskers in head-fixed freely behaving animals were subject to a series of data analysis. Ank3-1b-/- , but not the wild-type (WT) mice, fails to discriminate the novel object from familiar object in a standard NOR test. Results. 1. The CSD plot of the air-puff induced cortical responses are very robust and highly reproducible during repeated experiments. The signatures of current sinks and sources are significantly different between Ank3-1b-/- and wild-type controls. 2. There were significant differences in the area under the curve and the half-width of the single air-puff induced PSTH curves between WT and Ank3-1b-/- mice. 4. Cortical neurons in different layers fires less synchronously in the Ank3-1b-/- mice. Conclusions. Our data demonstrate the circuit features underlying sensory processing deficits and explains how does the changes in the excitability of parvalbumin interneurons, causes sensory endophenotype. NIH.

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Primary somatosensory cortex is required for the consolidation of a one-session thermal detection task

Sensory detection tasks are amenable to cellular resolution recordings in head-fixed mice, but training is typically takes multiple sessions, thereby preventing access to the early consolidation phase. To address this, we developed a single session go/no-go thermal detection task for head-fixed mice with tight control of the stimuli and rewards. Mice were trained to report a 10°C cooling stimulus delivered to their forepaw by licking for a water reward. Remarkably, mice learnt the task within ~50 trials (n = 65 mice) without any prior exposure to the stimulus or reward. Rather than a gradual improvement in reporting throughout the training session, our data show that mice performed a switch in their behavior from poor to expert performance. To examine the impact of forepaw primary somatosensory cortex (fS1) on consolidation, we went on to manipulate fS1 activity after the end of the training session. Inhibition of fS1 by local pharmacological silencing or optogenetic

stimulation of GABA-ergic inhibitory interneurons <2 hours following the end of training impaired memory consolidation as measured by reduced task performance on the subsequent day, All other controls with difference in time and place of manipulation showed no effect on task performance. These data indicate that fS1 is involved in early consolidation of thermal learning. European Research Council (ERC-2015-CoG-682422)Deutsche Forschungsgemeinschaft (FOR 2143, SFB1315)Helmholtz SocietyHFSP (LT000359/2018)

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Emerging experience-dependent dynamics in primary somatosensory cortex reflect behavioral adaptation

The primary somatosensory cortex (S1) is classically described as the origin of neuronal signals in response to tactile stimuli. In a recent study we observed that S1 not only relays ascending sensory signals but also plays an important role in mediating long-term adaptive context-dependent behaviors. Our finding suggests a signal transfer of these context-dependent changes between different brain structures along the sensory-motor arc, where S1 is transducing signals necessary for adaptive behavior. To understand the mechanism of this transfer, we are currently exploring the manipulation of corticothalamic neurons in behaving mice. We are optogenetically activating neurons in layer 6, which are cortical gain modulators that project across cortical layers and to the thalamus (L6ct). Manipulation of L6CT neurons produces bidirectional effects, resulting in either excitation or suppression of thalamic neurons. Our pilot experiments suggest that targeted L6CT manipulation has a bidirectional effect on behavior. Animals are highly sensitive to higher light intensities; strong repetitive activation causes an increase in “guessing” behavior (false alarms). Weak light levels cause a change in the slope of the psychometric curve towards optimal detection of whisker stimuli. Our findings suggest that this circuit could be the node through which signals from several brain areas interact making it critical for an animals’ survival strategies. NIH Brain R01NS104928, RF1NS128896

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An ultra-fast two-photon microscope for sustained, low-light in vivo voltage imaging of neuronal populations in mouse cortex

Understanding the complexity of neural networks in vivo requires simultaneous recordings of neuronal populations with action potential resolution. Genetically-encoded voltage indicators (GEVIs) featuring fast dynamics necessitate the development of kilohertz-rate two-photon (2P) imaging systems. Existing high-speed 2P microscopes scan restricted field of views (FOVs), limiting the number of simultaneously imaged neurons. We developed an Ultra-Fast 2-Photon (UF2P) microscope which is capable of full-frame kilohertz-speed imaging of a 400x400µm2 FOV of up to ~300µm deep in mouse cortex. A combination of temporal and spatial multiplexing was applied in the system. A 920nm-wavelength, 31.25MHz repetition rate laser was used to deliver laser pulses that were temporally multiplexed into 4 beamlets. Each beamlet was spatially multiplexed into two beams spaced 200µm apart at sample. Photons from multiplexed beams were resolved by a multi-anode photomultiplier tube (spatial) and digital gating (temporal). We applied the UF2P microscope with

novel positive-going GEVIs (SpikeyGi and SpikeyGi2) for in vivo voltage imaging in mouse cortex. A self-supervised denoising algorithm model (DeepVID) was trained for reducing shot noise in low photon-flux condition. Through combining all techniques above, we achieved simultaneous high-speed, deep-tissue imaging of >100 densely-labeled neurons in awake behaving mice for over an hour with minimal photobleaching, thermal effect and photodamage.

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Single genomic enhancers drive experience-dependent GABAergic plasticity to maintain sensory processing in the adult cortex

Experience-dependent plasticity of synapses modulates information processing in neural circuits and is essential for cognitive functions. Genomic enhancers are thought to modulate specific sets of synapses by regulating experience-induced transcription to thereby promote neural circuit plasticity. However, this idea remains untested. Thus, here we analyze the cellular and circuit functions of the genomic mechanisms that control the experience-induced transcription of Igf1 (Insulin-like growth factor 1) in disinhibitory VIP interneurons in the adult visual cortex. We find that two sensory-induced enhancers selectively and cooperatively drive sensory-induced Igf1 transcription and that these enhancers homeostatically control the ratio between excitation and inhibition (E/I-ratio) and neural activity in VIP interneurons to thereby restrict visual acuity. Thus, single experience-regulated enhancers are essential for maintaining sensory processing. Since cortical plasticity scales with neural activity in VIP interneurons, this also suggests that experience-induced transcription restricts plasticity in adult neural circuits to preserve the brain's functional integrity.

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Directed motor actions and choice signaling drive cortical acetylcholine dynamics.

Numerous cognitive functions including attention and learning are influenced by the dynamic patterns of acetylcholine release across the brain. How acetylcholine mediates these functions in cortex remains unclear, as the relationship between cortical acetylcholine and behavioral events has not been precisely measured across task learning. To dissect this relationship, we quantified motor behavior and sub-second acetylcholine dynamics in primary somatosensory cortex during acquisition and performance of a tactile-guided object localization task. We found that acetylcholine dynamics were directly attributable to whisker motion and licking, rather than sensory cues or reward delivery. As task performance improved across training, acetylcholine release associated with the first lick in a trial became dramatically and specifically potentiated, paralleling the emergence of a choice-signaling basis for this motor action. These results show that acetylcholine dynamics in sensory cortex are driven by directed motor actions to gather information and act upon it.

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