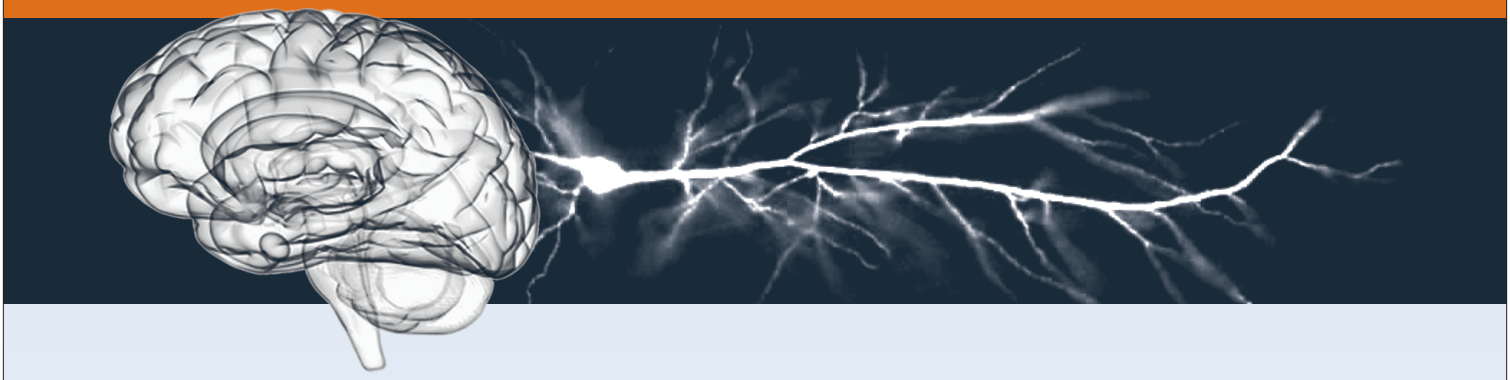
UT Austin Conference on Learning & Memory



Hosted by The Center for Learning and Memory
The University of Texas at Austin

APRIL 26–27, 2019

KEYNOTE SPEAKER

Sheena Josselyn
The Hospital for Sick Children
University of Toronto

SESSIONS SPEAKERS

Audrey Brumback, The University of Texas at Austin
Lu Chen, Stanford University School of Medicine
Daniel Colón-Ramos, Yale University School of Medicine
Lila Davachi, Columbia University
Norbert Fortin, University of California, Irvine
Michael Halassa, Massachusetts Institute of Technology
Elizabeth Hillman, Columbia University
Karla Kaun, Brown University
Nancy Kopell, Boston University
Jennifer Li, Harvard University
Sergiu Pasca, Stanford University
A. David Redish, University of Minnesota
Drew Robson, Harvard University
Per Sederberg, University of Virginia
Jason Shepherd, University of Utah
Ryohei Yasuda, Max Planck Florida Institute for Neuroscience
Yi Zou, University of California, Santa Cruz

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The 2019 Austin Conference on Learning & Memory is supported by a grant from the NINDS

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Yi Zuo, University of California, Santa Cruz

Conference Schedule

All conference sessions will take place in the Texas Union Shirley Bird Perry Ballroom (UNB 3.202).

FRIDAY, APRIL 26, 2019

7:30–8:20 Breakfast

8:20–8:30 Welcome
Dan Johnston, The University of Texas at Austin
Director, Center for Learning & Memory

8:30–10:15 Session 1: Temporal Coding in Episodic Memory
Session Co-chairs:
Alison Preston, The University of Texas at Austin, Center for Learning & Memory
Norbert Fortin, University of California, Irvine, Department of Neurobiology and Behavior

8:30–8:45 Norbert Fortin, University of California, Irvine
Department of Neurobiology and Behavior
Introduction to the field: *"A brief historical perspective on temporal coding, sequences, and memory: It's about time"*

8:45–9:15 A. David Redish, University of Minnesota
Department of Neuroscience
"Remember the future and imagining the past: Studies in mental time travel"

9:15–9:45 Lila Davachi, Columbia University
Department of Psychology
"Transcending time in the brain: How event memories are constructed from experience"

9:45–10:15 Per Sederberg, University of Virginia
Department of Psychology
"Neural representations over wide spatiotemporal scales support learning in an uncertain world"

10:15–10:45 Break

10:45–12:30 Session 2: Synaptic Plasticity of Learning and Memory
Session Co-chairs:
Kristen Harris, The University of Texas at Austin, Center for Learning & Memory
Yi Zuo, University of California, Santa Cruz, Department of Molecular Cell and Developmental Biology

10:45–11:00 Yi Zuo, University of California, Santa Cruz
Department of Molecular Cell and Developmental Biology
Introduction to the field: *"Molecular signaling in the postsynaptic arena"*

11:00–11:30 Ryohei Yasuda, Max Planck Florida Institute for Neuroscience
"Biochemical signal computation in dendritic spines"

11:30–12:00 Jason Shepherd, University of Utah
Department of Neurobiology and Anatomy
"Viral-like mechanisms of synaptic plasticity"

12:00–12:30 Lu Chen, Stanford University School of Medicine
Departments of Psychiatry & Behavioral Sciences, Neurosurgery
"Retinoic acid receptor RARalpha signaling in synaptic plasticity and Hebbian learning"

12:30–1:45 Lunch

1:45–3:05 **Session 3: Speakers invited from Poster Abstract Submissions**
Session Chair:
Laura Colgin, The University of Texas at Austin
Assistant Director, Center for Learning & Memory

1:45–2:05 Kirstie Cummings, Icahn School of Medicine at Mount Sinai
Department of Neuroscience
"Prefrontal somatostatin interneurons encode fear memory"

2:05–2:25 Matthew Mendoza, UT Southwestern Medical Center, Dallas
Department of Neuroscience
"*KIBRA Regulates Synaptic Plasticity by Altering AMPA Receptor Expression in an Age-Dependent Manner"*

2:25–2:45 Jagruti Pattadkal, The University of Texas at Austin
Department of Neuroscience
"The functional organization of area MT neurons revealed by 2-photon microscopy in awake marmosets"

2:45–3:05 James Kragel, Northwestern University Feinberg School of Medicine
Department of Medical Social Sciences
"Hippocampal theta coordinates memory processes during visual exploration"

3:05–3:25 Break

3:25–6:00 **General Poster Session I, even numbered posters present**

3:25–6:00 Happy hour, complimentary beer and wine

SATURDAY, APRIL 27, 2019

7:30–8:15 Breakfast

8:15–10:00 **Session 4: Neurodevelopmental Disorders of Learning and Memory**
Session Co-chairs:
Audrey Brumback, The University of Texas at Austin, Center for Learning & Memory
Michael Halassa, Massachusetts Institute of Technology, Department of Brain and Cognitive Science

8:15–8:30 Audrey Brumback, The University of Texas at Austin
Center for Learning & Memory
Introduction to the field: *"Discovery science: the foundation for breakthrough therapies in neurodevelopmental disorders"*

8:30–9:00 Michael Halassa, Massachusetts Institute of Technology
Department of Brain and Cognitive Science
"Frontothalamic architectures for cognitive control and flexibility"

9:00–9:30 Nancy Kopell, Boston University
Department of Mathematics and Statistics
"Brain rhythms and working memory in the parietal cortex"

9:30–10:00 Sergiu Pasca, Stanford University
Department of Psychiatry and Behavioral Sciences
"Assembling three-dimensional models of the human brain to study development and disease"

10:00–10:15	**Break**
10:15–12:45	**General Poster Session II, odd numbered posters present**
12:45–1:45	**Lunch**
1:45–3:40	**Session 5: Comparative Learning and Memory** Session Co-chairs: Jon Pierce, The University of Texas at Austin, Center for Learning & Memory Jennifer Li, Harvard University, The Rowland Institute
1:45–2:00	Jennifer Li, Harvard University The Rowland Institute Introduction to the field: *"Searching for primitives of learning and memory using small animals and big tools"*
2:00–2:25	Daniel Colón-Ramos, Yale University School of Medicine Departments of Cell Biology and Neuroscience *"Actuating a memory: How C. elegans remembers a learned behavioral preference"*
2:25–2:50	Karla Kaun, Brown University Department of Neuroscience *"Neuromolecular mechanisms that predict and encode alcohol associated preference"*
2:50–3:15	Drew Robson, Harvard University The Rowland Institute *"State machines: uncovering the neural implementation of motivational states"*
3:15–3:40	Elizabeth Hillman, Columbia University Department of Biomedical Engineering *"'Resting-state' brain-wide activity across scales and organisms"*
3:40–4:00	**Break**
4:00–5:15	**Session 6: Keynote Presentation** Sheena Josselyn**,** Hospital for Sick Children, The University of Toronto "*Making and Breaking Memories"*
5:15–5:25	**Presentation of poster contest awards** Dan Johnston, The University of Texas at Austin Director, Center for Learning & Memory
5:25–6:45	**Keynote Reception,** complimentary beer, wine and appetizers

Poster Abstracts

**Denotes the presenting author for each poster.*

[1] Wireless Stimulation and Recording for *in-vivo* Electrophysiology

James Morizio, Ph.D.[1]* , Robby Padia[1]

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Within a lifetime one of five people will be affected by a neurological disease which inspires the need for improved life science research equipment to understand the many mysteries of the nervous system. Learning and memory experiments that includes *in-vivo* electrophysiology and behavior equipment play a significant role in diagnosing and understanding these neurological diseases. Over the last two decades Triangle BioSystems International (TBSI) has developed wireless technology for neural recording and stimulation used for *in-vivo* electrophysiology applications on freely moving mice, rats and non-human primates. Novel integrated telemetric headstage systems can now replace cumbersome tethered recording equipment to record local field potentials as EEG, ECOG and EMG along with single unit (or spikes) signals while providing electrical and optogenetic stimulation for combination studies. These head mounted and implantable systems are used in research experiments investigating Alzheimer's, Dementia, Parkinson, Epilepsy, ALS and many other neurological disorders in academic or pharmaceutical laboratories all around the world. System level concepts for telemetric recording on 128 simultaneous channels and bipolar constant current electrical stimulation and optogenetic stimulation on 16 channels will be described. Key design challenges and tradeoffs of these wireless technologies used with behavior equipment will be explained for head mounted and implantable systems. A variety of animal experiments and test data will be presented.

[2] Double dissociation of familiarity and working memory in rhesus monkeys (*Macaca mulatta*)

Ryan J. Brady[1,2,*], Robert R. Hampton[1,2]

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[2]Yerkes National Primate Research Center, 954 Gatewood Rd NE, Atlanta, GA 30329
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Monkeys have been found to actively rehearse memoranda when tested with repeating stimuli, but not with trial-unique stimuli. This difference may exist because monkeys have difficulty processing trial-unique stimuli in a way that permits active maintenance in working memory. Alternatively, monkeys may have maintained trial-unique images in working memory in past studies, but the relative familiarity of to-be-remembered stimuli compared to never before seen distractors in classic recognition memory paradigms may be such a strong determinant of recognition performance that evidence of working memory was obscured. We contrasted these two hypotheses with a procedure that attenuated the utility of familiarity as a mnemonic signal permitting a more sensitive assessment of working memory. The familiarity attenuation caused a large decrease in accuracy with trial-unique but not with repeating stimuli. Conversely, concurrent cognitive load during the memory interval resulted in a large decrease in accuracy with repeating stimuli but not trial-unique stimuli. When we combined the familiarity attenuation procedure with concurrent cognitive load, we observed clear evidence of working memory with trial-unique stimuli. These results constitute a double dissociation of familiarity and working memory in rhesus monkeys, and show working memory for trial-unique stimuli in monkeys.

[3]

Multiple timescale responses account for adaptation across cortical sensory modality

Dylan J. Barbera[1]*, Kenneth W. Latimer[2], Michael Sokoletsky[3], Bashara Awaad[4], Israel Nelken[4], Ilan Lampl[3], Adrienne Fairhall[2], Nicholas J. Priebe[1]

[1]University of Texas at Austin, [2]University of Washington, Seattle, [3]Weizmann Institute of Science, Rehovot, Israel, [4]The Hebrew University of Jerusalem, Jerusalem, Israel
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Sensory systems encounter remarkably diverse stimuli in the environment. This presents a challenge to individual neurons, which exhibit a relatively narrow dynamic range. To overcome this, sensory neurons adjust their gain to optimize their response sensitivity to modulations in input, thereby increasing their effective bandwidth. This process, termed adaptation, is ubiquitous across sensory systems. It is possible that adaptation results from a change in the state of the neural system, resulting in response dynamics that depend on stimulus conditions. Alternatively, adaptation could be viewed as an emergent property of a fixed, but complex, sensory response composed of multiple timescales. To distinguish between these two possibilities, we sought to determine whether a simple static filter model, derived from neural responses to stimuli that vary considerably in their temporal statistics, could account for adaptive sensory responses. We measured the membrane potential responses of individual neurons to discrete, punctate stimuli delivered at a wide range of fixed and non-fixed frequencies in the visual, somatosensory and auditory cortices. We find that the adaptive profile of the responses is largely preserved across these three areas. Furthermore, we demonstrate that these adaptive responses can emerge from a simple model based on the integration of filters operating at multiple time scales. Therefore, adaptation can be described as an emergent phenomena of a fixed sensory response operating at multiple timescales.

[4]

Subcortical binocular integration for vergence eye movements in mice

Veronica Choi* and Nicholas J. Priebe

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We stabilize the dynamic visual world on our retina by moving our eyes in response to motion signals we receive. Coordinated movements between the two eyes are characterized by version when both eyes move in the same direction and vergence when the two eye move differently. Vergence eye movements have been proposed to be important for tracking objects in three dimensions and may be elicited in primates by both differences in the spatial signals, or disparity, or by differences in the motion that the two eyes receive. These vergence eye movements require the integration of left and right eye inputs, but it remains unclear which neural circuits are responsible for the integration that leads to these eye movements. To address this issue, we measured vergence eye movements in mice using a stereoscopic stimulus that is known to elicit vergence eye movements in primates. We found that the primary signal for vergence eye movements is the difference in motion presented to each eye, whereas spatial disparity cues had little impact on vergence. We also found that the vergence eye movements we observed in mice were not affected by silencing visual cortex, or by manipulations that disrupt the normal development of binocularity in visual cortex. Instead, we demonstrate that right and left eye motion cues in rodents could be described by a summation of motion signals that occurs in subcortical structures.

◆ [5]

The functional organization of area MT neurons revealed by 2-photon microscopy in awake marmosets

J. Pattadkal[1]*, Boris V. Zemelman[1] and Nicholas Priebe[1]

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Area MT contains neurons that are exquisitely sensitive to visual motion and, based on extracellular recordings, is functionally organized for direction. Neurons within a cortical direction column share direction preferences, and preferences smoothly shift across cortex, much like the functional architecture for orientation selectivity in primary visual cortex of primates. The large-scale organization of area MT has not been accessible to optical imaging and electrode arrays, since in the macaque it is located near the bottom of the superior temporal sulcus. To examine the functional architecture of area MT and assay the selectivity of inhibitory neurons, we used the marmoset (*Callithrix jacchus*). These primates have lissencephalic brains in which we have access to activity of large neuronal populations. We used 2-photon microscopy to record from several hundred neurons at single-cell resolution over a 1 mm^2 region of area MT in awake marmosets. GCaMP expression was induced by injecting AAV constructs with promoters that provided specific expression in interneurons within area MT. The motion selectivity of the interneurons was assessed using a full-field patch of random dots moving in different directions. GCaMP signals from inhibitory neurons revealed similar degrees of motion selectivity as that found from excitatory neurons (median DSI = 0.38, n = 301 cells). Nearby neurons tend to share direction preference, forming a map of direction preference with a period of approximately 300 microns. Finally, we found that the degree of orientation selectivity in MT neurons is weaker (median OSI=0.13) than direction selectivity. In sum, we have revealed the fine functional organization of area MT using 2-photon microscopy in awake marmosets and have demonstrated that MT inhibitory neurons are as direction selective as their excitatory neuron counterparts.

◆ This abstract was selected for a Best Abstract Award and the content will be presented as a talk in session 3 in lieu of a poster.

[6]

Mice discriminate stereoscopic surfaces without fixating in depth

Jason M Samonds*, Veronica Choi, Nicholas J Priebe

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Stereopsis is a ubiquitous feature of higher mammalian vision, but little is known about if and how lower mammals, such as mice, use stereoscopic vision. When we presented random dot stereograms to mice, they were able to discriminate near from far depths over a range of disparities with diminishing performance for small and large binocular disparities. Based on neurophysiological measurements, the range of disparities represented in the visual cortex aligns with the behavior, but covers a broader range than expected based on geometric predictions for any single depth. When we examined their binocular eye movements, we found that mice did not vary alignment to varying disparities like primates. Their eyes generally converged when making saccades relative to their average gaze, but then diverged back to the original alignment while fixating to maintain alignment. Although mice share fundamental characteristics of stereoscopic vision with primates and carnivores, their more limited coordination of eye movements and wider neuronal representation suggest that they may employ a more primitive strategy for stereopsis.

[7]

A 1080p Enhanced Image Sensor Module for Head-Mounted Microscope

Jill Juneau*, Guillaume Duret, Savva Morozov, Jacob Robinson,
Francois St-Pierre and Caleb Kemere

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We present the design and *in vivo* results from an enhanced image sensor module for head-mounted microscopes which incorporates the latest CMOS image sensor technology and provides 1080p video along with increased sensitivity, resolution and frame rates. The design is built upon the open-source Miniscope platform and is compatible with the Miniscope Data Acquisition Board as well as the single cable serializer/deserializer system. The new image sensor printed circuit board, with a size of 13mm by 22mm, incorporates a Sony IMX290LLR sensor with 2.13M pixels, 2.9um pixel size and up to 30db of analog gain. For a frame rate of 30 seconds, the maximum frame size is 1920 horizontal pixels by 1080 vertical pixels. However, significantly increased frame rates can be achieved by reducing the image height size. Additionally, the 3-D printed optics housing is updated for the larger sensor size as well as a new easy lock baseplate method.

We demonstrate the camera with *in vivo* imaging of the CA1 region of the hippocampus in freely behaving mice injected with GCaMP6f. Furthermore, we show preliminary results from *in vitro* and *in vivo* imaging of a genetically-encoded voltage indicator.

[8]

Clusterless Hidden Markov Models for Sequential Neural Activity

Etienne Ackermann*, Joshua Chu, and Caleb Kemere

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We have recently demonstrated that we can learn latent variable representations (specifically using hidden Markov models, HMMs) directly from sharp wave ripple associated population burst events (PBEs), whose dynamics are consistent with temporal replay sequences, and where the latent states correspond to a spatial map of the environment. We have further shown that our latent variable model approach can identify many of the same events as the commonly used Bayesian decoding approach, with comparable classification accuracy. Even though these short-duration PBEs often have rich sequential dynamics, the sequences have noticeably lower fidelity than those during animal behavior. It has been shown that by including additional hard-to-sort spikes (using clusterless decoding techniques, as opposed to standard Bayesian decoding of sorted units), the fidelity of similar short-duration sequences (e.g., theta sequences) can be improved significantly. Consequently, we propose and develop an unsupervised clusterless hidden Markov model, which will enable us to analyze behavior-free sequential neural activity at fine timescales, with increased fidelity compared to our previous HMMs that relied on having access to sorted units. Here we present the novel clusterless HMM, as well as a characterization of the model performance on simulated data, and explain when such a model may prove useful for the analysis of real neural data.

Funding: This work was supported by an NSF CAREER award (CBET-1351692), an NSF BRAIN EAGER award (IOS-1550994), an HFSP Young Investigator's award (RGY0088), and seed funding from the Ken Kennedy Institute for Information Technology.

[9]

Selective disruption of hippocampal sharp-wave ripples leads to impaired object-place recognition memory

Shayok Dutta[1]*, Ariel K. Feldman[2,3], and Caleb Kemere[1,4]

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Rodents have an innate curiosity to explore novel contexts and objects resulting in them spending more time with novel objects and locations as opposed to familiar ones. Extensive work through lesion studies have demonstrated this novelty preference to be hippocampally dependent via novel object test (NOT) paradigms. More recent work has not only correlated hippocampal CA1 signatures, such as fast-gamma oscillations, to be of importance in NOT object-place recognition memories but also demonstrated predictable changes in other hippocampal events, sharp-wave ripples (SWRs). Specifically, the latter events, SWRs, have been shown to increase after encoding of novel objects; however, the concomitant spiking activity has not been correlated with object-place pairings leading us to question the role of these events in encoding objects and place. To interrogate the role of SWRs in encoding novelty, we selectively modulate of SWR activity using our previously engineering closed-loop, open-source SWR detection system during various NOTs. Preliminary results indicate that suppression of SWR activity during object encoding and post encoding sleep sessions impair object-place recognition memory of familiar objects in novel locations but not of novel objects in novel locations. We look to further understand the role of SWRs along with its co-occurring neural activity that would lead to such a deficit in recognition memory by selectively interacting with particular portions of the event. Altogether, our preliminary findings suggest SWRs play a role in object-place pairing consolidation as opposed to simply broadcasting the presence of novelty.

Funding: This work was supported by an NSF CAREER award (CBET-1351692), an NSF BRAIN EAGER award (IOS-1550994), an HFSP Young Investigator's award (RGY0088), and seed funding from the Ken Kennedy Institute for Information Technology.

[10]

Hippocampal Encoding of Space During Navigation of Acoustically Defined Virtual Environment

Sibo Gao[1]*,Zakir H. Mridha[2], Ph.D., Wenhao Zhang[2], Ph.D., Matthew J. McGinley, Ph.D[2], Caleb Kemere[1,2], Ph.D.

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Auditory cues play an important role in navigation for animals especially when the visual system cannot detect objects or prey in the dark. However, little is known about how the auditory system and the hippocampus interact to use auditory cues for memory-guided navigation. In this study, we present a new paradigm where sensory stimuli associated with space are auditory rather than visual cues. Contrary to traditional navigation tasks where animals can visually see the surroundings, we use a virtual environment where animals must learn to use acoustic cues to navigate the virtual track. Head-fixed animals, walking on a cylindrical treadmill, have shown robust anticipatory licking of reward in an acoustically defined zone. We performed high-channel (128) electrophysiology in hippocampal CA1 to examine mechanisms for hippocampal coding. We used automated spike sorting algorithm to extract large number of units from our high-channel recordings. To date, we have observed head-fixed animals can perform acoustically guided navigation in a virtual environment. We identified units that exhibits place-cell characteristics that showed spatial selectivity and observed place-fields distributed along the virtual track. Our results suggest that memory-guided navigation is possible with exclusively acoustic cues. The virtual environment paradigm developed here will enable explorations of new types of experimental approaches to study how acoustic features are integrated into the neural circuits underlying navigation.

[11]

Nelpy: A Powerful Data Analysis Tool for Electrophysiology

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Recent advances in neural recording technology have enabled hundreds to thousands of channels. As bottlenecks shift away from data acquisition toward data analysis, it is imperative to have fast, flexible tools that can support large data. Here we introduce nelpy (**N**euro**el**ectro**p**hysiolog**y**), a Python software package that enables the neuroscientist to process data in a convenient object-oriented manner. Nelpy supports a range of data commonly encountered by electrophysiologists. These include sampled analog signals, spike trains, and binned spike trains, with each of these objects allowing fast time or indexed-based data access. Since these containers are specialized instances of more general parent objects, users can define custom objects without requiring large-scale rewrite of the code. In addition to convenient containerization, nelpy provides a flexible plotting library for quick data visualization and exploration.

The nelpy ecosystem is readily extended by submodules and external packages that use the core interfaces. We show examples by performing Bayesian decoding on neural spike trains for replay analysis, as well as spectral analyses implemented by our custom plugin package. Finally, to handle different computing needs, we demonstrate the use of nelpy (1) on a distributed cluster, (2) with GPU acceleration, and (3) with out-of-core-memory support enabled. We believe nelpy's speed, scalability, and user friendliness reduce the analysis bottlenecks frequently experienced by neuroscientists and aid the reliability and reproducibility of results from large-scale experiments.

[12]

A Novel Patch-Based Foraging Task in Acoustic Virtual Reality

James Webb[1]*, Jack Shi[1,2], Anton Banta[1,2,3], Zakir Mridha[1,2], Wenhao Zhang[1,2], Daeyeol Lee[4], Caleb Kemere[1,3] & Matthew J McGinley[1,2,3,4]

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To study decision-making in animals, many experimental designs are constructed to analyze neural activity with defined periods while controlling for external perturbations (e.g. two-alternative forced choice tasks). While these studies have provided much insight, natural scenarios often require animals to learn a different decision-making process. In many environments, finite amounts of a resource are concentrated in areas termed patches. To harvest the resource, animals must continually sample the depleting resource while also deciding whether to leave the current patch for a replenished one. The learning of this neuroeconomic decision in various natural environments is well-supported by literature in ethology and behavioral ecology but has been rarely studied in neuroscience.

We have created a virtual patch-based foraging task in which head-fixed mice learn to navigate acoustic space on a cylindrical treadmill to forage for a sucrose solution reward. While tone cloud is played, the mouse may freely choose to lick, receiving a reward that decays over time, or to run, after which pink noise is played until the animal has traveled a specified distance to the next patch. Population analyses of reward, lick, and walking statistics indicate that animals have learned to harvest reward in patches while running between them. We also have recorded from dorsal anterior cingulate cortex (dACC) with silicon microprobes during the task. Preliminary results suggest that dACC neural activity is associated with patch-leaving decisions. Future experiments will test behavioral adaptability to changing environments and the precise role of dACC in foraging decisions.

[13]

Parental elevated salt consumption in mice and the development of autism-like behavior in the offspring

Kazi Farhana Afroz*, Kajal Parikh, Varsha Mishra, Shree Patel,
Noah Reyes, Karina Alvina

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with no known etiology or cure. Recent studies have identified a possible causal relationship between parental autoimmune disorders and ASD in the offspring. It is known that elevated salt consumption has a significant effect on the immune system where it can induce pro-inflammatory cytokines and reduce macrophage functionality. Therefore, we hypothesize that high-salt diet (HSD) induces autoimmunity and can ultimately contribute to the development of ASD in the offspring. To test our hypothesis, we fed mice with high-NaCl chow and NaCl in their drinking water for 8-weeks while Control groups (CD) were fed with low NaCl chow and regular water. Then we paired HSD- or CD-fed males and females. The offspring from CD and HSD breeding pairs were then weaned and kept for behavioral analysis at 8 weeks-old. HSD parental group showed high stress, anxiety-like behavior, and impaired spatial memory. In the offspring, male mice from HSD parents showed less social interaction, exploration, along with increased repetitive behaviors in comparison with the offspring from CD-fed mice. Our results support the idea that parental HSD might increase the chances of ASD-like behaviors in the offspring. We are currently investigating mechanisms underlying these findings.

[14]

Experimental Manipulation of Psychological Control Scenarios: Implications for Exercise and Memory Research

Jeremiah Blough[1]* and Paul D. Loprinzi[1]

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There has been a great neglect of how manipulations and variations of control activities influences the relationship between exercise and memory function. Also, rarely assessed are participant outcome expectations of the imposed experimental manipulation, which can have great impact on any causal inferences made from an experiment. Thus, the purpose of this experiment was to evaluate the extent to which variations in control activities influence memory function as well as to investigate the participants' memory expectations for the various conditions. A within-subject, counterbalanced experimental design, was employed. Across four visits, participants (N=24; M_{age}=21.0 y) engaged in four tasks, including an acute exercise session and three cognitive-engagement control tasks of varying degrees of cognitive engagement and valence, namely reading neutral text, video, and puzzle completion. Participants' perceived expectations for how each condition would improve their memory performance was also assessed. After each condition, three cognitive outcomes were evaluated, including a word-list memory task, a comprehensive episodic memory task, and a cognitively-related planning task. We did not observe any differential effects of the control tasks on objectively-determined cognitive performance or perceived expectations. Our outcome expectation results demonstrated that, despite no observed differences on objective cognitive performance, participants expected the acute exercise stimulus (vs. the control tasks) to have a more beneficial effect on cognition. This exercise-related discrepancy between objective cognition performance and outcome expectation provides suggestive evidence that a placebo effect (expectations) may be less applicable in the exercise-cognition domain. Since we observed no differences in objective cognitive performance or outcome expectations across the three evaluated control tasks, future studies may wish to employ either of these control tasks, which should not compromise making comparisons across studies.

[15]

Effects of Intensity-Specific Acute Exercise on Memory Interference

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The objective of this study was to evaluate the role of intensity-specific acute exercise on memory interference. We hypothesized that acute exercise, particularly high-intensity exercise, would enhance episodic memory as well as attenuate both proactive and retroactive memory interference. A counterbalanced, randomized controlled, within-subject design, was employed. Young adults (N=19, M_{age}=20.32y) completed three counterbalanced visits, including a control visit, moderate-intensity exercise (50% of HRR; heart rate reserve) and vigorous-intensity exercise (80% of HRR). To evaluate memory interference, the AB-DE AC-FG paired associate task was implemented for each laboratory visit. Number of correctly recalled words from List 1 (AB-DE) was statistically significantly ($F(2)=4.63$, $p=.01$, $\eta^2_p=.205$) higher for the vigorous intensity condition (M=6.53) as compared to moderate (M=6.11) and control (M=5.0) conditions. Although high-intensity acute exercise had less memory interference, there was no statistically significant differences between proactive interference or retroactive interference across the experimental conditions. This experiment provides evidence for an intensity-specific effect of acute exercise on enhancing episodic memory, with some suggestive evidence of a possible memory interference attenuation via exercise.

[16]

Identification of Stimulated Synapses through 3D Electron Microscopy

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The hippocampal slice model of long-term potentiation (LTP) is a useful platform for investigating synaptic plasticity, but an ultrastructural marker for synapses that have undergone plasticity is lacking. Consequently, we have devised a single AAV construct that expresses ChR2-sfGFP and mAPEX2 under the control of a human synapsin promoter. This construct allows optically-stimulated axons to be identified and reconstructed using 3D electron microscopy. Our goal has been to confirm that this approach can induce LTP at hippocampal CA3 to CA1 pyramidal neuron synapses and reveal stimulated axons through subsequent EM. Adult SVE129 male mice were injected with the AAV vector unilaterally into hippocampal area CA3. LTP induced using 50 Hz trains of light pulses produced a similar increase in the slope in the ipsilateral and contralateral slices and lasted at least 3 hrs. However, optical stimulation of labeled commissural fibers terminating on the contralateral CA3 neurons might inadvertently recruit unlabeled Schaffer collaterals. To prevent unlabeled axon recruitment, we severed area CA3 in slices contralateral to the virus injection site. Our results suggest that 1) optically-evoked LTP is supported entirely by the ChR2-expressing axons and 2) mAPEX2 labeling successfully reveals ultrastructural changes at potentiated synapses.

[17]

Greater pontine mossy fiber recruitment may account for rapid cerebellar motor learning in two mouse models of post-traumatic stress disorder

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Severe trauma can result in pathological remodeling of neural circuits that profoundly affects memory and cognitive function, the proposed biological substrate of post-traumatic stress disorder (PTSD). A major feature of PTSD is altered cortico-cerebellar interactions, but little is understood about mechanisms driving this phenotype. To study cortical and cerebellar contributions to stress-induced network dysfunction, we used a classical delay eyelid conditioning task in two mouse models of PTSD, social isolation and acute electric shock. Following either stress protocol, we trained head-fixed mice (n = 14-18 per all groups, both sexes) to associate a peripheral light conditioned stimulus (CS) with a corneal air-puff unconditioned stimulus. To test for cerebellum-intrinsic versus extrinsic contributions, we partially de-coupled the cerebellum from its cortical inputs by replacing the light CS with direct electrical stimulation of the pontine mossy fiber bundle. Stressed animals learned the peripheral CS task faster than controls, a phenotype consistent with hypervigilance to sensory stimuli. However, learning differences disappeared when intensity-controlled mossy fiber stimulation was used as CS, revealing that differences in mossy fiber inputs to the cerebellum can account for learning differences in stressed animals. Notably, absence of learning differences with mossy fiber CS suggests that intrinsic cerebellar circuitry and climbing fiber input from the inferior olive may not contribute to pathological cortico-cerebellar interactions in PTSD. This finding puts important constraints on the underlying mechanisms of pathological cortico-cerebellar dynamics and offers a tractable experimental framework for biochemical and circuit analyses.

[18]

Investigating the role of WWC2 in synaptic and morphological development

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Learning and memory exhibit dynamic age-dependent regulation, yet the maturation of cellular or circuit-level mechanisms underlying adaptive cognition remains poorly understood. The WW- and C2-domain containing (WWC) protein family presents a promising target for studying the age-regulated processes, from synapse to circuit, that support learning and memory. We find that the differentially localized synaptic proteins WWC1 (aka KIBRA, at excitatory synapses) and WWC2 (at inhibitory synapses) exhibit peak expression coinciding with synaptogenesis. Additionally, both have been implicated in multiple neurodevelopmental disorders, consistent with roles in structural/functional brain maturation.

While it is known that *KIBRA* knockout mice exhibit impaired memory and adult-specific synaptic plasticity deficits along with aberrant spine and dendritic morphology, very little is known about the function of WWC2 in the brain. Therefore, we have begun studying the contributions of WWC2 to synaptic and morphological development.

Using WWC2 conditional knockout hippocampal cultures, we find that WWC2 KO neurons exhibit increased density and size of inhibitory synapses along with decreased dendritic complexity, suggesting a role in structural and functional brain development. By learning how WWC2 regulates synapse formation and establishment of dendritic morphology, and determining the consequences of disrupting these WWC2-dependent processes as the brain matures, these studies will reveal how early-development processes impact future capacity for synaptic plasticity and circuit dynamics that underlie adaptive cognition.

[19]

Investigating KIBRA-dependent regulation of memory-related circuit function and maturation using in-vivo recordings

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The circuit-level mechanisms that orchestrate cognition and underlie maturation of the brain's neural network remain elusive. Thus, an integrated understanding of how molecular and synaptic perturbations contribute to circuit function/plasticity over development will be invaluable. Mounting evidence implicates KIBRA in developmentally-regulated learning and memory functions, making KIBRA an ideal target to reveal mechanisms by which information processing is integrated across multiple levels to support cognition. However, the circuit-level role of KIBRA remains unknown. Human studies demonstrate that KIBRA gene variants are linked to variation in memory performance, and mice lacking Kibra exhibit impaired learning and memory. Although KIBRA is expressed throughout development, plasticity deficits do not emerge until young adulthood in KIBRA knockout mice, suggesting either that KIBRA is involved in adolescent brain maturation or that age-dependent mechanistic differences confer juvenile-selective resilience to KIBRA deletion. To assess the role of KIBRA in adult circuit function and postnatal circuit maturation, we utilize in vivo electrophysiology in freely behaving KIBRA constitutive or adult conditional knockout mice. By examining neural oscillations during multiple behavioral states in the hippocampus and anterior cingulate cortex, we obtain information about coordinated population activity and communication within and between these brain regions. Our findings support a role for KIBRA in HC-ACC circuit function and maturation. Moreover, we demonstrate the feasibility of obtaining chronic neural recordings in juvenile mice.

◆ [20]

KIBRA Regulates Synaptic Plasticity by Altering AMPA Receptor Expression in an Age-Dependent Manner

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Memory formation and storage is a dynamic process that changes throughout our lifespan. Previous evidence has implicated the KIBRA gene and KIBRA protein binding partners with various age-emergent neurological diseases such as Schizophrenia, Alzheimer's, and Autism Spectrum Disorders. While there is a growing body of human literature implicating KIBRA in learning and memory, KIBRA's molecular function and contribution to cognitive maturation remains poorly understood. Interestingly, despite being expressed throughout early postnatal development, germline deletion of KIBRA impairs synaptic plasticity selectively in adult rodents. Given this unique age-dependent function of KIBRA in synaptic plasticity, we hypothesized that KIBRA either facilitates adolescent brain development or that KIBRA serves a unique role in the adult brain, which thereby renders the adult brain selectively vulnerable to a loss of KIBRA. Here, using an inducible KIBRA knockout mouse, we demonstrate that acutely reducing KIBRA expression in adult forebrain excitatory neurons reduces long-term potentiation (LTP), but has no effect on long-term depression (LTD). In contrast, acute reduction of KIBRA in juvenile forebrain excitatory neurons had no influence on LTP. Surprisingly, the adult-specific deficits in LTP were associated with a decrease in total AMPA receptor expression after LTP induction, suggesting that KIBRA might serve to stabilize newly synthesized AMPA receptors following LTP induction. These results suggest that KIBRA serves a unique functional role in the adult brain by regulating AMPA expression.

◆ This abstract was selected for a Best Abstract Award and the content will be presented as a talk in session 3 in lieu of a poster.

[21]

Novel mechanisms of neuronal death associated with ischemic stroke

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Stroke is a major cause of death and disability in the United States, affecting approximately 800,000 people and resulting in ~140,000 deaths every year. Ischemic stroke accounts for about 87% of strokes, and results from loss of blood flow to the brain that damages and kills neurons. Understanding mechanisms of neuronal death associated with ischemic stroke is thus an essential component of creating better treatment and therapeutic strategies for ischemic stroke patients. We have identified a novel, isoform-specific regulation of the protein KIAA0513 in ischemic stroke. In healthy brain tissue, KIAA0513 long splice variants (A and B) are robustly expressed throughout the neocortex whereas short splice variants (C and D) show very low expression. However, ischemic stroke in a mouse model robustly upregulates expression KIAA0513 short variants. We find that cultured neurons overexpressing KIAA0513-C/D show dendritic beading, a morphological marker of neuronal injury and death, supporting the idea the KIAA0513-C/D promotes neuronal death. Additionally, cultured neurons treated with NMDA to induce excitotoxicity and mimic neuronal injury during ischemic stroke show upregulation of KIAA0513-C/D, suggesting that the origin of elevated KIAA0513 short variants in ischemic brain tissue is at least in part neuronal. We are currently investigating mechanisms of cell death induction by KIAA0513. Thus far, our results indicate that short variants do not induce necrosis and may regulate apoptosis. This study investigating a novel regulator of neuronal death after ischemic injury will reveal important insight into signaling pathways that may serve as new therapeutic targets for neuroprotection.

[22]

The Effects of Exercise on Chemotherapy-Induced Cognitive Impairment

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Chemotherapy-induced cognitive impairment (CICI) is commonly reported by human breast cancer patients, generally in the form of lapses in memory and decreases in executive functioning. In this study we use a pre-clinical model to determine if long term exposure to cardiovascular exercise (running) may act as a protective factor against the development of CICI symptoms in a transgenic breast cancer mouse model. Previous pre-clinical studies have shown that post-treatment exercise reduces memory dysfunction and increases rates of hippocampal neurogenesis in rodents. Neural regions typically associated with CICI include the hippocampus (memory) and frontal lobe (executive functioning). To assess hippocampal and frontal lobe function in transgenic tumorogenic mice and in wild type controls, mice were given a pre-treatment and post-treatment behavioral test battery including spatial water maze, novel object recognition, context fear conditioning, and conditioned associative learning. Behavioral tests indicate that Tg subjects have reduced cognitive functioning with some savings in the fear conditioning and Morris water maze tasks for mice who engaged in pre-treatment running. We additionally observed larger tumor volume for mice who engaged in pre-treatment running, suggesting that long-term exercise may actually enhance rates of tumor growth in animals genetically pre-disposed to developing tumors in the running condition.

[23]

Neuronal subset-specific deletion of *Pten* results in aberrant Wnt signaling and memory impairments

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The canonical Wnt and PI3K/Akt/mTOR pathways both play critical roles in brain development early in life. There is extensive evidence of how each pathway is involved in neuronal and synaptic maturation, however, how these molecular networks interact requires further investigation. The present study examines the effect of neuronal subset-specific deletion of phosphatase and tensin homolog (*Pten*) in mice on Wnt signaling protein levels and associated cognitive impairments. PTEN functions as a negative regulator of the PI3K/Akt/mTOR pathway, and mutations in *Pten* can result in cognitive and behavioral impairments. We found that deletion of *Pten* resulted in elevated Dvl2, Wnt5a/b, and Naked2, along with decreased GSK3β hippocampal synaptosome protein expression compared to wild type mice. Aberrations in the canonical Wnt pathway were associated with learning and memory deficits in *Pten* knockout mice, specifically in novel object recognition and the Lashley maze. This study demonstrates that deletion of *Pten* not only significantly impacts PI3K/Akt/mTOR signaling, but affects proper functioning of the Wnt signaling pathway. Overall, these findings will help elucidate how the PI3K/Akt/mTOR pathway intersects with Wnt signaling to result in cognitive impairments, specifically in memory.

[24]

Age-dependent impacts on fear learning following high omega-3 diet in the *Fmr1* knockout mouse

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Mice with deletion of *Fmr1* have been shown to have learning and memory deficits as well as alterations in hippocampal neuroinflammatory signaling markers. For our study, we examined whether administration of omega-3 fatty acids prenatally through weaning or from weaning through adulthood was sufficient to rescue learning and memory deficits in *Fmr1* knockout (KO) mice, in association with changes in inflammatory signaling. In a prenatal paradigm, breeding pairs were put on one of the three diet conditions (standard lab chow, EPA/DHA enriched chow, or a diet controlling for the fat increase) one week prior to breeding until weaning postnatal day (PD) 21. In a post-weaning paradigm, *Fmr1* wildtype (WT) and KO mice were assigned to one of three dietary conditions upon weaning at PD21. Results indicate that prenatal dietary treatment with EPA/DHA rescued impaired acquisition of a fear response in the delay fear conditioning task in adulthood in the KO. Conversely, postnatal treatment impaired acquisition of a fear response, as well as contextual fear conditioning and cued recall 24 hours later. Hippocampal expression of interleukin 6 (IL-6) was significantly downregulated post-weaning EPA/DHA exposure, while prenatal exposure reduced IL-1β and brain-derived neurotrophic factor (BDNF). These results suggest that the timing of the dietary intervention is important for predicting the impact on the cognitive and neuroimmune phenotype of the *Fmr1* KO mouse.

[25]

Phase-tuned neuronal firing encodes human contextual representations for navigational goals

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What is the human neuronal code underlying our ability to navigate? The hippocampus and medial temporal lobe (MTL) are hypothesized to support the representation of spatial contextual information, such as a prospective navigational goal, yet the mechanism by which this is instantiated at the single neuron level in humans remains poorly understood. We tested whether human MTL neurons encode information about prospective navigational goals using either 1) modulations in their firing rate or 2) changes in the timing of their firing relative to theta oscillations, a form of phase coding. We analyzed a dataset that simultaneously measured human single-neuron and oscillatory activity from MTL and frontal regions during a goal-directed navigation task (Jacobs et al., 2010; Miller et al., 2015). We identify neurons in the medial temporal lobe with firing-rate modulations for specific navigational goals, as well as during navigational planning and goal arrival. Further, using a novel oscillation detection algorithm, we identify phase-locked neural firing that encodes information about a person's prospective navigational goal in the absence of firing rate changes. These results provide evidence for navigational planning and contextual accounts of human MTL function at the single-neuron level. More generally, our findings identify phase-coded neuronal firing as a component of the human neural code. Future work can explore if other components of experience such as time are also encoded using a phase-coding scheme.

[26]

Presynaptic axonal boutons grow as vesicle count drops during late phase of LTP

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Long term potentiation (LTP) is the sustained increase in evoked response following the delivery of high-frequency stimulation. In the hippocampus, LTP is the cellular correlate of learning and memory. There are many ultra-structural changes that occur at hippocampal synapses several hours after LTP. Most of this work has previously focused on changes in postsynaptic structures. For example, it is well documented that postsynaptic densities (PSDs) and dendritic spines (the site of most excitatory synapses) are enlarged several hours following LTP induction (Bourne and Harris, 2011). However, less is known about presynaptic structure changes in the same paradigm. Previously we showed that two hours following LTP there is a significant drop in the reserve pool of synaptic vesicles, with a larger drop occurring at boutons that contain mitochondria (Smith et al., 2016). While it is tempting to speculate that the vesicles become more mobile between boutons, we also see a decrease in transport packets (groups of <10 vesicles in inter-bouton regions) two hours following LTP (Bourne et al., 2013). Here we have used serial section electron microscopy combined with Cell Blender tools to measure the presynaptic bouton surface area in stratum radiatum of CA1 in hippocampal slices that have received either control or LTP stimulation in order to test the hypothesis that the reserve pool of vesicles contributes to presynaptic bouton growth after LTP.

[27]

SER composition in dendritic spines of rat hippocampal CA1 and dentate gyrus receiving entorhinal afferents

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The hippocampus, critically involved in learning and memory, receives excitatory inputs from the entorhinal cortex at axo-spinous synapses on dendrites of the middle (MML) and outer (OML) molecular layers of the dentate gyrus, and in Stratum Lacunosum-Moleculare (SLM) of area CA1. Additionally, CA1 pyramidal cells receive Schaffer collateral inputs in Stratum Radiatum (SR). A subset of spines contains smooth endoplasmic reticulum (SER) as single tubules or as a complex spine apparatus (SA). SER regulates calcium signaling, lipid and protein synthesis, and trafficking throughout dendrites. Hence, we hypothesized that the relative distribution of SER to dendritic spines may differ depending on position in the dendritic arbor. We analyzed SER and SA distribution in dendritic spines of the MML, OML, SLM, and SR by three-dimensional reconstruction based on serial section electron microscopy (3DEM). From these hippocampal layers, we sampled dendritic segments of average caliber as measured by their microtubule content. In all of the four layers, spines with an SER tubule or an SA had significantly larger synapses than those without. The SLM dendrites had significantly fewer synapses and spines than MML, OML, or SR. However, more of the SLM spines contained an SER tubule or an SA than the other three layers. Importantly, the density of spines with any SER did not differ significantly across the four layers. Thus, SER might enter dendritic spines at a relatively fixed distance along the dendrites independent of spine density. The differential patterns in CA1 and dentate may serve to regulate dendritic integration and synaptic plasticity of the entorhinal inputs depending on the specific locations of the postsynaptic target.

[28]

The role of fragile X mental retardation protein in striatal plasticity and drug-related behaviors

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Cocaine, and other drugs of abuse, are known to alter dendritic spine density and synaptic strength of medium spiny neurons (MSNs) in the nucleus accumbens (NAc) and dorsal striatum (DS), implicating such changes in connectivity in the development and/or maintenance of addiction. However, key regulators of this process remain unclear. The fragile X mental retardation protein (FMRP), an RNA binding protein which controls the translation of hundreds of brain RNAs, has been shown to regulate spine density in multiple brain regions. Our work has highlighted FMRP's function in the promotion of basal spine stability, as well as in limiting cocaine-induced increases in dendritic branching and spine density, in multiple striatal sub-regions. Here, we continue to examine the role of FMRP in striatal cell plasticity and how this process relates to the development of addiction-related behaviors in mice, using both embryonic mouse cortical-striatal cell co-culture and *in vivo* mouse drug self-administration models. In the absence of FMRP, cultured striatal cells show no differences in synaptic puncta density after 10 days *in vitro* (DIV) but develop a significant deficit in puncta by 14 DIV, suggesting that FMRP plays an important role in striatal cell synapse formation and maintenance. Further, our preliminary *in vivo* drug self-administration data suggest that FMRP may be required for shifts in hedonic preferences associated with repeated drug exposure.

[29]

Does cognitive impairment in metabolic syndrome begin with the posterior cerebellum?

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The posterior cerebellum is the neuroanatomical structure most strongly implicated in metabolic syndrome (MetS) (Kotkowski et al., 2019). In light of this, we hypothesized that cognitive decline often reported in MetS is related to posterior cerebellar atrophy and not to the hippocampus, as has been previously suggested. We performed post-hoc analyses on voxel-based morphometric magnetic resonance imaging data from young participants (n = 104, aged 18-35 years), comparing imaging data and behavior scores derived from a battery of neuropsychological tests selected for their relevance to the cerebellar cognitive affective syndrome (CCAS, also known as Schmahmann's syndrome). We found preliminary evidence that early cognitive effects of MetS are most closely related to posterior cerebellar function, consistent with neuroanatomical findings. We propose implementing the CCAS/Schmahman syndrome scale in future investigations seeking to assess cognitive function relating to MetS and its comorbidities like type 2 diabetes, cardiovascular disease, and obesity.

[30]

Overexpression of microRNA-33 blocks allopregnanolone-induced state-dependent learning

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Sex steroids can modulate emotional behavior in both rodents and humans. We have previously shown that allopregnanolone (ALLO), a progesterone metabolite, can induce state-dependent contextual fear when infused into the bed nucleus of the stria terminalis (BNST) of male rats. Because ALLO is a strong potentiator of $GABA_A$ receptors, the state dependence it confers may involve regulation of GABAergic tone. In mice, intra-hippocampal infusion of gaboxadol induces state-dependent contextual fear by suppressing mir-33, a microRNA that regulates GABA-related proteins. To determine if mir-33 contributes to ALLO-induced state-dependent learning, we bilaterally injected a virus designed to overexpress it into the BNST of adult males; controls received blank virus. Two weeks post-injection, animals received intra-BNST infusions of either ALLO (8 mg/ul) or vehicle (VEH; 30% b-cyclodextrin) before conditioning with 5 tone-footshock pairings. On subsequent days, context and tone tests followed infusions of ALLO only. VEH-trained, ALLO-tested controls displayed low levels of contextual freezing compared to ALLO-ALLO controls. In contrast, mir-33 injected rats from both treatment groups displayed freezing similar to ALLO-ALLO controls. Cued freezing was similar for all groups. Thus, overexpression of mir-33 in the BNST appears to block induction of state-dependent contextual fear by ALLO, suggesting a role for a GABA-mediated molecular pathway.

[31]

Signaled Active Avoidance Performance is Context-Dependent

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After Pavlovian fear conditioning, the expression of conditioned fear is context-independent: rats that learn an association between a conditioned stimulus (CS) and an aversive unconditioned stimulus (US) in one context will show robust fear responses, such as freezing, to the CS in a different context. It is unclear whether other learned defensive responses, such as active avoidance behavior, are context-independent. Here we examined whether two-way signaled active avoidance behavior in rats is affected by a context shift. Sprague-Dawley rats received four days of signaled avoidance conditioning which consisted of thirty tone warning signals (2 kHz, 80 dB, 15 s) paired with footshock (0.7 mA, 0.5 s) per day. Rats could avoid the footshock US and terminate the warning signal by shuttling from one side of the apparatus to the other prior to US onset. After conditioning, the rats had two counterbalanced tests in either the conditioning context or in a shifted context. In both tests, 10 tones were presented absent shock and avoidance responses did not terminate the tone (i.e. both tests were 'reinforcement-free'). The rats performed significantly fewer avoidance responses in the shifted context compared to the original context. This was accompanied by an increase in freezing to the warning signal in the shifted context. Hence, unlike Pavlovian fear conditioning, active avoidance conditioning is context-dependent. Future work will examine the neural circuits mediating the context-dependence of avoidance responses.

[32]

Contextual regulation of flight behavior in rats is mediated by the bed nucleus of the stria terminalis

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Recent work (Fadok et al., 2017) has developed a modified Pavlovian fear conditioning procedure in which a serial conditioned stimulus (SCS) consisting of serial presentations of pure tone (7 kHz) and white noise (1-20 kHz), followed by a footshock unconditioned stimulus (US), elicits freezing and flight responses (e.g. escape jumps and increased movement speed) to tone and white noise presentations, respectively, in mice. It is further shown that the switching from freezing to flight behavior is gated by the central nucleus of the amygdala (CeA), and flight responses are only elicited within the conditioning context (Fadok et al., 2017). Here, we replicate these behavioral findings in male and female Long-Evans rats and further investigate how flight responses are contextually regulated. Using unsignaled footshocks we show that flight responses can be elicited within a threatening context that has never previously hosted the SCS which suggests that flight is dependent upon contextual fear. Moreover, using the $GABA_A$ agonist muscimol, we show that reversible inactivation of either the bed nucleus of the stria terminalis (BNST) or the CeA, but not the ventral hippocampus, diminishes flight responses within the conditioning context. These findings advance our understanding of the neural circuitry underlying the contextual regulation of active defensive behavior by demonstrating that flight responses are dependent upon contextual fear and that this effect is mediated by the BNST.

[33]

Nucleus reuniens influences medial prefrontal cortex and hippocampal neuronal activity during retrieval of extinguished fear memories

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Coordinated activity between the medial prefrontal cortex (mPFC) and hippocampus (HPC) is essential for encoding and retrieving spatial, working and contextual memories. The nucleus reuniens (RE) is a ventral midline thalamic nucleus that has a role in synchronizing activity in the HPC and mPFC. In Pavlovian fear conditioning, we have recently showed that RE inactivation impairs both the acquisition of hippocampal-dependent contextual fear memories as well as the extinction of fear to an auditory conditioned stimulus (CS). We hypothesized that the extinction deficit may be due to RE inactivation impairing behaviorally relevant neural activity in the mPFC and HPC. To test this idea, we examined the influence of RE inactivation on the induction of c-fos in mPFC and HPC by an extinguished conditional stimulus (CS). Consistent with our hypotheses, we found that inactivation of RE impaired the expression of extinction and this was associated with decreased c-fos expression in both the mPFC and HPC. We are currently exploring the functional role for RE projections to mPFC or HPC (or both) in extinction retrieval using an intersectional optogenetic strategy. Taken together, these data show that RE has a crucial role regulating neuronal activity in the mPFC and HPC that promotes successful retrieval of extinguished fear memories.

[34]

Bilateral, ipsilateral, and contralateral inactivations of dorsal and ventral hippocampus during a spatial reference memory task

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The hippocampus underlies episodic memory and spatial navigation. In rats, it is elongated with a dorsal (septal) and ventral (temporal) region (paralleling posterior/ anterior hippocampus in humans). The dorsal hippocampus is associated with spatial, and the ventral to emotional behavior. Less is known regarding how these regions interact during information processing. Anatomical connectivity suggests a flow of information from ventral to dorsal regions, conversely there are also commissural connections to the contra-lateral hippocampus.

The current study examined the extent to which information from the ventral hippocampus impacts processing in the ipsi- and contra-lateral dorsal hippocampus following the acquisition of a spatial task. Rats were trained on a spatial reference version of the water maze followed by muscimol inactivation of different hippocampal subregions in a within-animal repeated design.

Combined dorsal and ventral inactivation produced a severe impairment in spatial performance. Inactivation of only the dorsal or ventral regions resulted in intermediate impairment with performance. Contralateral inactivation resulted in deficits almost equivalent to full hippocampus inactivation, while ipsilateral inactivation resulted in little impairment. The results suggest that for spatial processing the hippocampus functions as a single integrated structure along the longitudinal axis, with dorsal regions dependent upon input from the ventral regions.

[35]

Isolation and analysis of Supramammillary Nucleus neurons projecting to the Hippocampus, Basolateral Amygdala and Prefrontal Cortex

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The Supramammillary Nucleus (SuM) of the hypothalamus projects prominently to the hippocampus (HPC) and a variety of other cortical and subcortical regions. SuM lesions impair spatial memory, context fear conditioning, and avoidance behaviors. While these studies demonstrate the behavioral importance of SuM, little is known about circuit mechanisms governing these effects. Using retrograde Adeno-Associated Viruses (rAAVs) and Cre-lox mediated recombination, we have isolated projection-specific populations of SuM neurons. We found that hippocampal-projecting SuM cells send collateral projections to the basolateral amygdala (BLA) and prefrontal cortex (PFC). Furthermore, we found that the population of hippocampus-projecting SuM cells includes separate BLA-co-projecting and PFC-co-projecting subsets. Experiments in progress are testing the hypothesis that these distinct populations of SuM cells modulate hippocampus-BLA and hippocampus-PFC interactions. Based on evidence that hippocampus-BLA interactions mediate acquisition and expression of conditioned fear, we predict that hippocampus-BLA-projecting SuM cells modulate acquisition and expression of hippocampus-dependent fear. In contrast, based on evidence that hippocampus-PFC interactions modulate fear extinction and consolidation of fear, we predict that hippocampus-PFC-projecting SuM cells modulate these processes. In summary, our data lead us to hypothesize that SuM contains distinct hippocampus-BLA and hippocampus-PFC projecting populations that modulate distinct aspects of fear learning and behavior.

[36]

A mouse model of stress-enhanced fear and anxiety-like behavior

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Stressful experiences can cause long-lasting sensitization of fear and anxiety that extends beyond the circumstances of the initial trauma. However, the mechanisms underlying stress-induced fear and anxiety are not well understood. It is debated whether sensitization is a non-associative phenomenon or reflects generalization of a learned Pavlovian association. We have constructed a mouse model of stress-enhanced fear and anxiety-like behavior. C57bl6/j or 129svev/Jax mice received four 1-mA foot shocks or equivalent context exposure without shock. Shock exposure suppressed open field exploration, potentiated freezing in response to a loud noise presented in a neutral context, and enhanced subsequent fear conditioning in a novel context. To determine whether footshock-induced sensitization is associative or non-associative, additional groups of mice received footshocks followed by extinction of the shock-paired context. Extinction training restored normal open field exploration but failed to attenuate noise-elicited freezing or subsequent fear conditioning. Chemogenetic inhibition of the basolateral amygdala during the first shock session prevented acquisition of contextual fear and blocked the effects of shock on open field exploration and noise-induced fear, demonstrating that both associative fear conditioning and sensitization require basolateral amygdala (BLA). Together, these findings indicate that stress-induced sensitization involves associative and non-associative components. Stress-enhanced anxiety-like behavior likely reflects generalization of conditioned contextual fear, whereas stress-enhanced fear and stress-enhanced fear learning are distinct forms of non-associative plasticity.

[37]

Classifying confidence level in correct rejection responses using single-trial EEG

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In this study, we trained leave-one-subject-out memory classifiers (Liao et al, 2018) to discriminate two different confidence levels (Sure New and Maybe New) of correct rejection responses in recognition memory retrieval tasks using temporal information during the recognition phase in four EEG datasets (Mollison and Curran, 2012) on a single-trial basis. The classifiers were trained separately on each of the datasets to give higher output for the Sure New responses. We showed that it is possible to predict subjects' confidence level of correct rejection responses with classifiers trained with data from different subjects. This decision could be based on familiarity with Sure New decisions representing less familiarity than Maybe New decisions or it could be based on confidence with Sure New decisions representing a more confident decision. In order to investigate this issue, we looked at projections of the remember(R) and know(K) responses onto the classification vector induced by the classifier trained to distinguish Sure New from Maybe New. This was done for trials with correct and incorrect source recollection conditions. The projections of R responses consistently received higher (more like Sure New) scores than the projection of K responses in both correct and incorrect information recollection conditions. This suggests that the EEG responses distinguishing Sure New vs Maybe New decisions reflect confidence more strongly than familiarity.

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[38]

The effects of acamprosate and $CaCl^2$ on prefrontal cortical function depend on the history of alcohol exposure

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Alcohol abuse impairs prefrontal cortex (PFC) function. Acamprosate can reduce craving in both animal models and human alcoholics, and may reduce relapse by restoring balance of glutamatergic synaptic transmission in the PFC. We have previously shown that alcohol dependence induced by chronic-intermittent ethanol (CIE) exposure leads to increased N-methyl-D-aspartate receptor (NMDAR) function, causing aberrant synaptic plasticity and disrupting normal PFC function. Treatment with acamprosate, or its active moiety calcium (CaCl2), recovered the behavioral deficits in a rule-shifting task, but did not significantly affect the synaptic dysfunction.

In order to better distinguish alcohol-induced effects on learning processes and goal-directed behavior from the pharmacological effects of high levels of alcohol, we examined if self-administration of alcohol has similar effects on behavior and synaptic plasticity, and if so, whether these changes can be ameliorated by acamprosate or CaCl2. Alcohol-exposed animals showed impairments in rule shifting, as well as an up-regulation of the ratio of NMDAR:AMPAR currents at PFC pyramidal neurons, both of which were reversed by acamprosate or CaCl2. Mice that were exposed to high levels of alcohol via CIE in addition to operant alcohol self-administration showed the same alcohol-induced increase in the NMDAR:AMPAR ratio; however, under these conditions neither acamprosate or CaCl2 restored normal NMDAR:AMPAR ratios. These results suggest that even low levels of daily alcohol consumption alter synaptic function in the medial PFC and impair PFC-dependent cognitive flexibility. These results also indicate that the effect of acamprosate (or calcium) depends on the previous history of alcohol exposure. Acamprosate appears to be more effective at altering glutamatergic transmission in the PFC if mice drink under goal-directed conditions.

[39]

Dopamine and norepinephrine transporter inhibitors act synergistically to enhance long-term memory

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Psychostimulants (e.g., amphetamine and methylphenidate) are highly effective cognitive enhancers, yet have a high potential for addiction. It is widely believed that norepinephrine transporter (NET) inhibition is exclusively responsible for the procognitive effects of psychostimulants. However, increasing evidence suggests that dopamine transporter (DAT) inhibition is also required for psychostimulant-induced long-term memory (LTM) enhancement. Although DAT inhibition is responsible for the addictive potential of psychostimulants, drugs with weak affinity for DAT may not produce addiction. In the present study, we examined the combined effects of strong NET inhibition (e.g., atomoxetine, nisoxetine) and weak DAT inhibition (e.g., bupropion) on LTM in mice using Pavlovian fear conditioning. Mice were trained with a single tone-shock pairing and tested one week later for long-term context and tone fear memory. While individually these NET and DAT inhibitors had no effect on LTM across a range of doses, the combination of certain doses significantly enhanced LTM relative to saline controls. Additionally, combined NET and DAT inhibition did not produce reinforcement on a conditioned place preference test. We propose that a pharmaceutical combination of strong NET and weak DAT inhibition could lead to the development of a highly effective memory-enhancing medication that lacks the potential for addiction.

[40]

Systematic functional analysis of 21st chromosome genes using *C. elegans*

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Down syndrome (DS), caused by trisomy of the 21st chromosome, leads to lifelong cognitive impairment. Efforts to understand this disorder first require an understanding of the genes encoded on the 21st chromosome (HSA21). While progress has been made using traditional mouse models, *C. elegans* represents a model complementary to uncovering the *in vivo* function of genes. Using RNAi and loss-of-function mutants, we systematically investigated the role of all HSA21 orthologs, excluding keratin-encoding genes, in viability and neuronal function. We identified ten HSA21 orthologs that are required for neuromuscular behavior. We also found that three of these genes are required for normal release of the neurotransmitter acetylcholine. This includes a known synaptic gene unc-26 (SYNJ1), as well as uncharacterized genes pdxk-1 (PDXK) and mtq-2 (N6ATM1). Furthermore, we found that the glutamine methyltransferase MTQ-2 localizes to cholinergic synapses where it appears to regulate neurotransmission via methylation of a Gα/o signaling protein. Going forward, we are overexpressing each of the HSA21 orthologs in worm and investigating which are subject to either direct or indirect forms of compensation. Differences in compensation could underlie the variable penetrance and expressivity in individuals with DS. As the first systematic functional analysis of HSA21 orthologs, our study may serve as a platform to understand genes that underlie phenotypes associated with DS.

[41]

APP-induced patterned neurodegeneration is exacerbated by *APOE4* in *C. elegans*

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Variations in the age of onset and progression of Alzheimer's disease (AD) has been linked to genetic variants in the amyloid precursor protein (*APP*) and apolipoprotein E (*APOE*). Both an extra copy or any number of gain-of-function mutations in *APP* considerably lower the age of AD onset. Additionally, the ε4 allele of *APOE* (*APOE4*) hastens and exacerbates the progression of early and late onset forms of AD compared to the other isoforms (*APOE3* and *APOE2*). Current *in vivo* models to study the interactions between APP and APOE4 to influence neurodegeneration are lacking. Previous studies in our lab have shown that expression of human *APP* induces specific, age-related neurodegeneration in the nematode C. elegans. Here we have genetically engineered worms to express both *APP* and *APOE4*. Live fluorescent microscopy confirms that APOE4 (but not APOE3) acts synergistically with APP to hasten and expand the pattern of cholinergic neurodegeneration caused by APP. Further, we show that APOE4 (but not APOE3) specifically affects egg-laying laying behavior, while motor coordination remains normal. The age-related decline and severity of egg laying correlates with degeneration of identified neurons critical for this behavior. This convenient worm model of neurodegeneration can be used to determine the molecular mechanisms underlying how APP and APOE4 synergize to cause cell death in specific neuron populations while leaving others intact.

[42]

Long-term activity drives branching of the receptive ending in a *C. elegans* sensory neuron

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Neuronal activity often leads to alterations in gene expression and cellular architecture. The nematode *Caenorhabditis elegans*, owing to its compact translucent nervous system, has proven to be a convenient system in which to study conserved aspects of the development and plasticity of neuronal morphology. Here we focus on one sensory neuron in the worm, termed URX, which senses oxygen and signals tonically proportional to environmental oxygen. Previous studies have reported that URX has variable branched endings at its dendritic sensory tip. By controlling oxygen levels and analyzing mutants, we found that these branched endings grow over time as a consequence of neuronal activity. Furthermore, we observed that the branches contain microtubules, but do not appear to harbor the guanylyl cyclase GCY-35, a central component of the oxygen sensory transduction pathway. Interestingly, we found that although URX dendritic tips grow branches in response to long-term activity, the degree of branch elaboration does not correlate with oxygen sensitivity at the cellular or the behavioral level. We suggest that URX will provide a useful system in which to identify molecular mechanisms that drive activity-dependent morphological changes in neurons and to parse the relationship between sensory neural receptive ending plasticity and neuronal sensitivity.

[43]

Exploring the 2R/TMEM97-mediated neuroprotective pathway in a *C. elegans* model of Alzheimer 's disease

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New pharmacological approaches are required for untreatable Alzheimer's disease (AD). We previously showed that small molecule ligands of the sigma-2 receptor (σ2R/Tmem97) were neuroprotective in a C. elegans model of APP. Deletion of the worm ortholog of σ2R/Tmem97 resulted in the same level of neuroprotection and prevented further ligand action. This strongly suggests that these ligands convey neuroprotection in vivo via σ2R/Tmem97. Moreover, these ligands also reduced cognitive deficits in a transgenic APP mouse model, demonstrating the translational potential for C. elegans in AD research. We have extended our analysis of *σ2R/Tmem97 ligands and found that they* also convey protection against neurodegeneration caused synergistically by APP and APOE4 in our new C. elegans model.

To study the mechanism of action for these novel ligands on the poorly understood σ2R/Tmem97, we are now turning to investigate the in vivo expression pattern of σ2R/Tmem97. We are generating transcriptional and translational fluorescent reporters using the native σ2R/Tmem97 promoter in C. elegans. Advanced understanding of the cellular and subcellular localization of σ2R/Tmem97 may yield clues on the mechanism of action for a new class of neuroprotective drugs that show promise for treating AD.

[44]

Suppression of defective motor and learning patterns in Parkinsonian *C. Elegans*

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Parkinson's disease (PD) is a neurodegenerative disorder caused partly by the loss of dopamine neurons. Dopamine is a conserved neuromodulator that aids in the transition between different motor patterns such as swimming, walking, or running and in the transition between different cognitive states. This is observed across many species, including mice, flies, and nematodes. The *cat-2* mutant strain of the nematode *C. elegans* has a deletion in the gene encoding tyrosine hydroxylase, an enzyme required to synthesize dopamine. Our lab recently demonstrated that the *cat-2* mutant shares aspects of PD patient dysfunction through its inability to transition normally between the "swimming" and "crawling" motor patterns; the *cat-2* mutant is also unable to learn associations between environmental salt concentrations and starvation conditions. Currently, PD treatments boost residual dopamine signaling and cannot maintain function once dopamine neurons completely degenerate. To search for ways to overcome motor dysfunction with dopamine absent, we performed a forward genetic screen to identify mutations that suppress poor motor transition in *cat-2* mutant. We found several suppressor mutants that displayed improved motor and memory function. This information could provide insight into repair of dopamine-deficient neural circuitry in higher level animals and possible approaches to help late-stage PD patients.

[45]

BDNF in the infralimbic cortex is necessary for the therapeutic effects of fear extinction after chronic stress in male and female rats

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Existing antidepressants are effective for some individuals, but are ineffective in treating the residual symptoms of cognitive dysfunction that are associated with stress-related psychiatric disorders such as PTSD and depression. Stress-related psychiatric disorders share a common dysfunction in the medial prefrontal cortex (mPFC), such that individuals with these disorders perform poorly on mPFC-dependent tasks such as set-shifting, a form of cognitive flexibility. We can model stress-induced cognitive dysfunction in set shifting using chronic unpredictable stress (CUS) in rodents and measuring their performance on the attentional set shifting task (AST). Behavioral therapies such as exposure therapy can be effective in ameliorating cognitive dysfunction associated with PTSD and depression. However, little is understood about the neurobiological mechanisms underlying behavioral interventions. We have previously shown that fear extinction, (i.e. learning that an innocuous cue previously associated with a fearful stimulus no longer predicts that stimulus) can be used to model the effects of exposure therapy on cognitive flexibility that has been compromised in chronically stressed rats. Further, we have shown that fear extinction (FE) requires *de novo* protein synthesis in the infralimbic (IL) region to exert its therapeutic effects on set shifting. Additionally, extinction learning induces the phosphorylation of the BDNF receptor TrkB, and the phosphorylation of ribosomal protein S6, a downstream factor of BDNF-TrkB, in the medial prefrontal cortex. Thus, we hypothesized that infralimbic BDNF may mediate the protein synthesis and plasticity processes that are necessary for the therapeutic effects of extinction in stressed animals. To test this hypothesis, male and female rats were chronically implanted with guide cannulae targeting the IL. Rats underwent stress or control conditions, and prior to extinction, received either a neutralizing antibody against BDNF or a sheep IgG control into the IL. 24 hours after extinction, animals were tested on the attentional set shifting test to evaluate set shifting performance. Preliminary results suggest that blocking BDNF at the time of extinction blocks the therapeutic effect of extinction on set shifting after stress in both sexes. Thus, infralimbic BDNF is necessary for the therapeutic effects of extinction on set shifting after chronic stress in both sexes.

[46]

Memory for speech of varying intelligibility

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Talkers spontaneously adopt hyperarticulated speech (clear speech, CLS) in response to environmental noise or when talking to a listener with hearing impairment or non-native proficiency. The benefit of the listener-oriented CLS on word recognition in noise is well-established for native and non-native listeners (Smiljanić & Bradlow, 2009). The effect of CLS on memory for spoken sentences is less well explored. The present paper reports findings from experiments examining recognition memory (RM) and recall (RE) for sentences of varying intelligibility by native and non-native English listeners. In RM, listeners were exposed to the casual (fast) and CLS sentences and were then tested on either the audio sentences (within-modal) or written sentences (cross-modal). They had to identify test sentences as old or new. In RE, listeners had to write down what they remembered after the exposure. Results showed enhanced RM and RE for CLS compared to casual sentences for both native and non-native listeners. The results suggest that more cognitive resources remain available for storing information in memory during processing of easier-to-understand CLS (cf. effortfulness hypothesis, McCoy et al., 2005). Non-native listeners' RM and RE were also improved by signal clarity despite processing speech signals in a cognitively more demanding second language.

[47]

Neural evidence for reinstatement of associative memories in children and adults

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The ability to retrieve memories undergoes pronounced development across childhood. Adults can retrieve information from degraded or partially overlapping cues, whereas younger children require nearly exact overlap with the original experience (Ackerman, 1982). In adults, functional magnetic resonance imaging (fMRI) evidence has shown that hippocampal patterns are reinstated during memory retrieval (Mack & Preston, 2016) and may drive reactivation of the initial experience in sensory regions (Polyn et al., 2005). Hence, one possible explanation for differences in memory retrieval across development is that children exhibit less robust sensory reinstatement relative to adults. In the present research, we used pattern analysis of fMRI activation to test reinstatement of specific memory elements at different ages. Children (7-10 years) and adults (18-30 years) learned a series of object-scene and object-face associations. Following learning, we correlated fMRI activation patterns during retrieval of the target items with the corresponding activation patterns evoked during initial perception of items from the same stimulus category (faces or scenes). Preliminary findings (N=21 children and 22 adults) show neural reinstatement across development. Nevertheless, whereas adults reinstated both faces and scenes, children only reinstated scenes. These findings provide initial support that children can reinstate prior experiences while also highlighting developmental differences.

[48]

Events with common structure become organized within a hierarchical cognitive map in hippocampus and frontoparietal cortex

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Recent research suggests that the episodic memory system links individual events according to their shared features, providing a cognitive map that supports inference about unobserved relationships among event elements. However, less is known about how people generalize information learned in one setting to another, distinct setting that has similar structure but no obvious shared features. We examined learning of higher-order structure in an associative learning task where participants were instructed to learn pairs of novel objects (AB, BC) that were drawn from distinct triads (ABC), each with three unique objects. fMRI was used to measure the neural representation of each object before and after learning. Previous analysis of this study found that learning of the overlapping AB and BC pairs of each triad caused the hippocampal representations of indirectly related items (A, C) to become more similar, reflecting second-order associations. There is also a third-order organization present in this task; participants learned 12 different triads in the task, which each included the same structure of overlapping pairs of novel objects. We found that representations in hippocampus and frontoparietal cortex reflect this higher-order organization, showing a consistent geometric relationship that allowed us to predict the relationships between item activity patterns across triads. Furthermore, participants with greater organization across triads in hippocampus and lateral parietal cortex were subsequently able to infer indirect associations within each triad more quickly. Our results suggest that anterior hippocampus and frontoparietal regions represent a cognitive map consisting of a hierarchical structure that generalizes across settings and supports inference about individual relationships.

[49]

Signal Translation between EEG and ECoG to improve non-invasive based BCI performance

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Electroencephalography (EEG) is electrical signals measured on the scalp and electrocorticography (ECoG) is electrical potentials recorded either above or below the dura matter, where it requires the brain surgery to implant the recorded electrodes in the brain. Based on the recording location, ECoG provides better signal spatial resolution and better signal to noise ratio (SNR). Therefore, nowadays, only ECoG-based Brain-Computer Interface (BCI) is demonstrated successful. Moreover, although the research group from Iran showed 81.4 % accuracy for Hold and Grasp Task for EEG-based BCI and another group from University of Minnesota showed 80 % accuracy for Reach and Grasp Task, the performance is still not good enough since there exists one fail every five tasks. Last but not least, because of the "distortion" effect resulted from skull on EEG, further complicated controlling application will be too hard to achieve. I hypothesize to estimate ECoG from EEG, and the performance of BCI based on the estimation can significantly be improved. In this project, I employ nonlinear principal component analysis (NLPCA) to reduce the dimension of ECoG signals. Then build a forward model from the perspective of physiology and statistical analysis to predict the EEG from ECoG. Next, inverse the structure of the forward model to obtain the inverse model to predict ECoG from EEG. Future work is to demonstrate the improvement by comparing the performance of pure EEG-based BCI and that of predicted ECoG-based BCI.

[50]

Hippocampal-parietal interactions during retrieval of true versus false memories

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Previous fMRI literature has established a core episodic memory retrieval network comprising of the hippocampus and parietal locations including the angular gyrus and posterior cingulate cortex, among other areas. Specifically, this retrieval network can be closely examined in free recall, where existing human studies would predict one would observe significant differences in brain activity that can discern between correct and incorrect retrieval events (list intrusions). However, existing EEG studies have not independently characterized brain activity within the core retrieval network and have not been able to examine connectivity relationships between these regions and the hippocampal and frontal cortex. We employed a data set consisting of 100 human patients implanted with laterally inserted stereo-EEG electrodes procedure mapping purposes who performed free recall. Ultimately, we found significant differences in gamma activity in the angular gyrus, precuneus, posterior cingulate, and posterior hippocampus between true and false memory retrieval events. We further observed that the left angular gyrus exhibits a unique cross frequency coupling pattern within this network. Finally, we compared brain connectivity between true and false memories, revealing significant hemispheric asymmetry, with relatively sparse left-sided functional connections compared to the right hemisphere. Overall, our results shed new light on brain regions critical for item retrieval, especially for temporal contextual information.

[51]

Hippocampal theta oscillations distinguish recollected from recognized memory items in associative recognition memory

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Dual process theory holds that distinct physiological mechanisms underlie the mnemonic functions of recognition and recollection, with the latter constituting a hippocampal-dependent process incorporating associations between items, spatial context, temporal context, or some other memory feature. But it remains an unanswered question as to which specific oscillatory patterns in the hippocampus or within wider episodic memory networks support this recognition/recollection distinction. The goal of investigating hippocampal oscillatory patterns to test predictions of dual process theory motivated us to apply the associative recognition (AR) paradigm to intracranial EEG patients with depth electrodes inserted into both cerebral hemispheres. We compared oscillatory activity in the hippocampus between item pairs correctly assessed as intact (successful associative memory, recollection) versus those incorrectly called rearranged but recognized as old (failed associative memory but successful recognition). We observed a power increase in the slow-theta frequency (2-4 Hz) range that was strongest in the posterior hippocampus during memory retrieval ($p < 0.05$ for one continuous cycle of oscillation, FDR corrected). Our findings provide direct electrophysiological evidence that hippocampal theta specifically may support recollection but not recognition processes in human memory circuits, and that this distinction relies on hippocampal activity during both memory encoding and retrieval.

[52]

Bidirectional hippocampal-prefrontal interactions during episodic memory processing

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A critical and emerging question in human episodic memory is how the hippocampus interacts with the prefrontal cortex during encoding and retrieval of items and their context. The biased competition model, synthesized using rodent models, postulates that during memory encoding, the hippocampus transmits contextual information to the prefrontal cortex, but during retrieval, this information is transmitted back to the hippocampus to govern selection of an appropriate memory trace. This "reversal of information flow" concept has been tested directly in rodents by examining theta oscillations. However, commensurate human data have not been uncovered. With the goal of specifically testing predictions of the biased competition model, we analyzed a data set of 76 individuals who performed an episodic memory paradigm with intracranial electrodes simultaneously inserted into the hippocampus and multiple prefrontal locations. Simultaneous recording allowed us to quantify the precise onset times of gamma band activation for the cortex relative to the hippocampus. We observed that the left anterior VLPFC exhibited activity onset that was significantly later than the hippocampus (14 msec) during memory encoding but significantly preceded activation onset in the hippocampus (10 msec) during memory retrieval. Our results provide direct human evidence to support the biased competition model. We discuss how our observations fit with a wider picture of brain activity during memory encoding.

[53]

Ontogeny of coordinated representations in the hippocampal-prefrontal network during spatial learning

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During spatial learning and cognition, hippocampal spatial maps are thought to interact with the prefrontal cortex (PFC) for evaluation and selection of task-relevant information to promote effective behavior. However, the specific nature of these task-relevant representations, the relative timescales at which they emerge in the hippocampus and PFC during learning, and how they support subsequent stable task performance is still unclear. To address these questions, we continuously and simultaneously recorded the same neuronal ensembles in PFC and hippocampal CA1 area in rats (n = 6) throughout learning of a novel spatial alternation task in a single day. We found that improvements in behavioral performance were closely associated with the stabilization and refinement of spatial representations, which emerged in parallel in both CA1 and PFC. Additionally, we observed the co-development of two types of task-dependent representations in CA1 and PFC during learning. First, activity patterns became more distinctive in different running directions occurring in the same spatial location (i.e., directional selectivity). Second, neurons developed trajectory-dependent activity, representing not only instantaneous position but also the past and future choices (i.e., choice selectivity). Our results suggest that spatial learning elicits coordinated changes in context-selective representations in both the hippocampus and PFC. The emergence of these stable representations from a naïve state reflects the establishment of hippocampal-prefrontal associations that are important for learning rules in novel environments, and can therefore provide the neural basis to support memory guided behavior.

[54]

Hippocampal-prefrontal replay mediates retrospection and prospection for spatial choice learning

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Goal-directed spatial learning requires remembering and retrieving critical paths or choices to a desired goal, a process that requires hippocampal-prefrontal circuits. In the hippocampus, awake replay of place-cell sequences can represent behavioral paths in either forward or reverse order, and is coordinated with prefrontal activity for memory reactivation, providing a potential mechanism for spatial learning. However, little is known about the specific roles of reverse and forward replay during the course of learning, and the connection between coordinated hippocampal-prefrontal reactivation and goal-directed choice behavior. We therefore continuously recorded the same hippocampal-prefrontal ensembles in rats (n = 6) throughout learning of a W-track spatial alternation task within a single-day. We found that all available past and future choices were preferentially replayed at reward wells by reverse and forward hippocampal sequences, respectively. During working-memory update, reverse replay predicted actual past choices only during initial learning. During reference-memory update, forward replay predicting correct future paths emerged only after learning. Furthermore, prefrontal cells reactivated more coherently with hippocampal place cells during the replay of behaviorally relevant trajectories (i.e., immediate past or future) than during that of irrelevant ones. Our findings reveal a shift from reverse-replay-based evaluative learning to forward-replay-based prospective planning, with prefrontal filtering of behaviorally relevant paths during learning and memory-guided choices.

[55]

A robust signature of grid code readout in place field statistics

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Hippocampal place cells integrate multimodal sensory information for constructing a spatial map of the physical environment. A major input to place cells comes from the medial entorhinal cortex, which contains grid cells whose regular hexagonal firing fields provide an efficient spatial metric for path integration. While place cells have been found throughout the hippocampus, it is unclear what spatial information is represented in different hippocampal subregions and to what extent each subregion is driven by grid cells. To this end, we studied the influence of grid cell inputs on the statistics of place fields in downstream place cells using a linear model with a variety of learned or random connections. We found that, in all model variants, the spatial frequencies associated with grid cell firing are overrepresented in the power spectral density (PSD) of the place field distribution in both 1D and 2D environments. When place cells remap in a different environment, these overrepresented peaks in the PSD remain invariant. Moreover, these peaks in the PSD persist over a range of noise levels, and could thus serve as a robust signature of grid code readout. Therefore, our theoretical study provides a testable prediction for information flow from grid cells to place cells in individual hippocampal subregions.

[56]

The Domain-Specificity of Serial Order Working Memory: An Individual Differences Approach

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Making a turn while driving is simple: turn on the indicator, check for cars, then turn. Two types of information are required to perform this sequence of events: information about the items (i.e., the correct indicator), and the serial order of those items (i.e., checking before turning rather than vice-versa). The capacity for remembering temporal order information is important to many cognitive functions, including working memory (WM). In both verbal and nonverbal WM, this capacity has been shown to dissociate from item-identity processing. We investigated whether serial order WM is shared for sequences from different content domains with an individual differences approach. One hundred and fifty-three participants performed sequence matching tasks with verbal (letters and words) and nonverbal (locations and arrows) stimuli. The accuracy of detecting mismatched item-identity and serial order information in sequences was used to operationalize item and order WM in these tasks. Domain-general vs. domain-specific serial order WM hypotheses were compared using structural equation modeling and nested model comparison. The domain-specific model with dissociated item and serial order latent variables in both verbal and nonverbal domains has the best fit, suggesting separate serial order WM capacities for verbal and nonverbal sequences.

[57]

Bimodal representation of information in the hippocampal theta oscillation during reward-associated navigation

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Successful navigation requires accurate encoding of current location and prediction of future outcomes based on prior behavior, and hippocampal place cells are believed to play a central role in these processes. During active exploration, place cells display "phase precession" with respect to the ongoing 4-12 Hz theta rhythm, firing at progressively earlier phases of theta as the rat traverses a cell's place field. Across place cell populations, phase precession is hypothesized to produce theta sequences, temporally organized sequences of neural firing which encode short virtual trajectories. It is currently unclear how theta sequences facilitate encoding and prediction during spatial navigation. Here, we show for the first time that during a memory-dependent task, a third of hippocampal CA1 cells (bimodal neurons) fire prominently at both the trough and peak of theta, respectively displaying canonical phase precession and, surprisingly, phase procession, while the remainder preferentially fire at the trough of theta. At a population level, bimodal neurons contribute to two distinct forms of theta sequences which arise consecutively within the same theta oscillation: a prospective sequence encoding a trajectory in the same direction as the animal's movement, and a retrospective sequence encoding a trajectory in the opposite direction. Firing within the prospective vs. retrospective sequence is independently modulated, indicating that bimodal place cells may be driven by two distinct sources of theta-frequency input that are phase offset by approximately 180°. Finally, we observe stronger firing in retrospective, but not prospective, sequences as rats approach goal locations, implicating this novel process in successful memory retrieval and behavioral performance.

[58]

Egr1 Recruits Tet1 to Shape the Brain Methylome during Early Postnatal Development

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Early growth response gene-1 (Egr1) is a critical transcription factor involved in neuronal plasticity and memory formation. With a rapid increase in expression during the first few weeks after birth, Egr1 controls the selection, maturation and functional integration of newborn neurons. The regulation of Egr1-mediated gene expression has been shown to be under methylation control. However, Egr1 target sites and their epigenetic regulation in the nervous system remains largely unknown. In this study, we performed ChIP-seq for EGR1 in mouse frontal cortex and identified a large number of EGR1 binding sites with their cell-type specific methylation (CSM) patterns established during postnatal frontal cortex development. More specifically, the CpG dinucleotides within these EGR1 binding sites become hypo-methylated in mature neurons but remain heavily methylated in glia. We further demonstrated that EGR1 recruits a DNA demethylase TET1 to remove DNA methylation at EGR1 binding sites and activate downstream genes. In addition, we found that the frontal cortices from knockout mice with the loss of Egr1 or Tet1 share strikingly similar profiles in both gene expression and DNA methylation. In summary, our study reveals Egr1 as a key mediator for gene-environment interactions shaping brain methylome together with Tet1 during early postnatal development and provides an important new insight into how early life experience may shape the brain methylome.

[59]

Dissociation between the role of the centrally-projecting Edinger Westphal nucleus (EWcp) in ethanol-induced conditioned place preference(CPP) and ethanol drinking.

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The transition from moderate to excessive drinking is likely due, in part, to alcoholinduced adaptations within the CRF system. In this system, the centrally-projecting Edinger Westphal nucleus, the main source of brain Urocortin 1, is known to be sensitive to, and regulate alcohol intake. Here, we assessed the role of the EWcp in ethanol-seeking by manipulating its neuronal activity. Pharmacological inhibition of EWcp (muscimol + baclofen) increased body temperature, and prevented the increase of c-Fos following an ethanol injection . Additionally, inhibition of EWcp during ethanol-induced CPP testing resulted in increased locomotor activity. However, there was no effect on CPP expression or acquisition. Conversely, chemogenetic activation of the EWcp via injection of Clozapine-N-Oxide decreased ethanol drinking in a choice procedure. Moreover, this decrease in ethanol intake can be attributed in part to glutamatergic neurons, as selective activation of Vglut2-positive neurons in the EWcp also decreased ethanol intake. Together, these data suggest that inhibition of the EWcp is not sufficient to alter ethanol-induced CPP, but chemogenetic activation of the EWcp can decrease ethanol intake. When considered in light of previous studies, these data suggest that the EWcp may play a more selective role in modulating certain ethanol-seeking behaviors.

[60]

High-density, three-dimensional ultraflexible electrode array: towards stable recording of thousands

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The brain is a massively-interconnected and constantly-evolving network of specialized circuits, a systematic understanding of which requires an interface that functions at diverse spatial and temporal scales. Implanted electrodes provide a unique approach to decipher brain circuitry by allowing for time-resolved electrical detection of individual neuron activity. However, conventional intracortical recordings are often sparse, and importantly, unstable over long term. Our recent progress on ultraflexible nanoelectronic threads (NETs) has demonstrated marked long-term stable recording and seamless probe-tissue integration. Here we present our on-going efforts of massively expanding this platform with the focus on further miniaturizing the probe dimensions and maximizing the recording density. We will show our recent progress on the resulting volumetric recordings in rodent brains, in both cortical and deeper structures.

[61]

Long-term tracking of neuronal clusters with ultraflexible electrode arrays

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The brain is characterized by massively connected and constantly-changing networks of neurons communicating in milliseconds. Therefore, reliably tracking the evolution of local neuronal clusters with high temporal resolution across chronic timescales is highly valuable to the functional mapping of the brain. Conventional rigid extracellular electrode arrays offer time-resolved parallel recording of large number of neurons in the short term. However, their capability to follow same neurons longitudinally remain elusive due to gradual deterioration of cell-electrode interface caused by mechanical mismatch induced chronic neuroinflammatory response. In addition, such mechanical mismatch generates excessive micro-movement between neuron and recording arrays, resulting in longitudinally inconsistent recorded waveforms from same neurons, which compromise traditional unsupervised spike sorting algorithms that base on constant waveform assumptions. To further expand the limit of electrical recording technology, we developed ultraflexible celluar-dimensioned probes that seamlessly integrate with neural tissues to mitigate foreign body response. The probe consists of closely spaced electrodes with overlapping detection range and hence trilateralization capability which allows tracking of slowly changes in neuron locations possibly due to cell migration. We strategically combined supervised and unsupervised algorithms to balance spike sorting efficiency while enabling linking of gradually changing waveform in a consistent manner with reasonable amount of manual input. Twice weekly head fixed recording sessions on mice demonstrated chronically reliable recordings with stable unit yield, amplitude, electrode impedance. A separate continuous freely moving recording for over 30 days greatly improved tracking yield and resolution compared with intermittent counterparts. Finally, we applied these arrays to study cell movements, network connectivity and evolution in mice sensory cortices.

[62]

Bridging single-neuron recording and cortex-wide optical acquisition

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Neural circuits span diverse spatial scales: they consist of nearby clusters of neurons as well as neurons distributed across multiple brain areas. Technically, electrical recording by implanted electrodes allows for millisecond resolution detection of individual neuron activity, but can typically only sample a small portion of all neurons involved in a circuit. Optical measurements of neuronal activity, in contrast, permit high spatial-resolution mapping of a large number of neurons, but typically penetrate < 1 mm in depth and have compromised temporal resolution. It is therefore desired to combine the complementary advantages of optical and electrical measurements. Here we demonstrate a method that combines ultraflexible neural electrodes with cortex-wide polymer cranial window to enable simultaneous recording from individual neurons and large-scale optical imaging of neural activity for long-term studies. We show that this setting flexibly allows for concurrent implementation of multiple neural recording and modulation techniques, including spatially resolved recordings at multiple regions and in deep structures, epi-fluorescence imaging across cortex, two-photon imaging at multiple cortical regions, and optogenetics.

[63]

Mechanistic explanations for spatial navigation deficits in old age

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Numerous studies have reported a progressive loss of spatial navigation abilities in old age, but we have only limited understanding of the causes and neuronal mechanisms underlying this decline. One important navigation strategy is path integration: it enables the continuous tracking of one's position in space by integrating self-motion cues, and it serves as a building block for cognitive maps. In a first experiment, we combined tests of path integration performance in subjects of different ages with a novel computational model that allowed us to decompose distinct causes of path integration error. We found that the dominant source of age-related errors was a growth in unbiased internal noise in older adults' path integration computations. Given the importance of so-called grid cells for spatial navigation functions, we hypothesized that neuronal noise from impaired grid cell firing might account for this increased internal path integration noise. In a second experiment, we therefore used fMRI and a virtual reality navigation task in healthy young and older adults, to investigate the mesoscopic firing signature of grid cell populations (i.e., grid-like representations). Indeed, we found that grid-cell-like representations in entorhinal cortex were compromised in old age. Most strikingly, individual magnitudes of grid-cell-like representations in older adults were predictive of their path integration errors, suggesting that compromised grid-cell-like representations might serve as a key explanation for age-related path integration deficits. Together, these findings not only advance our understanding of the specific contributors to path integration error, they also help elucidate the mechanisms that underlie age-related decline in higher-order cognitive functions such as spatial navigation.

[64]

The involvement of the left infralimbic prefrontal cortex in anxiety and fear extinction resistance after a single prolonged stress procedure

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Rats submitted to the single prolonged stress (SPS) procedure demonstrate impaired fear extinction and increased anxiety, similar to those behavioral and physiological symptoms observed in posttraumatic stress disorder patients. Converging evidence indicates that functional lateralization of the mPFC in the control of emotional states is observed after stress. In this sense, our hypothesis is that loss of tonic left mPFC (LmPFC) inhibitory control over right mPFC is related to the loss of resilience, contributing to the development of maladaptive responses, like impaired fear extinction and enhanced anxiety after the SPS. Here, we used an optogenetic approach to activate (with channelrhodopsin) glutamatergic neurons in the left infralimbic region of the mPFC in SPS rats for 15 minutes each day for 7 consecutive days. Rats were then submitted to the elevated plus maze and auditory fear condition. Our preliminary data demonstrated that activating left IL increases open arm exploration activity and enhances extinction of conditioned fear. Our results suggest that the left IL glutamatergic system is affected by SPS and SPS effects on anxiety and extinction can be reversed with daily stimulation of the left IL.

[65]

Vagus Nerve Stimulation promotes cross-modality extinction generalization between auditory and olfactory cues

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Vagus nerve stimulation (VNS) has been shown to enhance and generalize extinction of auditory fear conditioning in rats. Here we tested whether VNS can enhance extinction of olfactory fear and promote extinction generalization across auditory and olfactory sensory modalities. Male Sprague Dawley rats were implanted with a stimulating cuff around the vagus nerve. After recovery, the rats received two days of fear conditioning where an olfactory cue (o-CS; 100 µl of 10% amyl acetate) and an auditory cue (a-CS; 9 kHz tones, 30-sec, 75 dB) were concomitantly paired to 8 footshocks/day (US; 1-sec, 0.8 mA). Seventy-two hours later, the rats were given three days of sham or VNS-paired extinction (5 stimulations, 30-sec at 0.4 mA). Rats were then tested for avoidance to o-CS or freezing to the a-CS in a different context 48 h after extinction. We found that VNS rats paired with the o-CS displayed reduced avoidance in the olfactory test. We also found that VNS-paired with the a-CS decreased avoidance to the olfactory cue. VNS paired with the o-CS during extinction reduced freezing when rats were presented to the auditory cue. These results suggest that VNS enhances extinction of olfactory fear and promotes a degree of extinction generalization across different sensory modalities. Generalization-enhancing effects of VNS could contribute to improve efficacy of exposure-based therapies.

[66]

Longitudinal multimodal mapping of neural activity and blood flow reveals neurovascular dissociations in an awake mouse model of microinfarcts

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Brain functions and dysfunctions involve complex interactions between neuronal and other cellular and vascular activities at diverse spatiotemporal scales. This vast complexity demands novel technologies that are able to simultaneously resolve multifaceted brain activities at sufficient spatiotemporal resolutions, and to longitudinally track their evolution over a long span of time. Here we demonstrate the development of a longitudinal multimodal neural platform that enables simultaneous mapping of neural activity and cerebral blood flow (CBF) in the same behaving brain. This multimodal neural platform combines intracortical neural recording using the ultraflexible nanoelectronic neural threads that permit exceptional tissue-compatibility, and a wide-field imaging system capable to quantifying both CBF and inducing photothrombotic lesions at controlled locations, size and onset time. We demonstrate the application of this multimodal neural interface in a mouse model of microinfarcts, for which the microscopic ischemic injuries are often associated with vascular dementia but are too small in size to be detected using conventional techniques. In the acute sections following the awake induction of microinfarcts, we observe short-lasting neuronal bursting preceding peri-infarct depolarizations and uncoupling between CBF and neural activity that depends on the severity of the focal ischemia. The neurovascular uncoupling becomes the most severe at the sub-acute phases, for which reperfusion in the occluded arterioles and nearby tissue occurs in the absence of neural recovery. The neurovascular disassociation persists into chronic phases, the duration of which depends on ischemic severity. By spatially resolving and longitudinally tracking the neurovascular response to microinfarcts, we reveal their pathological evolution and demonstrate the need for direct neurological interrogations for evaluating brain impairment and recovery.

[67]

Thalamic physiology in the Fragile X mouse model of autism

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The medial prefrontal cortex (mPFC) and its reciprocal connection with mediodorsal (MD) thalamus are involved in executive functioning and social behavior. Our previous work demonstrated that the neurons that provide the main excitatory input from mPFC→MD are hypoexcitable in multiple mouse models of autism including fragile X syndrome model mice. Though there are extensive bodies of work on thalamic physiology in sensory and motor thalamic regions, virtually nothing is known about the physiology of neurons in the MD thalamus that provide reciprocal inputs to the mPFC.

Here, we measured the intrinsic electrophysiological properties of neurons in the three main subdivisions of MD thalamus (medial, central, and lateral MD). To explore neurons specifically involved in the reciprocal connections between mPFC and MD, we recorded from retrogradely-labeled neurons that project from MD to mPFC. We find that the physiology of MD neurons is heterogeneous: prefrontal-projecting neurons in the three subregions of MD thalamus have distinct electrophysiological properties. We next tested the hypothesis that neurons in the three MD subregions would be differentially affected by loss of the fragile X syndrome gene FMR1. Indeed, we found that the excitability of neurons in specific MD subregions was not affected uniformly by FMR1 knockout. Future work will delineate cellular mechanisms for these differences and the role of these specific populations of MD neurons in animal behavior.

[68]

Prefrontal corticothalamic circuitry in the regulation of social behaviors

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The medial prefrontal cortex (mPFC) plays a key role in regulating social behaviors, however the precise underlying neural circuitry is unclear. The medial dorsal thalamus (MD) is one of main postsynaptic partners of the mPFC. Here, we explored the role of the PFC→MD pathway in mPFC-dependent social behaviors. Previously we found that optogenetic activation of dopamine receptor 2 positive (DRD2+) neurons (which target subcortically projecting neurons) in mPFC decreased social interactions in mice. In the prenatal valproic acid exposure (VPA) mouse model of autism, we found that inhibition of these same DRD2+ mPFC neurons increased social interaction. Here, we have replicated these findings, and optogenetically manipulated specific mPFC→MD inputs during social behavioral tasks in VPA autism model mice. We found that inhibition of mPFC terminals in MD was sufficient to increase social behavior in VPA mice. In FMR1 KO mice, we found abnormalities in social exploration. We eliminated general hyperactivity, anxiety, increased interest in novelty, and olfactory sensitivity as factors in this change. Our ongoing experiments are dissecting how mPFC cell types connect to MD and their links to abnormal social behavior in autism in both VPA and fragile X mouse models.

[69]

Exploring thalamic physiology in an animal model of autism spectrum disorder

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This project involves the study of neurons that project from the prefrontal cortex to the medial dorsal nucleus of the thalamus, creating a neural circuit. The action potentials of the cells in the autism mouse models were compared to the action potentials of cells in the wild-type mouse models (serving as the control). Evaluating the action potentials gives information on how the neurons are firing and transmitting information to one another; discrepancies between the data sets may be indicative of underlying abnormalities in the brain.

To collect action potential data from these cells, cell recordings were performed. A pipette was inserted into a neuron in the prefrontal cortex on a brain slice from the experimental mouse. The addition of current from the pipette triggers action potentials in the cells, so once the pipette was continuous with the cell, the amount of current added and the current's duration were manipulated in various trials. There was an electrode containing a wire coated in chloride ions that was used to measure the amount of current present in the cell. Following this, the action potential data collected was analyzed through MATLAB.

Currently, the data are being analyzed in MATLAB. These findings will be of significance, as they build on previous research regarding other circuits implicated in autism mouse models. This will ultimately be the driver for the development of targeted circuit-based therapeutics for patients with autism.

[70]

Category selectivity and sensory reinstatement in human neocortex

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The sensory reinstatement hypothesis posits that brain regions involved in stimulus encoding are reactivated to support memory retrieval. While neuroimaging studies provide supporting evidence, the functional neuroanatomy of these effects often differs between studies and insight into the temporal dynamics of reinstatement is limited. To overcome these limitations, we utilized human intracranial electrophysiology to investigate the spatial and temporal properties of sensory reinstatement. We focused on reinstatement activity in the human ventral visual pathway. We asked if face selectivity was predictive of reinstatement activity during face stimulus retrieval. Face selective areas were first identified using a visual object localizer. Next, participants learned word and famous face pairs, and were subsequently asked to retrieve the associated face image when only given only word cues. Spectral analysis revealed strong increases in high-gamma range (70-150 Hz) activity during the encoding of word-face pairs in all face-selective electrodes. Interestingly, only a subset of these electrodes displayed reinstatement activity during retrieval. Furthermore, these reinstatement effects were more temporally delayed than encoding responses and significantly larger for hits vs. correct rejection trials. These findings provide direct electrophysiological support for sensory reinstatement in human neocortex occurring within a subset of stimulus-selective regions. Such a dissociation may be critical to understanding how memory-driven reactivation approximates prior perception in the absence of relevant sensory inputs.

◆ **[71]**

Prefrontal somatostatin interneurons encode fear memory

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In addition to excitatory projection neurons, prefrontal cortex harbors a network of local inhibitory neurons composed mainly of parvalbumin- (PV-INs) and somatostatin-expressing (SST-INs) interneurons. Intriguingly, *in vivo* electrophysiological recordings indicated that in contrast to conditioned stimulus (CS)-evoked spiking of projection neurons, fear memory expression is associated with suppression of activity in prelimbic (PL) PV-INs. However, it remains unclear how fear conditioning might drive these dynamic changes in prefrontal population activity. We performed immunohistochemical c-Fos staining and observed that PL layer 2/3 SST-INs are activated in response to both fear memory acquisition and retrieval. Correspondingly, whole-cell recordings from acute brain slices indicate that fear conditioning leads to a lamina-specific increase excitatory synaptic transmission in SST-INs but not PV-INs. Moreover, fiber photometry recordings indicated that PL SST-INs exhibit a learning-dependent enhancement in CS-evoked activity. Together, these data suggest that SST-INs may be important for fear learning and/or memory expression. In support of this idea, *in vivo* optogenetic activation or silencing of SST-INs promoted or suppressed fear memory expression, respectively. Optogenetics-assisted electrophysiological recordings in PL revealed that SST-INs provide monosynaptic input onto PV-INs. Importantly, these inputs exhibited learning-dependent plasticity, indicating a potential role for SST-INs in disinhibition of fear-related excitatory projection neurons. In line with this role, c-Fos staining in animals where SST-INs were optogenetically activated revealed that PL is disinhibited and as a result, relevant long-range target structures are engaged. Overall, our results suggest that SST-INs may play a key role in gating fear-related prelimbic circuitry and their expression of synaptic plasticity after fear conditioning could constitute a mechanism for memory storage.

◆ **This abstract was selected for a Best Abstract Award and the content will be presented as both a talk in session 3 and as a poster.**

[72]

Dysfunction of Inhibitory Interneuron Signaling in Fragile-X Syndrome

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Fragile X Syndrome (FXS) is the most commonly inherited form of intellectual disability and the leading genetic cause of autism. Patients with FXS exhibit increased incidence of epilepsy, sensory hypersensitivity, and anxiety among other cognitive impairments. Recent data suggests that a lack of inhibitory/excitatory balance in the brain may be a major contributor to the debilitating cognitive deficits in FXS. While there is an extensive body literature investigating excitatory pyramidal neurons and synaptic transmission, the impact of aberrant inhibitory activity is largely unknown. We focused on two integral inhibitory interneuron subtypes in the hippocampus: *somatostatin expressing* (SOM) and *parvalbumin expressing* (PV) interneurons. SOM interneurons specifically target pyramidal cell dendrites and control synaptic plasticity, while PV interneurons target pyramidal cell bodies and control cell ensemble activation. Using whole-cell current clamp recordings, we measured subthreshold (i.e. input resistance, resting membrane potential) and suprathreshold (i.e. action potential threshold) properties of SOM and PV cells in wild-type and *fmr1*$^{-/y}$ mice. We observed a depolarized resting membrane potential and decreased input resistance in the SOM interneurons of *fmr1*$^{-/y}$ mice. Additionally, SOM neurons in *fmr1*$^{-/y}$ mice exhibited decreased AP number to the same current injections compared to WT mice. There was no apparent phenotype in the PV interneurons of *fmr1*$^{-/y}$ mice in either subthreshold or suprathreshold properties. Due to their distinct connections, SOM and PV cells to contribute to different functional aspects of the hippocampal microcircuit and alterations of either interneuron subtype in FXS would impair information processing in the hippocampus.

[73]

Dysfunctional temporoammonic pathway LTP in a mouse model of Fragile X syndrome.

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Fragile X syndrome (FXS) is the most common monogenetic cause of autism and intellectual disability. Although the genetic underpinnings of FXS are well understood, the neurophysiological basis for the intellectual deficits remain largely unknown. Our lab has identified dendritic channelopathies in FXS affecting integrative processes in CA1 neurons of the hippocampus, a structure critical for learning and memory. Here, we use the *fmr1-/y* mouse model of FXS and a combination of somatic and dendritic current clamp recordings paired with 2-photon calcium imaging to investigate the impact of dendritic channelopathies in FXS on synaptic transmission and plasticity of temporoammonic (TA) synapses from the entorhinal cortex onto CA1 neurons. Following theta burst stimulation, TA synapses in *fmr1-/y* CA1 neurons showed significantly smaller LTP (8.8 ± 21.8%) compared to wild type CA1 neurons (324.4 ± 74.4%). 2-photon imaging revealed significantly smaller dendritic calcium signals during 100 Hz burst stimulation of TA inputs in *fmr1-/y* CA1 neurons (14.29 $\%\Delta F/F_0$) compared to wild type CA1 neurons (57.36 $\%\Delta F/F_0$). We interrogated NMDA receptor efficacy at TA synapses and found no differences in NMDA function between wild type and *fmr1-/y* neurons. Therefore, we hypothesize that there is insufficient dendritic depolarization, and subsequent calcium influx through voltage gated calcium channels, during TA-TBS in *fmr1-/y* neurons to promote LTP. Interestingly, simultaneous stimulation of both TA and Schaffer collateral synapses results in comparable levels of potentiation between wild type and *fmr1-/y* neurons, indicating that, despite the lack of TA LTP during single pathway stimulation, TA synapses in *fmr1-/y* neurons are able to undergo normal LTP. Our findings, showing such robust changes in neuronal plasticity in a disorder characterized by deficits in learning and memory, hold significant implications for future research into specific therapies for individuals with FXS.

[74]

Persistent co-activity patterns of neurons in the medial entorhinal cortex across waking and sleep states are not explained by similar patterns of place cell co-activity

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Multiple spatially selective subtypes of neurons, including head direction cells and grid cells, are found within the medial entorhinal cortex of rats and other species. The question of which mechanisms drive these neurons' activity patterns remains an area of active study. Continuous attractor network models posit that recurrent connectivity between grid cells controls their patterns of co-activation, whereas alternative models point to correlated inputs from sensory cortex or hippocampus. To clarify this issue, we recorded single units from the superficial layers (II/III) of the medial entorhinal cortex in six rats performing active exploratory behaviors and throughout subsequent overnight sleep. We found that the degree of spatial overlap between neurons' firing patterns observed during active waking behaviors predicted neuronal co-activity patterns during REM and non-REM sleep, when sensory inputs are absent. This relationship was observed for grid cell pairs from the same module, but not for grid cell pairs from different modules, further supporting recurrent connectivity as the mechanism for grid field formation. Through analyses of place cell recordings, along with modeling and simulations, we also found that medial entorhinal cell co-activity patterns were not explained by similar place cell activity patterns. These results suggest that, barring grid-like structured input from other cortical areas, local recurrent connectivity drives the co-activity of spatially selective cells in the superficial layers of medial entorhinal cortex across behavioral states.

[75]

Impaired CA2 place cell remapping in response to social olfactory stimuli in a rat model of Fragile X Syndrome

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The CA2 region of the hippocampus has been implicated in social memory. A recent study showed that CA2 place cell firing patterns change ("remap") during social interactions, a trait which is not apparent in CA1 place cells (Alexander et al., Nature Communications 2016). Our preliminary results show that CA2 place cells remap after a rat interacts with a familiar rat's empty homecage that contains only the rat's odors. On the contrary, CA2 place cells do not remap in response to interactions with an identical cage containing the rat, but with clean bedding and no familiar rat odors (Mably et al., SfN abstracts, 2018). These results suggest that CA2 place cells remap in response to the olfactory content of social experiences. Interestingly, preliminary data using a rat model of Fragile X Syndrome (FMR1 knockout rats or "FXS rats") suggest that CA2 place cell remapping does not occur in response to olfactory social stimuli in FXS rats compared to wildtype control rats. Necessary control experiments to assess CA2 place cell responses to non-social odors in control and FXS rats are ongoing and will also be discussed.

[76]

Corticotropin-releasing factor (CRF) neurons in the paraventricular thalamus balance food seeking with the risk of predation

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Survival depends on a balance between approaching food and avoiding the risk of being attacked by a predator. However, which neuronal circuits integrate reward and fear information remains unknown. Neurons in the paraventricular thalamus (PVT) respond to both reward and fear-associated cues, making this region a potential candidate for this integration. To test this hypothesis, Long-Evans adult rats were exposed to a conflict task in which audiovisual cues predicting the presence of sucrose were presented concomitantly with a fear-inducing stimulus (predator odor). Single-unit recordings from anterior PVT (aPVT) revealed two distinct populations of neurons responding to either predator odor or reward cues. aPVT responses to sucrose cues correlated with food-seeking behavior, and were attenuated during predator odor exposure. Chemogenetic inactivation of aPVT projections to the Nucleus Accumbens (NAc) reduced defensive responses and increased food seeking. Interestingly, exposure to predator odor activated corticotropin-releasing factor (CRF) neurons in the aPVT, and photoactivation of these neurons mimicked the avoidance responses and food-seeking suppression induced by predator odor. Slice recordings from NAc neurons demonstrated that photoactivation of $aPVT^{CRF}$ fibers in the NAc elicited large excitatory postsynaptic responses, suggesting that activity in $aPVT^{CRF}$-NAC pathway regulates the balance between fear and food-seeking responses.

[77]

Effects of different fasting regimens on innate fear responses in rats

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Overcoming aversive situations (e.g. predator threat) in order to obtain food is crucial to survival in nature. However, which brain regions regulate food-seeking and fear responses, and how food shortage interferes with this regulation, remains unknown. The paraventricular thalamus (PVT) has been implicated in both food-seeking and fear responses, making this region an important candidate to study. To investigate, male Long-Evans rats were trained to press a lever for sucrose during the presentation of audiovisual cues. Next, rats previously exposed to 24h or 72h of fasting were exposed to the audiovisual cues in the presence of either predator odor (PO) or neutral odor (control). Compared to controls, the 24h PO group showed robust defensive behaviors (avoidance, risk-assessment, freezing) and suppression of food-seeking responses (lever presses, appetitive vocalization). Interestingly, defensive behaviors and food-seeking responses in the 72h PO group were similar to controls. Accordingly, rats exposed to 24h of fasting, but not 72h, showed increased expression of the neuronal activity marker cFos in the PVT following PO exposure, when compared to controls. These results suggest that suppression of food-seeking responses during predator threat exposure correlates with PVT activity, and is regulated by the duration of food deprivation.

[78]

Foraging at the edge of fear: neural correlates of memory discrimination in the prelimbic cortex

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The ability to identify and discriminate cues associated with reward and aversive stimuli allows an organism to select the most appropriate response. Neurons in the prelimbic prefrontal cortex (PL) respond to reward and threat cues. However, how PL activity correlates with animals' decision-making to approach or avoid such cues remains unknown. To address this question, male Long-Evans rats with single-unit recording electrodes in PL were trained to press a lever for sucrose during the presentation of audiovisual cues. Next, rats were fear conditioned by pairing a neutral odor with electrical footshocks. During the test session, rats were exposed to three phases: only audiovisual cues (baseline), only odor cues (fear), or both simultaneously (decision-making, DM). Interestingly, two subpopulations of rats emerged during DM: rats that continued pressing with an increased latency of 37% (*pressers*) vs. rats that remained in the hidden area and showed complete food-seeking suppression (*avoiders*). During DM, reward-cue responses in PL neurons continued the same for *pressers*, but were completely abolished for *avoiders*. Compared to *avoiders*, *pressers* learned the reward-cue association quicker and showed more PL responses to reward cues during the baseline, suggesting that PL activity serves as a predictor for animal's decision-making during reward-fear conflict.

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[79]

Disrupted hippocampal synaptic plasticity in the *Scn1b* knockout model of Dravet syndrome

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Dravet Syndrome (DS) is a genetic form of epilepsy caused by mutations in the *SCN1A* or *SCN1B* gene. *SCN1B* codes for b1, a protein subunit that interacts with voltage-gated ion channels important for neuronal excitability and synaptic plasticity. Here, we used an *Scn1b* knock-out (KO) mouse model of DS, with wild-type (WT) littermates serving as controls, to examine the effects of loss of b1 on hippocampal synaptic plasticity. We recorded synaptic responses (fEPSPs) from CA1 of the hippocampus while stimulating afferent axons, and used a theta burst stimulation paradigm to induce synaptic plasticity. With this paradigm, we were able to induce long-term potentiation (LTP) in the slices from WT mice. However, our data revealed a deficit in plasticity in KO littermates. Recent data shows that *Scn1b* KO mice may have a delay in GABAergic maturation, and we examined how a $GABA_A$ antagonist affects synaptic plasticity. Interestingly, there was an even greater disruption of plasticity in the KO slices when we blocked GABAergic transmission. Our data supports our hypothesis because of the deficit of LTP in KO mice in and out of the $GABA_A$ antagonist, which all suggest there is a delay in GABAergic maturation in the mice. Our next study will be to continue the experiments and to examine the effects of the $GABA_A$ antagonist on WT mice.

[80]

Altered excitability and synaptic integration in a mouse model of Dravet syndrome

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Dravet syndrome (DS) is a genetic encephalopathy associated with prolonged seizures, developmental delays, cognitive deficits, and a high rate of mortality. DS has limited treatment options, in part due to our lack of understanding of the cellular and circuit level disruptions that underlie the phenotype. Mutations in *SCN1B*, which encodes the voltage-gated ion channel auxiliary b1 subunit, have been linked to DS. b1 associates with and modifies the actions of multiple types of ion channels that are vital regulators of action potential initiation and dendritic excitability. The goal of this study is to investigate how loss of b1 alters intrinsic excitability and synaptic properties of hippocampal neurons in order to better understand the neurophysiological changes leading to the complex phenotypes of DS. Here we performed whole cell patch clamp recordings from CA1 pyramidal cells (PCs) in acute hippocampal slices from *Scn1b* knockout (KO) mice and their wild-type (WT) littermates. Our data show that CA1 PCs from *Scn1b* KOs are hyperexcitable, firing more action potentials in response to current injection compared to WTs, without a change in threshold. KO neurons also demonstrated modest increases in input resistance and I_h, and reduced capacitance. These changes in intrinsic properties were coupled with complex changes in synaptic inputs to CA1 PCs. We found that PCs from KO mice displayed larger and prolonged depolarization in response afferent stimulation, but smaller excitatory and inhibitory post-synaptic currents. KO neurons also demonstrated a higher probability and faster rate of firing in response to physiological patterns of synaptic stimulation. Together our data suggest that modest changes in intrinsic excitability and synaptic properties leads to a great enhancement of synaptic integration and input/output functions in *Scn1b* KO neurons, thereby, fundamentally altering network excitability and the control of information processing in the hippocampus.

◆ **[81]**

Hippocampal theta coordinates memory processes during visual exploration

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The hippocampus supports memory encoding and retrieval, with distinct phases of theta oscillations modulating the amplitude of gamma-band activity during each process. Encoding and retrieval operations dynamically interact over rapid timescales, especially when sensory information conflicts with memory. The ability to link hippocampal dynamics to specific memory-guided behaviors has been limited by experiments that lack the temporal resolution to identify when encoding and retrieval occur. To resolve this issue, we simultaneously tracked eye movements and hippocampal field potentials while neurosurgical patients performed a spatial memory task. Novelty-driven fixations increased phase locking to the theta rhythm, which predicted successful memory performance. Theta to gamma phase amplitude coupling increased during these viewing behaviors and predicted forgetting of prior memories. In contrast, theta phase-locking preceded fixations initiated by memory retrieval, indicating that the hippocampus drives memory-guided eye movements. These findings suggest that theta oscillations in the hippocampus support learning through two interleaved processes: strengthening the encoding of novel information and guiding exploration based on prior experience.

◆ **This abstract was selected for a Best Abstract Award and the content will be presented as a talk in session 3 in lieu of a poster.**

[82]

The immediate early gene *Arc* is critical to the persistence of NMDAR-dependent LTD but not LTP

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Activity-Regulated Cytoskeletal protein (*Arc*) is critical to the persistence of long-term memory. Arc regulates AMPAR endocytosis, decreasing synaptic strength. However, *Arc* mRNA and protein expression is increased after the induction of long-term potentiation (LTP), which increases synaptic strength. While some studies have found LTP to be attenuated in the absence of Arc, these results have yet to be explained in relation to synaptic weakening. To elucidate the synapse specific ways in which Arc may regulate long-term memory, we used hippocampal slices from Arc knockout animals (ArcKO) and wildtype (WT) littermates to evaluate the role of *Arc* in long-term depression (LTD) and LTP at CA3-CA1 synapses, *in vitro*. LTD was significantly attenuated in slices from ArcKO animals, compared to WT controls. There was no difference in LTP between the groups using a high frequency stimulation protocol. Surprisingly, when using a theta burst stimulation protocol that is purported to be more physiologically relevant than high frequency stimulation, LTP was significantly enhanced in the ArcKO slices. These results indicate that Arc regulates LTD persistence but not LTP, suggesting that one role in long-term memory may be the regulation of synaptic weakening. Further, paradigms used to induce LTP may stimulate expression of genes unrelated to enhancement of synaptic strength. This expression pattern may be explained by *Arc's* ability to form capsid structures that package RNA for transfer between cells, potentially controlling cellular networks rather than specific synapses.

[83]

Effect of time and speed on hippocampal slow and fast theta rhythm in freely behaving mice

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Hippocampal theta (6-12 Hz) oscillations co-vary with different aspects of rodent cognition and behavior. Cognitively, recent research has highlighted the effect of time on hippocampal processing (Gereke et al 2018), suggesting that theta oscillations play a role in organizing temporal information in the brain. Behaviorally, theta activity correlates with the animal's running speed, which indicates that theta oscillations may process rapidly changing spatial information. However, it is unknown how speed and time interact to modulate theta oscillations within the hippocampus. Understanding the combined effects of both speed and time on the theta rhythm should help uncover how theta simultaneously organizes different aspects of cognition and behavior. Here, we hypothesized that hippocampal theta oscillations are modulated by both speed and time independently, and, depending on the cognitive state of the animal, theta oscillations will be disproportionally affected by one process more than the other. To test this hypothesis, we studied hippocampal theta oscillations while rodents performed a novel/familiar paradigm task. We used 32-channel silicon probes arrayed across the CA1-to-DG axis to record *in vivo* local field potential signals in wild-type mice (n = 6) during this task. Here, we present four major findings: (1) novelty is specifically associated with fast theta oscillations (8-10 Hz) in all layers of the hippocampus; (2) time is associated with slow theta power (6-7 Hz) in CA1, independent of task type (novel or familiar); (3) running speed is associated with a dissociation of slow and fast power in all layers (CA1-to-DG); (4) the correlation between theta power and speed in novel environments is weak. These results suggest a different role for slow and fast theta oscillations: slow theta rhythm reflects memory load, and fast theta rhythm reflects early episodic memory encoding.

[84]

The role of dopaminergic signaling in vocal learning and vocal fluency

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Dopaminergic circuits regulate important physiological brain's functions including the signaling of reward prediction error, motivation, control of movements and cognition. The dysfunction of dopaminergic transmission is recognized as a core alteration in several devastating neurological and psychiatric disorders. It's not fully appreciated whether and how alteration of a functional segregated dopaminergic circuit can result in variety of pathological symptoms in neurological disorders. Here, we found optogenetic excitation of VTA-vocal basal ganglia pathway in singing zebra finches can not only elicit positive reinforcement learning in the pitch of targeted song elements, but also lead to pathological vocal repetition, mainly in the non-targeted song elements, when this manipulation persists for several consecutive days. Although the changes in pitch and repetition occurs in parallel during optical stimulation, the recovery rate of repetition and pitch are usually asymmetrical and independent of each other. In contrast, optogenetic inhibition of the same dopaminergic pathway elicited negative reinforcement learning in the pitch of targeted song elements, but we failed to observe abnormal vocal repetition during the course of optical inhibition. This study demonstrates that overactivation of a dopaminergic pathway, which is essential for vocal learning, causes pathological vocal repetitive behavior resembling stuttering.

[85]

Habituation of feeding behavior in Hydra Vulgaris

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Cnidarians have a simple nervous system, a nerve net, with neurons distributed across the body, and lacking ganglia or any form of cephalization. With this simple nervous system, cnidarians can habituate, a form of non-associative memory. Yet, how a diffuse nerve net can encode habituation remains unknown.

To address this, we use the cnidarian Hydra vulgaris. Hydra is a small (0.5-1.5 cm in length) fresh-water polyp, with only 600-2000 neurons. We generated transgenic animals expressing the genetically-encoded calcium sensor GCaMP6s in the entire nervous system. Being transparent, Hydra provides a unique opportunity to image the entire neural activity of a freely-moving animal under a microscope.

To test if Hydra habituates to chemical stimuli, reduced-glutathione (GTH), that induces feeding behavior, was applied. During feeding, Hydra exhibits a sequential behavior including tentacle writhing and balling as tentacle length becomes shorter compared to the control ($p = 0.0012$). After repeated GTH applications, the induced robust shortenings of tentacles becomes smaller ($p = 0.9997$) suggesting that Hydra habituates to GTH-induced feeding.

To understand the neural mechanisms of habituation, the neuronal activity during GTH- induced feeding was studied using Hydra expressing GCaMP6s in its neurons. Upon GTH exposure, neurons in every tentacle were strongly activated. After repeated activation, neurons stopped responding, and there was no further tentacle writhing or balling. In future experiments, the causal relationships between neuronal activity and behavior will be tested using optogenetics.

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[86]

Removing thoughts via replacement, suppression, and clearing

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Removing unwanted thoughts from working memory (WM) is a critical cognitive process that enables an efficient use of its limited capacity (Lewis-Peacock et al., 2018). Recent evidence (Banich et al., 2015) suggests that brain regions involved in cognitive control are differentially engaged depending on how information is removed: *replacing* it with a different one, *suppressing* it, or *clearing* all thoughts from mind. Here we addressed the heretofore intractable issue of understanding how these removal processes alter the representation of thoughts during their removal from WM. On each trial, participants (N=47) memorized a target picture (a face, a fruit, or a scene) and then were instructed to maintain the memory or to perform one of the three removal operations. Employing multi-voxel pattern analysis (MVPA) on fMRI data collected every 470 ms, we were able to demonstrate that replacing, suppressing, and clearing are distinct neural processes that act upon WM information in different ways. By tracking the information contents of WM during the removal operations, we found that *replacing* an item was the quickest way to remove information, followed by *clearing* and then *suppressing*. Furthermore, these operations had different impacts on the encoding of new information. Whereas maintaining an item interfered with encoding of the next item, suppressing an item led to the greatest release from this proactive interference ($p = .002$), followed by replacing ($p = .11$), and then clearing ($p = .99$). These results provide an exciting new window into the unique neural processes and consequences of removing information from WM.

[87]

Changing cognitive control for prospective memory in dynamic environments

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Prospective memory (PM) refers to our ability to delay the execution of an intended action until the appropriate time or situation has arrived. Previous behavioral and neuroimaging evidence suggests that individuals can switch their allocation of working memory and attentional resources to support either *proactive* control (characterized by maintenance of prospective information in working memory and monitoring of the environment for relevant cues) or *reactive* control (relying on "bottom-up" cue-response associations) for PM in situations with markedly different, but stable, external demands. However, how people use these PM strategies in less stable, dynamic situations is still unclear. We designed a fMRI experiment where participants (N=30) identified the reappearance of a trial-specific PM target while also performing an ongoing, orthogonal visual search task (on oriented arrows) that fluctuated in difficulty over time. Analyses of behavioral and fMRI data determined that as demands increased across a trial, the behavioral (dual-task interference costs on RTs, or "PM cost") and the fMRI (MVPA classifier evidence) markers of proactive control dropped significantly, indicating a likely change in PM strategy from proactive to reactive control on these trials. Interestingly, we found that incorporating behavioral measures of proactive control with neural measures produced the best trial-by-trial prediction of accuracy on the PM task. These results provide insight into how individuals gradually adapt to changing demands on attention and memory resources in complex, dynamic environments.

[88]

Distraction recovery depends on prioritization in working memory

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A hallmark of working memory is that the retained information is resilient to distraction. However, there may be situations in which working memories are more susceptible to disruption than others. Recent behavioral evidence suggests that distraction might differentially impact working memories stored in high- vs. low-priority states. To evaluate neural correlates of this idea, we trained category-level fMRI pattern classifiers (N=17) and decoded memory representations of images during delays both before and after a distractor task. After encoding two images, a cue indicated which one of the items would likely be tested. This led to the neural prioritization, indicated by stronger classifier evidence, for the cued item over the uncued item. Then a distracting event (visual change detection) occurred that disrupted the neural signature for both items. After distraction, a second cue indicated whether the high-priority item or low-priority item would be tested after another short delay. Participants were able to recover the neural representation for either of these items and respond accurately. However, the recovery of high-priority items showed greater neural disruption, evidenced by weaker fMRI classification for those items after distraction ($p<.05$). These results suggest that the neural representation of low-priority memories may be more resilient to distraction.

[89]

Separation of items from their context observed via fMRI pattern analysis of item-method directed forgetting

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This study examined the hypothesis that contextual processing contributes to the intentional forgetting of individual items as it does for lists of items (Sahakyan et al., 2013). Healthy participants (N= 24) were first shown a list of words to remember in the fMRI scanner. Each word was separated by the appearance of three task-irrelevant scene images. These scenes served as a 'tag' of mental context (Gershman et al., 2013), enabling participants to form incidental associations between items (words) and their encoding context (scenes). The studied words (but not the scenes) were then presented again in an item-method directed forgetting (DF) task, where each word was followed by an instruction to either forget or remember the word. Categorical fMRI pattern classifiers were trained to identify word- and scene-related brain activity from separate data and then applied to the DF data to provide a measure of item and context processing on each trial. The experiment concluded with a recognition memory test for the previously presented words along with novel lures. Behavioral results show a significant directed-forgetting effect, with worse memory for items accompanied by a forget instruction ($p < .001$. Neural results show that the intention to forget an item led to a decrease in item processing (lower word-related activity, $p < .001$), along with an increase in the reactivation of prior contextual information (increased scene-related activity, $p < .001$). Together, these results may reflect the active unbinding of an item from its original encoding context to support its intentional forgetting.

[90]

Reinstatement of mental context resolves conflicts between fear and extinction memories

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Following fear conditioning, extinction learning introduces competition between fear and extinction memories (Bouton, M. E., 2002). The expression of extinction is contextually-specific, while fear generalizes to novel contexts. (Maren et al., 2013). Neurally, the acquisition and expression of extinction is regulated by a circuit including the ventro-medial prefrontal cortex (vmPFC), however many neuroimaging studies fail to observe vmPFC activity during extinction tests (Quirk & Mueller, 2008; Fullana et al., 2018). Recent models of human episodic memory emphasize mental context as an important factor for successful memory encoding and retrieval (Sederberg et al., 2008). We test the hypothesis that if subjects reinstate an extinction mental context, then the degree of reinstatement should relate to extinction circuit neural activity. Secondly, if subjects are reinstating an extinction mental context, then the neural patterns of activity observed during extinction encoding should be similar to the observed patterns of activity during extinction retrieval. Additionally, we hypothesized that patients with post-traumatic stress disorder (PTSD) would show deficits in these processes. 24 hours after Pavlovian conditioning, healthy controls and PTSD patients (N=48) were tested for extinction retrieval and mental context reinstatement. In healthy controls, multi-variate pattern analysis decoded extinction mental context reinstatement was significantly correlated with univariate activity throughout the extinction circuit. In the vmPFC, extinction encoding-to-retrieval neural pattern similarity was significantly greater for controls compared to patients. These results support a novel mental context model of how competition is resolved between fear and extinction memories, and may help explain the aberrant fear expression characteristic of PTSD.

Notes

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