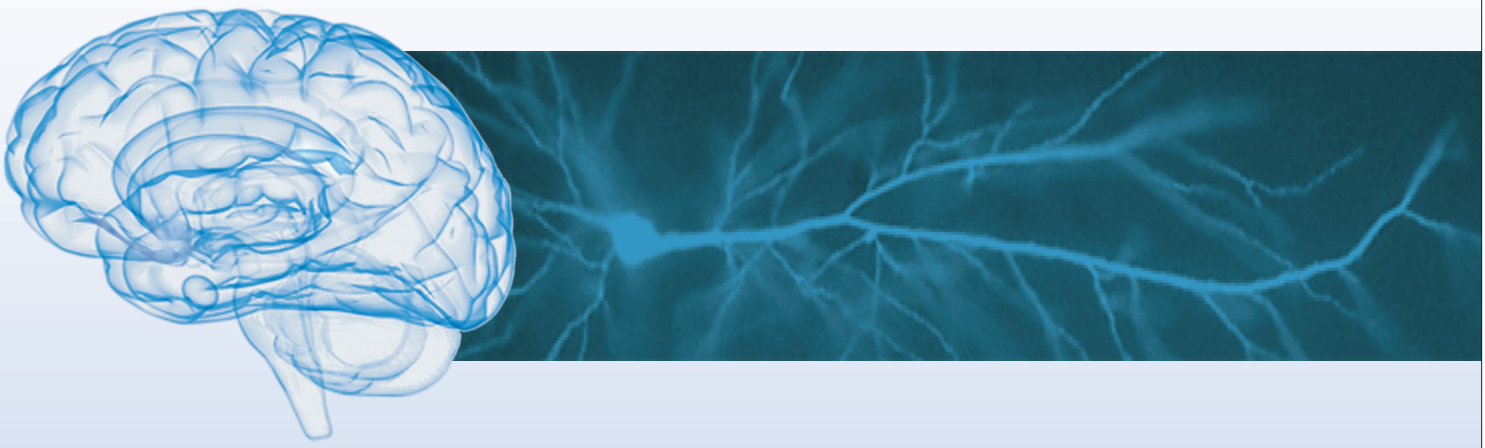

UT Austin Conference on Learning & Memory

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

APRIL 24–25, 2015

KEYNOTE SPEAKER

David Anderson
Howard Hughes Medical Institute
California Institute of Technology

SESSION SPEAKERS

Carol Barnes
Nicolas Brunel
Elizabeth Buffalo
Surya Ganguli
Zachary Kilpatrick
Brice Kuhl
Attila Losonczy
Jeffrey Magee
Geoffrey Murphy
Yael Niv
Jie Shen
Sharon Thompson-Schill
Nicholas Turk-Browne

Acknowledgements

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Conference Schedule

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

FRIDAY, APRIL 24, 2015

8:00am	Breakfast
8:45–10:45	**Session 1: Human Approaches to the Study of Learning & Memory** Session Co-Chairs: Jarrod Lewis-Peacock, The University of Texas at Austin, Center for Learning & Memory Sean Polyn, Vanderbilt University, Department of Psychology
8:45–9:25	Sharon Thompson-Schill, University of Pennsylvania Department of Psychology, Center for Cognitive Neuroscience *"Conceptual Integration"*
9:25–10:05	Brice Kuhl, New York University Department of Psychology, Center for Neural Science *"Neural representations of overlapping experiences: avoiding memory interference"*
10:05–10:45	Nicholas Turk-Browne, Princeton University Department of Psychology *"Interactions between attention and memory in the human brain"*
10:45–12:30	**Session 2: General Poster Session I-** even numbered posters present
12:30–1:30	Lunch
1:30–3:30	**Session 3: Computational Approaches to the Study of Learning & Memory** Session Co-Chairs: Ila Fiete, The University of Texas at Austin, Center for Learning & Memory Zachary Kilpatrick, University of Houston, Department of Mathematics
1:30–2:10	Nicolas Brunel, University of Chicago Departments of Statistics and Neurobiology *"Inferring learning rules in cortex"*
2:10–2:50	Zachary Kilpatrick, University of Houston Department of Mathematics *"Stochastic model of evidence accumulation in dynamic environments"*
2:50–3:30	Yael Niv, Princeton University Department of Psychology, Princeton Neuroscience Institute *"Shallow learning with deep memory: How latent structure saves the day"*
3:30–3:40	Break

3:40–5:20 **Session 4: Speakers selected from submitted poster abstracts**
Session Chair: Dan Johnston, The University of Texas at Austin, Director, Center for Learning & Memory

3:40–4:05 Shannon Farris, National Institutes of Health
National Institute of Environmental Health Sciences
"CA2 place cells link social and contextual information with representations of space"

4:05–4:30 Margaret Schlichting, The University of Texas at Austin
Center for Learning & Memory
"Structural development of hippocampal subfields is related to statistical learning and inference"

4:30–4:55 Travis D. Goode, Texas A&M University
Department of Psychology and Institute for Neuroscience
"Combinatorial DREADD silencing of ventral hippocampal neurons projecting to infralimbic cortex prevents fear renewal"

4:55–5:20 Ruben Tikidji-Hamburyan, LSU Health Science Center New Orleans
Department of Cell Biology and Anatomy
"Resonant interneurons can increase robustness of gamma oscillations"

5:20–6:20 Cocktails- *cash bar*

6:20 Dinner

SATURDAY, APRIL 25, 2015

8:00am Breakfast

8:45–10:45 **Session 5: Synaptic Approaches to the Study of Learning & Memory**
Session Co-Chairs:
Boris Zemelman, The University of Texas at Austin, Center for Learning & Memory
Attila Losonczy, Columbia University, Department of Neuroscience

8:45–9:25 Geoffrey Murphy, University of Michigan
Department of Physiology, Molecular & Behavioral Neuroscience Institute
"L-Type Voltage Gated Calcium Channels in Maladaptive Fear"

9:25–10:05 Jie Shen, Harvard Medical School
Department of Neurology, Center for Neurologic Disease
"Presenilin in learning and memory, synaptic function and Alzheimer's disease"

10:05–10:45 Jeffrey Magee, Janelia Research Campus
Howard Hughes Medical Institute
"A low-level computation in cortical microcircuits"

Conference Schedule

SATURDAY, APRIL 25, 2015 *(CONTINUED)*

10:45–12:30	**Session 6: General Poster Session II-** odd numbered posters present
12:30–1:30	Lunch
1:30–3:30	**Session 7: Systems Approaches to the Study of Learning & Memory** Session Co-Chairs: Laura Colgin, University of Texas at Austin, Center for Learning & Memory David Foster, The Johns Hopkins University School of Medicine, Department of Neuroscience
1:30–2:10	Carol Barnes, University of Arizona Departments of Psychology, Neurology & Neuroscience, McKnight Brain Institute *"Impact of aging on neural circuits critical for memory"*
2:10–2:50	Elizabeth Buffalo, University of Washington, Seattle Department of Physiology and Biophysics *"Bridging the Gap between the Spatial and Mnemonic Views of the Hippocampus"*
2:50–3:30	Attila Losonczy, Columbia University Department of Neuroscience, Kavli Institute for Brain Science *"Functional imaging hippocampal circuit dynamics in behaving mice"*
3:30–4:10	Surya Ganguli, Stanford University Department of Applied Physics "*The functional contribution of synaptic complexity to learning and memory"*
4:10–4:20	Break
4:20–5:30	**Session 8: Keynote Speaker** David Anderson, California Institute of Technology Department of Biology, Howard Hughes Medical Institute *"Internal states and behavioral decisions: the paradox of sex and violence"*
5:30	Presentation of on-site poster competition awards
5:40–6:15	Cocktails- *cash bar*
6:15	Banquet

Poster Abstracts

**Denotes the presenting author for each poster.*

[1] Amygdala Modulation of Cerebellar Learning

Sean J. Farley* and John H. Freeman
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We examined the mechanisms underlying amygdala modulation of cerebellar learning. Rats were trained in a cerebellum-dependent associative motor learning task, delay eyeblink conditioning, while the central nucleus of the amygdala (CeA) was inactivated bilaterally. Training trials consisted of a pure tone conditioned stimulus (CS) paired with a periorbital stimulation unconditioned stimulus. Multiple tetrode recordings were collected from the cerebellar anterior interpositus nucleus during training sessions in rats given muscimol or vehicle infusions into the CeA. Profound deficits in learning and learning-related neuronal activity during acquisition and retention were observed in rats with amygdala inactivation compared to controls. After the inactivation phase during acquisition, rats were able to reach the same learning criterion as the control group. Short-latency neuronal responses never developed in rats originally trained during amygdala inactivation, but were robust in the controls. Monosynaptic projections from the CeA and parts of the auditory CS input pathway were investigated with anterograde and retrograde axonal tracers. An axonal projection from the CeA to the lateral basilar pontine nuclei was identified. Collectively, these findings suggest that the amygdala may gate auditory CS input to the cerebellum through projections to the pontine nuclei during associative motor learning.

[2] Anterior Cingulate Cortical Control in Visual Attention

Jangjin Kim*, Ka H. Ng, and John H. Freeman
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The dorsal anterior cingulate cortex (dACC) has been proposed to control selective attention. However, the mechanisms of how dACC neuronal firing and theta rhythms contribute to visual attention have not been examined. In the current study, dACC neuronal activity was recorded from multiple tetrodes while the rat performed a dACC-dependent visual attentional task using a touchscreen apparatus. On every trial, the rats were required to attend to the task-relevant visual stimulus while ignoring a task-irrelevant stimulus. Neuronal spike activity and theta were analyzed during task event periods (i.e., pre-trial, cue-onset, cuing/maintenance, and choice button selection). Both spike activity and theta power decreased during correct trials. Specifically, the spike activity was inhibited during the initial cuing phase for task-relevant stimulus selection and theta power was suppressed in the middle of cuing for maintaining the task information. Cross-correlation analysis showed that spike firing preceded theta in the pre-trial and maintenance periods when the rat made correct choices, whereas theta preceded spikes on the incorrect trials. Also, coherence in the correct trials was higher than incorrect trials during the maintenance period. Lastly, there was higher phase synchrony between dACC spikes and theta during the pre-trial period of the correct trials. The results show that dACC activity should be orchestrated in time and phase before cue-onset for the successful performance. The synchronized dACC activity leads the suppression of both dACC and theta during the correct selection and maintenance of task information. The results suggest that inhibited, yet synchronous, dACC firing is necessary for rodent visual attention tasks.

**[3] Resonant interneurons can increase robustness of gamma oscillations

Ruben Tikidji-Hamburyan[1*], Joan José Martínez[2], John A. White[2],
Carmen C. Canavier[1,3]
[1]Department of Cell Biology and Anatomy, LSUHSC, New Orleans, LA; [2]Department of Bioengineering, University of Utah, Salt Lake City, UT; [3]Neuroscience center, LSUHSC, New Orleans, LA
*rtikid@lsuhsc.edu

Gamma oscillations are believed to play a critical role in in information processing encoding and retrieval. Inhibitory interneuronal network gamma (ING) oscillations may arise from a coupled oscillator mechanism in which individual neurons oscillate, or from a population oscillator in which individual neurons fire sparsely and stochastically. All ING mechanisms, including the one proposed herein, rely on alternating waves of inhibition and windows of opportunity for spiking. The coupled oscillator model implemented with Wang and Buzsaki model neurons is not sufficiently robust to heterogeneity in excitatory drive, and therefore intrinsic frequency, to account for in vitro models of ING. Similarly, the stochastic population oscillator model is characterized by sparse firing, whereas in ING both in vivo and in vitro interneurons do not fire sparsely, but rather on average every other cycle. We substituted so-called resonator neural models, which exhibit class 2 excitability and post-inhibitory rebound (PIR), for the integrators that are typically utilized. This results in much greater robustness to heterogeneity that actually increases as the average participation in spikes per cycle approximates physiological levels. Moreover, dynamic clamp experiments on entorhinal cortical basket cells support the idea that PIR can serve as a network gamma mechanism.

**** This poster was selected for a Best Abstract Award and the content will be presented as a talk in session 4 in lieu of a poster. ****

[4] Frequency-dependent input processing in hippocampal CA1 pyramidal neurons

Crescent L. Combe[1], Ruben Tikidji-Hamburyan[2], Carmen C. Canavier[1,2]
and Sonia Gasparini[1,2*]
[1]Neuroscience Center and [2]Department of Cell Biology and Anatomy, LSU Health Sciences Center, New Orleans, LA
*sgaspa1@lsuhsc.edu

Gamma oscillations are hypothesized to play a role in learning and memory. Two frequency bands, slow (25-50 Hz) and fast (65-90 Hz) gamma, have been identified in area CA1 of the rodent hippocampus. Slow gamma is phase-locked to activity in area CA3 and presumably driven by the Schaffer Collaterals, whereas fast gamma is phase-locked to activity in the medial entorhinal cortex and presumably driven by the Perforant Path. We used a combination of computational modeling and *in vitro* electrophysiology to test the mechanisms underlying the hypothesized selectivity of Schaffer Collateral vs. Perforant Path synapses for their respective input frequencies. Electrical stimulation of the Schaffer Collateral fibers at either slow gamma (40 Hz) or fast gamma (100 Hz) frequencies preferentially elicited spiking at slow gamma in CA1 neurons. This low-pass filtering tendency was greatly attenuated by perfusing the Ca^{2+}-activated K^+ channel blocker apamin. In contrast, stimulation of Perforant Path fibers at fast gamma frequencies was required to elicit any spikes. The number of spikes elicited was decreased in the presence of the NMDA glutamatergic antagonist APV. These results confirm our model simulations, which suggest that CA1 neurons might behave as low-pass filters in response to Schaffer Collateral activation and high-pass filters in response to Perforant Path activation, due to a combination of intrinsic and synaptic mechanisms.

[5] The RNA-binding protein Sam68 and the proteasome coordinate synaptic protein abundance during long term plasticity

Matthew E. Klein*, Thomas J. Younts, Pablo E. Castillo,
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Local protein homeostasis is crucial for most forms of long-term synaptic plasticity, a cellular correlate for learning and memory. Current models of metabotropic glutamate receptor mediated long-term depression (mGluR-LTD) suggest that rapid, local synthesis of key proteins is necessary for the induction and expression of LTD. We find that mGluR activation leads not only to translation, but also to protein degradation by the proteasome. Surprisingly, mGluR-LTD can be induced in the absence of translation if the proteasome is concurrently inhibited. Moreover, proteasome inhibition can rescue mGluR-LTD in mice null for the RNA binding protein Sam68, which we show here lack mGluR-dependent translation and LTD. We propose that Sam68-mediated translation helps to counterbalance degradation, ensuring that protein levels briefly remain above a permissive threshold during LTD induction.

Additionally, we have begun to explore the role of Sam68 and local translation in presynaptic forms of plasticity. Currently, it is unclear if presynaptic protein synthesis is necessary for long-term plasticity in the mature mammalian brain. We show, for the first time, that Sam68-mediated translation is required for LTD of inhibitory transmission (iLTD) expressed at presynaptic terminals. Our results provide a framework for understanding how synaptic protein abundance is tightly coordinated by Sam68-mediated translation and proteasomal degradation during synaptic plasticity.

[6] Synaptic localization of β-actin mRNA by the RNA binding protein ZBP1 regulates neuronal activity

Adina R. Buxbaum[1,2*], Bin Wu[1], Young J. Yoon[1], Jason S. Rosenberg[1],
Robert H. Singer[1,2]
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Activity dependent modifications in the molecular composition of neurons and synapses underlie normal brain function and behavioral changes. mRNA localization and translation at synaptic contacts contribute to the activity dependent alteration of the local synaptic proteome. Local actin remodeling underlies spinogenesis and structural plasticity. However, the contribution of local actin mRNA dynamics to synaptic transmission and plasticity at the level of individual synapses is poorly understood. By visualizing the entire complement of endogenous, single ß-actin mRNAs in individual cultured neurons we were able to quantify the relationship of mRNAs with synapses across the dendritic arbor. We investigated the role of ß-actin mRNA at synapses by use of a transgenic mouse lacking the RNA regulatory protein Zipcode Binding Protein I (ZBP1), which is known to transport ß-actin mRNA into dendrites and regulate its translation. Loss of ZBP1 inhibited activity dependent localization of mRNA to synapses and decreased synaptic activity as measured by GCaMP3 calcium imaging in spines. ZBP1$^{-/-}$ neurons also exhibited a reduced frequency of calcium transients in the soma. Since local translation of ß-actin mRNA is thought to play an important role in synaptic function, we proposed that artificial capture of mRNAs at synapses would alter neuronal activity. Tethering ß-actin mRNA to post synaptic densities partially rescued calcium transients in ZBP1$^{-/-}$ neurons. Taken together, activity dependent proper mRNA trafficking and positioning with respect to synapses likely plays an important role in ensuring efficient synaptic transmission and cell firing.

[7] Extension of the sensitive period for imprinting in chickens by manipulating experience-dependent translation initiation

G. Batista[1*], M. Costa-Mattioli[2] & J.L. Pena[1]
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[2]*Baylor College of Medicine, Department of Neuroscience, Houston,TX*
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The brain can be transiently sensitive to learning during short periods of time, known as sensitive periods (SP). Extending SPs may thus permit behavioral plasticity beyond early stages in life. Experience-dependent protein synthesis underlying long-term memory formation is a potential target for SPs extension. We tested this idea using imprinting in chickens as a learning task. We trained chickens to recognize an object paired to a sound on a computer screen, to test visual and auditory imprinting. Using Western Blotting and pharmacology we investigated whether eIF2α and mTORC1, which can independently regulate translation initiation, affect imprinting.

Non-phophorylated eIF2α, which enhances translation initiation, was increased in the area involved in auditory imprinting but not in the site for visual imprinting. Accordingly, manipulation of this pathway either blocked or triggered consolidation of auditory, but not visual, memory. Notably, facilitating translation initiation through eIF2α also extended the critical period for auditory imprinting.

The mTORC1 pathway was activated in both visual and auditory areas. However, blocking mTORC1 with Rapamycin only disrupted the formation of visual memories. In addition, we found that thyroid hormones, which can extend the critical period for visual imprinting, induce mTORC1 activation. Together, these data strongly suggest that the formation of auditory and visual long-term memory is mediated by two independent pathways that regulate translation initiation. Furthermore, manipulating these pathways can extend the SP for imprinting in each sensory modality.

[8] Modulating hippocampal-cortical brain networks and memory using repetitive transcranial magnetic stimulation (rTMS)

Jane X. Wang* & Joel L. Voss
Department of Medical Social Sciences, Ken and Ruth Davee Department of Neurology, and Interdepartmental Neuroscience Program. Northwestern University Feinberg School of Medicine, Chicago, IL
* janewang@northwestern.edu

Many feats of memory have been associated with interactions among a distributed set of brain regions forming a hippocampal-cortical network. This network is disrupted in a variety of neurological and neuropsychiatric conditions that have memory impairment as a chief symptom. We have therefore developed methods to target and manipulate this network using noninvasive electromagnetic stimulation. We used a multi-day regimen of repetitive transcranial magnetic stimulation targeted to locations of lateral parietal cortex found for each individual based on subject-specific resting state connectivity during functional magnetic resonance imaging. Lasting enhancements of network connectivity and memory were observed, implicating localized long-term plasticity selective for targeted brain regions including hippocampus. Importantly, enhancements of functional connectivity and memory performance persisted long after stimulation, up to 15 days on average. In addition, we found increases in theta power during rest over medial parietal electrodes as a result of stimulation, compared to a sham condition. Targeted noninvasive stimulation of hippocampal-cortical networks is therefore a promising new approach that could have significant impact on impairments of memory and cognition in a variety of disorders.

[9] Age–related cognitive impairments correlate with CAV1.2 protein expression in area CA1 of dorsal hippocampus

Daniel M. Curlik II[1*], Xiao-Wen Yu[1], Felix Nunez[1], Marcia D. Antion[1],
M. Matthew Oh[1], John F. Disterhoft[1]
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The calcium (Ca^{2+}) hypothesis of aging predicts that age-related cognitive impairments result from disruption of Ca^{2+} homeostasis. In aged animals Ca^{2+} influx is increased in CA1 pyramidal neurons, resulting in a decrease in the intrinsic excitability of those cells. Increased Ca^{2+} entry through L-type voltage gated Ca^{2+} channels (LVCCs) is believed to mediate these age-related biophysical and behavioral deficits, as bath application of LVCC antagonists increases intrinsic excitability of aged CA1 pyramidal neurons *in vitro*, and systemic administration of those antagonists also ameliorates age-related cognitive impairments *in vivo.* Therefore, an age-related increase in the number, and/or function, of LVCCs in CA1 pyramidal neurons is believed to mediate age-related cognitive deficits. There are two subtypes of LVCC in CA1, the $Ca_v1.2$ and $Ca_v1.3$ subtypes. To determine whether activity of $Ca_v1.2$ mediates age-related cognitive impairments we designed adeno-associative viral (AAV) short hairpin RNA (shRNA) to reduce expression of $Ca_v1.2$ in dorsal CA1. In young rats AAV-shRNA reduced $Ca_v1.2$ protein expression by 40%. Surprisingly, no reduction of $Ca_v1.2$ protein was observed in aged virally-injected animals. Aged rats were impaired during water maze training and fear conditioning, however viral administration did not ameliorate those impairments. Regardless, very strong correlations were observed between cognitive measures and $Ca_v1.2$ protein in dorsal CA1of aged, but not young, rats. Together, these results suggest that an age-related increase in the number and/or function of $Ca_v1.2$ channels in dorsal CA1 mediates age-related cognitive impairments. Therefore, compounds and/or manipulations that block $Ca_v1.2$ in CA1 pyramidal neurons may ameliorate these age-related deficits. Ongoing research will explore this possibility using pharmacological manipulations to extend results of previous *in vivo* systemic injection studies, by determining whether intra-hippocampal blockade of L-type channels ameliorates age-related biophysical and cognitive deficits.

This work was supported by NIH R37 AG008796 & R01 AG017139 to John F. Disterhoft; T32 AG20506 & P30 AG13854 to Daniel M. Curlik

[10] Temporal order spatial navigation: A behavioral analysis using a radial arm water maze

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Episodic memory involves the storage and retrieval of details from a particular event. Remembering an experience, such as meeting someone at a poster, entails remembering "what" happened, "where" that event occurred (e.g. UT Austin Conference), and "when" it occurred (e.g. before lunchtime). To date, most rat studies have focused on the "what" and "where" aspects of hippocampal processing. The current study is a task that also includes "when," by teaching two groups of Fisher-344 rats (N = 10 and N = 6), a spatial temporal order paradigm using a radial arm water maze. In this study, there is no food reward, instead the rats had to swim through the maze to reach a platform at the end of a goal arm.

We examined the learning curve in relation to the sequence length, and the maximum sequence length rats could achieve. In addition, we performed manipulations to determine the degree to which this was a visuospatial task, and the sensitivity of performing the sequence after a temporal disruption. Now that we have developed a reliable task for spatial temporal sequence training, we will determine the effects of inactivating specific subregions of dorsal/ventral hippocampus and medial prefrontal cortex on sequence memory.

[11] Activation of basal forebrain GABAergic projection neurons alters mPFC-mediated working memory performance in young F344 rats

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Working memory is a prefrontal cortical (PFC) supported executive function in which information is maintained for short durations in the absence of persistent sensory input. The ability to maintain an internal representation in working memory stores is thought to be mediated by the persistent excitation of pyramidal neuronal networks within the PFC. GABAergic interneurons within these PFC circuits are thought to provide essential spatial and temporal specificity in this system. Shifts in the excitatory-inhibitory dynamics within the prefrontal cortex in conditions such as schizophrenia or aging have been directly linked to cognitive deficits, including impaired working memory. Notably, in addition to the local inhibitory circuitry, the PFC receives GABAergic projections from the magnocellular preoptic (MCPO) area in the basal forebrain. These afferents synapse primarily on GABAergic interneurons and thus are well-positioned to regulate excitatory-inhibitory dynamics in this circuitry and possibly influence working memory function. To date, however, the role of these GABAergic basal forebrain afferents in PFC-supported cognition has not been well characterized. In this study, a pharmacological approach was used to assess how modulation of GABAergic basal forebrain neuronal activity affects working memory performance in young adult male F344 rats. Rats were surgically implanted with guide cannula aimed at the MCPO and trained on an operant-based delayed response test of working memory. In this task, rats were required to remember the location of a sample lever over a delay period (0-24 s) to obtain a food reward. After reaching stable, baseline performance, rats received microinjections of the M3 muscarinic receptor agonist cevimeline (5 µg and 10 µg) or vehicle directly into the MCPO immediately prior to testing using a within-subjects design. Cevimeline was chosen because of anatomical and electrophysiological data demonstrating that this M3 muscarinic cholinergic receptor agonist, selectively activates basal forebrain GABAergic projection neurons. Cevimeline significantly enhanced working memory performance compared to vehicle conditions, particularly at long delays. These data support a role for GABAergic basal forebrain-PFC projections in working memory. Future work will further delineate this circuit and the contribution of other neurochemically distinct basal forebrain projection systems to PFC-supported cognition using pharmacological and optogenetic approaches to achieve cell type specificity.

Supported by AG029421 and the McKnight Brain Research Foundation.

[12] Loss of GIRK2-Containing Channels in Pyramidal Neurons Selectively Impairs Aversive Learning and Memory, and Underlying Plasticity

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Cognitive dysfunction occurs in many debilitating conditions including Alzheimer's disease, Down syndrome, post-traumatic stress and mood disorders. The dorsal hippocampus is a critical regulator for cognitive processes of learning and memory, particularly for spatial and contextual associations. Several lines of evidence indicate that G protein-gated inwardly rectifying K^+ (GIRK) channels, which couple to metabotropic receptors and produce neuronal inhibition, are important regulators of hippocampal-dependent cognition. However, evidence derives from constitutive gain or loss of function models. Here, we asked whether *Girk2*, specifically in pyramidal neurons, is necessary for normal hippocampal-dependent associative learning and memory, and underlying plasticity. Using conditional genetic, molecular biologic, electrophysiologic and behavioral techniques we demonstrate for the first time that loss of *Girk2* in pyramidal neurons (and not GABA neurons) selectively impairs hippocampal-dependent contextual fear learning and memory, while preserving Barnes Maze cognition. Excitability of dorsal CA1 pyramidal neurons is increased, depotentiation of LTP is prevented and LTD at the Schaffer-collateral synapse is exaggerated by *Girk2* ablation in pyramidal neurons. Our findings support the working hypothesis that *Girk2* in CA1 pyramidal neurons of the dorsal hippocampus is necessary for normal cognitive processing and underlying synaptic plasticity. Our data implicate GIRKs as an important molecular target for disorders affected by cognitive dysfunction.

[13] Sodium butyrate increases contextual fear expression in sign- but not goal-trackers

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Pavlovian conditioned approach behavior has been previously used to identify rats that display enhanced fear expression in response to either cues (sign-trackers; STs) or context (goal- trackers; GTs) following fear conditioning (FC). Levels of histone acetylation in brain regions such as the dorsal hippocampus (dHPC) are critical in consolidating contextual FC and may underlie individual variation in contextual fear expression. Therefore, we hypothesized that low levels of contextual fear expression in STs are a result of decreased acetylation following contextual FC. In Experiment 1, we showed that STs express less contextual fear than GTs following contextual FC, despite equal levels of contextual fear during conditioning. In Experiment 2, we demonstrated that sodium butyrate (200 mg/kg; 10 mL/kg), a histone deacetylase (HDAC) inhibitor, given 1 h prior to contextual FC, enhances contextual fear expression in STs, but not GTs. This is the first demonstration that a HDAC inhibitor given before contextual FC can enhance contextual fear expression in some subjects but not others, and suggests that individual variation in histone acetylation during contextual fear conditioning may underlie individual variation in contextual fear expression. In addition, these results may contribute to a neurobiological explanation of why some individuals but not others develop posttraumatic stress disorder.

[14] Regulation of a Cerebellar Voltage-Gated Ion Channels and Cerebellum-Dependent Learning and Memory

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*jrfuchs@uvm.edu

Eyeblink conditioning (EBC) is governed by sites of plasticity in the cerebellar cortex and the interpositus nucleus. However, the cellular mechanisms supporting EBC are poorly understood. The voltage-gated potassium channel alpha-subunit Kv1.2 is densely expressed at basket cell (BC) axon terminals where they form inhibitory synapses with Purkinje cells (PCs) and PC dendrites, Kv1.2 surface expression is regulated by secretin, and secretin is released from depolarized PCs as a retrograde messenger. Our previous work has shown that intra-cerebellar blockade of Kv1.2 facilitates EBC while intra-cerebellar infusions of secretin or a secretin receptor antagonist facilitated or impaired EBC, respectively. In the current work, we addressed the question of whether EBC regulates surface expression of Kv1.2 in cerebellar cortex. Rats received three days of either delay EBC, explicitly unpaired stimuli presentations, or no stimuli, and cerebellar tissue was harvested and analyzed via biotinylation/western blot (WB) and multiphoton microscopy (MP) techniques. The Unpaired group showed significantly less surface Kv1.2 as measured by MP and a trend towards greater surface Kv1.2 across BC axon terminals and PC dendrites as measured by WB. We hypothesize that inhibition of the inferior olive by the generation of conditioned eyeblink responses contributes to differences observed between the Paired and Unpaired groups. A follow-up experiment will examine surface expression of Kv1.2 in cerebellar cortex earlier in acquisition.

**[15] CA2 place cells link social and contextual information with representations of space

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The hippocampus supports a cognitive map of space and is critical for encoding declarative memory (who, what, when, where). Until recently, very little was known about the behavioral function of hippocampal subfield CA2. Recent studies have shown that CA2 is essential for social, or 'who' memory, as shown by the loss of social recognition memory in both the vasopressin 1B receptor knock-out mice (Wersinger *et al*., 2002) and in mice with CA2 output silenced by tetanus toxin (Hitti & Siegelbaum, 2014). Recent studies have also supported a role for CA2 in spatial information processing (Mankin *et al.*, 2015). However, how CA2 integrates both social and spatial information is unknown. In this study, we have taken two independent approaches of querying CA2 pyramidal cell activity to determine how CA2 neurons respond to spatial and social exploration.

We performed *in vivo* electrophysiology in awake, behaving rats to measure firing rate and place field properties of CA2 neurons during spatial exploration and social exposure. Similarly, in separate cohorts of rats we measured immediate early gene expression after the same tasks using multiplexed fluorescent *in situ* hybridization. Both methods independently demonstrated that CA2 neuronal activity is modulated by spatial exploration but not further enhanced by social stimulation. However, *in vivo* recordings demonstrated that place field locations were shifted in CA2 neurons upon social stimulation. This pronounced global remapping was not specific to social stimulation, as the same magnitude of remapping occurred upon novel object exposure. Thus, we have discovered an unanticipated mechanism by which CA2 neurons could encode 'who' and 'what' memories by linking social and object representations with spatial representations. These data provide compelling evidence for how the hippocampus can integrate both declarative and spatial information in order to create meaningful representations of experiences.

**** This poster was selected for a Best Abstract Award and the content will be presented as a talk in session 4 in lieu of a poster. ****

[16] Credit Assignment in Movement-Dependent Reinforcement Learning

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If a diner reaches across the table and knocks over her espresso, the absence of anticipated reward should be attributed to a failure of coordination, rather than diminish her love of coffee. A psychological "credit assignment" mechanism could act to prevent the reward system from indiscriminately assigning valence to stimuli (and events associated with them) by virtue of a representation of the underlying causes of reward and punishment. To test this idea, we developed a novel reward task that signals movement errors. We show that the salience of sensorimotor error signals influences participant's decisions, and may facilitate a form of credit assignment. Furthermore, individuals with degeneration of the cerebellum — a neural structure strongly associated with the computation of sensorimotor error signals — deviate in choice behavior from healthy controls, but only under conditions with potential execution failures. These data suggest that cerebellar processing may play a role in movement-dependent decision-making and reinforcement learning. Lastly, a modeling analysis offers two mechanistic accounts of the results, one in which reward signals are directly modulated by sensorimotor error signals, and another in which decision-making relies on an internal model of motor competence to guide choices.

[17] CVS-N2cΔG Rabies Strain Enhances Trans-synaptic Neuronal Expression and Manipulation

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Virally-based trans-synaptic tracing technologies constitute a powerful experimental tool for neuronal circuit mapping and manipulation. The SAD-B19 deletion-mutant rabies virus (RABV) vaccine strain permits unambiguous identification of mono-synaptic inputs to genetically defined neurons but suffers from two major drawbacks: (i) the efficiency of trans-synaptic virus spread is poor, and (ii) viral cytoxicity severely constrains functional studies – neurons in which SAD-B19 variants express channelrhodopsin typically die within days.

To overcome this problem we have explored the utility of the highly neurotropic CVS-N2c rabies virus strain. Through a deletion-mutant strategy we generated a CVS-N2cΔG strain that attenuates the virulence of the parental strain, permitting us to explore its neural features. We find that that the CVS-N2cΔG strain, after complimentation by its native glycoprotein, exhibits a dramatic enhancement in trans-synaptic transport and a marked reduction in neurotoxicity. As a consequence, the CVS-N2cΔG strain permits effective optogenetic manipulation of neuronal activity.

[18] Hippocampal long-term potentiation supports recent, but not remote, recognition memory in rats

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By infusing zeta inhibitory peptide (ZIP) into the dorsal hippocampus, spatial memory in rodents can be erased by reversing established long-term potentiation (LTP). It has not been shown previously that other forms of memory, such as recognition memory, are also supported by hippocampal LTP. Our study tested recognition memory in rats following a stereotaxic infusion of ZIP throughout the dorsal, intermediate, and ventral hippocampus, targeting the entire structure. Rats infused with ZIP 3-7 days after training on the Novel Object Recognition task showed impaired object recognition memory compared to control rats (those infused with aCSF). In contrast, rats infused with ZIP one month after training performed similar to control rats. The ability to form new memories after ZIP infusions remained intact. These results lead us to suggest that enhanced recognition memory for recent events is supported by hippocampal LTP, which can be reversed by infusion of ZIP throughout the hippocampus.

[19] Modeling the Hemodynamic Response Function for Prediction Errors in the Human Ventral Striatum

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Recent years have seen a proliferation of studies in which computational models are used to specify precisely a set of hypotheses regarding reinforcement learning and decision making in humans, which are then tested against data from functional magnetic resonance imaging (fMRI). fMRI research proceeds by using information provided by the blood oxygenation level dependent (BOLD) signal to make inferences about the underlying neural activation. The focus of much of this model-based fMRI effort has been on the ventral striatum (VS), where the BOLD response has been shown to reflect reward prediction error signals (momentary differences between expected and obtained outcomes) from dopaminergic afferents.

To make sensible inferences from fMRI data it is important to accurately model the hemodynamic response function (HRF), i.e., the hemodynamic response evoked by a punctate neural event. Acanonical HRF, mapped for sensory cortical regions, is commonly used for analyzing activity throughout the brain despite the fact that hemodynamics are known to vary across regions, in particular in subcortical areas such as the VS. Here we use data from an experiment focused on learning from prediction errors to fit a VS-specific HRF function.

Our results show that the VS HRF differs significantly from the canonical HRF, most importantly peaking at 6 sec rather than at 5 sec. We demonstrate the superiority of the VS HRF in modeling data by showing that it increases statistical power. This result is particularly relevant to fMRI studies of reinforcement learning and decision making as many of these rely on fine analysis of the VS BOLD activity to distinguish between important but subtle differences in computational models of learning and choice. We therefore recommend the use of this new HRF for future fMRI studies of the ventral striatum.

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[20] A predictive framework for evaluating models of semantic organization in free recall

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Research in free recall has demonstrated that semantic associations reliably influence the organization of search through episodic memory. However, the specific structure of these associations and the mechanisms by which they influence memory search remain unclear. We introduce a likelihood-based model-comparison technique, which embeds a model of semantic structure within the context maintenance and retrieval (CMR) model of human memory search. Within this framework, model variants are evaluated in terms of their ability to predict the specific sequence in which items are recalled. We compare two prominent models of semantic structure, latent semantic analysis (LSA) and word association spaces (WAS), and find that models using WAS greatly outperform those using LSA. Furthermore, we find that models using an item-based semantic cuing mechanism, where retrieved items influence semantic organization, predict recall sequences more accurately than models where both temporal and semantic organization are driven by the same contextual cues.

[21] Isoform-specific modulation of neuronal voltage-gated Na+ channels by GSK3

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In recent years, glycogen synthase kinase 3 (GSK3) has been implicated as a dysregulated protein of interest in long term depression (LTD) and several neuropsychiatric disorders, including Alzheimer's disease. We have previously shown that GSK3 inhibition results in a potentiation of peak current densities in the neuronal voltage-gated sodium channel type 1.2 ($Na_v1.2$) and that this effect is likely mediated by a GSK3-dependent phosphorylation of T^{1966} in the carboxy-terminal tail. Imaging studies suggest that GSK3 phosphorylation might influence Na_v recycling, turnover, and/or trafficking without affecting the channel total pool. Along with $Na_v1.2$, other isoforms of Na_v channels are commonly found in the brain, including $Na_v1.1$ and $Na_v1.6$, which we hypothesized would show similar functional modifications and phosphorylations by GSK3. While $Na_v1.1$ showed a similar potentiation to $Na_v1.2$ in GSK3-inhibited conditions, $Na_v1.6$ current densities were suppressed. Given the sequence similarity between $Na_v1.2$ and $Na_v1.1$ and sequence dissimilarity with $Na_v1.6$, it is likely that GSK3 phosphorylation results in divergent consequences depending on Na_v subtype. Preliminary mass spectrometry data suggest that GSK3 phosphorylates $Na_v1.1$ at T^{1979} and $Na_v1.6$ at T^{1936}, which lends further support to the hypothesis that Na_v channels have differential responses to GSK3 phosphorylation.

[22] Identification of Akt-GSK3-Nav1.6 sodium channel signaling pathway as a therapeutic target against psychiatric disorders

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Vulnerability to psychiatric disorders is intimately interlinked with environmental factors that can protect individuals against these afflictions. By modulation of specific genetic programs in the mesocortico-limbic circuit, enriched environmental conditions (EC) can exert protective effects against depression- and addiction-related behaviors. However, how these genetic programs translate into molecular and cellular changes at the circuitry level is still poorly understood. In search for EC-induced cellular pathways relevant for affective disorders and addiction, we conducted an unbiased transcriptomic study in the nucleus accumbens (NAc) of rats raised in EC and isolated conditions (IC). Bioinformatics analysis of regulated transcripts indicates that EC leads to decreased transcript levels of several proteins involved in the PI3K-Akt signaling pathway compared to the IC group, including GSK3beta and the voltage-gated sodium channel Nav1.6. With a combination of viral-vector genetic silencing, patch-clamp electrophysiology and behavioral studies, we provide data demonstrating that genetic silencing of either GSK3beta or Nav1.6 channel or pharmacological suppression of Akt-GSK3 pathway leads to decreased sodium current in heterogeneous expressing system, reduced firing and suppression of sodium-persistent currents in NA medium spiny neurons, and reducing anxiety-like behavior. Taken together, these findings provide evidence for a new complex role of Akt-GSK3 signaling pathway in regulating mesocortico-limbic circuits through an effect on Nav channels that plays a significant role in controlling neuronal excitability.

[23] Targeting protein: Protein interaction sites "hotspots" within the macromolecular complex of the voltage-gated sodium channels as a novel drug development approach

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Fibroblast growth factor 14 (FGF14) is a functionally relevant accessory protein of the neuronal Nav channel. Through a monomeric interaction with the intracellular C-terminus of Nav channels, FGF14 modulates Na^+ currents in a Nav isoform-specific manner serving as a fine-tuning regulator of excitability. In previous studies we have reconstituted the FGF14:Nav1.6 complex in live cells using the split-luciferase complementation assay (LCA) and through site-direct mutagenesis identified "hot-spots" at the FGF14 surface critical for binding to Nav1.6. Based on *in silico* studies, we have designed short peptide fragments that align with the FGF14 β12-strand and β8-β9 loop and validated their in-cell activity as inhibitors of the FGF14:Nav1.6 complex. One peptide, Fpep1, we have generated novel peptidomimetics that are currently being evaluated. Small molecule inhibitors (SMI) and/or peptidomimetics targeting druggable pockets at the FGF14 β8-β9 and β12 might give rise to a new class of unconventional protein: protein interaction-based allosteric modulators of Nav channels. We expect our studies to have a broad impact in the drug design against a wide range of still untreatable brain disorders associated with Nav channel dysfunction.

[24] Genetic deletion of *Fgf14* recapitulates molecular, cellular and circuit alterations underlying cognitive impairment associated with human psychiatric disorders

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Cognitive processing is highly dependent on the functional integrity of Gamma-Amino-Butyric Acid (GABA) interneurons in the brain. These cells regulate excitability of principal neurons balancing the excitatory/inhibitory tone of cortical networks. Reduced function of parvalbumin interneurons (PVIs) and disruption of GABAergic synapses result in desynchronized cortical circuitry associated with cognitive impairment across many psychiatric disorders including schizophrenia, bipolar disease, and depression. Yet, the mechanisms underlying these phenotypes are still poorly understood. Here, we show that in animal models genetic deletion of fibroblast growth factor 14 (*Fgf14*), a resident protein of the axonal initial segment (AIS), regulator of neuronal excitability and synaptic transmission, and an emerging brain disease-associated factor, leads to loss of PVIs hippocampal CA1 region, a critical area for cognitive function. This cellular phenotype associates with decreased expression of glutamic acid decarboxylase 67 (GAD67) and vesicular GABA transporter (VGAT) at GABAergic presynaptic puncta. Coincides with loss in frequency and amplitude of spontaneous and miniature inhibitory synaptic events in CA1 pyramidal neurons, reduced *in vivo* gamma frequency oscillations and impaired working memory. Together these phenotypes recapitulate salient molecular, cellular, functional and behavioral features associated with cognitive impairment in complex brain disorders, adding FGF14 to the repertoire of potential risk factors for psychiatric disorders.

[25] Regulation of adult neurogenesis by FGF14 as a potential mechanistic link to human brain disorders

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Adult neurogenesis, the production of mature neurons from progenitor cells in the adult mammalian brain, is linked to the etiology of neurodegenerative and psychiatric disorders. However, a thorough understanding of the molecular elements at the base of adult neurogenesis remains elusive. Identifying new factors required for neural stem cell proliferation, migration, maturation and integration into the synaptic hippocampal circuit could inform the pathogenesis of a variety of brain disorders. Using a combination of BrdU incorporation studies and confocal imaging, we discovered that genetic deletion of fibroblast growth factor 14 (*fgf14*), a brain disease-associated factor that controls neuronal excitability and synaptic plasticity, leads to previously undescribed alterations in adult neurogenesis in the dentate gyrus (DG) of the hippocampal region. We show that *fgf14-/-* mice exhibit an increase in the immature population of doublecortin and calretinin positive neurons and a reduction in mature neurons expressing calbindin, while early progenitor stem cells in the DG remained intact. In humans mutations of the *fgf14* gene are the genetic cause of spinocerebellar ataxia 27, a complex neurodegenerative disorder associated with cognitive and motor deficits. Thus, while providing evidence for a novel regulator of adult neurogenesis, this study provides potential new insights to the complex pathology associated with disrupted FGF14 function in human diseases.

[26] Context discrimination in Alzheimer's disease model mice reveals neurogenesis mechanisms

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The Tg2576 mouse model recapitulates early Alzheimer's disease (AD) pathology including hippocampal cognitive deficits, Aβ oligomer accumulation, and central insulin resistance. The insulin-sensitizing drug and peroxisome proliferator activated receptor γ (PPARγ) agonist, rosiglitazone (RSG), improves Tg2576 cognitive performance in hippocampus-dependent memory tasks. Context discrimination fear conditioning is a hippocampus-dependent learning and memory task designed to test an animal's ability to distinguish between two highly similar yet different environments in which context 'A' is paired with a foot shock and context 'B' is the safe context. Since adult-born neurons arising from neurogenesis within the dentate gyrus (DG) sub granular zone are thought to be necessary for context discrimination and RSG restores DG mature/immature neuronal population ratios to wild type levels, we postulated that RSG-treated Tg2576 would perform better in a context discrimination task compared to untreated Tg2576 and wildtype mice. Interestingly, we found that untreated Tg2576 mice exhibited superior context discrimination compared to all other groups and RSG treatment improved wildtype performance over that of untreated. Furthermore, RSG-treated Tg2576 context discrimination performance was equivalent to RSG-treated wildtype mice. The data presented here suggest that the neurogenesis-dependent changes observed inTg2576 pattern separation memory is normalized by RSG treatments.

[27] Superimposing Status Epilepticus on NS-PTEN Haploinsufficient and Wild Type Mice Results in Long-term Alterations in Leaning and Behavior

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Rationale: Seizures can result in significant impairments in learning and in autistic-like behavioral deficits. Here, we evaluated the effects of superimposing seizures in mice that are haploinsufficient for the Phosphatase and tensin homolog (PTEN) gene. PTEN is a negative repressor for the PI3K/AKT pathway and plays a significant role in learning and autism.
Methods: Pten heterozygous (HT) and wildtype (WT) adult mice received either injections of kainic acid (20 mg/kg; intraperitoneal) to induce status epilepticus or saline in adulthood. We examined their behavior through a battery of behavioral tests: open field, elevated plus maze, marble burying, social chamber test, trace fear conditioning, and Morris water maze.
Results: We found that the HT seizure mice showed significant increase in activity in the open field ($p < 0.05$). The WT mice and HT mice with seizures had a decrease in social interaction in the social chamber test. WT mice with seizures had a deficit in the probe test of MWM test. The HT mice with seizures displayed enhanced learning in trace fear conditioning compared to controls, $p < 0.05$.
Conclusions: These findings demonstrate that superimposing a seizure on a genetic mutation can result in some long-term alterations in activity and social behavior in mice. However, the haploinsufficient mice were protected against the learning deficits that occur with seizures.

[28] Comparing the long-term effects of seizures at different ages of development on learning and memory

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One of the most devastating aspects of developmental epilepsy is the long-term impact on learning and memory. We administered the chemoconvulsant kainic acid to induce seizures in postnatal day (PD) 7 and 10 mice. The subjects were then tested in a battery of behavioral tests in adulthood: open field activity, elevated-plus maze, light-dark test, conditioned fear, novel object recognition, and Morris water maze. The mice with PD 10 seizures showed a consistent increase in anxiety in all three behavioral tests that measure changes in anxiety. They spent less time in the center of an open field test ($p < 0.05$); less time in the open arms of the plus-maze test ($p < 0.05$); and showed fewer transitions between the light to dark areas compared to the controls ($p < 0.05$). The PD 10 seizure mice showed no differences in tone fear conditioning but had a deficit in spatial learning. They had a longer latency to reach the hidden platform across the 8 trials of testing ($p < 0.01$) and significant differences in the probe trial test ($p < 0.05$). We found that seizures on PD 7 did not produce any long-term deficits on any of the measures. These results demonstrate that mice with one insult of status epilepticus on postnatal day 10 have a long-lasting increase in spatial learning and anxiety.

[29] A Single Pre-training Seizure Impairs Long Term Memory in Mice

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Past studies that utilized the flurothyl model of seizure induction have demonstrated impairments in spatial learning and memory in neonatal and adult rats. These studies focused on inducing several seizures and later examining learning and memory. The impact of a single acute seizure on learning and memory has not been investigated in mice. In this study, we placed adult 129SvEvTac mice in an inhalation chamber where the animals were exposed to the inhalant flurothyl until a behavioral seizure was induced. One hour or six hours later we examined associative learning and memory using delay fear conditioning. We then examined the acquisition of the associative conditioning by testing the mice 24 hr post-seizure. Mice that had experienced a single seizure 1 hr prior to training showed a significant impairment in associative conditioning to the stimulus compared to controls. However, the seizure mice were no different in their freezing behavior in a new context compared to controls. Mice that had experienced a seizure 6 hr prior to training did not show any difference in freezing behavior 24 hr after a seizure when presented with the conditioned stimulus or in the new context as compared to controls. These findings suggest that a single acute flurothyl seizure induced 1 hr but not 6 hr prior to associative learning impairs long term fear memory.

[30] Effects of the antioxidant n-acetyl cysteine on behavioral and neurophysiological deficits induced by developmental NMDA-R antagonism

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Treatment with N-methyl-D-aspartic acid (NMDA-R) receptor antagonists result in symptoms that closely mimic those seen in schizophrenia. Recently we reported that adult mice treated with ketamine on postnatal days (PND) 7, 9 and 11 showed 1) loss of parvalbumin (PV) immunoreactivity in the medial prefrontal cortex (mPFC); 2) severe attentional deficits in a set-shifting task; 3) reduced GABA release in layer 2/3 of the PFC; 4) upregulated NMDA-R function in PV cells, resulting in aberrant synaptic integration. Ketamine-induced loss of PV can be caused by oxidative stress. Here we investigated whether treatment with the antioxidant n-acetyl cysteine (NAC) during development would prevent the loss of PV expression in adult animals and also could prevent the behavioral and neurophysiological deficits.d earlier. Animals were treated with ketamine or saline, respectively and received NAC from PND 5 until weaning via subcutaneous injections, and subsequently in their drinking water until the day of experiment. NAC improved the performance of ketamine-treated animals in the set-shifting task to near control levels. Similarly, miniature IPSCs from pyramidal cells in layer 2/3 were restored to control levels. Ongoing experiments will quantify the PV expression in the mPFC and changes in the NMDA:AMPA ratio in layer 2/3 PV cells.

[31] Vagus Nerve Stimulation Modulates Plasticity in the Prefrontal Cortex-Amygdala Pathway and Enhances Extinction of Drug-Seeking Behavior

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Cocaine addiction can cause maladaptive neuroplasticity that persists long after cessation of drug taking. The relative permanence of cue associations formed during drug taking contributes to the difficulties in treating addiction. Exposure to these cues can trigger relapse to drug use. Breaking the cue/drug association via extinction learning is one approach to preventing relapse. Vagus nerve stimulation (VNS) has previously been shown to enhance extinction of conditioned fear and to alter neural plasticity in fronto-limbic circuits. Here we trained animals to self-administer cocaine and extinguished them in the presence or absence of VNS. VNS-treated animals had increased rates of extinction and showed reductions in cue-induced reinstatement.

After reinstatement, in-vivo local field potential recordings in the basolateral amygdala (BLA) of anesthetized animals showed VNS-induced changes in plasticity in the pathway between the medial prefrontal cortex (PFC) and the BLA. Stimulation of the infralimbic PFC (900 pulses at 1Hz) induced LTD in Sham-VNS animals but caused no change in VNS animals. The data suggest that VNS facilitates extinction and reduces reinstatement by modulating the projection from the PFC to the BLA.

These findings provide systems-level information about neural plasticity during extinction and suggest a novel approach for drug addiction therapies.

[32] Viral delivery of RNAi to amygdala neurons leads to neurotoxicity and deficits in Pavlovian fear conditioning

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The use of viral vector technology to deliver RNAi to cells of the nervous system of many model organisms has been widely utilized by neuroscientists to study the influence of genes on behavior. However, there have been numerous reports that this approach can lead to neurotoxicity. Here we report that adeno-associated viruses designed to express control short-hairpin RNAs (shRNA) and shRNAs designed to target known plasticity associated genes (i.e. Arc, Egr1 and GluN2A), impair auditory fear conditioning when expressed in basal and lateral amygdala nuclei. Our results indicate that the impairments in Pavlovian fear conditioning were due to the viruses harboring shRNA genes and were not due to surgery, the virus itself or viral mediated GFP expression, and these results were dose dependent. Infusion of viruses designed to harbor shRNAs into the BLA did not induce obvious morphological changes to the cells/tissue at any dose of virus tested, however, did increase microglial activation at high titers (3.16E13 GC/mL; 1ul/side), but was not increased at lower titers (1.0E13 – 1.6E12 GC/mL; 1ul/side). In conclusion, we believe that the use of RNAi may not be a reliable way to examine the relationship between specific genes and behavior.

[33] High-Fat Diet Induces Sex-Dependent Alterations in Spatial Memory, Hippocampal CA1 Excitability and Metabolic Signaling in the Long-Evans Rat

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Alarming increases in metabolic disorder associated with obesity necessitate focusing on the effects of dietary fat intake on brain and cognitive function. Here we investigated the effects of a high-fat (HF) diet on spatial object recognition (SOR), on CA1 hippocampal neuron excitability, and on metabolic signaling

Male and female Long-Evans rats were fed from weaning either a control (14% fat) or HF diet (57.6% fat) for 6-10 wk prior to experimentation. Spatial memory was assessed in an SOR task and serum samples were collected for biochemical analyses. Current-clamp recordings were made to assess post-burst AHPs. After baseline recordings, slices were perfused with insulin to assess insulin-sensitivity of neurons.

Both HF males and HF females showed reductions in CA1 excitability via enhanced AHPs. HF female neurons had significantly larger mAHPs and longer duration sAHPs than those from HF males, which were also less excitable after eating the diet. Interestingly, HF females retained neuronal insulin sensitivity whereas their HF male counterparts did not. Additionally HF males had significant elevations in resting blood glucose levels, impaired glucose tolerance testing, and reductions in circulating insulin – all used clinically to diagnose type II diabetes. HF females (despite the enhancement of AHPs) showed no change in resting glucose or glucose tolerance and a striking decrease in insulin. Since there is enhanced prevalence of Alzheimer's in the diabetic and female population, these sex-dependent changes in hippocampus may have significant consequences in brain development, brain aging and cognitive decline. Studies are underway to further assess the mechanism involved in what may be a sexually divergent pathway of obesity induced metabolic dysfunction and cognitive impairment.

[34] The effects of Vagus nerve stimulation on anxiety

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Trauma-related disorders, such as posttraumatic stress disorder (PTSD), are typically treated with cognitive behavioral therapy. In one form of cognitive behavior therapy, exposure therapy, patients are repeatedly exposed to the cues that elicit conditioned fear or maladaptive behavioral responses. Over time, conditioned responses are extinguished. Because successful extinction requires learning of new associations with conditioned cues, many studies have examined the effects of memory enhancing drugs as adjuncts to exposure therapy. Although this approach is effective in fear-conditioned rats, results in humans with PTSD remain inconsistent. One possible explanation for this discrepancy is, when the conditioned response is not sufficiently extinguished, memory-enhancing drugs could reinforce the association between the cue and the inappropriate fear response. Optimal adjunct treatments to exposure therapy should reduce the anxiety produced by the conditioned cues while enhancing consolidation of fear extinction. Unfortunately, most anxiety-reducing drugs impair memory consolidation and thus interfere with progress in exposure therapy. Vagus nerve stimulation (VNS) is an FDA-approved treatment for the prevention of seizures. Recent research indicates that VNS enhances memory consolidation in rats and humans, and training-induced cortical plasticity and rehabilitation in animal models of stroke and tinnitus. We recently found that VNS pairing with unreinforced exposure to conditioned cues enhanced extinction of conditioned fear in rats. This effect could be due to enhanced consolidation of fear extinction. Alternatively, or additionally, VNS may facilitate extinction learning by reducing anxiety during exposure to the conditioned cues. Reduced anxiety has been observed in humans suffering from disorders such as epilepsy following chronic VNS. However, whether VNS has direct anxiolytic effects remains unknown. The objective of this study was to examine the effects of VNS administration on anxiety in male Sprague-Dawley rats. Vagus nerve stimulation was administered to rats prior to testing on an elevated plus maze. Animals treated with VNS spent significantly more time in the open arms of the elevated plus maze, and had significantly reduced levels of corticosterone compared to sham-stimulated controls. The finding the VNS reduces anxiety in rats, paired with evidence that VNS can enhance memory consolidation suggest that VNS could be used as an adjunct to exposure therapy for the treatment of trauma-related disorders such as PTSD.

[35] Memory enhancement by targeting Cdk5 signaling and NR2B regulation

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Learning and memory deficits are characteristic for many neurological and psychiatric disorders. Memory enhancement is considered a valid strategy to counteract cognitive deficits. The N-methyl-D-aspartate receptor (NMDAR) and in particular its NR2B subunit are fundamentally involved in mnemonic functions. Overexpression of NR2B in glutamatergic neurons improves synaptic plasticity and memory. The protein kinase cyclin-dependent kinase 5 (Cdk5) has been critically linked to synaptic plasticity and memory function via NMDAR regulation. However the molecular interplay between Cdk5 and NMDAR is not fully understood.

Here we show that Cdk5 knock-out as well as overexpression of the Cdk5 activator p25 lead to improved memory performance in mice. We find that the molecular mechanisms underlying this memory enhancement are linked to NR2B function. NR2B is phosphorylated by Cdk5, which is itself controlled by neuronal activity and regulates the receptor's cell surface expression. Based on the sequence surrounding the Cdk5 phosphorylation site, we developed small interfering peptides (siP) that selectively disrupt NR2B–Cdk5 interaction. Application of the siP in hippocampal slices increases NR2B surface levels and facilitates synaptic transmission. Accordingly, intra-hippocampal infusion of the siP improved fear memory *in vivo.*

Taken together, our results show a molecular mechanism that critically regulates NR2B function via Cdk5. A small molecule targeting this mechanism acted as a memory enhancer and hence may serve as the basis for the development of more effective therapeutics for memory impairment as well as age-dependent cognitive decline.

[36] Noradrenergic blockade stabilizes prefrontal activity and enables fear extinction under stress

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Stress-induced impairments in extinction learning are believed to sustain post-traumatic stress disorder (PTSD). Noradrenergic signaling may contribute to extinction impairments by modulating medial prefrontal cortical (mPFC) circuits involved in fear regulation. Here we demonstrate that aversive fear conditioning rapidly and persistently alters spontaneous single-unit activity in the prelimbic and infralimbic subdivisions of the mPFC in behaving rats. These conditioning-induced changes in mPFC firing were mitigated by systemic administration of propranolol, a b-noradrenergic receptor antagonist. Moreover, propranolol administration dampened the stress-induced impairment in extinction observed when extinction training is delivered shortly after fear conditioning. These findings suggest that b-adrenoceptors mediate stress-induced changes in mPFC spike firing that contribute to extinction impairments. Propranolol may be a helpful adjunct to behavioral therapy for PTSD, particularly in patients who have recently experienced trauma.

**[37] Combinatorial DREADD silencing of ventral hippocampal neurons projecting to infralimbic cortex prevents fear renewal

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Interactions between the ventral hippocampus (vHPC) and the prefrontal cortex have been implicated in the renewal of fear outside of the extinction context, but the roles of specific circuits in these regions during renewal are essentially unknown. Here, we used designer receptors exclusively activated by designer drugs (DREADDs) to selectively silence vHPC circuits during fear renewal. Rats received bilateral infusions into the vHPC of either non-Cre-dependent inhibitory DREADD virus (AAV[8]-CaMKIIα-hM4D[G_i]-mCherry) or a Cre-dependent DREADD silencer (AAV[5]-hSyn-DIO-hM4D[G_i]-mCherry). Rats that received Cre-dependent DREADD virus into the vHPC were also infused with a retrograde Cre virus (CAV2-Cre) in the infralimbic cortex (IL) to induce DREADD expression in vHPC:IL circuits. Following sufficient time for virus expression after surgery, rats were treated (i.p.) with clozapine *N*-oxide (CNO) or vehicle 30 min prior to inducing renewal to a conditioned stimulus (CS) outside of its extinction context. Systemic injection of CNO causes inhibitory DREADD-expressing cells to reversibly inactivate. As predicted, DREADD-mediated inactivation of the vHPC or vHPC:IL circuits in particular disrupted fear renewal as compared to rats injected with vehicle or expressing control virus. The data suggest that vHPC input to the prefrontal cortex is necessary for renewal, which could be a potential target of future therapeutic interventions.

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**** This poster was selected for a Best Abstract Award and the content will be presented as a talk in session 4. ****

[38] State-dependent effects of allopregnanolone on contextual fear learning

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Contextual conditioning often involves a variety of exteroceptive stimuli. In the case of Pavlovian fear conditioning in rodents, it can include olfactory and visual cues. Contextual conditioning, however, can also involve interoceptive stimuli such as a physiological state induced by systemic as well as intracranial administration of drugs. Under these circumstances, state-dependent learning can occur, such that memory retrieval is most efficient when testing occurs in the same drug state as learning. Previous work in our laboratory suggests that allopregnanolone (ALLO) impairs contextual freezing by acting at $GABA_A$ receptors in the bed nucleus of the stria terminalis (BNST). Here, we sought to determine if the effect of ALLO on contextual freezing is a result of state-dependent learning. Following cannulae implantation and recovery, adult male rats were given infusions of either ALLO (2 µg/side) or vehicle (30% β-cyclodextrin) into the BNST and after 10 min, trained with 5 tone-shock pairings. The following day, rats were infused with either the same or different drug given before training and tested in the conditioning context for 10 min. Results indicate that subjects trained and tested in the same drug state have increased levels of freezing compared to subjects trained and tested in a different state. These findings suggest that infusion of ALLO into the BNST results in state-dependent learning. To explore whether the effects of ALLO are specific to the BNST, we will study the effects of ALLO infusion into the basolateral amygdala, a key region involved in Pavlovian fear conditioning that has not been implicated in state-dependent learning.

[39] Latent variable modeling of sequential hippocampal reactivation

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Neuronal firing patterns are often preserved and repeated in a time-compressed manner (called replay or neural reactivation), but it remains challenging to (i) identify and (ii) quantitatively assess these events from extracellularly recorded neural data. Here I show how latent variable models (hidden Markov models in particular) can be used to identify and quantify putative sequences of reactivation—commonly believed to be critical for understanding learning, and memory consolidation in the hippocampus.

[40] Stochastic Motion of Bumps in Planar Neural Fields

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We analyze the effects of spatiotemporal noise on stationary pulse solutions (bumps) in neural field equations on planar domains. Neural fields are integrodifferential equations whose integral kernel describes the strength and polarity of synaptic interactions between neurons at different spatial locations of the network. Fluctuations in neural activity are modeled as a Langevin equation. Noise causes bumps to wander diffusively. We derive effective equations describing the bump dynamics as Brownian motion in two-dimensions. The diffusion coefficient can then be computed explicitly. We also consider weak external inputs that can pin the bump so that it obeys an Ornstein-Uhlenbeck process with coefficients determined by input shape. Inputs reshape the effective potential that guides the dynamics of the bump position, so it tends to lie near attractors which can be single points or contours in the plane. Our perturbative analysis can then be used to show the bump position evolves as a multivariate Ornstein-Uhlenbeck process whose relaxation constants are determined by the shape of the input.

[41] Involvement of the JAK/STAT3 Signaling Pathway in Ketamine-induced Synaptic Plasticity

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Ketamine, an NMDA receptor antagonist known clinically for its fast-acting antidepressant effects, is believed to bring about its therapeutic action by modulating neuronal plasticity. For example, rodents subjected to chronic stress exhibit both the cognitive deficits characteristic of depression, as well as dendritic atrophy in associated cortical regions, and notably an acute systemic injection of a low, sub-anesthetic dose of ketamine corrects both the behavioral and cellular deficits induced by chronic stress. At a molecular level, ketamine administration has been shown to evoke an increased expression of synaptic proteins, such as the activity regulated cytoskeleton (ARC) protein, that mediate processes of synaptic plasticity. However, to date, the molecular mechanism(s) underlying ketamine's therapeutic effect are still uncertain. Therefore, in the present study we investigated the novel role of the JAK/STAT3 pathway, in ketamine's therapeutic action.

Reversal learning, a form of cognitive flexibility predominantly mediated by the orbitofrontal cortex (OFC), is defined as the ability to adapt one's behavior in response to a change (or reversal) of rewarding contingencies. Our laboratory has shown that rats exposed to chronic intermittent cold stress (CIC, 6h at 4C for 2 weeks), exhibit a reversal-learning deficit. Therefore, our initial study examined the efficacy ketamine on the reversal-learning deficits caused by CIC stress. In parallel with previous work, we found that an acute injection of ketamine (10 mg/kg, i.p.) given 24 h prior to behavioral testing had a therapeutic effect on cognitive performance in CIC-stressed rats.

Previously, we have shown that reversal learning is impaired by inhibition of the JAK/STAT3 pathway. Therefore, we hypothesized that the JAK/STAT3 pathway may modulate ketamine's therapeutic effects on reversal learning. A preliminary experiment indicated that ketamine (10 mg/kg, i.p.) induces phosphorylation of JAK/STAT3 proteins within the OFC, and subsequently, in support of our hypothesis, we found that pharmacological inhibition of the JAK/STAT3 pathway 24h prior to reversal testing prevented ketamine's therapeutic effects on reversal learning.

To further investigate the molecular mechanism behind these behavioral data, we conducted a series of studies using a cortical neuronal cell line, A1A1, that expresses functional NMDA and AMPA receptors. In line with our *in vivo* studies, ketamine activated the JAK/STAT3 pathway in A1A1 cells, and also increased the levels of the synaptic plasticity marker, ARC. Importantly, knock-down of JAK1 prevented the ketamine-induced ARC expression, indicating that the JAK/STAT3 pathway may participate in synaptic plasticity.

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[42] Picture This! A Meta-Analysis Comparing Affective Salience of Words vs. Images

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fMRI studies exploring emotional memory encoding use a variety of experimental-design strategies and stimuli types, with event-related studies using word or picture stimuli being most common. Lesion-deficit correlations suggest different hemispheric specializations for these two types of stimuli. Despite the large size of the neuroimaging literature, no publications have compared the neural systems recruited by these two stimulus categories. In this meta-analysis we compared the neural systems recruited during emotional-stimulus encoding for picture and word stimuli, restricting our sample to event-related, peer-reviewed, fMRI studies. Our results indicated that both stimulus types yielded statistically robust and distinct regions of activation convergence in medial-temporal, memory-specific brain regions with picture-driven responses expressing bilateral activation and word-driven responses expressing left-lateralized activation in the parahippocampal gyrus. This is the first demonstration of a medial-lateral differentiation of the parahippocampal gyrus for picture and word stimuli.

[43] Mapping the electrophysiological and morphological properties of CA1 pyramidal neurons along the longitudinal hippocampal axis

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Differences in behavioral roles, anatomical connectivity and molecular gene expression patterns in dorsal, intermediate and ventral regions of the hippocampus are well characterized. Recently we reported that dorsal CA1 neurons are less excitable than ventral neurons. There is little or no information for how neurons in the intermediate hippocampus compare to those from the dorsal and ventral ends. Also, it is not known whether the transition of properties along the dorsoventral axis is graded or abrupt. In this study we developed a novel method to predict the dorsoventral position of hippocampal slices. Using current clamp recordings combined with this novel methodology, we found that CA1 neurons in dorsal, intermediate and ventral hippocampus have distinct properties. Here we show that the resting membrane potential, input resistance, resonance frequency and firing output of CA1 neurons decrease from the ventral to the dorsal end. We also observed increases in dendritic surface area and number of dendritic branches in both apical and basal dendrites from the ventral to dorsal end. Furthermore, we observed a gradual transition in these properties of CA1 neurons from dorsal to intermediate hippocampus. The change in neuronal properties from intermediate to ventral hippocampus was, however, abrupt. Overall, the findings from this study highlight the heterogeneity in CA1 neuronal properties along the entire dorsoventral axis of hippocampus.

[44] Fragile X mice show substantial learning impairments in a prefrontal-dependent trace eyeblink conditioning task.

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Fragile X syndrome (FXS) is the most prevalent heritable cause of mental disability, resulting from a loss-of-function mutation specifically in the *fmr1* gene, making the *fmr1-/y* mouse a particularly suitable disease model. Some of the cognitive inflexibility and working memory deficits observed in FXS patients are recapitulated in the *fmr1-/y* mouse, which has been attributed to developmental and ongoing abnormalities in synaptic and cellular function in the medial prefrontal cortex (mPFC; Bray et al., 2011; Kreuger et al., 2011). We trained *fmr1-/y* mice in an associational learning task (trace eyeblink conditioning) that depends on working memory mechanisms in the mPFC for acquisition. The majority of *fmr1-/y* mice were severely impaired and failed to acquire the task (9/11 mice), while only a small proportion of C57/Bl6 control mice did not meet criterion (4/16 mice). Importantly, 5/6 of the *fmr1-/y* mice tested were able to learn a prefrontal-independent version of the task (delay eyeblink conditioning), although with some deficit relative to controls as previously reported (Koekkoek et al., 2005). *In vivo* recordings and *in vitro* analysis of the cellular properties of mPFC cells between learners and non-learning *fmr1-/y* mice will provide substantial insight regarding the prefrontal dysfunction that underlies the learning and working memory deficits observed in FXS patients.

[45] Cell-type specific channelopathies in the prefrontal cortex of the *fmr1-/y* mouse model of Fragile X syndrome

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Fragile X syndrome (FXS) is caused by a single gene mutation resulting in the loss of expression of fragile X mental retardation protein (FMRP). FXS patients display several behavioral phenotypes associated with prefrontal cortex (PFC) dysfunction. Voltage-gated ion channels, some of which are targets of FMRP-regulation, heavily influence prefrontal neuron function. In *fmr1-/y* mouse L5 pyramidal neurons of PFC, we tested for alterations to ion channels critical in regulating neural excitability. Using somatic and dendritic patch clamp recordings we provide evidence that the functional expression of h-channels (I_h) is down-regulated, whereas A-type K^+ channel function is up-regulated in pyramidal tract-projecting (PT) neurons in the *fmr1-/y* mouse PFC. This is the opposite pattern of results from published findings from hippocampus where I_h is up-regulated and A-type K+ channel function is down-regulated. Additionally, we find that K_v1-mediated current is down-regulated at the soma of *fmr1-/y* PT neurons, resulting in increased excitability. Importantly, these K^+ channel differences do not extend to neighboring intratelencephalic-projecting (IT) neurons. Thus, the absence of FMRP has divergent effects on the function of individual types of ion channels not only between brain regions, but also across cell types within the same brain region. Given the importance of ion channels in regulating neural circuits, these results suggest cell-type specific phenotypes for the disease.

[46] Matlab-based automated patch clamp system for awake behaving mice

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Automation has been an important part of biomedical research for decades, and the use of automated and robotic systems is now standard for such tasks as DNA sequencing and high-throughput screening. Recently, Kodandaramaiah and colleagues (Nat. Methods, 2012) demonstrated, using anesthetized animals, the feasibility of automating blind patch clamp recordings *in vivo*. Blind patch is a good target for automation because it is a complex yet highly stereotyped process that revolves around analysis of a single signal (electrode impedance) and movement along a single axis. Here, we introduce an automated system for blind patch clamp recordings from awake, head-fixed mice running on a wheel. The system employs equipment that is standard for patch recording rigs, moderately priced, or simple to make. It is written entirely in Matlab, a programming environment with an enormous user base in the neuroscience community. Using this system, we obtained 19 recordings from neurons in the prefrontal cortex of awake mice. Recordings had series resistances that averaged 52 ± 4 MΩ and required 5.7 ± 0.6 attempts to obtain. These numbers are comparable to those of experienced electrophysiologists working manually; and this system should be useful to many cellular electrophysiologists who study awake behaving mice.

[47] Representation of novel and familiar object-place associations during slow and fast gamma rhythms in freely behaving rats

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Hippocampal gamma oscillations are thought to play a role in memory operations by coordinating the activity of neurons that code related information. We used a hippocampal-dependent novel object recognition (NOR) task to investigate the roles of slow and fast gamma rhythms in memory encoding of novel object-place associations and memory retrieval of familiar object-place associations. Because the level of hippocampal dependence varies depending on the type of novelty involved, we examined gamma activity during three conditions: a novel object placed in a familiar location, a familiar object placed in a novel location, and a novel object placed in a novel location. The strongest and most consistent effects were observed for fast gamma during the novel object-novel place condition. We found that fast, but not slow, gamma power in CA1 significantly increased during exploration of novel objects in novel locations compared to familiar object-place associations. Moreover, CA1 place cell spikes were more strongly phase-locked to fast gamma during exploration of novel object-novel place associations compared to exploration of familiar object-place associations. We also found that CA1 place cells with fields close to the novel object/novel location exhibited firing rates that were significantly higher during fast gamma than during slow gamma. These results support the hypothesis that fast gamma conveys novel sensory information from MEC to CA1 during encoding of new object-place associations.

[48] Place cells use different spatial and temporal codes during slow and fast gamma rhythms

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The hippocampus is central to episodic memory and spatial navigation, both of which rely on sequences of spatio-temporal information. 'Theta sequences' are temporally compressed representations of spatial paths by place cells, hippocampal neurons that represent specific locations. These sequences activate within individual cycles of the extracellular theta oscillation (~6–10 Hz) and may be important for the encoding or retrieval of spatial memories. A second type of oscillation in the hippocampus, gamma (~25–100 Hz), is thought to interact with theta to temporally organize theta sequences. However, it remains unclear how theta sequences are affected by different slow (~25–55 Hz) and fast (~60–100 Hz) subtypes of gamma, which reflect different spatial coding modes in the hippocampus. In rats running on a linear track, we found that sequences during slow gamma showed a greater degree of temporal compression and extended further ahead of the animal compared to sequences during fast gamma, which were more likely to represent current locations in real time. Moreover, the slow gamma phases at which spikes occurred shifted as the sequence progressed, such that earlier locations were coded by spikes at early slow gamma phases and later locations were coded by spikes at late slow gamma phases. In contrast, place cells tended to fire at the same fast gamma phase, regardless of where their place field was located. These findings suggest that place cell sequences that code future paths activate within a slow gamma cycle on a compressed time scale, whereas sequences that represent the ongoing trajectory activate across successive fast gamma cycles at the behavioral time scale.

[49] The role of contextual information in retrieval-induced forgetting

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Context refers to the many facets of information that characterize the situation in which a specific episodic memory occurs — placing the memory in space and time. Recent memory models suggest that memory retrieval uses contextual information as a "spotlight" for probing memories during recall (Polyn et al., 2009; Sederberg et al., 2008). These models are driven by the idea that increased overlap of features between memory probes and memory traces enable easier access (Eich, 1985; Murnane and Phelps, 1995). Additionally, there is evidence of competitive dynamics between co-activating memories which can lead to subsequent memory weakening for non-target memories (Anderson et al., 1994, 2000). However, the relationship between this memory weakening effect and contextual information at retrieval is unknown.

In this experiment, we explore the relationship between contextual information and retrieval-induced forgetting by using partial contextual information in a cued retrieval task. Images of objects are first encoded in environments which contain overlapping and unique contextual layers: a scene photograph, color, and coherent dot-motion direction. The combination of contextual layers are unique to each object image, but a subset of contextual layers are potentially shared across objects. These contextual layers are then used as cues in a retrieval task designed to induce selective competitive dynamics amongst the associated object memories.

Preliminary behavioral results suggest that the amount of shared contextual information for objects during encoding is predictive of negative memory strength for non-target objects after a cued retrieval task. Further, in an fMRI experiment, pattern similarity analysis will be used during cued retrieval to measure memory reactivation; in a data-driven approach, these measures will provide a neural indicator of memories most likely to be weakened during retrieval.

[50] Shifting the granularity of context-based predictions modulates memory pruning

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The brain continuously updates its memories of past experiences in order to generate timely predictions to efficiently guide behavior. Correct predictions can facilitate task-relevant neural processing and enhance behavioral performance. Incorrect predictions lead to processing inefficiencies and behavioral costs. The neural friction induced between an incorrectly predicted event and the processing of the actual event can trigger "memory pruning" by which the memories used to generate that misprediction are weakened through competitive neural dynamics. Recent evidence has shown that the temporal context of our experience (e.g., that event B follows event A) is used to generate implicit predictions that can lead to memory pruning (Kim, Lewis-Peacock, Norman, & Turk-Browne, 2014). However, the process by which the brain incorporates contextual information to tune its predictive processing remains poorly understood. Here, we investigate whether memory pruning of specific items can be avoided when context information supports more general predictions (e.g., category-level predictions vs. item-specific ones). Subjects will undergo sequential learning of non-adjacent pairs consisting of one cue item and three associates (e.g., cup-camel, cup-tree, cup-shoe). This arrangement should lead to item-specific predictions that when violated trigger memory pruning. However, when the three associates are related (e.g., they are "animals", as in apple-bear, apple-rabbit, apple-elephant), we hypothesize that predictions will shift from item to category on subsequent cue presentations (e.g. apple will predict "animal", not elephant). This shift in prediction specificity should eliminate memory pruning of the individual associate items. To test this, we will apply multivoxel pattern analysis to fMRI data during this learning task to track the specificity of context-based predictions, and we will relate these predictions to subsequent memory consequences. We anticipate two results: (1) retrograde memory benefits for the pruning-free items and (2) anterograde memory costs for the items encountered in category-level prediction mode.

[51] Calibrating the usage of working memory for prospective remembering

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How do we remember to execute goals at the appropriate time? Prospective memory can be achieved using proactive control by actively maintaining the goal in working memory or using reactive control by relying on external cues to retrieve the goal when necessary. The flexible choice of strategy involves effort and performance tradeoffs. We developed an fMRI study to assess how the dynamic selection of strategy varies with cognitive load. Each trial began with a picture target (a face or scene), followed by a variable-length sequence of 2-sec memory probes containing four pictures and a field of moving dots. Participants balanced two goals: 1) to make repeated direction-of-motion judgments about the dots; and 2) to identify when the picture target reappeared. The motion coherence of the dots were parametrically varied across trials in an effort to modulate resource consumption, thereby shifting cognitive control strategies, in the dual-task. Higher coherence made the dot judgements easier, thus requiring fewer resources and favoring a proactive control strategy. Lower coherence made the judgments harder, increasing the viability of a reactive control strategy. We recorded fMRI data every 1s and used multivariate pattern analysis to decode the contents of working memory and decipher control strategies. We sought to identify the neural signature associated with prospective memory success on a subject-by-subject basis across low- and high-resource consumption conditions. Ultimately, our goal is to use this model to provide individualized fMRI neurofeedback by titrating the coherence of the dot motion task from moment to moment. This will modulate demands on shared cognitive resources in an effort to maximize the incidence of the brain states associated with prospective remembering, thereby boosting performance on the complex, but ecologically valid dual task.

[52] Adult hippocampal neurogenesis modulates fear learning through associative and nonassociative mechanisms

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Adult hippocampal neurogenesis is believed to support hippocampus-dependent learning and emotional regulation. These putative functions of adult neurogenesis have typically been studied in isolation, and little is known about how they interact to produce adaptive behavior. We used trace fear conditioning as a model system to elucidate mechanisms through which adult hippocampal neurogenesis modulates processing of aversive experience. To achieve a specific ablation of neurogenesis, we generated transgenic mice that express herpes simplex virus thymidine kinase specifically in neural progenitors and immature neurons. Intra-cerebralventricular injection of the prodrug ganciclovir caused a robust suppression of neurogenesis without suppressing gliogenesis. Neurogenesis ablation via this method or targeted x-irradiation caused an increase in context conditioning in trace but not delay fear conditioning. The data suggest that this phenotype represents opposing effects of neurogenesis ablation on associative and nonassociative components of fear learning. Arrest of neurogenesis sensitizes mice to nonassociative effects of fear conditioning, as evidenced by increased anxiety-like behavior in the open field after (but not in the absence of) fear conditioning. In addition, arrest of neurogenesis impairs associative trace conditioning, but this impairment can be masked by nonassociative fear. The results suggest that adult neurogenesis modulates emotional learning via two distinct but opposing mechanisms: it supports associative trace conditioning while also buffering against the generalized fear and anxiety caused by fear conditioning.

[53] Bidirectional modulation of context fear in the dentate gyrus

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Recent studies have demonstrated the importance of the hippocampal dentate gyrus (DG) in the acquisition of contextual fear memories. However, the neural substrates that underlie extinction of context fear have not yet been clearly defined. Here, we utilize optogenetic and chemogenetic methods to assess the role of the DG in contextual extinction learning in mice. To rapidly and reversibly manipulate neural activity during behavior, an adeno-associated viral (AAV) vector was used to drive expression of the light activated chloride pump halorhodopsin specifically within the DG. Optogenetic inhibition of the dorsal DG impairs fear learning, while dentate inhibition during extinction prevents extinction learning, with mice maintaining a high level of freezing across five days of extinction training relative to controls. The increased freezing in mice experiencing dentate inhibition was not due to an effect on expression of fear learning or freezing behavior, as there is no effect on retrieval of either fear or extinction memories. To further examine the role of the DG in context learning, we employed a chemogenetic approach to increase activation of dentate granule cells (DGCs) during either fear conditioning or extinction. Interestingly, increased activation of DGCs during conditioning impaired learning, similarly to inhibition. However, increasing excitability of DGCs during extinction training enhances extinction learning, leading to a maximal reduction in freezing after a single extinction session. Together these data identify the dorsal DG as a critical component in the neural circuitry of context extinction and a potential therapeutic target for the treatment of emotional disorders related to aberrant fear learning.

[54] Learning activates expression of Zif268 in mature hippocampal neurons but suppresses Zif268 in immature hippocampal neurons

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The dentate gyrus continuously generates neurons in adulthood, but how and when these adult-born neurons participate in hippocampal function is not fully understood. As newborn neurons mature, they exhibit changes in excitability and activity. While depolarizing inputs are important for the adult-born neuron to integrate into the circuit, many studies have failed to detect activity of immature adult-born neurons *in vivo* under conditions that activate mature neurons. To investigate the development of adult-born neuron activity, we characterized expression of the immediate early gene (IEG) Zif268 in mature and immature granule cells after exposure to a novel environment, an enriched environment, or water maze acquisition. We found that while Zif268 expression in the general granule cell population peaks 1 hour after exposure to a novel environment and significantly declines by 8 hours post-exposure, the percentage of Doublecortin+ (DCX+) immature granule cells coexpressing Zif268 was depressed relative to home cage for at least 8h after novel environment exposure. We also found that all three behavioral procedures suppressed Zif268 expression in DCX+ immature neurons relative to homecage, whereas these procedures evoked a significant increase in zif268 expression both in the general granule cell population and in 6 week-old adult-born neurons. We next quantified how IEG expression in response to a novel environment changes as a function of cell age in the DCX+ population, which ranged in age from 0 to 4 weeks. Novel environment exposure activated Zif268 expression in 2-week-old adult born neurons but suppressed expression in 3- and 4-week-old neurons. In summary, hippocampus-dependent information processing activates expression of Zif268 in 2-week-old and mature hippocampal granule cells but suppresses Zif268 expression 3-4-week-old granule cells. We hypothesize that suppression of IEG expression in adult-born granule cells could function to prevent neurons from undergoing synaptic plasticity while immature, or may support learning-induced apoptosis, which has been observed in immature adult-born granule cells.

[55] Timing of context preexposure affects strength of fear conditioning

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Contextual fear conditioning (CFC) is an associative learning paradigm that requires an animal to form a mental representation of the surrounding contextual elements before an aversive stimulus may become associated with those elements. Models of CFC posit that such mental representations can be acquired during passive exploration of an environment. Consistent with this idea, context preexposure can alleviate the conditioning deficit caused by delivering a shock immediately after the animal is placed in the context. Current models of CFC assert that context preexposure is required for CFC acquisition but make no predictions about how variation in the temporal interval between context preexposure and conditioning will affect learning. Because the synaptic and anatomical substrates of context memory change over time after acquisition of the memory, we predicted that the interval between context preexposure and conditioning would affect the strength of conditioning. We found that context preexposure 72h or 24h before single-shock CFC produced higher conditioned fear than did preexposure 1min before or contiguous with conditioning. Next we asked whether the effect of preexposure timing was mediated through enhanced context fear acquisition or increased resistance to extinction. We tested whether variation in the timing of context preexposure affects sensitivity to postshock context exposure, a manipulation that potently extinguishes context fear. Again, increased preexposure-to-conditioning intervals were associated with higher freezing; however, the timing of context preexposure and postshock duration did not interact, suggesting that these manipulations independently affect the strength of conditioning. In summary, the data show that CFC acquisition is enhanced when sufficient time elapses between context preexposure and conditioning,. We hypothesize that CFC acquisition is enhanced when it involves reactivation of a previously acquired context memory as opposed to simultaneous acquisition of a context memory and a context-shock association.

[56] The alignment of functional selectivity in V1 following ocular misalignment

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Disruption in the visual field before the critical period can change how the neurons in the primary visual cortex integrate binocular inputs. Strabismus (ocular misalignment) during development leads to cortical neurons that are almost exclusively monocular when measured by spike rate.The traditional interpretation for this phenomenon is an underlying reduction, or even elimination, of the synaptic input to the cortical neuron from the non-preferred eye via activity-dependent competition. Since this interpretation has relied almost exclusively on recording of suprathreshold activity (spiking), which is indirectly related to synaptic input, we measured subthreshold membrane potential responses to assess the changes in functional selectivity following ocular misalignment.

Following surgically-induced strabismus in cats before the critical period (p12) we used whole-cell recordings *in vivo* to measure the activities of the cortical neurons in adult animals. We compared each neurons preference for orientation, spatial frequency, and contrast sensitivity for both the right and left eyes. We find a surprising match between these selectivity of the neurons for the right and left eyes at the level of membrane potential. Right and left eye inputs in strabismus animals share orientation preference, spatial frequency preference, and contrast sensitivity despite the increased degree of monocularity in these neurons. While we do uncover some variance in selectivity between the right and left eye inputs, this degree of variances matches that found in normal animals. These direct measurements of input selectivity following strabismus reveal that despite the lack of correlation between the images that the left and right eyes provide, the underlying selectivity of the neurons is maintained.

[57] Loss of Binocular Disparity Selectivity Following Monocular Deprivation in Mouse V1

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Experience dependent plasticity during the critical period of development shapes anatomical and functional elements of cortical circuits. In primary visual cortex (V1) of mice, neurons in binocular zone shift preference toward the ipsilateral eye if the contralateral eye is occluded during the critical period. This shift equalizes the relative contribution of input from each eye. Here we tested how this increased ocular input affects binocular disparity selectivity of V1 neurons, a response property arising from the integration of ocular inputs. Using two-photon calcium imaging we measured ocular dominance (OD) and disparity selectivity of neurons in the binocular zone of mice after occluding one eye during the critical period. Surprisingly, a decrease in disparity sensitivity accompanied increased binocularity in deprived animals. Decreased disparity tuning was most pronounced in moderately binocular neurons, as measured by ocular dominance. These data suggest the enhanced binocularity resulting from OD plasticity is at least partially nonfunctional due to a loss of disparity selectivity, suggesting synaptic input misalignment during deprived visual experience.

[58] Bidirectional regulation of the alpha2/delta-2 calcium channel subunit following induction of chemical LTD or LTP

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A fundamental property of neurons thought to underlie learning and memory is the ability to alter synaptic strength through changes in neuronal activity. Protein synthesis is necessary for different types of synaptic plasticity such as long term potentiation (LTP) and long term depression (LTD). The decision for a synapse to undergo LTP or LTD requires activation of specific receptors that often activate common signaling pathways such as the ERK/MAPK and PI3K/mTOR pathways and promote protein synthesis of plasticity related proteins. There is increasing evidence that voltage-gated calcium channels are involved in both LTP and LTD. In this study we identify the calcium channel subunit Cacna2d2 as one of these plasticity related proteins whose translation is regulated in a bidirectional manner depending on whether LTD or LTP is induced. When mGluR-LTD was induced in slices and in hippocampal cultures we observed an increase in Cacna2d2 protein expression. Furthermore, Cacna2d2 protein levels increase in the dendrites and colocalize with PSD95. Conversely when chemical L-LTP was induced with forskolin we observed a decrease in Cacna2d2 dendritic protein expression. Since the Fragile X mental retardation protein (FMRP) has been shown to regulate protein synthesis mediated by group I mGluR activation we measured Cacna2d2 protein levels in Fmr1 knockout mice and found can increase suggesting that Cacna2d2 may also be regulated by FMRP. Finally we show that overexpressing Cacna2d2 in primary hippocampal neurons leads to a decrease in GluR1 surface labeling suggesting that Cacna2d2 may be involved in glutamate receptor trafficking. Collectively, our results suggest that competitive forms of long-lasting plasticity promote bidirectional changes in the auxiliary calcium channel subunit Cacna2d2 which may serve as a switch dictating the strength of the synapse.

[59] Alcohol Exposure Alters the Dendritic Expression and Function of the $GABA_B$ Receptor

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Alcohol use disorders display comorbidity to a range of mental disorders; including major depressive disorder. The initial use of alcohol has also been suggested to be a form of self-medication for individuals with major depression. Recently it has been discovered that blockade of N-methyl-D-aspartate receptor (NMDAR) by rapid antidepressant induces a functional switch in gamma-aminobutyric acid B receptors ($GABA_BR$) at the synapse, as well as increased dendritic expression. $GABA_BR$ switches from activating G-protein-gated inwardly rectifying potassium channels to facilitating L-type calcium channels. This increase in calcium entry activates synaptic signaling pathways that promote local protein synthesis at the synapse required for long-term changes in synaptic efficacy.

Ethanol is a known NMDAR antagonist, and preliminary results suggest ethanol exposure also causes new synthesis and function of $GABA_BR$ and activates this rapid antidepressant pathway. We aim to further our understanding of the rapid antidepressant effects of ethanol, by exploring mechanisms of new $GABA_BR$ synthesis with acute ethanol exposure. $GABA_BR$ mRNA is a target of the RNA-binding protein Fragile-X Mental Retardation Protein (FMRP). Preliminary results suggest that ethanol exposure leads to a rapid reduction in dendritic FMRP. Thus, we propose that the increase in $GABA_BR$ expression is due to decreased dendritic activity of FMRP leading to local protein synthesis after ethanol exposure in the dendrites.

We tested the hypothesis that ethanol modulates dendritic $GABA_BR$ expression through FMRP activity by using immunocytochemistry of cultured hippocampal neurons and western blot analysis of hippocampal synaptoneurosomes after ethanol treatment. We will next test the hypothesis that local protein synthesis of $GABA_BR$ at the synapse is promoted by ethanol exposure.

Our studies suggest that $GABA_BR$ expression and function are altered with ethanol treatment *in vitro* and *in vivo*, and that these changes in $GABA_BR$ expression may be due to a decrease in FMRP negative regulation of the $GABA_BR$. Our preliminary results thus far support the theory that ethanol may act similarly to rapid antidepressants in regards to the expression and function of the $GABA_BR$. Supported by grants from NIH/NIAAA to the INIA-West consortium.

[60] Analysis of proteins that rapidly change upon mTORC1 repression identifies PARK7 as a novel protein aberrantly expressed in Tuberous Sclerosis Complex

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Many neurobiological processes involve mTORC1 which is the core of activity-dependent translation. To determine the role of mTORC1 subcellular activation in protein expression, we employed an unbiased, large-scale proteomic approach. We provide evidence that brief repression of mTORC1 activity *in vivo* by rapamycin has little affect globally, yet leads to significant remodeling of synaptic proteins, in particular those proteins that reside in the postsynaptic density (PSD). We also found that curtailing the activity of mTORC1 bidirectionally alters the expression of proteins associated with epilepsy, Alzheimer's disease (AD), and autism spectrum disorders (ASD)— disorders with dysregulated mTORC1 activity. Through protein-protein interaction network analysis, we identified common proteins among these mTORC1-related diseases including PARK7, implicated in Parkinson's disease, but not epilepsy, AD, or ASD. We provide evidence that the protein expression of PARK7, including new protein synthesis, is sensitive to mTORC1 inhibition. Using cultured neurons from a mouse model of tuberous sclerosis complex (TSC), a disease displaying both epilepsy and ASD phenotypes and has overactive mTOR signaling, we show that PARK7 protein is elevated in the dendrites. We provide a comprehensive view of mTORC1 and its role in regulating regional protein expression in normal and diseased states.

**[61] Structural development of hippocampal subfields is related to statistical learning and inference

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Recent work suggests that the human hippocampus undergoes protracted development, which may explain improvements in memory from childhood to adulthood. However, the hippocampus is a heterogeneous structure that comprises several distinct subfields, and little is known about how they develop. Although the hippocampus is primarily known for its critical role in the encoding and retrieval of individual episodes, it has also been implicated in coding relationships that generalize across experiences. In the present study, we investigated the relationship between hippocampal subfield structure and generalization performance from ages 630. We found lower performance among children relative to adults in two tasks thought to require hippocampal generalization: associative inference and statistical learning. Consistent with the notion that hippocampal structures continue to mature into adolescence, we observed hippocampal volume decreases over development that were primarily driven by changes in the hippocampal head. Moreover, after accounting for age effects, we found relationships between hippocampal head volumes and generalization performance. These results paralleled the volume decreases we observed over development, with smaller volumes being associated with superior behavior. These data show that hippocampal structure relates to individual differences in the ability to integrate across related experiences and may not reach maturity until adulthood.

**** This poster was selected for a Best Abstract Award and the content will be presented as a talk in session 4 in lieu of a poster. ****

[62] The evolution of category knowledge: Linking learning models to the dynamics of neural representations

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Learning theories posit that during the course of learning, attention is tuned to relevant information. Formal learning models suggest that changes in attention during learning are reflected by an evolving representational space that is increasingly biased towards diagnostic features. Although recent evidence suggests that after learning, attention-weighted knowledge is present in neural representations, a link between the evolution of attention and the dynamics of neural representation during learning has yet to be demonstrated. Here, we extend neural pattern similarity and model-based fMRI analyses to investigate the neural mechanisms of learning-based shifts in category representations. During fMRI scanning, participants learned to categorize complex objects across three category learning tasks. A learning model was fit to participants' behavior to derive latent measures of attention weights to object features, which were used to construct similarity matrices characterizing each participant's attention-biased object representations throughout learning. A searchlight analysis compared similarity matrices of the neural representations of the objects over time with model-derived similarity matrices. We found correspondence between model and neural similarity in regions associated with higher-level object representations including lateral occipital and posterior parietal cortex, and in regions of lateral prefrontal cortex. Interestingly, hippocampus also showed evidence of attention-biased object representations during learning. These results highlight the underappreciated role of MTL-based processes in category learning and provide strong neural evidence for the attention mechanisms proposed by prominent category learning theories.

[63] Dealing with the uncertainty: binary decision making in the cerebellum

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Dealing with noisy and variable sensory inputs is an inevitable issue living organisms must face daily. The cerebellum is known to receive vast sensory and proprioceptive inputs, however little is known about how the cerebellum deals with the uncertainty in these inputs. In order to address this question, we used delay eyelid conditioning paradigm in the rabbit – because of the relatively direct way that it engages the cerebellum, combined with tetrode recordings from the cerebellar cortex. To gain full control over the intensity and temporal characteristics of input to the cerebellum, we used electrical stimulation of mossy fiber inputs as the conditioned stimulus (CS). After an initial phase of training, we introduced CS-alone probe trials that were altered systematically in different ways from the original CS. Our results indicate that under all conditions the cerebellum makes a binary choice at the behavioral level: either to make a conditioned response with an amplitude and timing appropriate to its previous training, or to not make a response at all. Simultaneous recordings from Purkinje cells, the output neurons of the cerebellar cortex, allowed us to localize such decision to be the result of computation in the cerebellar cortex. These data demonstrate a novel computational principle that the cerebellum implements when faced with uncertainty in a sensory input.

[64] Accelerated learning in transgenic mouse model of Alzheimer's disease

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Trace conditioning is a highly conserved form of associative learning in mammals. The neural circuitry required for this cognitive task has been described, however cellular mechanisms that support it are not well understood. As such, variations in performance across animal strains are potentially informative. We have also discovered a difference between 3xTg Alzheimer's disease (AD) model mice and non-transgenic controls in acquisition of trace conditioning tasks. Paradoxically, 2-3 month old, otherwise asymptomatic, 3xTg animals learn our trace eyelid task more rapidly than non-transgenic controls. This difference extends to trace fear conditioning, as 3xTg mice display enhanced freezing to context, but not to tone. Two hypotheses may explain our findings: accelerated learning could present as an advantage at the outset, but may produce cognitive dysfunction over time; alternatively, the enhancement may be compensatory, indicative of aberrant network operations. Both phenomena could be features of disease onset. Upcoming experiments will examine the age dependence of accelerated learning. To explore the underlying cellular mechanisms, we will also test the sufficiency of individual 3xTg AD proteins for conferring a learning advantage, as well as correlate cell intrinsic properties with identified learning phenotypes.

[65] Functional investigation of hippocampal CA1 circuit activity during learning

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Diverse cell classes in the hippocampal CA1 region work in concert to support associative memory formation. We have identified a hippocampus-dependent trace conditioning task that is amenable to a head-fixed configuration. We have also adapted a minimally disruptive surgical preparation for accessing the dorsal hippocampus in mice for 2-photon functional GCaMP imaging. Using this experimental framework, we have succeeded in monitoring hippocampal microcircuit operations longitudinally for up to two months, returning to the same field of view on each day of training. In addition to following transformations within the full neuronal ensemble, we have used a variety of viral and transgenics-based methods to label specific neuron classes for imaging. Here we present initial observations on the response profiles of these individual classes of hippocampal neurons, as well as the evolution of cell population dynamics during learning. In future experiments, we plan to examine cell activity during the trace interval to elucidate the role of hippocampal neurons during this cognitive task.

[66] Activity-dependent postsynaptic modulation of intrinsic membrane properties is altered in hippocampal CA1 pyramidal neurons in mouse models of familial Alzheimer's disease

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Presenilin1 (PS1) mutations are responsible for the vast majority of familial Alzheimer's disease (FAD) cases. Amino acid substitutions, such as M146V, linked to the most aggressive form of early-onset FAD, produce intracellular calcium mishandling. However, it is unclear how this initial change in cell function leads to cognitive decline. We have measured intrinsic membrane properties of hippocampal CA1 pyramidal neurons in 5–8 week old 3xTg mice, PS1(M146V) mice and aged-matched non-transgenic (NTg) animals *in vitro*. At this age, neuronal calcium dysfunction has been observed in the absence of additional pathology, providing a useful platform for examining disease onset. Despite similar passive and active membrane properties, we were able to detect a dramatic difference in intrinsic plasticity related to postsynaptic calcium handling. Bath application of the group I mGluR agonist DHPG (20 μM)—to evoke calcium release from endoplasmic reticulum—produced a significantly smaller increase in input resistance in CA1 pyramidal neurons of 3xTg and PS1(M146V) mice compared to NTg controls. Because this increase in input resistance is believed to underly homeostatic regulation of excitability associated with synaptic plasticity, these data suggest that postsynaptic intrinsic plasticity deficits may contribute to cognitive decline in AD.

[67] Developmental organization of smooth endoplasmic reticulum within developing CA1 hippocampal dendrites

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The smooth endoplasmic reticulum is a membranous organelle that forms a network of tubules, vesicles, and cisterns. This network plays a role in the regulation of intracellular calcium, trafficking of integral membrane and synaptic proteins, and the metabolism of lipids. The SER network varies along dendrites, where small SER tubules alternate with regions that contain broad cisterns of SER. The number of spines along developing dendrites doubles between postnatal day (P) 15 and P21, and age that has about 80% of total dendritic spines relative to young adult rats (P55-70). We used three-dimensional reconstruction from serial section electron microscopy (3DEM) to assess relationships between this robust synaptogenesis and the maturation of dendritic SER. The volume of SER was well-correlated with the total synaptic input in adult but not at P15. We hypothesized that an increase in SER volume should accompany the increased synaptic input in P21 dendrites. We found a developmental increase in dendritic SER volume that was well correlated with the maturation of total synaptic input. Our findings support the hypothesis that the dendritic SER scales as spine density and synapse size mature across age.

[68] Complexity of dendritic SER increases at enlarging synapses during LTP

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Smooth endoplasmic reticulum (SER) forms a membranous network that extends throughout neurons. SER regulates intracellular calcium and the posttranslational modification and trafficking of membrane and proteins. As the structure of dendritic SER shifts from a tubular to a more complex, branched form, the movement of membrane cargo slows and delivery to nearby spines increases. Here, we discovered changes in the structural complexity of SER that have important functional implications during long-term potentiation (LTP) in the adult rat hippocampus. By 2 hours after the induction of LTP with theta-burst stimulation, synapse enlargement was greatest on spines that contained SER. More spines had an elaborate spine apparatus than a simple tubule of SER. The SER in dendritic shafts became more complex beneath spines with both polyribosomes and SER, and less complex along aspiny dendritic regions. The findings suggest that local changes in dendritic SER support enhanced growth of specific synapses during LTP.

[69] Structural changes of presynaptic boutons and Mitochondria associated with LTP in p15 and adult hippocampus

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Hippocampal LTP involves changes in presynaptic function. Many steps of the synaptic vesicle cycle require mitochondrial ATP, but little is known about the relationship between mitochondria, vesicle cycling, and LTP. To determine whether mitochondrial proximity and presynaptic vesicles are related in immature axons, we used serial section microscopy to make 3D reconstructions (3DEM) of CA1 axonal boutons in perfusion-fixed brains from postnatal day 15 (P15) male rats. We separated boutons by mitochondrial proximity into three populations with distinct vesicle compositions. To ascertain whether these populations behaved differently after LTP, we delivered control or theta burst stimulation (TBS) to independent sites in the middle of s. radiatum of acute hippocampal slices from P15 and adult rats and used 3DEM to evaluate changes in synaptic structure. 30 minutes after TBS, boutons containing mitochondria lost docked vesicles. By 2 hours post-TBS, boutons with mitochondria had also lost non-docked vesicles. Vesicle composition remained unchanged in boutons without mitochondria. We also studied LTP-related changes in axonal mitochondrial dimensions and distribution. At 2 hours post-TBS, P15 mitochondria became smaller but not more frequent; in adults, they became larger and less frequent. Mitochondrial internal structure also changed following LTP: their matrices became condensed and their cristae widened, implying increased respiration. Our findings demonstrate an LTP-associated increase in mitochondrial activity to meet the demands of active boutons.

[70] Automated Transmission-Mode Scanning Electron Microscopy (tSEM) for Large Volume Analysis at Nanoscale Resolution

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Transmission-mode scanning electron microscopy (tSEM) on a field emission SEM platform was developed for efficient and cost-effective imaging of circuit-scale volumes from brain at nanoscale resolution. Image area was maximized while optimizing the resolution and dynamic range necessary for discriminating key subcellular structures, such as small axonal, dendritic and glial processes, synapses, smooth endoplasmic reticulum, vesicles, microtubules, polyribosomes, and endosomes which are critical for neuronal function. Individual image fields from the tSEM system were up to 4,295 mm^2 (65.54 mm per side) at 2 nm pixel size, contrasting with image fields from a modern transmission electron microscope (TEM) system, which were only 66.59 mm^2 (8.160 mm per side) at the same pixel size. The tSEM produced outstanding images and had reduced distortion and drift relative to TEM. Automated stage and scan control in tSEM easily provided unattended serial section imaging and montaging. Lens and scan properties on both TEM and SEM platforms revealed no significant nonlinear distortions within a central field of ~100 mm^2 and produced near-perfect image registration across serial sections using the computational elastic alignment tool in Fiji/TrakEM2 software, and reliable geometric measurements from RECONSTRUCTTM or Fiji/TrakEM2 software. Axial resolution limits the analysis of small structures contained within a section (~45 nm). Since this new tSEM is non-destructive, objects within a section can be explored at finer axial resolution in TEM tomography with current methods. Future development of tSEM tomography promises thinner axial resolution producing nearly isotropic voxels and should provide within-section analyses of structures without changing platforms. Brain was the test system given our interest in synaptic connectivity and plasticity; however, the new tSEM system is readily applicable to other biological systems.

[71] Contrasting onset age of hippocampal LTP and dendritic spines in rats versus mice

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We have determined the onset age during development for LTP lasting more than 3 hours in rats and mice as a basis for testing whether dendritic spines are required. Previously, we found that the onset age for enduring LTP induced by theta-burst stimulation (TBS) is postnatal day (P)12 in hippocampal area CA1 of Long Evans rats (Cao and Harris, 2012). In addition, we found that prior to P20, control test-pulses delivered even as slowly as 1 pulse/5 minutes produced synaptic depression. The onset of test pulse-induced depression was faster at shorter inter-pulse intervals. After P21, test-pulses no longer influenced baseline responsivity, which remained stable at all inter-pulse intervals (30 seconds – 5 minutes) for many hours *in vitro*. At P8-P11, TBS reversed the test-pulse depression; however, no potentiation was produced above the original naïve response. An additional episode of TBS delivered 30-120 minutes after the first TBS produced enduring LTP at P10-P11, but not at younger ages in rats.

Recently, we examined the developmental profiles of test-pulse depression and enduring LTP in C57BL/6 mice. In mice, test pulse-induced depression occurred until P60 and the degree of depression was dependent on the number of test pulses delivered rather than frequency contrasting with rats. In the mice, TBS first induced enduring LTP reliably at about P34-36. Unlike in rats, an additional episode of TBS did not produce LTP in younger mice.

Preliminary results from our lab show P12 to be the onset age of mature dendritic spines in rat hippocampal area CA1, suggesting they are necessary for enduring LTP. Prior work shows dendritic spines occur by P24 (Nikonenko et al., 2013) in C57BL/6 mouse hippocampal area CA1, suggesting dendritic spines may be necessary, but not sufficient for enduring LTP in the mouse.

[72] Memory and visual search in immersive environments

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Memory may be an important determinant of attention allocation during daily behaviors, and is known to guides visual search in two-dimensional images. However, it is unclear how these findings extend to three-dimensional environments. We aimed to determine to what extent memory for context guides search in three-dimensional vs. two-dimensional environments, and the role of task in such guidance. Eye movements were tracked in an immersive virtual reality apartment with two rooms. Subjects explored one room for one minute and searched for targets in either room for 40 trials, including searches for geometric objects and realistic context objects. We found that one-minute exploration prior to search does not aid later search much in the same room unless targets were present during exploration in both 2D and 3D. However, search efficiency increased rapidly when a target was searched repeatedly, and the improvement came from reducing time in incorrect room. There was no benefit of previous experience for search of context objects that had previously been task-irrelevant. The results suggest that spatial memory facilitates search primarily when developed during task-relevant experience. More extensive experience may be required for memory for task-irrelevant context or incidental fixations on context objects to aid subsequent search.

[73] Developmental changes in autonomous observational and interactive feedback-based category learning, between childhood and adulthood

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As children start attending school they are more likely to face situations where they have to autonomously learn about novel object categories (e.g. by reading a picture book with descriptions of novel animals). Such an autonomous observational category learning (OCL) gradually complements interactive feedback-based category learning (FBCL) where a child hypothesize the nature of a novel object, act based on his prediction, and then receives feedback indicating the correctness of his prediction. Here we tested OCL and FBCL skills of elementary school children and adults. In both conditions participants performed complex rule-based categorization tasks that required associating novel objects with novel category-labels. We expected children to perform better in FBCL tasks than in OCL tasks, whereas adults to be skilled in both tasks. As hypothesized, in early-phase learning children performed better in FBCL tasks than in OCL tasks. Unexpectedly, adults performed best in OCL tasks. Early-phase FBCL performances in the two age groups were matched, but the OCL performances of adults were higher than those of children. Moreover, performances in post learning categorization tasks that did not require label recollection indicate that in FBCL tasks children were likely to directly learn the associations between an object and a category label, whereas in the OCL tasks they were likely to first learn which feature-dimensions are relevant. These findings shed light on developmental changes in cognitive control and learning mechanisms, and they are with implications for educational settings.

[74] Structural Remodeling of Adult Cortical Neurons during Motor Skill Learning

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Although prevalent, a critical understanding of experience- dependent plasticity in the adult mammalian brain remains elusive. In order to uncover the relative time course of experience- dependent synaptic changes that occur in the adult brain during learning, individual dendrites within the motor cortex of mice expressing YFP in a subset of layer V cortical pyramidal neurons were repeatedly imaged using *in vivo* two photon microscopy throughout novel motor skill learning. Adult mice (4.5 to 6mo) were trained for 15 days on the Pasta Matrix Task, and changes in spine turnover were tracked on days 3,6,10 and 15 respectively. Motor training induced a significant increase in formation followed by selective elimination of spines within motor cortex with no net change in spine density. Interestingly, only 3 days of training was sufficient to selectively stabilize newly formed spines. Finally, training induced a significantly greater spine density on apical branches of YFP-labeled layer V neurons within layer 2/3 of motor cortex as assessed histologically with confocal microscopy.

[75] Exponential capacity and robust error correction in Hopfield networks

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Noise is ubiquitous in the brain, limiting how networks of neurons represent and propagate information. Consequently, the brain must encode signals redundantly and recover them from degraded input. This redundancy restricts the representational capacity of networks. Current models of memory storage and error correction yield either weak increases in capacity with network size or poor robustness to noise, and the tradeoff between capacity and robustness is not well-understood.

We demonstrate that Hopfield networks, which are canonical models of neural computation, can combine high capacity with robust error correction: the networks can store exponentially-increasing numbers of states, and network dynamics corrects a fixed fraction of errors, regardless of network size.

To construct these networks, we map the decoding constraints of expander codes, a type of error-correcting code, onto the energy function of a Hopfield network. In general, neural network dynamics are too limited to decode the constraints of an error-correcting code. Expander codes are sparse bipartite graphs where few nodes co-occur in multiple constraints. This allows for simple, local decoding and a neural implementation.

Our results demonstrate that the structures of certain important error-correcting codes, wherein sparse constraints produce high-dimensional systems with large capacity and robustness, might apply to neural architectures.

[76] An attractor model of probabilistic localization

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During navigation, animals integrate a wide range of cues of varying reliability. Optimal integration of these cues requires an explicit coding of reliability whereas reliability-unaware strategies are typically costly and error-prone. How the brain computes a location estimate on the basis of sensory cues of varying reliability is still largely unknown.

In our model, an animal runs on a one-dimensional track and encounters landmarks at specific positions. Both path integration and perceived landmark location are corrupted by Gaussian noise. The optimal location estimator in this case is given by a Kalman filter. We search for a network implementation of the Kalman filter in terms of a bump attractor, where bump position encodes the location of the animal and bump height encodes the reliability.

For Gaussian tuning curves, the stable manifold of such an attractor is non-linear, and we require a proper non-linearity to project out deviations from the stable manifold. We show that an attractor with a divisive-normalization-type non-linearity can support Gaussian tuning curves of variable height. We then generalize the model to allow for a location update in response to a velocity signal, integration of landmark information and reliability decay in absence of landmarks. We finally show that our network performance is very close to that of the optimal Kalman filter.

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