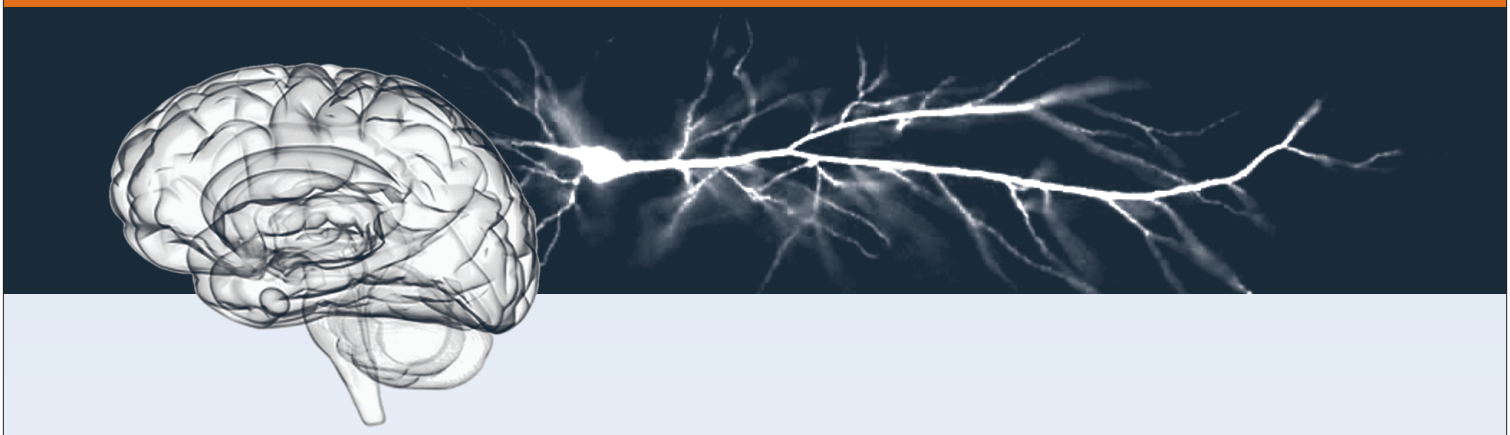
UT Austin Conference on Learning & Memory



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

APRIL 28-29, 2017

KEYNOTE SPEAKER
Larry Abbott
Columbia University

SESSION SPEAKERS
Michael Anderson, University of Cambridge
Chiara Cirelli, University of Wisconsin, Madison
Ron Davis, The Scripps Research Institute Florida
Loren Frank, University of California, San Francisco
Takao Hensch, Harvard University
Andrew King, University of Oxford
Lisa Marshall, University of Lübeck
Miguel Nicolelis, Duke University
Greg Quirk, University of Puerto Rico
Philip Sabes, University of California, San Francisco
Nanthia Suthana, University of California, Los Angeles
Gina Turrigiano, Brandeis University

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Dragana Rogulja, Harvard University
Nanthia Suthana, The University of California, Los Angeles
Moriel Zelikowsky, California Institute of Technology

Conference Schedule

All conference sessions will take place in the Texas Union Shirley Bird Perry Ballroom (3.202)
All meals will be served in the Texas Union Santa Rita Suite (3.502)

FRIDAY, APRIL 28, 2017

7:45-8:30am Breakfast

8:30-10:45 **Session 1: Brain Machine Interface**
Session Co-Chairs:
Mike Mauk, The University of Texas at Austin, Center for Learning & Memory
Nanthia Suthana, The University of California, Los Angeles, Departments of Psychiatry and Biobehavioral Science, Neurosurgery, Psychology

8:30-8:45 Nanthia Suthana, The University of California, Los Angeles
Introduction to the field

8:45-9:25 Miguel Nicolelis, Duke University
Departments of Neurobiology, Biomedical Engineering, Psychology, Neuroscience
"Brain-machine interfaces: from basic science to neurological rehabilitation"

9:25-10:05 Nanthia Suthana, The University of California, Los Angeles
Departments of Psychiatry and Biobehavioral Science, Neurosurgery, Psychology
"Optimization of intracranial stimulation for enhancement of episodic memory"

10:05-10:45 Philip Sabes, The University of California, San Francisco
Department of Physiology
"Toward high bandwidth, bi-directional neural interfaces"

10:45-12:45 **General Poster Session 1** – even numbered posters present

12:45-1:45 Lunch- Santa Rita Suite (3.502)

1:45-4:00pm **Session 2: Sleep & Memory**
Session Co-Chairs:
Laura Colgin, The University of Texas at Austin, Center for Learning & Memory
Dragana Rogulja, Harvard University, Department of Neurobiology

1:45-2:00 Dragana Rogulja, Harvard University
Introduction to the field

2:00-2:40 Chiara Cirelli, The University of Wisconsin, Madison
Department of Psychiatry
"Sleep and Synaptic Renormalization"

2:40-3:20 Loren Frank, The University of California, San Francisco
Department of Physiology, Howard Hughes Medical Institute
"Discrete memories from continuous experiences"

3:20-4:00 Lisa Marshall, University of Lübeck
Institute of Experimental and Clinical Pharmacology and Toxicology
"*Sleep spindles and efficiency of slow oscillatory-transcranial direct current stimulation (SO-tDCS)"*

4:00-4:20 Break

4:20-6:00 **Session 3: Poster Speakers**
Session Chair:
Dan Johnston, The University of Texas at Austin, Center for Learning & Memory

4:20-4:40 Chun-Ting Wu, Baylor College of Medicine
Department of Molecular and Cellular Biology
"Hippocampal awake replay in fear memory retrieval"

4:40-5:00 Tracy Wang, The University of Texas at Austin
Center for Learning and Memory
"Intentional forgetting via memory weakening in sensory cortex"

5:00-5:20 Crescent L. Combe, LSU Health Sciences Center
Department of Cell Biology and Anatomy
"Intrinsic mechanisms of frequency selectivity in CA1 pyramidal neurons"

5:20-5:40 Hector Zurita, University of Texas at San Antonio
Department of Biology
"A layer-specific corticofugal input to the mouse superior colliculus"

5:40-6:00 Hannah Monday, Albert Einstein College of Medicine
Department of Neuroscience
"*The role of presynaptic protein synthesis in long-term plasticity of GABA release"*

6:00-6:40 Cocktail Hour- Quadrangle Room (3.304)
- cash bar

6:40 Dinner- Santa Rita Suite (3.502)

SATURDAY, APRIL 29, 2017

7:45-8:30am Breakfast

8:30-10:45 **Session 4: Experience Dependent Plasticity**
Session Co-Chairs:
Nicholas Priebe & Nace Golding, The University of Texas at Austin, Center for Learning & Memory
Sandy Kuhlman, Carnegie Mellon University, Department of Biological Sciences

8:30-8:45 Sandy Kuhlman, Carnegie Mellon University
Introduction to the field

8:45-9:25 Takao Hensch, Harvard University
Department of Neurology, Center for Brain Science
"Parvalbumin, perineuronal nets and network plasticity"

9:25-10:05 Andrew King, University of Oxford
Department of Physiology, Anatomy and Genetics, The Wellcome Trust
'Learning to localize sound'

10:05-10:45 Gina Turrigiano, Brandeis University
Department of Biology
"*Self-tuning neurons and firing rate homeostasis"*

Conference Schedule

All conference sessions will take place in the Texas Union Shirley Bird Perry Ballroom (3.202)
All meals will be served in the Texas Union Santa Rita Suite (3.502)

SATURDAY, APRIL 29, 2017 *(CONTINUED)*

10:45-12:45	**General Poster Session 2** – odd numbered posters present
12:45-1:45	Lunch- Santa Rita Suite (3.502)
1:45-4:00	**Session 5: Memory Extinction & Forgetting** *Session Chairs:* Michael Drew, The University of Texas at Austin, Center for Learning & Memory Moriel Zelikowsky, California Institute of Technology, Department of Biology & Biological Engineering
1:45-2:00	Moriel Zelikowsky, California Institute of Technology *Introduction to the field*
2:00-2:40	Greg Quirk, University of Puerto Rico Departments of Psychiatry and Anatomy & Neurobiology *"Extinguishing learned fear vs. learned avoidance"*
2:40-3:20	Michael Anderson, University of Cambridge MRC Cognition and Brain Sciences Unit "*The Role of Hippocampal GABA in Enabling the Forgetting of Unwanted Memories"*
3:20-4:00	Ron Davis, The Scripps Research Institute Florida Department of Neuroscience *"Memory suppressor genes and active forgetting"*
4:00-4:20	Break
4:20-5:30	**Session 6: Keynote Speaker** Larry Abbott, Columbia University Department of Neuroscience, Physiology & Cellular Biophysics Center for Theoretical Neuroscience *"Recognition Memory in the Fly"*
5:30	Presentation of poster competition awards
5:40-6:30	Cocktail Hour- Quadrangle Room (3.304) - cash bar
6:30	Dinner- Santa Rita Suite (3.502)

Poster Abstracts

**Denotes the presenting author for each poster.*

[1] Muscarinic acetylcholine receptor antagonism decreases sign-tracking behavior in rats

Christopher J. Fitzpatrick[1]* and Jonathan D. Morrow[2]
[1]Neuroscience Graduate Program and [2]Department of Psychiatry, University of Michigan, Ann Arbor, MI
*cjfitzpa@umich.edu

Muscarinic acetylcholine receptors (mAChRs) facilitate dopamine (DA) transmission within the mesolimbic reward system. Our laboratory uses a Pavlovian conditioned approach (PCA) paradigm to investigate this system and addiction vulnerability in rats. Briefly, rats are repeatedly presented with a conditioned stimulus (CS; a lever) followed by the response-independent presentation of an unconditioned stimulus (US; a food pellet). Over multiple training sessions, two phenotypes can develop: sign-tracking (CS-directed behavior) and goal-tracking (US-directed behavior). Sign-trackers (STs) attribute incentive-motivational value to reward-related cues and are more vulnerable to addiction-like behaviors, such as cue-induced reinstatement of drug-seeking. In addition, sign-tracking behavior requires DA transmission within the mesolimbic reward system, therefore we hypothesized that mAChR antagonism would attenuate the acquisition and expression of sign-tracking behavior. In agreement with our hypothesis, scopolamine (0.3-3 mg/kg; i.p.), a nonselective mAChR antagonist, decreased the acquisition of sign-tracking behavior (and increased goal-tracking behavior) during nine daily PCA training sessions. Next, during an additional PCA training session, previously vehicle-treated rats received scopolamine (3 mg/kg), which reduced the expression of previously learned sign-tracking behavior in rats. Taken together, these results demonstrate that mAChRs modulate sign-tracking behavior and suggest that mAChR antagonism may be a viable strategy for addiction treatment.

[2] Context and Word Learning in Young Children

Katie Esterline[1]* and Rebecca Gómez[1]
[1]Department of Psychology, The University of Arizona, Tucson, AZ
*kesterline@email.arizona.edu

In adults, the hippocampus contributes to the formation of flexible memory representations. Importantly, the hippocampus develops protractedly and research suggests young children may instead be fusing objects to their background during word learning (Werchan & Gómez 2013) and object recognition (Edgin et al., 2014). Here, we test this possibility by manipulating context during a word-learning task. Children aged 2.5-, 3.5-, and 4-years received a brief, single exposure to two novel object-label pairs on a colored background. Immediately after training, children received four trials of a two-alternative forced choice test between the newly learned objects presented on the same or a different colored background than training. One sample t-tests were conducted to compare word learning to chance level performance (50%). As a group, 4-year-old children performed significantly greater than chance $t(51) = 3.28$, $p > .001$, however 2.5-year-olds did not $t(16) = 1.77$, $p = .10$. Interestingly, 3.5-year-old children tested in the same context condition performed better than chance $t(22) = 2.93$, $p > .001$, whereas 3.5-year-old children in the different context condition did not $t(24) = 0.84$, $p = .41$. Future research will further examine the impact of context on word learning in children and will test memory for single exposure word learning across delays.

[3] Development of memory for associations to similar versus distinct objects

Ji-Soo Kim* and Rebecca Gomez
University of Arizona, Tucson, AZ
*jkim4353@email.arizona.edu

The level of detail stored in memory is crucial for children's development because it allows for more computational flexibility. Children learned associations between specific puppets (Mr. Raccoon and Mr. Bunny) and highly similar or distinct objects. Children participated in a memory test for the associations after a 15 min delay. Children exhibited high memory for associations to distinct objects from 2.5 to 4.5 years of age (80%) that increased to 100% accuracy by age 5.5 years. Memory for the similar object associations was at chance at 3.5 and 4.5 years of age but increased significantly to 80% by age 4.5. The earlier development of retention for distinct versus similar object associations is expected given the protracted development of the trisynaptic pathway of the hippocampus and its ability to support pattern separation.

[4] The relationship between nap habits, gender and executive function in four-year olds

Ji-Soo Kim[1]*, Rebecca Gomez[1], YoonKyung Jeong[2]
[1]University of Arizona, Tucson, AZ, [2]Catholic University of Korea, Gyeonggi-do, South Korea
*jkim4353@email.arizona.edu

Most children discontinue daytime napping at the age of four. This study investigated the role of nap status and gender in executive functioning of four-year olds. Thirty-seven children living in the Gyeonggi-do area in South Korea participated in this study. A sleep diary kept by parents distinguished children's nap habits and their executive function was assessed using the Fish Flanker Task. Habitual nappers were better at shifting from the standard flanker to the reverse flanker. Habitual napper girls showed slower reaction time on incongruent trials during the standard flanker phase; however, they eventually reached the similar reaction time on the mixed phase. They also showed better performance on the incongruent trials on the reverse flanker during the mixed phase. Nighttime sleep duration was different depending on their nap status and gender; napper girls slept more at night than napper boys did. These results suggest that four-year olds may still receive a cognitive benefit from habitual naps, especially when they must shift between tasks. Total sleep duration may also be an important factor for executive function. Future studies need to take account of gender differences on sleep duration and its role of executive function.

[5] Low latency, Closed-Loop, Open-Source, Sharp-Wave Ripple Detection System

Shayok Dutta[1]* and Caleb Kemere[1,2]
[1]Electrical and Computer Engineering, Rice University; [2]Neuroscience, Baylor College of Medicine
*Shayok.Dutta@rice.edu

Sharp-wave ripples (SWRs) are coordinated bursts of ~150-250 Hz oscillations in the local field potential in hippocampal area CA1. At a network level, these transient events, lasting ~60-150 ms, co-occur with sequential spiking of pyramidal neurons in the area. SWRs and concomitant neural activity are associated with information propagation relating to memory consolidation, recall, and memory-guided decision making. Selective suppression of hippocampal activity upon online SWR detection has been established to cause impairments in memory consolidation and working memory. However, null results of cognitive impairments have also been reported with online disruption opening up questions about detection efficacy and the extent of SWR contribution to the learning or decision making processes. Here, we evaluate performance and discuss the capabilities of our ripple-detection system developed to interface with an open-source software platform (Trodes) and two hardware platforms (OpenEphys and SpikeGadgets). We show that our results, ~35-60 ms detection latencies with ~2 ms closed-loop latency while detecting >95% of events with <5 false detections per minute, are dependent upon both algorithmic tradeoffs and acquisition hardware. Finally, we discuss the potential limitations of online ripple disruptions. Overall, we anticipate our modular, open-source, real-time system will facilitate causal closed-loop neuroscience experiments.

** [6] Hippocampal awake replay in fear memory retrieval

Chun-Ting Wu[1,2]•, Daniel Haggerty[2], Caleb Kemere[4], Daoyun Ji[2,3]
[1]Neuroscience PhD Program, [2]Department of Molecular and Cellular Biology, and [3]Department of Neuroscience, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030. [4]Department of Electrical and Computer Engineering, Rice University, 6100 Main St, Houston TX 77005.
*chuntinw@bcm.edu

Hippocampal place cells are key to episodic memories. How these cells participate in memory retrieval remains unclear. Here, we designed a novel, linear inhibitory avoidance task to study the place cell activities underlying fear memory retrieval. In the task, the animals were first freely exploring on a track. After receiving foot-shocks at a shock zone (SZ) on the track, the animals acquired fear memory and displayed memory retrieval behavior: avoidance of the SZ. By recording from a population of place cells in the hippocampus, we found that place cells encoding the SZ were reactivated during the avoidance behavior, despite the fact that the animals did not enter the SZ. This reactivation occurred in ripple-associated awake replay of place cell sequences encoding the paths from the animal's current positions to the SZ, but not in place cell sequences within individual cycles of theta oscillation, suggesting that ripple oscillations and awake replay are involved in avoidance behavior and memory retrieval. In addition, we found that only the place cells encoding the SZ were more likely to be reactivated together in replay after the shocks, but not the remaining place cells, indicating that shock may induce a differential change in synaptic connections between different populations of place cells.

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

[7] Regulating the transport of active zone proteins

Kara R. Barber^@*, Julia Tanquary&, Keegan Bush^@%, Amanda Shaw^@%, Michael Woodson#, Michael Sherman# and Yogesh P. Wairkar^@*
Department of Neurology, University of Texas Medical Branch, Galveston TX 77555
^ George and Cynthia Mitchell Center for Neurodegenerative Diseases
@ Neuroscience Graduate Program
& Summer Undergraduate Research Program, UTMB
 # Sealy Center for Structural Biology, UTMB
*krbarber@utmb.edu

Processes that regulate synapse development and maintenance play a critical role in learning and memory formation. Active zones are presynaptic specializations directly apposed from postsynaptic densities. One process to maintain active zone integrity is the transport of active zone proteins via axonal transport. Our data suggests that overexpression of Par-1/MARK kinase, a protein whose misregulation has been implicated in Autism spectrum disorders (ASDs) and neurodegenerative disorders, lead to a specific block in the transport of an active zone protein component- Bruchpilot within axons. Consistent with a block in axonal transport, we find a decrease in number of active zones and reduced neurotransmission in flies overexpressing Par-1 kinase. Interestingly, we find that Par-1 acts independently of Tau-one of the most well studied substrates of Par-1, revealing a presynaptic function for Par-1 that is independent of Tau. Thus, our study suggests that the transport of active zone components is tightly regulated through distinct mechanisms.

[8] H2O2-induced oxidative stress stimulates alterations in the shape and density of dendritic spines

Thanh Lam[1]*, Joseph Duman[2], Lawrence Bronk[1], Connie Weng[1],
Wei Zhou[1] and David Grosshans[1]
[1]Departments of Radiation Oncology and Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [2]Department of Neuroscience, Baylor College of Medicine, Houston, Texas
*TTLam@mdanderson.org

In the mammalian brain dendritic spines house excitatory synapses, the sites at which neurons receive the signals from other neurons. Synaptic activity occurring at dendritic spines may provide the basis of memory. Differential spine structure and number may represent changes in synaptic strength and thus learning and memory. Our previous experiments have shown rapid and unexptected changes in the structure of spines following irradiation of neuronal cultures. We hypothesized that such changes are mediated by ionizing radiation-induced oxidative stress. In the current study we sought to study the effects of oxidative stress, using hydrogen peroxide, on the morphology and density of the dendritic spine. Our data shows that the hydrogen peroxide not only changes the density but also the shape of the spines. We also evaluated the protective effects of memantine, an NMDA-antagonist which may prevent cognitive dysfunction in patients receiving whole-brain radiotherapy, as it relates to hydrogen peroxide induce oxidative stress. Future studies will directly interrogate oxidative stress following radiation exposure using real time imaging.

[9] Accessing long-lasting extinction-resistant fear in rats using the M-Maze

Rimenez R. Souza[1]*, Nicole M. Robertson[1], David T. Pruit[1], Seth A. Hays[1,3], Robert L. Rennaker[1,2,3], Michael P. Kilgard[1,2,3], Christa K. McIntyre[1,2].
[1]Texas Biomedical Device Center, [2]School of Behavioral Sciences, [3]Department of Bioengineering. The University of Texas at Dallas, Richardson-TX.
*rxr166230@utdallas.edu

Posttraumatic stress disorder (PTSD) is a condition that involves long-lasting symptoms of exaggerated responses to reminders of a trauma. Several models of PTSD use Auditory Fear Conditioning (AFC) and track the reduction of freezing as a measure of extinction. However, impaired extinction is less often assessed by cessation of goal directed behaviors. Here we submitted rats to a 4-day variable AFC protocol, combining of 100% delayed, unpredictable delayed, and short and long trace fear conditioning. Conditioned responses (CR) were assessed using an M-shaped maze that automatically measured transit time between two pellet-rewarding nosepokes. Time to transit from one nosepoke to the other was 20 times greater when rats were exposed to the conditioned stimulus after AFC, indicating that the reminder disrupted normal goal directed behavior. Extinction of CR was impaired in rats exposed to the combined AFC protocol, when given weekly unreinforced exposures to the conditioned sound. Significant enhance in transit time was observed for up to 10 weeks. Spontaneous recovery and renewal were observed 4 weeks after completion of 10 weekly extinction sessions. Our findings suggest that persistent fear can be produced by varying AFC parameters, and support the use of goal directed behavior to investigate resistant fear extinction.

[10] Effects of vagus nerve stimulation on a rat model of PTSD

Lindsey J. Noble*, Venkat B. Meruva, Ashleigh Chuah, Kathleen A. Callahan,
Christa K. McIntyre
The University of Texas at Dallas
*lindsey.noble@utdallas.edu

Posttraumatic stress disorder (PTSD) can develop following a traumatic event. Symptoms of PTSD include hypervigilance, avoidance, and increased anxiety. Exposure therapy is a form of cognitive behavioral therapy that is commonly used to treat these symptoms. During exposure therapy, patients are repeatedly exposed to cues that remind them of the trauma until they learn healthier responses to those cues. However, PTSD patients show impairments in extinction learning, which may increase nonresponse rates and dropout rates. Adjuncts to exposure therapy could be utilized to increase the effectiveness by promoting successful extinction learning, VNS shows promise as an adjunct for exposure therapy because previous research indicates that it enhances memory consolidation in rats and in humans. We recently found that pairing VNS with extinction training enhance extinction and protect against relapse in the single prolonged stressor (SPS) rat model of PTSD that shows resistance to extinction. We also found that one week following VNS-paired extinction, symptoms of PTSD seen in the SPS model including: generalized anxiety, startle, avoidance, and social deficits were reversed. Current studies aim to elucidate the mechanism by which VNS enhances extinction, and alters PTSD symptoms that are not related to specific cues one week later.

[11] Calcium mimics the effects of acamprosate on cognitive deficits and synaptic function in chronic alcohol-exposed mice

Patrick Melugin* Fei Wu, Aarron Phensy, Sai Charan Chilumula, Hannah Fang,
Amogh Singhal, Rachel Weber, Sven Kroener
School of Behavioral and Brain Science, The University of Texas at Dallas
*prm160230@utdallas.edu

Drugs of abuse diminish the ability of the prefrontal cortex (PFC) to exert supervisory control over impulsive behaviors related to drug-seeking and relapse. Chronic alcohol exposure alters glutamatergic synaptic transmission, and specifically the upregulation of N-methyl-D-aspartate (NMDA) receptors in PFC pyramidal neurons may contribute to the loss of normal PFC function. Here we used operant self-administration and chronic intermittent ethanol (CIE) exposure in mice to assess alcohol-induced deficits across a range of behaviors, and investigated whether acamprosate, the leading medication approved for the maintenance of abstinence, can reverse these deficits. Further, we tested whether calcium, the active moiety in acamprosate, is sufficient to achieve the same effects. Our results indicate that both CIE and operant self-administration of alcohol impaired cognitive flexibility in an attentional set-shifting task. CIE-exposed animals also showed deficits in novel object recognition memory, but not spontaneous alternation, or social recognition memory. Alcohol self-administration also lead to changes in NMDAR function, similar to what we have previously observed in CIE-treated animals. Further, alcohol-induced changes in behavior and synaptic transmission were reversed by subchronic (3 days) treatment with either acamprosate or $CaCl_2$. Our results support the notion that acamprosate produces anti-relapse effects through its calcium moiety and suggest that inhibitory regulation of drug intake after withdrawal is related to improved cognitive function.

[12] The Development of a Viral Mediated CRISPR/Cas9 System with Doxycycline Dependent gRNA Expression for Inducible In vivo Genome Editing in the Amygdala

Christopher A. de Solis*, Anthony Ho, Roopashri Holehonnur and Jonathan E. Ploski
Department of Behavioral and Brain Sciences, University of Texas at Dallas
*cad130330@utdallas.edu

The RNA-guided Cas9 nuclease, from the type II prokaryotic Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR) adaptive immune system, has been adapted and utilized by scientists to edit the genomes of eukaryotic cells. Here, we report the development of a viral mediated CRISPR/Cas9 system that can be rendered inducible utilizing doxycycline (Dox) and can be delivered to cells in vitro and in vivo utilizing adeno-associated virus (AAV). Specifically, we developed an inducible gRNA (gRNAi) AAV vector that is designed to express the gRNA from a H1/TO promoter. This AAV vector is also designed to express the Tet repressor (TetR) to regulate the expression of the gRNAi in a Dox dependent manner. We show that H1/TO promoters of varying length and a U6/TO promoter can edit DNA with similar efficiency in vitro, in a Dox dependent manner. We also demonstrate that our inducible gRNAi vector can be used to edit the genomes of neurons in vivo within the mouse brain in a Dox dependent manner. Genome editing can be induced in vivo with this system by supplying animals Dox containing food for as little as 1 day. This system might be cross compatible with many existing S. pyogenes Cas9 systems (i.e., Cas9 mouse, CRISPRi, etc.), and therefore it likely can be used to render these systems inducible as well.

[13] Age Matters: The Role of KIBRA in Age-Related Changes in Synaptic Function

Matthew L. Mendoza[1,2]* and Lenora J. Volk[2,3]
[1]Neuroscience Graduate Program, UT Southwestern Medical Center, Dallas, TX, [2]Department of Neuroscience, UT Southwestern Medical Center, Dallas, TX, [3]Department of Psychiatry UT Southwestern Medical Center, Dallas, TX
*Matthew.Mendoza@utsouthwestern.edu

Our capacity to learn and remember changes dynamically throughout our lifespan. However, the molecular and synaptic basis for age-related changes in cognition remain poorly understood. Synaptic plasticity is a key cellular mechanism underlying cognitive functions such as learning and memory. Dynamic AMPA receptor (AMPAR) trafficking is critical for many forms of synaptic plasticity. AMPAR trafficking is regulated by multiple proteins, including the product of the human memory-related gene KIBRA. Interestingly, though KIBRA is expressed throughout development, genetic deletion of KIBRA leads to synaptic and cognitive impairments selectively in adult mice. Whether the loss of KIBRA progressively decreases synaptic function, or adult synapses are selectively vulnerability to a loss of KIBRA remains to be addressed. To determine if adult neurons are selectively vulnerable to a loss of KIBRA, we generated inducible knockout mice by breeding novel Kibra $^{floxed/floxed}$ mice with CaMKII Cre^{ERT2} mice. We find that reducing KIBRA expression selectively in excitatory forebrain neurons of adult mice reduces long-term potentiation (LTP). We observed no difference in basal synaptic transmission. These results support the idea that adult neurons are selectively vulnerable to loss of KIBRA. Ongoing studies will address associated cognitive consequences and synaptic mechanisms responsible for impaired plasticity in these mice.

[14] Automated quantitative analysis of high resolution fluorescent images of neuronal network cultures

C. Kayasandik[1]*, P. Negi[2], M. Papadakis[1], F Laezza[3], D. Labate[1]
[1]*Department of Mathematics, University of Houston, Houston, Texas*
[2]*Dept. of Engineering and Computer Science, University of Denver, Denver, Colorado*
[3]*Dept. of Pharmacology and Toxicology, Univ. of TX Medical Branch, Galveston, TX*
*kayasa89@math.uh.edu

Fluorescence confocal microscopy is a fundamental tool for molecular studies of neurons in culture and tissue. Combined with immunolabeling, fluorescence-based multispectral imaging is used to probe for localization and distribution of molecules at the single cell level resolution over cellular networks. Yet, despite remarkable advances in imaging acquisition, most image analysis tools still require a significant manual or semi-automated intensity-based thresholding for computing image masks and selecting region of interests making large-scale data processing inefficient, biased and poorly accurate. To overcome these limitations, we introduce an image processing pipeline targeted to fluorescence images of neuronal cultures and aimed at automatically extracting single-neuron trees from images of neuronal networks where neurites from different cells may overlap or run very close to each other. Our method applies directional multiscale representations for automated segmentation and soma detection and includes a novel tracing algorithm that utilizes sensitive geometric descriptors for accurate tracing and separation of neuronal trees. Through this framework, we can quantify the spatial distribution of specific analytes at the subcellular level from multispectral confocal images of neuronal networks in a fully automated mode. Fluorescence intensity and spatial distribution of proteins of interest are computed relative to the tree structure and automatically assigned to specific subcellular compartments of individual neurons. By enabling automated processing of multispectral fluorescence images with high accuracy, this framework advances state-of-the-art in image processing tailored to the needs of high-content screening facilitating biomarkers and new drug target discoveries.

[15] Optogenetic Suppression of mPFC Terminals and Cell Bodies in Nucleus Reuniens during Select Phases of a Spatial Working Memory Task

Maisson, D. J-N*. and Griffin, A. L.
Department of Psychological and Brain Sciences, University of Delaware
*dmaisson@psych.udel.edu

Our lab has shown that the nucleus Reuniens (Re), part of the ventral midline thalamus that is bi-directionally connected with the medial prefrontal cortex (mPFC) and the hippocampus, is critical for spatial working memory (SWM) and prefrontal-hippocampal oscillatory synchrony. However, questions remain about the distinct role that Re plays in SWM, including the degree to which components of the mPFC-Re-hippocampal circuit contribute to encoding and retrieval. The present study focused on the mPFC-Re pathway using optogenetic-silencing techniques to gain precise temporal control of the activity in this pathway during the sample (encoding) and choice (retrieval) phase of a delayed-nonmatch-to-position task. An AAV encoding the neural silencing opsin, ArchT, was delivered either into mPFC or the Re in separate groups of rats. Optical fibers, implanted into Re, allowed for silencing either of mPFC projections to Re or Re cell bodies during select trial phases on separate days. Our results show that mPFC-Re terminal suppression induced a deficit exclusively on choice-phase sessions. Conversely, Re suppression selectively impaired choice accuracy on sample-phase sessions. These results suggest that the retrieval of information to guide goal-directed behavior is dependent upon proper mPFC-Re communication, but that Re contributes to the initial encoding of spatial information.

[16] The role of cortico-thalamic circuitry in cocaine-seeking behavior

Kuhn BN*, Klumpner MS, & Flagel SB
University of Michigan, Neuroscience Graduate Program
*bnkuhn@umich.edu

Cues associated with reward can motivate maladaptive behaviors, such as drug addiction. For example, relapse often occurs following exposure to cues previously associated with the drug-taking experience. One brain region that has recently been recognized for its role in cue-induced drug-seeking behaviors is the paraventricular nucleus of the thalamus (PVT). Work from our lab suggests that the PVT may play an important role in mediating individual differences in the propensity for relapse. Here we used a dual-vector DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technique to specifically examine the effects of inhibiting afferents to the PVT from the prelimbic cortex (PrL), another brain region that has been implicated in drug-seeking behavior. Rats underwent 2 weeks of cocaine self-administration followed by 2 weeks of abstinence and then extinction. Prior to the test for cocaine-primed and cue-induced reinstatement, rats received an injection of vehicle or clozapine-N-oxide (CNO) to activate the inhibitory G_i-DREADD. CNO-induced inhibition of the PrL-PVT pathway decreased cocaine-seeking behavior during cue-induced reinstatement, but had no effect during cocaine-primed reinstatement. Thus, the PrL-PVT pathway appears to play a specific role in cue-mediated drug-seeking behavior.

[17] Forward genetic screening for fear conditioning mutants in mouse

Pin Xu[1]*, Kazuhiro Shimomura[2], Kimberley Brown[1], Vivek Kumar[3],
Joseph S. Takahashi[1,4]
[1]Department of Neuroscience, [4]Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX.
[2]Department of Neurology, Northwestern University, Feinberg School of Medicine, Chicago, IL
[3]The Jackson Laboratory, Bar Harbor, Maine.
*pin.xu@utsouthwestern.edu

Learning and memory are two fundamental cognitive processes and understanding the basic mechanisms has been a main goal in the field of neuroscience. However, the molecular foundation as well as the neural substrate underlying these biological events remain poorly understood.

A wide variety of genetic and behavioral paradigms have been employed to study learning and memory in several model organisms. In mice, reverse genetics, by targeting specific genes and pathways, has been useful for testing existing hypotheses. In comparison, forward genetic approaches that utilize unbiased mutagenesis throughout the genome, provide opportunities to identify novel regulators. Although this strategy has contributed to several breakthroughs in studies of circadian biology and drug addiction, it has not been effectively used to study learning and memory in mice.

Here, we report a forward genetic approach to identify novel regulators of learning and memory in mice. To this end, we used N-nitroso-N-ethylurea (ENU) mutagenesis to introduce mutations in the genome of C57BL/6J mice. The mutagenized males were bred for three generations to produce G3 mice for behavioral screening of both dominant and recessive mutations. We adopted a fear conditioning test that allowed for robust and high-throughput screening of mutants. Those that manifested either stronger or weaker fear responses (at least one standard deviation away from the mean) were selected for subsequent mapping studies. We employed a combination of quantitative trait loci (QTL) analysis and exome sequencing to identify causative mutations in multiple putants. With these approaches, we obtained and analyzed several putative mutant lines with either high or low freezing scores. Among low freezing lines, we successfully mapped one QTL on chr7. Taken together, our studies demonstrate that mouse forward genetics can serve as a powerful means to identify novel regulators of learning and memory.

** [18] Intrinsic mechanisms of frequency selectivity in CA1 pyramidal neurons

Crescent L. Combe[1]*, Carmen C. Canavier[1,2] and Sonia Gasparini[1,2]
Neuroscience Center[1] and Department of Cell Biology and Anatomy[2], LSU Health Sciences Center, New Orleans, LA
*ccomb1@lsuhsc.edu

Gamma oscillations are hypothesized to play a role in learning and memory. Two frequency bands, slow (25-50 Hz) and fast (65-100 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. We used a combination of computational modeling and in vitro electrophysiology in hippocampal slices to test the mechanisms underlying the hypothesized selectivity of Schaffer collateral synapses for slow gamma frequency input. Model predictions were that CA1 neurons behave as low-pass filters in response to Schaffer collateral activation due to a combination of intrinsic mechanisms. This was borne out in the experimental results: Electrical stimulation of the Schaffer collateral fibers at either slow gamma (40 Hz) or fast gamma (70 or 100 Hz) 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 or the broad-spectrum cholinergic agonist carbachol, and enhanced by blocking A-type K^+ channels with barium chloride. These results suggest that intrinsic properties of CA1 pyramidal neurons influence the frequencies at which CA1 synchronizes with activity in CA3, and point to cholinergic activation as one candidate that may modulate this behavior under different physiological conditions.

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

[19] Perisomatic SK channels control activity in neurons of the thalamic reticular nucleus (TRN)

Frederik Seibt* and Michael Beierlein
Department of Neurobiology & Anatomy, McGovern Medical School, Houston, TX
*Frederik.M.Seibt@uth.tmc.edu

GABAergic neurons of the thalamic reticular nucleus (TRN) are critically involved in controlling sensory information flow. TRN neurons express high densities of small-conductance calcium activated potassium (SK) channels, whose recruitment by calcium influx through dendritically expressed low-threshold T-type calcium channels underlies oscillatory burst firing during slow-wave sleep. However, we know little about the calcium sources leading to SK channel activation in tonic firing mode associated with waking states. Recording in thalamocortical slices derived from P13-17 mice, we found that single action potentials generated an SK channel-dependent afterhyperpolarization (AHP) which was blocked by specific antagonists for P/Q and N-type calcium channels, while antagonists for either R- or L-type calcium channels did not significantly influence AHP amplitudes. Furthermore, dialyzing neurons with EGTA had no effect on the AHP amplitude, suggesting that P/Q and N-type calcium channels form functional nanodomains with SK channels. While both action potentials and cholinergic synaptic inputs led to the activation of T-type calcium channels, we found that in tonic firing mode the resulting calcium increases were not sufficient to recruit SK channels.

Taken together, our results suggest that SK channels form distinct functional interactions with different classes of voltage-gated calcium channels, showing tight coupling to both P/Q and N-type calcium channels, but only loose and state-dependent coupling to T-type channels.

[20] Overexpression of the vesicular acetylcholine transporter alters short-term synaptic plasticity at cholinergic synapses

J. O'Malley[1, 2]*, R. Dasgupta[1, 2], F. Seibt[1], & M. Beierlein[1, 2]
[1]Department of Neurobiology & Anatomy, McGovern Medical School at UTHealth, and [2]University of Texas Graduate School of Biomedical Sciences, Houston, TX
*John.OMalley@uth.tmc.edu

Acetylcholine (ACh) signaling in the mammalian brain controls diverse cognitive functions, including learning, memory, and attention. At cholinergic synapses, ACh loading into vesicles is mediated by the actions of the vesicular acetylcholine transporter (VAChT). While previous studies have shown that overexpression of VAChT can lead to distinct behavioral deficits in learning and memory, it remains unclear how alterations in VAChT levels influence cholinergic synaptic signaling and plasticity. We have addressed this question by isolating cholinergic synaptic inputs from the basal forebrain and quantifying short-term plasticity of nicotinic receptor mediated responses in neurons of the thalamic reticular nucleus (TRN), using brain slices derived from ChAT-ChR2-EYFP (ChR2) and B6eGFPChAT transgenic mice which overexpress VAChT. We found that both transgenic lines displayed reduced short-term synaptic depression compared to synapses in WT animals. Surprisingly, for ChR2 mice reduced short-term depression was due to a lack of presynaptic muscarinic ACh receptor (mAChR)-mediated autoinhibition, even though functional mAChRs are expressed presynaptically. With autoinhibition blocked pharmacologically, B6eGFPChAT mice showed reduced depression as compared to WT, possibly due to differences in release probability. Our findings suggest that for different mouse models overexpression of VAChT can lead to distinct alterations in cholinergic synaptic plasticity.

[21] Cholinergic control of cortical circuit dynamics

Rajan Dasgupta[1,2]*, Frederik M. Seibt[1] and Michael Beierlein[1,2]
[1]Department of Neurobiology & Anatomy, McGovern Medical School at UTHealth and [2]University of Texas Graduate School of Biomedical Sciences, Houston, TX
*Rajan.Dasgupta@uth.tmc.edu

Cholinergic neurons of the basal forebrain (BF) form extensive projections to neocortex and are critically involved in mediating numerous cognitive processes. To understand how acetylcholine (ACh) shapes cortical computations, it is important to gain a better understanding of the underlying cellular and circuit mechanisms. However, how synaptically released ACh influences cellular targets and ultimately controls cortical circuit dynamics remains poorly understood. We addressed this question using a combination of in vitro electrophysiology and optogenetics in mouse somatosensory (barrel) cortex. We found that the activation of BF cholinergic afferents led to strong reduction of evoked cortical activity, with nicotinic receptors (nAChRs) mediating transient suppression, and muscarinic receptors (mAChRs) mediating prolonged suppression. Postsynaptic cholinergic responses were prominent in layer 4 and were primarily mediated by mAChRs, leading to long-lasting IPSCs in excitatory neurons and EPSCs in regular-spiking interneurons. In agreement, cholinergic suppression of cortical activity in the isolated layers 4-6 was entirely dependent on mAChR activation. In contrast, cholinergic responses in supragranular layers were predominantly mediated by nAChRs expressed by GABAergic interneurons. Taken together, our results indicate that cholinergic control of cortical network dynamics occurs over different time scales and is mediated by nAChRs and mAChRs-dependent mechanisms expressed in distinct cortical layers and cell types.

[22] Entorhinal–CA3 dual-input control of spike timing in the hippocampus by theta-gamma coupling

Fernandez-Ruiz, A.[1]*, Oliva, A.[1], Nagy, G. A.[3], Maurer, A. P.[4,5], Berényi, A.[6] and Buzsáki, G.[1,2]
[1]New York University Neuroscience Institute, New York University, New York, NY.
[2]Center for Neural Science, New York University, New York, NY. [3]Institute of Experimental Medicine of the Hungarian Academy of Sciences, Budapest. Hungary.
[4]Department of Neuroscience, McKnight Brain Institute, College of Medicine, University of Florida, Gainesville, FL.
\[5]Department of Biomedical Engineering, University of Florida, Gainesville, FL. [6]Department of Physiology, University of Szeged, Hungary
*antferrui@gmail.com

Theta-gamma phase coupling and spike timing within theta oscillations are prominent features of the hippocampus and are often related to navigation and memory. However, the mechanisms that give rise to these relationships are not well understood. Using high spatial resolution electrophysiology, we investigated the influence of CA3 and entorhinal inputs on the timing of CA1 neurons. The theta phase preference and excitatory strength of the afferent CA3 and entorhinal inputs effectively timed the principal neuron activity as well as regulated distinct CA1 interneuron populations. Place field activity of CA1 neurons is initiated by the EC3 input at the peak of theta and associated with a $gamma_M$ burst in str. LM. As the animal moves across the field, EC3 drive decreases and is supplemented by an increasing CA3 drive, as reflected by increasing power of $gamma_S$ in str. rad. Feedback potentiation of distal dendritic inhibition by CA1 place cells attenuates the EC3 input. Likewise, depression of proximal dendritic and perisomatic inhibition facilitates the impact of CA3. These combined upstream excitatory and local inhibitory effects result in a monotonic shift of spikes from the late to earlier phases of theta waves as the rat passes through the place field. These data support a general mechanism for several physiological phenomena, including laminar profile of theta oscillations, brain state- and task-dependent theta phase preference of spikes, spike theta phase-position correlations of place cells in different hippocampal subregions and sublayers. Thus, upstream inputs interact with local mechanisms to determine theta phase timing of hippocampal neurons to support memory and spatial navigation.

** [23] A layer-specific corticofugal input to the mouse superior colliculus

Hector Zurita*, Crystal Rock, Alfonso junior Apicella
Department of Biology, Neuroscience Institute, University of Texas at San Antonio, San Antonio, Texas
*hectorzurape@hotmail.com

In the auditory cortex (AC), corticofugal projections arise from each level of the auditory system and are considered to provide feedback "loops" important to modulate the flow of ascending information. It is well established that the cortex can modulate the response of neurons in the superior colliculus (SC) via descending corticofugal projections. However, little is known about the relative contribution of different pyramidal neurons to these projections in the SC. We addressed this question by taking advantage of retrograde neuronal tracing to directly examine the laminar distribution and electrophysiological properties of pyramidal neurons projecting from the AC to the SC of the mouse brain. Here we show that layer 5 cortico-superior-collicular pyramidal neurons act as bandpass filters, resonating with a broad peak at ~3 Hz, whereas layer 6 neurons act as low-pass filters. The dissimilar subthreshold properties of layer 5 and layer 6 cortico-superior-collicular pyramidal neurons can be described by differences in the hyperpolarization-activated cyclic nucleotide gated cation h-current (I_h). I_h also reduced the summation of short trains of artificial excitatory postsynaptic potentials injected at the soma of layer 5, but not layer 6, cortico-superior-collicular pyramidal neurons, indicating a differential dampening effect of I_h onto these neurons. Our results establish two layer-specific sub-classes of projection neurons to the SC that may serve separate functions in cortico-collicular circuits and that may be engaged differently during defense-like and/or orienting behavior.

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

[24] An Inhibitory Corticostriatal Pathway

Rock, C.*, Zurita, H., Wilson, C.J., Apicella, A.j.
University of Texas at San Antonio (UTSA)
*crystal.rock@utsa.edu

Striatal neuronal activity has been shown to be involved in movement, learning, and goal-directed behavior, therefore it is crucial to understand the corticostriatal connectivity pattern and dynamics that shape the flow of information in the striatum. It has been well established that cortical neurons regulate the activity of spiny projection neurons (SPNs) in the striatum through long-range glutamatergic/excitatory projections, while inhibition is thought to be mediated by local feed-forward and feed-back circuits. Here we demonstrate that the dorsal striatum also receives long-range GABAergic projections from the cortex. By taking advantage of optogenetic methods we were able to directly examine the functional effects of cortical GABAergic inputs to SPNs from the mouse auditory and motor cortex. We found that the cortex, via corticostriatal somatostatin neurons (CS-SOM), has a direct inhibitory influence on the output of the striatal SPNs. Our results describe a previously unknown corticostriatal long-range inhibitory circuit (CS-SOM inhibitory projections → striatal SPNs) underlying the control of spike timing/generation in SPNs and attributes a specific function to a genetically defined type of cortical neuron in corticostriatal communication.

** [25] The role of presynaptic protein synthesis in long-term plasticity of GABA release

Monday HR[1]*, Younts TJ[1,2], Dudok B[3], Klein ME[1], Jordan BA[1],
Katona I[3], Castillo PE[1]
[1]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, New York, NY 10461, USA. [2]Department of Neuroscience, Physiology and Pharmacology, University College London, Gower Street, London WC1E 6BT, UK
[3]Momentum Laboratory of Molecular Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest 1051, Hungary
*monday@mail.einstein.yu.edu

The ability of synapses to undergo changes in strength underlies information storage in the brain. The necessity of local postsynaptic protein synthesis in synaptic plasticity is well-established, but a role for presynaptic protein synthesis in the adult mammalian brain remains contentious. Using electrophysiology, fluorescent noncanonical amino acid tagging (FUNCAT) to visualize newly synthesized proteins, and super-resolution microscopy, we tested whether endocannabinoid-mediated long-term depression of inhibitory transmission (eCB-iLTD) requires presynaptic protein synthesis. We found that eCB-iLTD is blocked by inhibiting protein synthesis in the presynaptic neuron. Moreover, somatic translation and trafficking along microtubules are not required for iLTD, suggesting that translation in the presynaptic neuron occurs locally. Importantly, super-resolution microscopy revealed ribosomes in adult cannabinoid-1 receptor (CB_1R)-positive interneuron terminals. Using FUNCAT in hippocampal cultures, we discovered that activation of the CB_1R promotes protein synthesis. To determine the signaling pathways involved downstream of the CB_1R, we used pharmacology and electrophysiology. We found that eCB-iLTD involves signaling via the Akt-GSK3-mTOR pathway, but unexpectedly, PI3K and $G_{\beta\gamma}$ are not required. Thus, we provide direct evidence that local presynaptic translation is a critical mechanism for a form of long-term presynaptic plasticity in the mature mammalian brain. Furthermore, the identification of key players in a signaling pathway linking sustained activation of the CB_1R to the translation machinery may be important for developing therapies for diseases characterized by disrupted eCB-mediated plasticity, including schizophrenia, autism, and addiction.

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

[26] Molecular basis of activity-dependent bidirectional NMDA receptor plasticity

Stefano Lutzu[1]*, Karina Alviña[1] and Pablo E. Castillo[1]
Albert Einstein College of Medicine[1], Dominic P. Purpura Department of Neuroscience, Bronx, NY,10461 USA.
stefano.lutzu2@phd.einstein.yu.edu

NMDA receptors (NMDARs) are key mediators of synaptic plasticity and learning and memory. NMDARs have been shown to undergo activity-dependent bidirectional plasticity (i.e. NMDAR-LTP/LTD) at many central synapses but the molecular mechanisms underlying NMDAR plasticity remain poorly understood. In the hippocampus, physiologically-relevant coincident pre/postsynaptic burst activity induces robust bidirectional NMDAR plasticity at the mossy fiber-to-CA3 pyramidal cell (MF-CA3) synapse. While both NMDAR-LTP and LTD require postsynaptic calcium rise, the calcium sources differ, raising the possibility that distinct calcium dynamics determines the sign of NMDAR plasticity. To address this possibility, we combined 2 photon laser microscopy and electrophysiology in rat hippocampal slices to measure postsynaptic calcium transients (CaTs) during the induction of NMDAR plasticity. Specifically, we measured CaTs at thorny excrescences (TEs), the postsynaptic target of MFs onto CA3 pyramidal cells. CaTs were significantly larger during the induction of NMDAR-LTP than NMDAR-LTD, and this difference was also observed by 2 photon uncaging glutamate onto TEs, a manipulation that mimics glutamate release. Remarkably, the difference between NMDAR LTP and LTD-associated CaTs was abolished by pharmacological blockade of specific postsynaptic calcium sources. Thus, distinct postsynaptic calcium dynamics likely underlies the sign of NMDAR plasticity.

Supported by NIH R01 grants MH081935 and DA017392

[27] Presynaptic NMDA receptors contribute to short-term plasticity at mossy fiber-CA3 synapses

Pablo J. Lituma[1]*, Hyuangbae Kwon[1], Rafael Lujan[2], Pablo E. Castillo[1]
[1]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY 10461, USA. [2]Instituto de Investigacion en Discapacidades Neurologicas (IDINE), University of Castilla La Mancha, Spain
*pablo.lituma@phd.einstein.yu.edu

Neurotransmitter release is a highly regulated process that exquisitely controls the strength of neuronal communication. Presynaptic Ca^{2+} rise is a key component of this process not only for triggering synchronous, action-potential driven transmitter release, but also for facilitating neurotransmitter release during repetitive presynaptic activity. Hippocampal mossy fiber synapses, which carry the main excitatory input to the hippocampus proper, express uniquely robust activity-dependent facilitation. The molecular mechanisms underlying this form of short-term plasticity remain poorly understood, although glutamate autoreceptors may participate. Presynaptic NMDA receptors (preNMDARs) at the mossy fiber bouton have been reported more than three decades ago (Siegel et. al, PNAS, 1994) but their role remains unexplored. Here we test the hypothesis that preNMDARs likely due to their high Ca^{2+} permeability contribute to mossy fiber robust short-term facilitation. Using immunoelectron microscopy we identified the obligatory NMDAR subunit GluN1 in rat mossy fiber boutons. To assess the role of preNMDARs we used electrophysiology, selective pharmacology, and two-photon laser scanning microscopy in acute rat hippocampal slices. Bath application of MK-801 (50 μM) reduced both low-frequency (0.1 to 1.0 Hz steps) and burst-induced (5 stimuli, 25 Hz) facilitation when postsynaptic NMDARs were blocked by loading CA3 pyramidal cells with MK-801 (2 mM). Calcium imaging of mossy fiber giant boutons (200 μM, Fluo-5F intracellularly loaded into dentate granule cells) revealed a D-APV sensitive Ca^{2+} component during brief bursts of activity, suggesting preNMDARs participate in presynaptic Ca^{2+} rise. Together, our findings reveal that during repetitive activity preNMDARs facilitate glutamate release from mossy fiber boutons. Thus, preNMDARs may contribute significantly to dentate gyrus-CA3 information transfer.

Supported by R01 MH081935, F31 MH109267

[28] A brief flurothyl-induced seizure produces long-term anterograde memory deficits

Holley, A. J.[1]*, Binder, M. S.[1], Hodges, S. L.[2], Okoh, J. T.[1], & Lugo, J. N.[1,2]
[1]Department of Psychology and Neuroscience, Baylor University, Waco, TX 76798, USA. [2] Institute of Biomedical Studies, Baylor University, Waco, TX 76798, USA
*Andy_Holley@Baylor.edu

Introduction. Previous reports indicate a single seizure can cause transient learning and memory impairments in mice. The current study characterizes hippocampal-dependent learning and memory retention in mice after a seizure.

Methods. We placed male C57BL/6 mice into an inhalation chamber and infused flurothyl until a generalized seizure occurred. An hour later, mice underwent trace fear conditioning and were later tested for cued recall at 24 h and 1 wk. We used the open field and elevated plus maze to assess locomotor activity and anxiety 24 h and 1 wk after a single seizure. To test for generalized impairments we also used the accelerating rotarod test to examine motor learning and coordination starting 72 h after a single seizure.

Results. Memory tests revealed no differences between seizure and control groups at 24 h, but did show significant learning deficits at 1 wk. Open field test results indicated suppression of activity at 24 h, but not 1 wk following a seizure. The elevated plus maze test revealed no changes to anxiety at 24 h or 1 wk. The rotarod test did not reveal impairments in motor learning or coordination.

Conclusion. This data suggests that initially after a seizure new learning can be retained; however, hippocampal-dependent memory may decay over longer intervals. In contrast, cerebellar learning appears unaffected by a single seizure.

[29] Acute predator threat induces sex-specific hippocampal plasticity and contextual fear generalization

Damek Homiack[1]*, Emma O'Cinneide[1], Sema Hajmurad[2], and Laura Schrader[1,2]
[1]Brain Institute, [2]Cell and Molecular Biology, Tulane University New Orleans, LA
*dhomiack@tulane.edu

Post-traumatic stress disorder (PTSD) is characterized by the development of paradoxical memory disturbances characterized by powerful, intrusive memories with concurrent amnesia for details of the traumatic experience. However, in spite of evidence that women are at higher risk to develop PTSD, most animal research has focused on the processes by which male rodents develop adaptive fear memory. As such, the mechanisms which underlie the development of PTSD-like memory disturbances are poorly understood, particularly with respect to the female brain. In this investigation, we exposed adult male and female Wistar rats to the synthetic alarm pheromone 2,4,5-trimethylthiazole (TMT) to assess the activation of signaling cascades associated with hippocampus-dependent long-term memory and the development of generalized fear behavior.

Expression of phosphorylated CREB (S133), but not total CREB was dramatically reduced immediately following 30 minute TMT exposure throughout the male, but not the female hippocampus. Consistent with activation of the previously described CREB shut-off cascade, we also observed inactivation of ERK/MAPK and nuclear translocation of Jacob in the male hippocampus. Follow-up experiments showed that TMT exposure dampens glutamate reuptake, which may contribute to activation of the CREB shut-off cascade. To probe the long-term behavioral effects of predator odor exposure, we designed a novel predator odor context discrimination paradigm to assess the ability of TMT-exposed Wistar rats to distinguish between threat-associated and neutral contexts. We report that TMT-exposed female rats exhibited context discrimination impairments relative to TMT-exposed male rats, suggesting the intriguing possibility that females are more susceptible to developing generalized fear behavior following predator threat.

[30] Filial imprinting and experience-dependent social preferences are mediated by mTORC1 in newborn chickens

Gervasio Batista[1]*, Elena Dominguez[1], Jennifer L Johnson[2], Rodrigo Pavao[1], Mauro *Costa-Mattioli[2], Jose L Pena[1]*
[1]Department of Neuroscience, Albert Einstein College of Medicine. Bronx, New York.
[2]Department of Neuroscience, Baylor College of Medicine. Houston, Texas.
*gervasio.batista@phd.einstein.yu.edu

The mechanistic target of rapamycin complex 1 (mTORC1) regulates long-term memory formation and social behaviors in the adult brain. Yet little is known about mTORC1's function in memory formation during critical periods in early life. We addressed this question studying imprinting, a form of learning constrained to a critical period, and social preferences in newly hatched chicks. Previously, we found that translational control of protein synthesis is required for auditory imprinting and associated structural plasticity. Here we show that imprinting to virtual objects and artificial sounds activate mTORC1 in imprinting-relevant brain areas. Furthermore, while blockade of mTORC1 impaired both imprinting and structural plasticity, pharmacological activation of AKT/mTORC1 signaling restored imprinting beyond the critical period. Thus, our data demonstrate that mTORC1 underlies the formation of imprinted memories across sensory modalities and can be targeted to reopen the critical period. Using multi-tracking software we also assessed the emergence and stability of individual preferences in social groups over 2-hour interactions. Preliminary data indicate that transient blockade of mTORC1 disrupts the stability of individual preferences but it does not affect grouping behavior. Therefore, experience-dependent emergence of social preferences appears to rely on mTORC1 function. Our results uncover an unknown role of mTORC1 within critical periods for memory formation and social behaviors early in life.

[31] Medial entorhinal cortex grid and non-grid cells represent spatial location and environmental features via complementary coding schemes

Geoffrey W. Diehl[1]*, Olivia J. Hon[1], Stefan Leutgeb[1,2], and Jill K. Leutgeb[1*]
[1]Neurobiology Section and Center for Neural Circuits and Behavior, Division of Biological Sciences, University of California, San Diego, La Jolla, CA 92093, USA
[2]Kavli Institute for Brain and Mind, University of California, San Diego, La Jolla, CA
*GDiehl@UCSD.edu

The medial entorhinal cortex (mEC) is thought of as a hub for the representation and processing of spatial information based on the discovery of grid, border, and head-direction cells. Yet these three cell types represent only a small fraction of the total mEC population. We find that in addition to these well characterized classes, nearly all of the remaining two thirds of mEC cells could be categorized as spatially selective, with firing patterns that were highly reproducible across repeated explorations of the same environment. We refer to these cells as non-grid spatial cells. However, in response to manipulations of environmental features, such as box shape or box color, non-grid spatial cells completely changed their firing pattern such that two environments with only minor differences produced highly distinct spatial maps. At the same time, we found that grid cells retained their spatial alignment and predominantly responded to changes in environmental features with redistributed firing rates across their grid fields. Thus, mEC contains a joint representation of both spatial and environmental feature content, with grid and non-grid spatial cells utilizing distinct mechanisms to represent this multimodal information.

[32] Medial prefrontal cortex versus orbitofrontal cortex: teasing apart differences in plasticity after stress

Samantha Adler[1]*, Sarah Bulin[2], Michael Patton[1], Milena Girotti[1], David Morilak[1].
[1]*University of Texas Health San Antonio, San Antonio, TX, USA*
*adlersm@uthscsa.edu

Cognitive inflexibility is a symptom dimension shared by several stress-related psychiatric disorders that is poorly treated by current medications. To create better treatments, we need to know more about the neurobiology of stress effects on this symptom. In rodents, the attentional set-shifting task (AST) can be used to evaluate two types of cognitive flexibility: reversal learning, which is mediated by the orbitofrontal cortex (OFC), and extra-dimensional set-shifting, which is mediated by the medial prefrontal cortex (mPFC). We have identified two types of chronic stress that elicit deficits in each of these functions: chronic intermittent cold (CIC) stress impairs reversal learning ($p<.01$), while chronic unpredictable stress (CUS) impairs extra-dimensional set-shifting ($p<.05$). Each stress paradigm affects the output of the two brain regions very differently. Field potentials evoked acutely in the OFC by mediodorsothalamus (MDT) afferent stimulation in rats were potentiated after 2 weeks of CIC stress compared to baseline ($p<.01$). Conversely, MDT-evoked responses in the mPFC were decreased after two weeks of CUS ($p<.001$). Since changes in excitatory transmission are often accompanied by morphological changes in dendrites, we are now analyzing the differences in dendritic arborization and spine density after stress with Golgi staining. We expect stress-induced hyperactivity in the OFC to be associated with dendritic elaboration and increased spine density, and hypoactivity in the mPFC to be associated with dendritic retraction and decreased spine density.

[33] Developing sub-maximal fear extinction to model exposure therapy and adjunct treatment for psychiatric illnesses

Denisse Paredes* and David Morilak, Ph. D.
Department of Pharmacology, UT Health Science Center at San Antonio, TX
*paredesd@livemail.uthscsa.edu

Psychotherapy, especially in conjunction with pharmacotherapy, can improve symptoms of depression and increase remission rates in patients. Exposure therapy, a form of Cognitive Behavioral Therapy, shares many similarities to fear extinction learning. Our lab has previously shown that fear extinction (i.e. learning that an innocuous cue is no longer associated with a fearful stimulus) can be used to model the effects of exposure therapy on cognitive flexibility in chronically stressed rats. Thus, we can use this model of exposure therapy to understand the underlying mechanisms of adjunct treatment, with the ultimate goal of enhancing the effects of exposure therapy in a human population. The goal of these experiments is to investigate what variation of the extinction protocol will produce a sub-maximal therapeutic effect on measures of cognitive flexibility and coping style choice. In these experiments, animals were chronically stressed and received either 8 tones or 16 tones during fear extinction or received either 0.6, 0.8, or 1.0 mA of shock intensity during fear conditioning. If the therapeutic effects of extinction necessitate a longer tone exposure, (16 tones vs. 8 tones), then exposing the rats to 8 may diminish the effects of extinction on cognitive flexibility. Alternatively, lowering the shock during fear conditioning, may weaken the fear memory that allows animal to undergo fear extinction learning. It is also possible that increasing the shock voltage during fear extinction will make it more difficult for the animals to dissociate the shock from tone during fear extinction. Preliminary data suggest that decreasing tone exposure from 16 tones to 8 decreases the effect of fear extinction on immobility and burying behavior. Ongoing experiments will determine if varying the degree of shock intensity affects the therapeutic effects of fear extinction.

[34] Vortioxetine Treatment for Cognitive Impairment Associated with Androgen Deprivation Therapy (ADT) for Prostate Cancer

Suphada Lertphinyowong*, Sarah Bulin, Denisse Paredes, Alexandra Sharp
and David A. Morilak, Ph.D.
University of Texas Health San Antonio
*Lertphinyowo@uthscsa.edu

Cognitive impairment in prostate cancer patients after androgen deprivation therapy (ADT) is highly prevalent. 47-65% of ADT patients exhibit significant impairment in medial prefrontal cortex (mPFC) function, a brain region involved in cognitive functioning such as memory, attention and executive function. Vortioxetine is a novel, multi-modal antidepressant drug with a specific efficacy for cognitive impairment in depression. We have shown previously that vortioxetine was effective in reversing deficits in reversal learning on the Attentional Set-Shifting Test (AST) induced by chronic cold stress.

In this study, we sought to establish whether androgen deprivation in rats causes deficits in set-shifting on the AST, an mPFC-dependent cognitive flexibility task and if so, whether, chronic treatment with vortioxetine could rescue the deficits. Additionally, we investigated changes in functional plasticity induced by androgen deprivation and vortioxetine treatment by stimulating excitatory afferents from the medial dorsal thalamus (MDT) and recording evoked field potentials in the mPFC. We also investigated changes in gene expression in the brain using a microarray assay. Our preliminary data show that androgen deprivation by physical castration in male rats induced a deficit in cognitive flexibility, and chronic treatment with vortioxetine in the diet (28 mg/kg/day) was able to rescue the deficit. Androgen deprivation also induced a decrease in the afferent-evoked response in the mPFC. Results of the gene expression data are under analysis, and experiments are ongoing to determine if vortioxetine can rescue the afferent-evoked response.

[35] Context Discrimination in Alzheimer's Disease and Aging Mouse Models: Contributions of PPARγ Agonism, Microglia, Neurogenesis

Danelo Cortez* & Kelly T. Dineley
The University of Texas Medical Branch, Department of Neuroscience and Cell Biology, Department of Neurology and Mitchell Center for Neurodegenerative Diseases
*ibcortez@UTMB.EDU

Background: Converging evidence from animal and human studies suggest that an early target of Alzheimer's disease (AD) amyloid pathology is synaptic activity within the entorhinal cortex (EC), dentate gyrus, and Cornu Ammonis 3 (EC/DG/CA3) network. This hippocampal network underlies pattern separation, the ability to process overlapping environmental cues into unique representations and distinguish similar, yet non-identical contexts. Pattern separation is dependent on adult neurogenesis within the subgranular zone of the DG. We have previously shown that aged Tg2576 mice, a model for early AD that recapitulates amyloid pathology, hippocampal cognitive deficits and disrupted EC/DG/CA3 circuitry, all of which is alleviated by peroxisome proliferator activated receptor gamma (PPARγ) agonism with rosiglitazone (RSG). We postulated that cognitive tests that assess pattern separation would be altered in Tg2576 AD mice compared to littermate controls and that RSG treatment would normalize this behavior.

Methods: Context discrimination fear conditioning in combination with quantitative immunohistochemistry for neurogenesis proliferation and differentiation markers was used to reveal putative mechanisms contributing to the pattern separation behavioral phenotypes observed. Focal irradiation to the hippocampal subgranular zone was employed to verify the contribution of neurogenesis to the behavioral cognitive outcome measures.

Results: Untreated groups perform comparably in context discrimination while acute radiation treatment significantly impairs their ability to distinguish between similar contexts. Further, Rosiglitazone treatment improves wild type and wild type irradiated but not Tg2576 groups in context discrimination. Though, Quantitation of the immature neurons doublecortin reveal significantly less cells in irradiated groups while doublecortin abundance is unaltered in untreated and rosiglitazone treated wild type and Tg2576 groups.

Conclusions: Improved context discrimination in rosiglitazone treated wild type groups may not be due to the production of new born neurons but protection from chronic inflammation from aging or microglial activation, though further analysis of adult hippocampal neurogenesis is obligatory. Conversely, Tg2576 groups did not respond to rosiglitazone with/out radiation treatment suggesting AD pathology may disrupt pattern separation memory formation which is irreversible with PPARγ activation.

[36] Emotional Working Memory Training Improves Filtering Efficiency and Worry Symptoms of Individuals with High Trait Anxiety

Salahadin Lotfi[1]*, Maryam Ayazi[1], Ken Bennett[1], Christine Larson[1], Han-Joo Lee[1]
[1]*University of Wisconsin-Milwaukee*
*slotfi@uwm.edu

Anxiety is associated with excessive allocation of attentional resources toward threatening stimuli. This dysfunctional allocation allows unnecessary threat-related information to enter working memory (WM), consume cognitive resources (= filtering deficiency), and in turn interfere with ongoing behavior. Research shows that filtering efficiency (FE) can be improved using computerized WM training (WMT). The main purpose of study is to investigate the effects of an emotional WMT on EEG signatures and behavioral outcomes of individuals with high trait anxiety (HTA). EEG data can directly measure neural activity associated with FE in WM performance. Higher WM performance is linked to higher EEG beta frequencies and better FE of task-irrelevant information is associated with higher alpha frequencies in the parietal region. To this end, 21 undergraduates displaying HTA were randomly assigned to 9 sessions of online emotional dual N-back or 1-back minimal-dose trainings. Results revealed a significant pre-post increase in mean beta EEG frequency in parietal regions (P3, Pz, P4) only in the N-back condition. The N-back group also showed a trend ($p<0.06$) for increase alpha frequency after training. At behavioral levels, the N-back group showed a greater level of spatial WM performance and a significantly lower level of self-reported worrying, than the 1-back group. Our data suggest that emotional WMT can potentially serve as a cognitive intervention for anxious individuals by improving their ability to filter out irrelevant threatening information.

[37] Developing a Hippocampal Co-Atrophy Network Model Using Structural MACM from BrainMap's VBM Database

Eithan Kotkowski* and Peter T. Fox MD
UT Health San Antonio & The Research Imaging Institute
*Kotkowski@livemail.uthscsa.edu

The hippocampus has long been implicated in the pathogenesis of a number of psychiatric and neurological diseases including mild cognitive impairment (MCI), temporal lobe epilepsy (TLE), and Alzheimer's disease (AD). Evidence from recent functional meta-analytic connectivity modeling (MACM) studies of the hippocampus show distinct networks of co-activation between the hippocampus and specific brain regions (Robinson et al., 2015). In this study, we hypothesized that a network model of co-atrophy can be similarly derived using the MACM model from structural voxel-based morphometry (VBM) studies. We further hypothesized that the network model will exhibit significant loading on both structural (AD, MCI, etc.) and functional (memory) paradigms implicating the hippocampus. In this study, we seeded both hippocampi as a single region of interest (ROI) in the BrainMap® VBM database and found significant co-atrophy relationships with the bilateral structures of the parahippocampi, medial dorsal nuclei of the thalamus, insula, and caudate heads trans-diagnostically. Furthermore, using Lancaster et al. (2012)'s automated regional behavior analysis, we identified specific behavioral paradigms corresponding to BrainMap's functional database intrinsically related to our co-atrophy model; notably attention, explicit memory, and language (semantics). More importantly, using a novel plugin to assess atrophy foci from the VBM database, we identified disease states that appear to strongly correlate with our co-atrophy MACM model, namely MCI, AD, TLE, frontotemporal dementia (FTD), and schizophrenia.

[38] Role of competition between explicit and implicit learning in the effects of reward and punishment on visuomotor adaptation

Yanlong Song[1]* and Ann Smiley-Oyen[1]
[1]*Iowa State University*
*yanlongs@iastate.edu

Reward and punishment were revealed to have dissociable effects on online motor skill acquisition and offline motor memory consolidation. This study examined a possible cause of this dissociation from the perspective of competition between explicit learning and implicit learning. During learning to adapt to an abrupt visual perturbation in reaching a visual target, young healthy participants were provided with performance-based monetary reward or punishment. In the context of continuous visual feedback involving both explicit learning and implicit learning, punishment induced faster adaptation but reward markedly promoted offline consolidation expressed as savings. However, in the context of non-continuous visual feedback involving explicit learning, punishment still prompted faster adaptation but also showed comparable savings as reward. This inhibition was reduced by a declarative learning task immediately after the visuomotor adaptation in participants received punishment during the adaptation phase. In contrast, the declarative learning task had no influence on the consolidation of reward-induced visuomotor adaptation memory. These findings suggest that punishment, compared to reward, induced more efficient explicit learning in the adaptation phase but afterward competition between explicit memory and implicit memory suppressed consolidation of the punishment-induced motor memory.

[39] Synaptosomal Phospholipase D signaling in Memory Mechanisms

Balaji Krishnan* and Giulio Taglialatela
UTMB Mitchell Center for Neurodegenerative Diseases, Department of Neurology, University of Texas Medical Branch at Galveston, Galveston, TX 77555-1045
*bakrishn@UTMB.EDU

It is now well-estabished that memory deficits in Alzheimer's disease (AD), the most common and severe age-associated neurodegenerative dementia, start with synaptic dysfunction, however there is a need to understand the signaling mechanism underlying the progression of the memory deficits in AD towards an effective therapeutic intervention. Recent studies from our group have demonstrated a role for phospholipase D (PLD) as a key signaling element in the maintenance of long-term memory. Here, we present novel data showing differential expression of PLD isoforms (PLD1 and PLD2) in synaptosomal fractions in post-mortem AD brains compared to age-matched controls suggesting a role for PLD isoforms in mediating synaptic dysfunction associated with AD progression. We further observed, for the first time, that blocking the inducible PLD1 isoform was effective in preventing synaptic dysfunction and memory modeled in preclinical mouse models showing AD-like memory deficits using electrophysiological and behavioral studies.

Acknowledgements: The Mitchell Center for Neurodegenerative Diseases, NIA R01 AG042890

[40] Honey bees use sensory cues rather than nutritional information to evaluate food quality

Julie A Mustard[1]*, Valerie L Alvarez[1], Sofy Barocio[1], Jamie Mathews[1], Alexander Stoker[2], Kashif Malik[2]
[1]Department of Biology, University of Texas Rio Grande Valley, Brownsville TX; [2]School of Life Sciences, Arizona State University, Tempe AZ
*julie.mustard@utrgv.edu

Although honey bees will learn to respond to a reward associated with a positive gustatory stimulus in the short term, the formation of longer term memories is dependent on postingestive assessment of nutritional value. To examine the relationship between learning, taste and nutrition, the effects on learning of three sugars (sorbitol, mannitol and xylose) that bees can metabolize but not taste were investigated. Appetitive olfactory conditioning was used to condition bees to associate an odor with stimulation of the gustatory receptors on the antennal with sucrose and feeding with either sucrose, one of the metabolizable sugars, or no sugar. The results suggest that sorbitol and xylose, but not mannitol, support the formation of long term memory when paired with a positive gustatory stimulus. However, in a choice test, bees did not show a preference for solutions containing sucrose supplemented with the nutritional sugar compared to solutions containing sucrose alone. In addition, when feeders contained one of the three sugars alone, without sucrose as a gustatory signal, were provided, bees showed mortality rates similar to those seen for water alone suggesting that the bees were unable to determine that the solutions were nutritious. These data suggest that bees use gustatory cues rather than nutritional information when making decisions about food quality.

[41] Detection of occluding targets in natural backgrounds across the visual field.

R. Calen Walshe*, Stephen Sebastian, Wilson Geisler
The University of Texas at Austin
*calen.walshe@gmail.com

Detecting spatial patterns is a fundamental task solved by the human visual system. Two important constraints on detection performance are the variability that is found in natural scenes and the degradation of the image that occurs due to optical blurring and non-homogenous sampling of the retinal ganglion cell (RGC) mosaic across the visual field. Furthermore, most previous studies of detection performance have been conducted in the fovea with additive targets. However, image cues are different with occluding targets so these studies may not generalize well to occluding targets presented in the periphery. Here, we report eccentricity thresholds (eccentricity for 70% correct detection) for four different occluding targets presented in natural backgrounds at varying, but known, distances from the fovea. The luminance and contrast of the targets was fixed, and precise experimental control of the statistics (luminance, contrast and similarity) of the natural backgrounds was obtained using a novel method known as *constrained scene sampling* (Sebastian, Abrams & Geisler, submitted). Next, we describe a first-principles model, limited by known physiology of the human visual system and by the statistics of natural scenes, to compare with the pattern of observed thresholds. First, target-present and target-absent images are filtered by a modulation transfer function that approximates the optics of the human eye. Second, RGC responses are simulated by blurring and downsampling the optically-filtered image in a fashion consistent the midget RGCs at each retinal eccentricity. The model then combines luminance, pattern, and boundary information in the target region to predict detectability across the visual field. We show that a weighted combination of these three cues predicts the pattern of thresholds observed in our experiment. These results provide a characterization of the information that the human visual system is likely to be using when detecting occluding objects in the periphery.

[42] Simulated fMRI neurofeedback reveals principles of neural self-regulation

Ethan Oblak*, Jarrod A. Lewis-Peacock, James Sulzer
The University of Texas at Austin
*eoblak@utexas.edu

Direct manipulation of fine-grained patterns of brain activity can address causal questions of brain-behavior relationships. This is nearly impossible with non-invasive stimulation methods. Fortunately, this can be done by having people learn to self-regulate neuroimaging measurements of their brain activity patterns (e.g., using fMRI neurofeedback). This technique has transformative potential, but faces challenges. Many participants (~ 33%) are unable to self-regulate. Numerous experimental factors likely contribute to this problem, but they have not been systematically explored due to the cost and complexity of doing so in the MRI scanner. For example, the prescribed self-regulation strategy (cognitive or automatic) and feedback timing (continuous or intermittent) are often chosen arbitrarily, but these choices are critical, especially because of the sluggish hemodynamic signals of fMRI. Here, we developed a simulated neurofeedback environment to evaluate principles of neural self-regulation. Participants learned to regulate a simulated neurofeedback signal using a simple cognitive strategy (rotating a visual grating left or right to find a hidden target orientation). Continuous feedback led to faster regulation compared to intermittent feedback. When feedback was delayed and blurred (as in fMRI), we found that a computational model of automatic reward-based learning performed better with intermittent feedback. Our results suggest that different self-regulation mechanisms prefer different feedback schedules, which will help us to develop more effective neurofeedback paradigms.

[43] Inferring strongly recurrent circuits from activity data

Abhranil Das* and Ila Fiete
Center for Learning and Memory, the University of Texas at Austin
*abhranil.das@utexas.edu

Understanding neural circuit mechanism ultimately requires determining its connectivity. However, measuring connectivity is harder than recording neural activity, hence the interest in statistical methods to estimate connectivity from activity data.

Such methods have been applied to low-level sensory networks with some success (measured by activity prediction, not by comparison to true connectivity). To what extent can these methods infer memory networks (strongly recurrent networks that can sustain activity states)? To study this question, we implement a simple circuit whose weights can be dialed between 'sensory' and 'memory' regimes, and in which systematic errors in connectivity estimation can be clearly distinguished and characterized from that due to noise.

We show that even in fully observed memory networks with spike data from every neuron, estimation methods are biased toward inferring connections when they do not exist, owing to strongly correlated responses between neurons that are not directly connected. This bias is not remedied with more data, making memory circuit inference intractable with realistic data volumes.

We demonstrate that these results generalize to different generative and inference models, and show further that this is due to fundamental limits in the information contained in spikes from strongly connected networks.

Finally, we show that bias errors that arise in inferring partially observed networks are worsened when they are strongly recurrently connected.

[44] Unsupervised latent variable extraction from neural data to characterize processing across states

Rishidev Chaudhuri[1]*, Berk Gercek[1], Biraj Pandey[1] & Ila Fiete[1]
[1]*Center for Learning and Memory and Department of Neuroscience, The University of Texas at Austin, Austin, Texas, USA.*
*rishidev.chaudhuri@gmail.com

In circuits at the sensory and motor periphery and in rare instances in cognitive areas, the identity of the primary independent variable represented by the neural responses is known. This is the exception: In many brain regions or in different states (e.g. sleep), the independent encoded variable is unknown. To what extent is it possible to discover the identity of the independent variable and decode its value from neural data, without direct knowledge of what it is?

We present efforts to discover structure in multiple single-unit data, extract the unknown independent variable, and perform fully unsupervised decoding of it. Our method involves parameterizing low-dimensional manifold structure in high-dimensional data. We apply it to recordings from the mouse thalamus and postsubiculum (Peyrache et al., 2015) to examine neural circuit dynamics during awake exploration, REM, and slow-wave sleep (SWS).

The method discovers a ring structure, which it parameterizes to extract a circular variable, consistent with head direction coding in these circuits. The accuracy of unsupervised decoding of the latent variable on many sessions is on par with decoders constructed using head direction. Per-neuron tuning curves for the latent variable match (up to rotation) the actual head direction tuning curves. REM and SWS states fall on the waking manifold, showing—without the assumptions involved in applying awake-state encoding models to sleep decoding—that sleep and awake states share the same structure. Unlike waking, REM states perform a random walk on the circular variable, while SWS states sample a subset of angle values and make large jumps between them.

Thus, we show it is possible to discover the structure of a variable that drives neural responses and decode it without knowing its identity, simply from time-series neural data. Such approaches can help understand encoding and dynamics in neural circuits, across behavioral states.

[45] The coexistence of diverse spatial, velocity, and conjunctively tuned cells in heterogeneous networks that faithfully path integrate and localize

Tzuhsuan Ma[1]* and Ila R. Fiete[1]
[1]*Center for Learning and Memory and Department of Neuroscience, The University of Texas at Austin, Austin, TX 78712, USA*
*tzuhsuan@physics.utexas.edu

The hippocampus contains cells with a wide variety of very different spatial and velocity tuning profiles. This diversity includes single cells tuned to single features, single cells with mixed tuning to multiple features, different cells with different types of tuning to the same feature, and so on. It is unclear why this wide mix of tuning types exist. Hand-designed models built to estimate location by simply integrating a velocity input tend to require homogeneous connectivity and tuning, thus it is also unclear mechanistically how to build heterogeneous models that support integration. When faced with building neural models for tasks of sufficient complexity, the hand-designed approach hits a wall as our intuition fails.

Training recurrent neural networks is a versatile approach to finding solutions beyond our intuition, but this approach sometimes offers less insight about how the neurons are solving the problem than can be gained from studying a hand-designed network. To allow for the combination of both approaches, we consider tasks that are simple enough so that hand-designed networks can serve as the initial foundation, but complex enough that we need to further train the networks to accomplish them.

For a 1D spatial localization task in the presence of motion estimation errors and landmarks, we oberve the emergence of diverse types of tuning in a trained network, including pure position tuning, pure velocity tuning, and conjunctive tuning of position, direction and velocity. The cells of the trained network may be categorized as directional/non-directional grid/place cells or border cells. More importantly, after studying a trained network, we are able to distill the key ingredients in its connectivity responsible for its success. This allows us to understand how these specialized or multi-functional cells work together to perform spatial localization and gives insights about how the hippocampus can solve the navigation problem.

[46] Hippocampal coding arises from probabilistic self-localizationacross many ambiguous environments

Ingmar Kanitscheider* and Ila Fiete
Department of Neuroscience, UT Austin
*IKanitscheider@mail.clm.utexas.edu

Sensory noise and ambiguous cues make self-localization during navigation computationally challenging: Path integration causes location estimates to deteriorate quickly and landmarks are often spatially extended (e.g. walls) or look similar to other landmarks, thus providing only partial position information. Worse, in novel environments, landmark positions are unknown and must be learned while navigating. How brains perform these difficult computations is largely unknown. Engineering solutions require sophisticated probabilistic algorithms based on particle filters that update several hypotheses simultaneously over time, but are hard to map to biological neurons.

We define several problems that crystallize typical navigation challenges: Self-localization in a circular 1D environment with several indistinguishable landmarks, known circular and polygon-shaped 2D environments with extended, featureless boundary walls, and novel 2D polygon-shaped environments whose boundaries have to be learned during navigation. We take a model-free approach and generate neutrally plausible solutions by training recurrent networks with hidden layers, then scrutinize their performance, errors, and dynamics.

The networks learn to update their estimates through velocity integration, integrate landmark information, and use memory of the last landmark encounter to choose between competing location hypotheses. The network performance matches the optimal particle filter (known environments) and substantially outperforms pure path integration (unknown environments), evidence that it can learn new maps. Reminiscent of remapping, the hidden units dynamically switch their tuning to code for the relevant statistics at a given time, such as location relative to the last observed landmark or to absolute location. These results demonstrate that hard navigation tasks can be solved by deterministic networks and provide predictions for neural representations during real-world navigational
challenges.

[47] Regional Differences in h Channel Expression Along the Dorsoventral Axis of the Hippocampus In A Rodent Model of Temporal Lobe Epilepsy

Elizabeth Arnold* and Daniel Johnston
Center for Learning and Memory, The University of Texas at Austin
*Elizabeth.Arnold@utexas.edu

Temporal Lobe Epilepsy (TLE), affecting the hippocampus and surrounding cortices, is the most common focal epilepsy. Work from both humans and animal models of TLE suggest the hippocampus isn't uniformly affected by seizures. The ventral end of the longitudinal axis of the hippocampus is associated with increased cell loss, seizure initiation and axonal sprouting. Furthermore, TLE has been linked to profound changes in ion channel expression, called channelopathies, including a reduction in hyperpolarization-activated, h, channels. We hypothesized a reduction h channel expression might contribute to the vulnerability of the ventral hippocampus to seizures. To test this we used whole cell electrophysiology and immunohistochemistry to measure h channel expression in rats that had undergone status epilepticus (SE) six weeks earlier. Based on previous studies we had expected to see evidence of this h channelopathy in the ventral pole of hippocampal area CA1. Surprisingly, we found that h channel expression was reduced in dorsal, but not ventral CA1. We measured a decrease in HCN1 subunit expression in the dorsal dendrites, and a reduction in intrinsic properties associated with h. These data suggest that the presence of h-channelopathies associated with Temporal Lobe Epilepsy in CA1 neurons will be dependent on the dorsoventral location.

[48] Prefrontal cortex dysfunction in Fragile X mice depends on the continued absence of Fragile X Mental Retardation Protein in the adult brain

Raymond A. Chitwood[1,2]*, Jennifer J. Siegel[1]*, James M. Ding[1,2], Clayton Payne[1,2], William Taylor[1], Richard Gray[1], Boris V. Zemelman[1,2], Daniel Johnston[1,2]
*authors made equal contributions
[1]Center for Learning & Memory and [2]Department of Neuroscience, The University of Texas at Austin, Austin, Texas 78712
randy@mail.clm.utexas.edu

Fragile X Syndrome (FX) is considered a developmental disorder, arising from a mutation that disrupts the transcription of Fragile X Mental Retardation Protein (FMRP). However, FMRP regulates the transcription of other proteins and participates in protein-protein interactions throughout life. Therefore, it is likely that dysfunction is also due to the ongoing absence of FMRP in the adult brain. We show here that FX model mice lacking the gene encoding FMRP display significant deficits in a prefrontal cortex (PFC) dependent task, including an increase in the proportion of non-learners and a delay in the onset of learning. We then used conditional knockout (cKO) mice to eliminate FMRP only in the PFC of adult mice, and observe the same deficits. The results suggest that these deficits 1) are due to the absence of FMRP in the PFC alone, and 2) are not the result of developmental dysregulation. Furthermore, the PFC-associated deficits were rescued by initiating production of FMRP in adult conditional restoration (cON) mice, indicating that PFC dysfunction can be rescued post-development. The results suggest a dissociation between the roles of FMRP in neural function and in developmental dysregulation, and that PFC function can be restored in the adult FX brain.

[49] Excitatory/Inhibitory imbalance in PFC is associated with learning deficits in Fragile X model mice.

Jennifer J. Siegel[1]*, Raymond A. Chitwood[1,2], Richard Gray[1], Daniel Johnston[1,2]
[1]Center for Learning & Memory and [2]Department of Neuroscience
University of Texas at Austin, Austin, Texas 78712
*jenni@mail.clm.utexas.edu

Fragile X Syndrome (FX) is the most common monogenic cause of autism, arising from a mutation that disrupts the transcription of Fragile X Mental Retardation Protein (FMRP) throughout life. We have demonstrated that FX model mice lacking the gene encoding FMRP show significant impairments in the PFC-dependent task trace eyeblink conditioning. These impairments were recapitulated by blocking, or rescued by restoring, the production of FMRP in the PFC alone. Interestingly, with additional training some FX animals are able to express learning. We used single-unit recordings in the PFC of FX mice to investigate potential differences in PFC function between FX learners and nonlearners. The data reveal that interneurons in FX mice show aberrantly strong responses to training stimuli that were 2–4 fold higher than those observed in wild-type mice. With training, a decrease in these responses to wild-type levels was associated with the delayed expression of learning in FX mice, and was not observed in FX nonlearners. The results support the theory that an imbalance in the ratio of excitation to inhibition is associated with FX, and may result in learning disabilities. Furthermore, the results suggest that pharmacological manipulations that temper interneuron responses may restore cortical function in FX, providing a new strategy to treat FX in adult patients.

[50] Impaired temporoammonic pathway LTP in *fmr1-/y* CA1 neurons

Gregory Ordemann* and Darrin Brager
University of Texas at Austin, Center for Learning and Memory
*gordemann@utexas.edu

Fragile X syndrome (FXS) is the leading monogenetic cause of autism and intellectual disability. Dendritic dysfunction and changes in voltage-gated ion channels are rapidly expanding areas of research in FXS. The functional expression of h-channels (I_h) is higher in CA1 pyramidal neuron dendrites of the *fmr1-/y* mouse (Brager et al., 2012). In CA1 neurons, I_h plays a critical role in synaptic plasticity of temporoammonic (TA) inputs by limiting both synaptic integration and regulating dendritic calcium plateau potentials. Based on this, we hypothesized that the elevated dendritic I_h in *fmr1-/y* CA1 pyramidal neurons will impair TA-LTP. We used whole-cell current clamp recording to measure baseline and theta-burst stimulation (TBS) induced changes in TA-EPSPs. There was no significant difference in either paired-pulse ratio or input-output relationship between wildtype and *fmr1-/y* neurons. TBS significantly potentiated TA inputs in wildtype (430.48%±192.52) but not *fmr1-/y* slices (109.15%±44.56). During TBS wildtype neurons fired more spikes and greater depolarization compared with *fmr1-/y* neurons. Block of h-channels with intracellular application of ZD7288 did not restore TBS-LTP in *fmr1-/y* slices. Our results outline a previously unreported deficit in TA LTP in a model of FXS. Further study of the mechanism underlying this TA LTP impairment will involve dual stimulation of the Schaffer collateral and TA pathways and direct dendritic recordings.

[51] Adult Hippocampal Neurogenesis Modulates the Effect of Environmental Enrichment on Spatial Search in the Morris Water Maze

Francis Shue* and Michael R. Drew
Center for Learning and Memory, University of Texas at Austin, Austin, TX
*shuefrancis@gmail.com

Environmental enrichment (EE) increases the survival of adult-born neurons and enhances spatial learning and memory in the Morris Water Maze (MWM). Whether increased survival of adult-born neurons plays a causal role in EE is debated (Zhao et al., 2008). Our previous study (Meshi et al., 2006) demonstrated that suppression of adult neurogenesis via x-irradiation failed to block the effects of EE on MWM performance. However, this study, and many previous ones, focused on the time it takes an animal to find the platform in MWM, which ignores the possibility that animals can employ different search strategies to solve the task. We asked whether strategies choice is affected by EE or suppression of neurogenesis. To test this hypothesis, we re-analyzed the MWM data of Meshi et al. (2006), which included irradiated and sham-irradiated mice housed in either EE or standard housing (SH). We created an algorithm classify the search strategy into 3 categories: Non-Spatial, Intermediate, and Spatial. EE mice were more likely that SH mice to use Spatial strategies. In addition, there was a significant interaction between EE and irradiation, such that irradiated mice in EE used more Spatial Strategies than any other group. This interaction suggests that neurogenesis restrains the effects of EE rather than mediating them. We hypothesize that adult-born neurons reduce the precision of spatial memory, consistent with evidence that young adult-born neurons display less precise spatial tuning than their mature counterparts (Danielson et al., 2016).

[52] Dentate gyrus contributes to retrieval as well as encoding: Evidence from context fear conditioning, recall, and extinction

Brian E. Bernier[1]*, Anthony F. Lacagnina[1], Adam Ayoub[1], Boris V. Zemelman[1], Franklin B. Krasne[2] & Michael R. Drew[1]
[1]*Center for Learning and Memory, Department of Neuroscience, University of Texas at Austin, Austin, TX 78712, USA.*
[2]*Department of Psychology, University of California at Los Angeles, Los Angeles, CA 90095, USA*
*bbernier1@gmail.com

Dentate gyrus (DG) is widely thought to provide a teaching signal that enables hippocampal encoding of memories, but its role during retrieval is poorly understood. Some data and models suggest that DG plays no role in retrieval; others encourage the opposite conclusion. In an effort to resolve this controversy we evaluated the effects of optogenetic inhibition of dorsal DG during context fear conditioning, recall, generalization, and extinction. We found that (1) inhibition during training impaired context fear acquisition; (2) inhibition during recall did not impair fear expression in the training context, unless mice had to distinguish between similar feared and neutral contexts; (4) inhibition increased generalization of fear to an unfamiliar context that was similar to a feared one and impaired fear expression in the conditioned context when it was similar to a neutral one; (5) inhibition impaired fear extinction. These effects, as well as several seemingly contradictory published findings, could be reproduced by BACON, a physiologically realistic hippocampal model positing that acquisition and retrieval both involve coordinated activity in DG and CA3. Our findings thus suggest that DG contributes to retrieval and extinction, as well as to the initial establishment of context fear.

[53] Optogenetic interrogation of the contribution of dorsal and ventral adult-born neurons to context fear conditioning

Kylie A. Huckleberry[1]*, Francis Shue[1], Taylor Copeland[1], Raymond A. Chitwood[1], Weiling Yin[2], Michael R. Drew[1]
[1]*Center for Learning and Memory, University of Texas at Austin, Austin, Texas*
[2]*Division of Pharmacology and Toxicology, University of Texas at Austin, Austin, TX*
*kylie.a.huckleberry@gmail.com

The hippocampus contains one of the few neurogenic niches within the adult brain—the subgranular zone of the dentate gyrus (DG)—and exhibits significant functional heterogeneity along its dorsoventral axis. Although adult-born neurons within the DG have been implicated in many hippocampus-dependent behaviors, little is known about how the function of the adult-born neurons varies along this axis. We used a highly specific Nestin-CreER(T2) mouse line (Lagace et al., 2007; Sun et al., 2014) to induce expression of the light-activated neural silencer archaerhodopsin in ~30% of neural progenitor cells and their progeny. Optical fibers were implanted into the dorsal or ventral DG to selectively silence adult-born neurons in these regions. We first tested the contribution of ≤6-week-old dorsal and ventral adult-born dentate granule cells to acquisition of context fear memory by delivering laser illumination during training. Silencing neither the dorsal nor ventral adult-born neurons affected the activity burst during the shock, indicating that silencing did not alter shock sensitivity. Context memory expression was tested twenty-four hours after acquisition without laser illumination. Silencing both the dorsal and ventral adult-born neurons significantly decreased freezing during the context test. We next tested the contribution of ≤6-week-old dorsal adult-born granule cells to context memory retrieval and context generalization. Mice were trained without laser illumination but were tested with laser illumination in both an alternate similar context and the original training context. Silencing both the dorsal and ventral adult-born neurons significantly decreased freezing during testing in both contexts, but the ability to discriminate remained intact as the animals always froze more to the original than to the alternate context. Experiments are underway to assess how silencing the adult-born neurons affects non-hippocampus-dependent associative fear as well as how silencing the adult-born neurons affects local activity in the DG and CA3. In summary, silencing dorsal and ventral adult-born neurons during either training or testing reduced context fear memory.

[54] Capturing the functional importance of graded climbing fiber signaling

A. Fanning*, R. Chitwood, J. Siegel, D. Johnston and H. Nishiyama.
Department of Neuroscience, The University of Texas at Austin, Austin, TX 78712 USA
*alfanning10@gmail.com

For many forms of motor learning to occur, the brain produces error signals when there's a mismatch between expected and actual movement (or sensory perception), in order to change output to correct for subsequent movement. Climbing fibers (CFs), the axons originating from cells in the inferior olive, provide the cerebellum with error signals that are crucial for producing plasticity that allows for learned motor responses. CFs exhibit high-frequency bursts of 1-to-6 action potentials (100-500 Hz). Since CFs show a wide range of high-frequency burst sizes, it may be that CFs are providing additional information about the error that occurred that is encoded in burst size. Using calcium imaging of CFs during eyeblink conditioning, we show that CFs exhibit larger calcium transients to differentiate unexpected sensory events from spontaneous activity. CFs are also more reliably responsive to the unconditioned stimulus (air puff) before learning occurs, but switch to become more reliably responsive to the conditioned stimulus (light emitting diode) as learning progresses. As CFs become more reliably responsive to the conditioned stimulus, the calcium transients also become larger. We are currently working to see how CF burst size changes in response to the unconditioned stimulus as learning progresses, as well as how it correlates to the speed and strength of a learned response.

[55] Competition and forgetting during context-based episodic memory retrieval

Augustin Hennings*, Stephanie Jeanneret, Anthony Dutcher,
Mark Hollenbeck, and Jarrod A. Lewis-Peacock
Center for Learning & Memory, University of Texas at Austin
*achennings@utexas.edu

Recent memory models highlight the importance of contextual information for remembering episodic events (Polyn et al., 2009). A consequence of binding event memories with their context is that contextually related memories can interfere with the retrieval of targeted memories, leading to retrieval-induced forgetting (RIF) of the competing memories (Anderson et al., 2000). A model built to explain this effect describes a nonmonotonic "U-shaped" relationship between memory activation and changes in memory strength (Norman et al., 2007). Specifically, competing memories that activate to a moderate degree (vs. low or high activation) are more likely to be weakened and forgotten. However, the factors governing whether and how memories will activate and compete during retrieval are not well understood. Here, we test the hypothesis that events experienced closer in time will be more likely to compete later during memory retrieval, leading to RIF. Representational similarity analysis of fMRI data was used to identify object-specific representations in ventral visual cortex and to track reactivations during a cued-retrieval task. Preliminary data are consistent with our hypothesis. To strengthen our results, we are now working to improve the sensitivity of item-specific neural decoding by using a priori semantic clustering of the objects to train fMRI pattern classifiers on ad hoc object clusters, and by using shared-response modeling to combine data from multiple subjects.

[56] Cognitive flexibility improves both prospective and long-term remembering

Seth R. Koslov* & Jarrod A. Lewis-Peacock
Center for Learning & Memory, University of Texas at Austin
*koslov@utexas.edu

Prospective memory describes the ability to remember to perform goal-relevant actions in the future. The multiprocess view of prospective memory posits that two separable control mechanisms underlie this ability: proactive control, which involves maintenance of goal information in working memory and monitoring of the environment for relevant cues; and reactive control, involving the formation of cue-response associations which are later automatically retrieved from episodic memory. Individuals will often engage proactive and reactive control strategies appropriately when the demands of the task environment are stable. However, in environments of shifting task demands, sub-optimal strategy use oftentimes leads to performance costs and memory failures. Here, we sought to characterize the flexible choice of control strategies for prospective remembering in situations with rapidly varying task demands. Participants were asked to identify the reappearance of a picture target (a face or scene) while at the same time performing a visual search task. Afterwards, they were given a surprise memory test for the target items. Results indicate that the degree to which subjects appropriately adapt their control strategy (e.g., switching from a proactive strategy to a reactive strategy when overall task demands increase) predicts better delayed execution of goals and better long-term retention of those goals. Conversely, sticking with a non-adaptive strategy hurts both performance metrics, highlighting an important link between cognitive flexibility and memory.

** [57] Intentional forgetting via memory weakening in sensory cortex

Tracy H. Wang*, Katerina Placek, Jarrod A. Lewis-Peacock
Center for Learning & Memory, University of Texas at Austin
*Tracy.wang@utexas.edu

Forgetting can be understood as an adaptive, active, and often automatic process of curating memories. It can also be deliberate: the intention to forget can produce long-lasting forgetting. How does the brain accomplish this? Two successful strategies have been identified with distinct neural signatures: "direct suppression" attempts to squash the memory by engaging prefrontal control regions to inhibit processing in the hippocampus, whereas "thought substitution" attempts to replace the memory with alternatives from long-term memory through enhanced hippocampal engagement (Benoit and Anderson, 2012). Here, we explored whether a memory weakening mechanism that contributes to unintentional forgetting – in which moderately active memories get weakened through a process of oscillating inhibition in the brain regions supporting their representation (Lewis-Peacock & Norman, 2014) – is also active during deliberate forgetting. We hypothesized that intentional forgetting of visual memories can be accomplished by promoting moderate activation in visual brain regions. In a directed-forgetting task, fMRI pattern classifiers revealed that intentional forgetting was associated with stronger processing of the to-be-forgotten item in ventral temporal cortex. Consistent with our hypothesis, this produced a reliable nonmonotonic relationship between neural activation and memory performance such that moderate activity of an item was predictive of successful forgetting. These results suggest that sensory cortex may play a larger role in forgetting than previously appreciated.

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

[58] The precision of memory-based prediction biases memory pruning

Hyojeong Kim*, Margaret L. Schlichting, Alison R. Preston, & Jarrod A. Lewis-Peacock
Center for Learning & Memory, University of Texas at Austin
*hyojeongkim@utexas.edu

When the statistics of our experiences change, our memory is updated by weakening ("pruning") unreliable memories whose predictions are violated ("prediction errors," Kim et al., 2014). Here, our goal was to determine how the precision of prediction errors impacts memory pruning. We hypothesized that contexts that generate specific predictions ("I expect that one tiger") would lead to pruning of that memory when an unexpected item appeared instead, whereas contexts that generate generic predictions ("I expect some animal") would not. We tested this hypothesis by showing observers a sequence of objects for which we manipulated the transition probabilities. Cue items appeared four times either always followed by an item from a different category, or followed by items from a single category. We reasoned that prediction errors would decrease when cues reliably predict the category of the item when item prediction (identity) is violated. Consistent with our hypothesis, we found that the cues in the different-category condition led to pruning more often than the cues in the same-category condition. fMRI results indicate that only in the different-category condition did stronger predictions, which were always violated, lead to pruning. These results suggest that when memory predictions are broadened, prediction error decreases and episodic detail is more likely to be preserved. However, broader predictions also reduced the encoding of subsequent events, highlighting a tradeoff between preserving old memories and building new ones.

[59] Social learning and neural networks in a highly social fish

Mariana Rodriguez-Santiago[1,2]*, Lyndon A. Jordan[2,4], and Hans A. Hofmann[1,2,3]
[1]Institute for Neuroscience, [2]Dept. of Integrative Biology, [3]Center for Computational Biology and Bioinformatics, The University of Texas at Austin, Austin, TX, [4]Dept. of Collective Behavior, Max Planck Institute for Ornithology, Konstanz, Germany
*mari_rodriguez@utexas.edu

Social context greatly influences learning and decision-making. Social learning, the acquisition of environmental information through direct or indirect observation of others, is fundamental in this context. An individual's rank in a dominance hierarchy strongly influences how information is perceived and acquired. While learning mechanisms have been studied extensively at the individual level, the neural mechanisms underlying social learning have not been studied in much detail. Here we examined how social dominance influences learning of an associative task by group members. Using the African cichlid *Astatotilapia burtoni*, a model system in social neuroscience, we show that demonstrators enhance group learning compared to single individuals learning asocially. We quantified induction of the immediate-early gene c-Fos in candidate brain regions known to play a role in social behavior, learning, and memory. Our results show that neural activity patterns differ between social and individual learning. How individuals acquire and store salient information is thus highly dependent on the social context. Finally, we found that dopaminergic activity in the putative homolog of the mammalian striatum, a region associated with motivation and reward, was higher in groups that learned the task. These results provide novel insights into the behavioral and neural mechanisms underlying social learning in groups.

[60] Concurrent optical imaging and extracellular recording for longitudinal studies of behaving brain

Lan Luan[1,2], Colin T. Sullender[1], Zhengtuo Zhao[1], Xue Li[1], Hanlin Zhu[1], Xiaoling Wei[1], Raymond A. Chitwood[3], Jennifer J. Siegel[3], Andrew K. Dunn[1], Chong Xie[1]*

[1]Department of Biomedical Engineering, the University of Texas at Austin; [2]Department of Physics, the University of Texas at Austin; [3]Center for Learning and Memory, Institute for Neuroscience, the University of Texas at Austin, Austin

*chongxie@utexas.edu

Simultaneous intracortical electrical recording and optical imaging promise combinative advantages from the two complementary methodologies including large field of view, multi-modality and sub-micron resolution from optical imaging, and high temporal resolution at any tissue depth from electrical recording. However, combined implementation of both methods for longitudinal studies of behaving brain has not been achieved, in large part due to the lack of electrophysiological methods that record individual neurons at minimal tissue invasiveness and allow for convenient chronic optical access. Here we demonstrated in mouse models that a novel type of intracortical electrodes, the ultraflexible nanoelectronic threads (NETs), enabled chronic multimodal neural platform that combines electrical recording of neural activity and optical imaging. Using genetically encoded calcium sensors GCamp6 by viral transduction in the somatosensory cortex, we performed repeated two-photon imaging of Ca^{2+} transients simultaneously with electrical recording of action potentials. We also demonstrated simultaneous mapping of neural activity and hemodynamics by combining spatially resolved electrical recording with full field laser speckle contract imaging of cerebral blood flow in an ischemic model, which was also able to track the change of both neural activity and hemodynamic parameters over chronic time scales. These results show that the NETs enable novel multimodal neural platform for longitudinal, multimodal interrogation of behaving brain that can be applied to a variety of basic and applied neuroscience studies.

[61] Tracking and manipulation of neuronal clusters using ultraflexible electrode array

Zhengtuo Zhao[1]*, Hanlin Zhu[1], Xue Li[1], Xiaoling Wei[1], Lan Luan[1,2] and Chong Xie[1]

[1]Department of Biomedical Engineering, the University of Texas at Austin; [2]Department of Physics, the University of Texas at Austin

*zhengtuo@utexas.edu

The ability to reliably record, track and control neuronal clusters/ensembles are of great importance to basic and clinical neuroscience, as local circuitry/connections carry important functions. Assorted multi-site dense electrode arrays have been designed based on conventional structures, but their chronic recording capacity is often compromised by the instability of the tissue-probe interface. Ultraflexible, cellular-dimensioned neural electrodes have recently demonstrated seamless integration with brain tissue and reliable recording of individual neurons for several months. Here we show that a closely-spaced electrode array of 32 recording sites on the ultraflexible platform can detect and track over months a small neuronal cluster. We demonstrate the detection, isolation, position estimation, and connection mapping of each neuron in the cluster facilitated by the spatial-temporal correlation among the multiple electrodes. Using an open-source large scale sorting software (Klustaviewa) combined with customized waveform similarity based semi-automatic clustering algorithm, we show that many units can be repeatedly identified and tracked over eight weeks and longer. In vivo two-photon Imaging of neurons in vicinity of the probe confirmed a sufficiently stable tissue-electrode interface. Furthermore, we demonstrated the capability of manipulating the neuronal cluster by electrical stimulation, and by multifunctional probes constructed from conformal attachment of ultraflexible electrode arrays on conventional probes that combine optical stimulation, controlled drug infusion with extracellular recording of neural clusters.

[62] Ultra-flexible Brain Probes Form Reliable, Glial Scar Free Neural Integration

Lan Luan[1,2]*, Zhengtuo Zhao[1], Xiaoling Wei[1], Jennifer J. Siegel[3], Shams Kazmi[1], Robert A. Fowler[1], Andrew K. Dunn[1], Raymond A. Chitwood[3] and Chong Xie[1]

[1]Department of Biomedical Engineering, the University of Texas at Austin; [2]Department of Physics, the University of Texas at Austin; [3]Center for Learning and Memory, Institute for Neuroscience, the University of Texas at Austin, Austin, TX 78712–1192, USA.

*lluan@utexas.edu.

Implanted electrodes provide one of the most important neurotechniques by allowing for time-resolved acquisition of individual neuron electrical activity in the living brain. However, their recording stability and efficacy in both the short and long term pose limitations on their scientific and clinical applications. Conventional brain probes suffer from substantial recording condition changes in time scales as short as hours due to the micro-movements of the implanted electrodes relative to the brain tissue. Over a period of weeks to months, their recording performance often deteriorates due to sustained foreign body reactions. Here we show that ultra-flexible, subcellular sized brain probe architecture, the nano-electronic thread (NET), forms reliable, glial scar free neural-probe interface as verified by chronic neural recordings and tissue-probe interface characterizations. We observed that the electrode impedance, the noise level, the single-unit recording yield, and the signal amplitude remained stable during long-term implantation. We demonstrated that individual units can be reliably detected and tracked for months. *In vivo* two-photon imaging and postmortem histological analysis revealed seamless, subcellular integration of NET probes with the local cellular and vasculature networks. Significantly, we observed fully recovered capillaries with intact blood brain barrier, and complete absence of chronic neuronal degradation and glial scar. We continued to demonstrate further reduction in dimensions of individual NETs using advanced e-beam lithography techniques, and facile delivery of multiple NETs in densely packed linear arrays, which provide new opportunities for high density electrical recording in behaving animals by overcoming the current physical limitations.

[63] Impairments in spatial memory representations in freely moving 3xTg mice

Alexandra J. Mably[1,3]*, Dylan T. Jones[1,3], Brian J. Gereke[1,2] and Laura L. Colgin[1,2,3].

[1]Center for Learning and Memory, [2]Institute for Neuroscience, [3]Department of Neuroscience, University of Texas at Austin, Texas.

*amably@austin.utexas.edu

Spatial memory impairments are both a clinical feature of Alzheimer's disease (AD) and a characteristic common to many AD mouse models. The hippocampal formation, and hippocampal place cells, are thought to be essential for correct cognitive representation of spatial information. Therefore, a plausible hypothesis is that improper formation of place cells' spatial receptive fields (i.e., place fields), or instability of these fields over time, contributes to spatial memory impairments seen in AD. To assess whether place cell activity was aberrant in a mouse model of AD, we recorded place cells from hippocampal subfield CA1 of 3xTg and wildtype (Wt) mice traversing a familiar circular track. Mice ran three 10-minute sessions per day, and place fields were compared across laps and across sessions within each day. Place field locations and firing rates were significantly less stable across both laps and sessions in 3xTg mice compared to Wt mice. Furthermore, rhythmic coordination of place cell spiking was altered in 3xTg mice. Specifically, a smaller proportion of place cells from 3xTg mice were significantly phase-locked to theta and slow gamma rhythms. These results indicate a disruption in the cognitive representation of space in an AD mouse model and, with further investigation, may provide insights into the cellular mechanisms of spatial memory impairments in AD.

[64] Characterizing social behavior in a novel rat model of Fragile X Syndrome

Nicole L. Alexander*, Alexandra J. Mably, and Laura L. Colgin
Center for Learning and Memory, The University of Texas at Austin
*nalexander@utexas.edu

Fragile X Syndrome (FXS) is the most commonly inherited intellectual disability and only known genetic cause of autism spectrum disorder (ASD). FXS results in multiple behavioral disturbances including social behavior impairments; however, the underlying cellular mechanisms remain unknown. Several recent studies have suggested a role for hippocampal subregion CA2 in social behaviors. Recent work from the Colgin Lab showed that neurons in CA2, but not other hippocampal subregions, changed firing patterns in response to social interaction behaviors. This study aimed to characterize social behavior in a novel rat model of FXS as part of a larger project assessing whether social impairments in FXS rats are predicted by abnormal cellular responses in CA2. We hypothesized that FXS rats would show impaired social behaviors compared to control rats. To test this, FXS and control rats were tested in several social behavior paradigms designed to assess sociability, social novelty preference, and direct social interaction. Results showed that FXS rats display normal sociability and novelty preference but impairments in direct interaction measures. Ongoing recordings will assess the responses of neurons in CA2 and neighboring hippocampal subregions to social interactions. These results, combined with the behavioral data reported here, are expected to shed light on cellular mechanisms underlying social behavior deficits in FXS and may point toward novel therapeutic targets for FXS and ASD.

[65] Slow and Fast Gamma Rhythms in the Superficial Layers of Medial Entorhinal Cortex

John B. Trimper[1]*, Sean G. Trettel[1,2], Ernie Hwaun[1,2], Laura Lee Colgin[1,2,3]
[1]Center for Learning and Memory, University of Texas at Austin, Austin, Texas, USA.
[2]Institute for Neuroscience, University of Texas at Austin, Austin, Texas, USA.
[3]Department of Neuroscience, University of Texas at Austin, Austin, Texas, USA.
*jbtrimper@gmail.com

Slow and fast gamma are distinct rhythms that occur prominently in the hippocampus. However, the prominence of these rhythms in the superficial layers (II/III) of the medial entorhinal cortex (MEC), a primary input to hippocampus, has yet to be assessed. In particular, though fast gamma has been reported in MEC superficial layers, it remains unknown whether slow gamma is also present. Here, we recorded local field potentials from MEC superficial layers in five freely behaving rats to address this question. Analyses revealed that fast gamma was far more prevalent than slow gamma and that fast gamma occurred most often during theta-related behaviors (i.e., ambulation and REM sleep). Surprisingly, slow gamma was similarly absent during non-REM sleep, a state in which slow gamma occurs prominently in the hippocampus. Analyses of neuronal activity in MEC superficial layers revealed that "grid cell" firing was modulated by the phase of fast gamma during all three states (i.e., ambulation, REM, and nREM), with stronger modulation occurring during theta-associated states. In sum, slow gamma was rarely detected in MEC superficial layers, whereas fast gamma occurred prominently during theta-related states. These results suggest that fast gamma may facilitate the transfer of sensory information from MEC to hippocampus during active environmental exploration. Additional studies are needed to address the potential functional significance of fast gamma during REM sleep.

[66] Experience-Dependent Trends in CA1 Theta and Slow Gamma Rhythms in Freely Behaving Mice

Brian J Gereke[1]*, Alexandra J Mably[2,3], and Laura Lee Colgin[1,2,3]
[1]Institute for Neuroscience, University of Texas at Austin, Austin, Texas; [2]Center for Learning and Memory, University of Texas at Austin, Austin, Texas; [3]Department of Neuroscience, University of Texas at Austin, Austin, Texas
*bgereke@utexas.edu

CA1 place cells become more anticipatory with experience, an effect thought to be caused by plasticity in CA3-CA1 synapses. Theta (~6-12 Hz), slow gamma (~25-50 Hz), and fast gamma (~65-100 Hz) rhythms are thought to route information in the hippocampal network and coordinate place cell activity, yet it is unknown whether these rhythms exhibit experience-dependent changes concurrent with those observed in place cells. We addressed this question by examining recordings from mice traversing a familiar circular track for three sessions per day across multiple days. We found that slow gamma rhythms were suppressed in the early minutes of the first session of each day, though both theta and fast gamma rhythms were elevated during this same time period. The same pattern was not observed in later sessions. In the first minutes of the second and third sessions of each day, all three rhythms were elevated. Interestingly, theta was elevated to a greater degree in the first minutes of the first session than in the first minutes of later sessions. Additionally, all three rhythms were influenced by running speed in dynamic ways, with the influence of running speed on theta and slow gamma changing over time within and across sessions. These results raise the possibility that experience-dependent changes in hippocampal rhythms relate to changes in place cell activity that emerge with experience.

[67] Developmentally Restricted Long-term Potentiation of Glycinergic Inhibition onto Neurons of the Medial Superior Olive

Bradley D. Winters*, Nace L. Golding
University of Texas at Austin, Department of Neuroscience and Center for Learning and Memory
*bwinters@austin.utexas.edu

Glycinergic inhibitory inputs onto neurons of the medial superior olive (MSO) are important for processing of binaural timing-based sound localization cues. After hearing onset, the strength and subcellular location of these inhibitory inputs are dramatically altered. The cellular processes underlying these experience-dependent changes are not known. Using whole-cell recordings in gerbil brainstem slices, we find a novel form of inhibitory long-term potentiation (iLTP) that requires high-frequency (200 Hz) pairing of synaptic activation with action potential (AP) firing. NMDA receptor activation and calcium influx were key components of a cumulative mechanism that was sensitive to the rate and number of pairings. Linking reinforcement of inhibition to firing would provide a mechanism to preserve inhibitory inputs that are well timed with binaural excitation. The ability to induce iLTP was eliminated over the first two weeks of hearing and correlated with decreasing AP amplitude and backpropagation. Increasing depolarization during the induction protocol by replacing APs with voltage clamp steps was able to rescue iLTP, indicating the regulation of synaptic plasticity by the developing intrinsic properties of these neurons. Progressive reduction in AP backpropagation would deprive distal inhibitory synapses of reinforcement and may help establish the mature, soma biased pattern of inhibition.

[68] Cerebellar cortex mechanisms supporting extinction and reacquisition of conditioned eyelid responses at different interstimulus intervals

Hunter E. Halverson*, Andrei Khilkevich and Michael D. Mauk
Center for Learning & Memory, University of Texas at Austin, Austin, TX 78712
*hunter.halverson@gmail.com

The cerebellar cortex is necessary for expression of properly timed conditioned eyelid responses (CRs) at different interstimulus intervals (ISIs). Cortical involvement in expression of CRs is clear, the mechanisms within the cortex supporting subsequent extinction and reacquisition of CRs at different ISIs have not been described. Relating changes in Purkinje cell (PC) and molecular layer interneuron (MLI) responses to the rate of extinction and reacquisition of CRs at different intervals is necessary to establish the cerebellar rules governing these processes. Time demands at different ISIs could lead to different interactions between PCs and MLIs and the rate of CR extinction observed at short and long intervals. Before training a 12 tetrode hyperdrive array was implanted dorsal to the ipsilateral (to the trained eye) anterior lobe. Neuronal activity was recorded during initial CR expression and extinction with delay conditioning using a 550 ms tone conditioned stimulus (CS) and 50 ms periorbital shock (2-3 mA) unconditioned stimulus (US). After initial training with a 500 ms ISI, shorter (ISI 250) and longer (ISI 750) intervals were used to investigate interactions between PC and MLI responses during extinction and reacquisition. Eyelid PCs were identified by the presence of short latency US-evoked complex spikes. Eyelid MLIs were identified by a two step process using baseline firing properties and correlation with eyelid CRs. Reacquisition at longer ISIs would often be contaminated (early CR onset) by training at shorter ISIs early within a session. This contamination during reacquisition would extinguish during the session. Extinction of CRs at longer intervals (ISI 500 and above) was faster than at shorter ISIs. Activity of eyelid PCs and MLI tracked CRs closely during extinction at longer ISIs and were more variable at shorter ISIs. These results suggest short intervals place time demands on the cerebellum that lead to decreased synchrony between PCs, MLIs and eyelid CRs during extinction.

[69] Ultrastructural identification of synapses receiving channelrhodopsin2-expressing axons following light-induced long-term potentiation

Masaaki Kuwajima[1]*, Guan Cao[1], Bridget L. Kajs[1], Boris V. Zemelman[1,2], Kristen M. Harris[1,2]
Center for Learning and Memory, Department of Neuroscience, The University of Texas at Austin, USA
*masa@clm.utexas.edu

Understanding the cellular mechanisms of learning and memory requires substantial improvement in our ability to identify the synapses involved. Unequivocal detection of changes in synapses and their subcellular components requires (1) confidence that specific synapses have been potentiated, and (2) their three-dimensional reconstruction from serial section electron microscopy (3DEM). We re-engineered a genetically encoded EM tag based on the plant ascorbate peroxidase to optimize its expression and targeting in mammalian neurons (mAPEX2), leading to enhanced contrast for 3DEM. An adeno-associated virus (AAV) vector was constructed to co-express mAPEX2 with Chr2-EGFP (channelrhodopsin2, ET/TC variant) as two proteins separated by the self-cleaving 2A peptide (P2A) from porcine teschovirus. The virus was injected unilaterally into the hippocampal area CA3 of adult mice. NMDAR-dependent long-term potentiation lasting for at least 3 hrs was induced at CA3 → CA1 synapses in acute hippocampal slices using high-frequency light pulses (λ = 473 nm at ~13.5 mW; 6 trains of 100 pulses at 50 Hz, pulse duration 1 ms, 10-15 s intervals between 100-pulse trains). At end of recording, the slices were chemically fixed and the mAPEX2-expressing axons in the area CA1 were then labeled with tyramide signal amplification reagent (conjugated with Alexa Fluor 488 or 647), which were visualized subsequently by post-embedding immunogold labeling with antibodies against the fluorescent dyes. Acute slices prepared from AAV-injected animals show outstanding ultrastructure for 3DEM analysis. Our new approach should greatly facilitate the elucidation of synapse-specific ultrastructural changes associated with long-term synaptic plasticity, a crucial step in understanding the cellular mechanisms of learning and memory.

Support: Brain Research Foundation (Scientific Innovations Award to KMH), Human Frontier Science Program (RGP0041 to BVZ), NIH (MH104319 and NS074644 to KMH; EY026446, EY026442, and NS094330 to BVZ), The University of Texas System (UT BRAIN Seed Grants NNRI 365222 and 365289 to BVZ);

[70] Spine Apparatus and PSD Area in Relation to Dendritic Caliber in Dentate Gyrus and CA1

Kate Dembny*, Alyssa Herbort, Kyle Zatyko, Corey Haines, Jordan Mackey, Masa Kuwajima, Kristen Harris
University of Texas at Austin, Institute for Neuroscience,
Center for Learning and Memory
*kate.dembny@gmail.com

Neurons communicate across specialized junctions called synapses. The strength of these synaptic connections can be regulated by the presence or absence of specific organelles, including the smooth endoplasmic reticulum (SER). Spine apparatus (SA) is a specialized form of SER that plays a role in calcium signaling, synthesis and modification of transmembrane proteins, and the regulation of efficacy of synaptic transmission. Neurons also contain microtubules, a cytoskeletal protein that plays a role in the movement of organelles throughout the cell. In previous studies, microtubule count has been used as a proxy for dendritic caliber, as shaft diameter can vary along the length of the dendrite, and a positive correlation between dendritic caliber and number of protrusions has been found. It was concluded that while dendrites in the SLM have fewer spines, they are more likely to contain spine apparatus and have larger PSDs. Additionally, spines in the SLM containing SER or SA had larger PSDs than those that did not. To determine this, brain tissue was taken from adult male Long Evans rats and was processed for serial section transmission electron microscopy (ssTEM). Reconstruct™ software was then used to create 3D renderings individual dendrites and their synapses and tag neuronal organelles.

[71] Effects of Test-Pulse and Theta Burst Stimulation on Dendritic Spine Formation in Developing Rat Hippocampal Area CA1

Corey Haines[2]*, Sindy Ventura[1], Marshall Drake[1,2], Guan Cao[3], and Kristen Harris[1,2]
[1] Center for Learning and Memory, Univ. Texas, Austin, TX; [2] University of Texas at Austin, Austin, TX; [3] PixarBio Corporation
*chaines@utexas.edu

Neurons communicate across specialized junctions called synapses that occur on small protrusions called dendritic spines. Theta-burst stimulation (TBS) is a robust stimulation protocol used to induce long term potentiation (LTP), a cellular mechanism for learning and memory. Previous studies have demonstrated that administering repeated bouts of TBS can induce late-phase LTP at postnatal day 10 (P10) in the rat hippocampus, earlier than previously observed at P12 when administering only one bout of TBS. Additionally, before P12 dendritic protrusions occur as immature filopodia rather than dendritic spines. Thus, we hypothesized that after administering one bout of TBS at P10 immature dendritic filopodia would undergo a morphological shift into mature dendritic spines. Hippocampal slices taken from six P10 male Long Evans rats either underwent perfusion fixation (naïve) or were implanted with one stimulating electrode near CA3 and one recording electrode in the middle of CA1 stratum radiatum. Test-pulse stimulation (TPS) was administered every 2 minutes to control and experimental slices, which also received one bout of TBS at 60 minutes after the start of TPS. Slices were prepared using serial section electron microscopy. Preliminary results suggest there is an increase in the number of dendritic spines at P10 after TPS and TBS.

[72] Functional dissection of neuronal classes and microcircuit dynamics of the claustrum

Roberta Leone*, Alan Carleton, Boris V Zemelman
Centre for Learning and Memory, UT-Austin; University of Geneva (CH).
*leone@austin.utexas.edu

The claustrum shares extensive and reciprocal connections with the cortex, but its dimensions, circuit composition and function are mostly unknown. In this study, we use novel molecular-genetic techniques and exploit existing cortical connectivity to identify and characterize the excitatory and inhibitory components of the claustrum. Based on cortical injections of fluorescent cholera toxin, we have identified proximate, non-overlapping sub-populations of efferent neurons that extend beyond the accepted borders of the mouse claustrum. Constituent neurons display distinct intrinsic properties such as regular spiking, adapting, stuttering, or bursting. We now extended these findings to precisely define the internal circuitry of the claustrum. Cortical excitatory neurons are pharmacogenetically activated to label post-synaptic cells in reporter mice, thus allowing us to identify claustral neurons that respond to specific cortical inputs. This approach is then combined with novel retrograde recombinant viruses, as well as patch clamp multiple recordings and selective optogenetic stimulation, to determine which neurons in the claustrum are affected by incoming cortical inputs, which efferent projection are activated, and how the excitatory and inhibitory components shape the claustro-cortical response. These studies represent the critical first step in uncovering circuit mechanisms of the claustrum and the role of this region in brain function.

[73] Eyeblink responses as a readout of network hyperactivity and learning in Alzheimer's disease model mice

Cheasequah Blevins*, Richard Gray, Dylan Barbera and Boris Zemelman
Center for Learning and Memory, Department of Neuroscience, The University of Texas at Austin
*cheasequah.blevins@gmail.com

Eyelid response paradigms have been used to study associative (eyeblink conditioning) and non-associative (sensitization of the startle response) learning. We employed high-speed videography to examine behavioral correlates of neuronal dysfunction in 3xTg and $PS1^{M146V}$ mouse models of Alzheimer's disease. Prominent features of AD in the patient population include hippocampal hyperactivity, increased anxiety and co-atrophy of the amygdala and hippocampus. While transgenic mouse models tend not to display cell loss or regional atrophy, they do typically exhibit increased anxiety behaviors and network hyperactivity. We find that young and aged AD mice do not have a deficit in acquisition of eyeblink conditioning: while genotype differences did not reach statistical significance, there was a trend toward more rapid learning in AD animals, measured as a decrease in the mean number of days to reach behavioral criterion, compared to non-transgenic controls. We also detect fear-potentiated acoustic startle, comprising the early development and persistence of fear-potentiated startle responses, during low volume tone-cued eyeblink training in young AD animals, but not control animals. Both behavioral outcomes can result from hyperactivity of the amygdalofugal projection to brainstem structures, such as pontine nuclei (eyeblink conditioning) and pontine reticular formation (acoustic startle). Future experiments will test the hypothesis that the observed behaviors in these model animals arise from AD-related hyperactivity and are specific to cell classes and projection targets of the amygdala.

[74] Unbiased discovery of gene regulatory motifs by suffix array kernel smoothing (SArKS)

Dennis Wylie*, Hans Hofmann and Boris V Zemelman
Center for Learning and Memory, Department of Neuroscience, Department of Integrative Biology, The University of Texas at Austin
*denniswylie@austin.utexas.edu

Precise targeting of neurons of a particular class is a key first step for studying cell type-specific functions within brain circuits. Such targeting is possible in engineered mouse lines, but not in less genetically tractable species. Indeed, fundamental rules governing differential gene expression in somatic cells are not known. We have developed a framework for identifying candidate DNA regulatory regions as a prelude to constructing short cell type-specific promoters for use in recombinant viral vectors. We describe a new analytical technique for de novo regulatory motif discovery, Suffix Array Kernel Smoothing (SArKS), designed to take full advantage of continuous differential expression metrics derived from modern RNAseq experiments. Here we apply SArKS to RNAseq data sets from multiple glutamatergic and GABAergic neuron classes to yield ranked non-coding sequence domains associated with gene expression in parvalbumin neurons. We observe distinct variants of known transcription factor binding sites (e.g., estrogen-related receptor binding sites) upstream and downstream of gene initiation sites, as well as in introns. Intriguingly, some enriched motifs appear to be related to transposable elements (B1 repeats) found throughout the genome. We are now investigating extending the SArKS methodology to the joining of the uncovered regions to build and test longer, promoter length expression regulatory domains.

[75] A robust ionotropic activator for brain-wide manipulation of neuronal function

Elizabeth Gardner*, Jimmy D Gollihar, Andrew D Ellington and Boris V Zemelman
Center for Learning and Memory, Department of Neuroscience, Department of Integrative Biology, The University of Texas at Austin
*egar18111@gmail.com

We aim to engineer orthogonal receptor/ligand pairs for pharmacogenetic regulation of multiple neuron populations. The novel receptors are based on purinergic P2X receptor architecture, and will be generated using directed evolution in yeast. We have examined all seven receptor subtypes to elucidate channel gating mechanisms, creating 1000 variants of each for *in silico* binding assays to a library of 20 ATP analogs. We have deployed the CPR (Compartmentalized Partnered Replication) positive selection and amplification system in yeast, amplifying candidate channel sequences in a calcium-dependent fashion from emulsified cell isolates. We have also designed a complementary negative selection circuit that inverts the calcium dependence. For our selection scheme, we describe the screening of human $P2X_{1-7}$ for proper targeting and function, demonstrate the first instance of mammalian ionotropic channel signaling in yeast, and characterize the kinetics of the $P2X_2$ receptor using this platform. We are now building mutant libraries via site-saturation mutagenesis of key ligand binding using a vector that will shuttle between yeast and mammalian cells. We ultimately expect to assay a pool of approximately 10^8 mutants for optimal gating. Candidates with be validated in mammalian fibroblasts and neurons using electrophysiological and optical techniques, and in the mouse brain using behavioral assays.

[76] A high precision method for activity-dependent neural circuit mapping

Nathaniel Nocera*, Alan Meis, Stephen Martin, Michael Drew and Boris Zemelman
Center for Learning and Memory, Department of Neuroscience, Department of Chemistry, The University of Texas at Austin
*nnocera@utexas.edu

A central goal in neuroscience is to identify brain circuitry supporting mental and behavioral states. We are developing a novel method for labeling and accessing such transient, behaviorally-relevant neuron assemblies in awake animals. The key unique features of our approach are its temporal precision, which matches the timescale of naturalistic behavior, and its ability to label multiple cell populations in the same animal, enabling state-specific cell ensembles to be directly compared. Our molecular-genetic technique is designed to identify activated neurons based on elevated intracellular calcium and then tag them using light. Light application is especially attractive because it is temporally precise: just as other optogenetic methods have aided neuronal circuit analysis by approximating the timescale of cell activity, so too does a light-dependent labeling technique illuminate functional cell assemblies. The technique is also entirely virus-based, and can therefore be used in multiple species without the reliance on transgenic animals. We anticipate that this methodology will be used to elucidate the neuronal substrates of diverse mental states, such as fear, hunger, depression, anxiety, and addiction, thereby advancing the exploration of critical brain networks.

[77] Accessing defined neuron classes in rodent and primate neocortex for imaging and manipulation

Preeti Mehta*, Bridget Kajs, Lauren Kreeger, Jagruti Pattadcal, Devon Greer, Eyal Seidemann, Nicholas Priebe and Boris Zemelman
Center for Learning and Memory, Center for Perceptual Systems, Department of Neuroscience, Department of Psychology, The University of Texas at Austin
*prtmht@gmail.com

An important question in brain research is how neurons and the circuits they form process information to produce behavior. To understand what happens in a human brain, it is necessary to study a brain of similar complexity, such as that of a primate. Like much of the brain, the neocortex consists of different classes of neurons that can excite, inhibit or modulate the activity of neighboring cells. Accessing these different neuron classes has traditionally required manipulating an animal's DNA, which is especially difficult in a primate. Here we describe our nascent efforts to target excitatory and key subsets of inhibitory neurons in the mammalian brain using recombinant adeno-associated viruses. To date, we have expressed heterologous proteins successfully, comprehensively and for periods lasting many months in excitatory and GABAergic inhibitory neurons in mice, gerbils, marmosets and macaques. Moreover, using interdependent viruses with engineered promoters, we can reliably access somatostatin-positive neurons. We are now testing expression systems for targeting subsets of parvalbumin, neuropeptide-Y and vasoactive intestinal polypeptide-positive GABAergic neurons. These advances will greatly enhance our ability to image and manipulate neural circuit elements across species.

[78] A novel molecular-genetic approach for targeting functional neuron classes in the central nucleus of the gerbil inferior colliculus

Lauren J. Kreeger*, Preeti Mehta, Nace L. Golding and Boris V. Zemelman
Center for Learning and Memory, Department of Neuroscience, The University of Texas at Austin
*laurenkreeger@utexas.edu

Understanding the organization of neural circuits is essential for studies of circuit function. Neurons in the central nucleus of the inferior colliculus (ICC), a midbrain auditory structure, exhibit diverse morphologies, postsynaptic targets, endogenous neurochemical markers, and electrophysiological properties, defying mapping and classification efforts. We aim to overcome these limitations and map ICC connectivity using recombinant viruses. By utilizing interdependent viruses, we have been able to achieve fluorescent protein expression in subpopulations of excitatory and inhibitory ICC neurons. We have characterized the labeled neurons by multiplexed *in situ* hybridization and targeted the neurons for whole-cell current clamp recordings to bridge the gap between endogenous neurochemical markers and cell intrinsic properties. The vast majority of the virally-targeted cells express cholecystokinin, a neuropeptide normally associated with excitatory and inhibitory neurons, and have a homogeneous "adapting" firing pattern. Indeed, this group can be further divided into excitatory and inhibitory populations on the basis of distinct action potential signatures. Both subpopulations have dense synaptic connections with nearby ICC neurons that display diverse firing patterns and morphologies. We also found that, outside of the intrinsic ICC circuit, the excitatory neurons project to the medial division of the medial geniculate nucleus. Ongoing experiments aim to determine the specific patterns of connectivity within the ICC and between the ICC and the auditory thalamus.

[79] Activity-dependent dendritic morphology and gene expression in sensory neuron pair URX in *C. elegans*

Jesse Cohn*, Nicole Zarate, Jonathan Pierce
Department of Neuroscience, University of Texas at Austin
*jcohn@utulsa.edu

Prolonged sensory input and chronic neural activity can lead to several downstream cellular alterations, such as morphological remodeling and changes in gene transcription. The pathways that lead to these changes are often unique in different cell types, and the streamlined nervous system of *C. elegans* offers a useful system for uncovering genes involved in these processes. To this end, we are investigating cellular changes in a chronically active neuron in *C. elegans* that senses environmental oxygen. This neuron, called URX, has sustained cGMP production in response to oxygen, which leads to continual calcium entry into the cell through cyclic-nucleotide gated ion channels. We found two consequences of chronic activity in the URX neurons. First, the dendritic endings of the neuron grow and branch in an activity-dependent manner. These dendritic tips are mainly actin based and are often studied as a model for synaptic remodeling. Secondly, a transcriptional reporter for a pro-apoptotic BH3-only protein is upregulated by this activity. To identify genes that influence these phenomena, we performed a forward genetic screen and intriguingly recovered a loss-of-function allele of the worm homolog of the CREB transcription factor. Despite its well-known importance in activity-dependent phenomena across neuroscience, surprisingly this is the first time CREB has been identified from an unbiased genetic screen in *C. elegans*. We are currently exploring several avenues to understand how it controls these activity-dependent cellular changes in URX.

[80] Mice use a cortical pathway to discriminate binocular motion direction

Veronica Choi*, Sung Jun Joo, Jason Samonds, Alexander C. Huk, Nicholas J. Priebe
The University of Texas at Austin
*v.choi88@gmail.com

Rodents have become increasingly popular to study neural processing as genetic tools are available to measure and manipulate their neural circuits. Rodent visual cortex has been extensively studied, but little is known about the visual signals used to guide behavior. Here we utilized a behavioral paradigm that demonstrates mice can use binocular information for visually-guided behavior. We trained animals to walk or stop depending upon binocular visual cues. Mice stopped for objects moving towards them and walked for other conditions. The cues for toward and away motion were only accessible by integrating the visual signals presented to each eye.
The mean walking speed of all animals were slower for the towards condition from all other conditions which indicates that mice are able to distinguish motion in depth signals, and integrate visual signals between their eyes. We also investigated if the monocular cells of the visual cortex are important in driving this behavior or the binocular cells in the visual cortex are required for the discrimination. Using optogenetic inactivation we first demonstrate the visual cortex is essential for the expression of this behavior and second that integration of visual cues between the eye occurs in binocular cells in visual cortex.

[81] Natural image and receptive field statistics predict saccade sizes

Jason M. Samonds,[1,2,3]* Wilson S. Geisler,[2,4] Nicholas J. Priebe[1,2,3]
Department of Neuroscience, University of Texas at Austin; [2]Center for Perceptual Systems, University of Texas at Austin; [3]Center for Learning and Memory, University of Texas at Austin; [4]Department of Psychology, University of Texas at Austin
*samondjm@gmail.com

Mice do not have a fovea like humans and other primates (Dräger and Olsen 1982; Jeon et al. 1998). This raises the question of why do mice make saccadic eye movements, since the primary function of saccades are to foveate a region of interest in a scene based on salience (Koch and Ullman 1985) and task demands (Yarbus, 1967; Hayhoe and Ballard 2005; Najemnik & Geisler 2005). Researchers have not previously examined rodent saccades in detail in the context of visual processing because their eye movements are thought primarily to stabilize gaze (Stahl 2004; Wallace et al. 2013). We find that saccades in mice share some properties with those in humans: saccade amplitude and frequency depends on image size. We hypothesized that another function of saccades that would benefit both humans and mice is to decorrelate incoming visual information so that neurons are minimally adapted and can continually sample non-redundant information. We characterized decorrelation distances in natural images for a wide range of neuronal receptive field sizes and find that this property can be used to predict saccade size distributions for a number of mammals, including non-human primates, cats, and mice. Our analysis suggests that receptive field sizes and the decorrelation of neuronal responses play an important role in the generation of saccadic eye movements.

[82] Whole cell recording of synaptic and intrinsic conductances in V1 of behaving monkeys

Baowang Li*, Nicholas Priebe, Eyal Seidemann
Center for Perceptual Systems, Department of Neuroscience,
The University of Texas at Austin
*libaowang@gmail.com

We seek to understand how neurons integrate and transform synaptic inputs into patterns of spiking activity by using whole-cell recordings from V1 of behaving macaques. These membrane potential (Vm) records provide a perspective on both the network and intrinsic state that has not previously been available in primates. Importantly, we also assay the membrane resistance (Rm) of cells which allows us to assess the state of the synaptic and intrinsic conductances. We make these measurements while presenting large and small visual stimuli. We obtained three major findings. First, visual stimulation depolarizes neurons and evokes large decreases in Rm. This is consistent with models in which visual stimulation dramatically shifts the state of the network (Tan et al., 2014) and increases the synaptic drive impinging on individual neurons (Borg-Graham et al., 1998). Second, in many V1 neurons, increasing stimulus size evokes smaller Vm depolarization. The synaptic basis of this surround suppression could be reduced excitation, increased inhibition (Haider et al., 2010), or reductions in both (Ozeki et al., 2009). We find that small stimuli evoke larger Rm changes than large stimuli, suggesting surround suppression emerges from a reduction in synaptic input instead of an increase in inhibition. Finally, we examined the relationship between fluctuations in Vm and Rm that are stimulus independent (i.e., fluctuations under identical visual conditions). Surprisingly, we find that stimulus-independent increases in Vm are associated with increases in Rm. This positive relationship may reflect intrinsic voltage-gated conductances or fluctuations in the balance between excitation and inhibition. To determine whether intrinsic mechanisms play a role we systematically shifted Vm while measuring Rm and have uncovered an intrinsic mechanism that increases Rm with Vm. Overall, our results provide important novel constraints to models of the intrinsic and synaptic conductances that underlie information processing by cortical neurons in behaving subjects.

[83] Medial prefrontal cortex supports flexible memory retrieval

Neal W Morton* and Alison R. Preston
The University of Texas at Austin
*neal.morton@austin.utexas.edu

Memories are not formed in isolation, but rather are learned in the context of a vast store of existing knowledge. In order to use this store of information flexibly, the memory system is thought to code information about relationships between different events. Medial prefrontal cortex (MPFC) has been proposed to facilitate the discovery of relationships by forming integrated memory traces that contain information about multiple events. To test this account, we had participants learn face-object and scene-object (denoted AB) pairs. Then fMRI data were collected while participants learned overlapping object-object (BC) associations. Finally, participants performed an associative inference task where they were tested on indirect associations between A and C items. Using multivariate pattern analysis, we found evidence of reactivation of related memories during learning of overlapping object-object associations. The degree of reactivation during encoding predicted individual differences in reaction time on the inference test, consistent with our prediction that memory reactivation would support successful memory integration, facilitating flexible use of memory. Furthermore, we found that during the inference task, MPFC and anterior hippocampus are more active during tests where there was greater memory reactivation during the corresponding object-object (BC) association. These results suggest that MPFC is selectively recruited during retrieval of integrated memories.

[84] Sequencing Effects on the Retention of Generalized Knowledge and Source Memory

*Sharon M. Noh and Alison R. Preston
The University of Texas at Austin
*smnoh@utexas.edu

Though the goal of learning is enhanced long-term retention, most training programs are validated solely on immediate performance. We used a category learning paradigm to assess the degree to which generalized knowledge and memory for detail is preserved as a function of training with different study schedules (blocked vs. interleaved) following a delay. Participants were trained to identify paintings by different artists for which half of the artists were studied in a blocked schedule (i.e., all paintings of the artist were presented sequentially), and the remainder were learned in an interleaved schedule (i.e., paintings for multiple artists were intermixed). After training, participants completed a generalization task and a memory task administered immediately after training, as well as after a 1-week delay. For the memory task, there was a main effect of delay such that memory declines were observed following the delay. For generalization, however, there was a schedule x delay interaction—interleaved training led to superior generalization performance (relative to blocked) immediately after training, but this difference was attenuated as the blocked condition showed improved performance following a week delay. These results suggest that although memory for detail declines over time, generalized knowledge is preserved and in some cases, improved.

[85] Hippocampal subfield coding of overlapping visual events

Robert J. Molitor*, Katherine R. Sherrill, Neal W. Morton, & Alison R. Preston
Center for Learning & Memory, University of Texas at Austin
*rjmolitor@utexas.edu;

Overlapping visual events can be encoded by the hippocampus (HPC) via pattern separation or memory integration. Computational modeling, supported by electrophysiological recordings from animals, suggests that HPC subfield dentate gyrus (DG) separates and orthogonalizes overlapping memories, whereas CA1 integrates overlapping memories. However, evidence of this subfield specialization in human HPC is lacking. Here, we manipulated the visual similarity of overlapping events in an associative inference task to investigate whether there are differences in subfield representations in human HPC. Participants studied initial face-shape or scene-shape pairs (AB), followed by overlapping shape-object pairs (BC). The shapes seen during BC learning were parametrically manipulated to be visually similar or visually dissimilar to shapes from AB learning. Finally, participants were tested on their ability to infer the indirect relationship between A and C items due to the overlapping B shape. Performance on tests of direct memory (BC) and inference (AC) varied as a function of visual similarity, indicating that our visual manipulation successfully altered memory formation. Planned fMRI analyses will use representational similarity analysis to assess the relationship between neural similarity of indirectly related A and C items as a function of visual similarity across events. We predict DG will show a non-monotonic relationship between neural differentiation and visual similarity, reflecting pattern separation. In contrast, we predict CA1 will exhibit a linear relationship between neural integration and visual similarity, reflecting memory integration. These data stand to bridge human and animal research regarding the functional specialization of HPC subfields in memory.

[86] Temporal structure learning facilitates inductive generalization

Athula Pudhiyidath[1]*, Anna Schapiro[2], & Alison Preston[1]
[1]*The University of Texas at Austin,* [2]*Harvard Medical School*
*athula.pud@utexas.edu

Life never stops moving forward, and yet we perceive events as discrete moments in time with both a beginning and an end. We glean temporal relationships among events by coding temporally proximal events similarly and distant events as distinct. To examine how these complex temporal codes can guide reasoning and learning, we created a novel adaptation of a temporal coding paradigm. In our study, adult participants were visually presented with a continuous stream of 21 novel 3D objects. Unbeknownst to participants, the objects were presented in an order that was in accordance with an underlying temporal structure that consisted of three groupings. Thus, there were hidden temporal regularities in the presentation order of these novel objects. After this exposure phase, participants completed an inductive generalization test in which they made judgments about which pairs of objects from the exposure phase lived in the same habitat; these corresponded to one of the three groupings in the temporal structure. Results revealed that participants' implicit knowledge of the objects' temporal structure was correlated with how well they could reason about the objects' shared habitats. These results suggest that that knowledge about temporal statistics may guide the ability to reason about the world.

[87] Modulatory Effects of the Estrous Cycle on Contextual Renewal of Appetitive and Fear Behavior after Extinction

Emily N. Hilz*, Marie H. Monfils, & Hongjoo J. Lee
The University of Texas at Austin
*emilyhilz@yahoo.com

As estrogen rises across the 5 day estrous cycle, synaptic plasticity increases in the hippocampus of adult female rats. The hippocampus plays an important role in contextual information processing, having been shown to modulate both renewal and memory retrieval of conditioned fear after extinction. In the present experiment, we examine whether the level of estrogen present during extinction – either low-estrogen during the metestrus/diestrus (M/D) phases of the estrous cycle or high-estrogen during the proestrus (P) phase of the estrous cycle – plays a role in contextual renewal of appetitive and fear behaviors.

Female and male Sprague-Dawley rats were exposed to both appetitive and fear acquisition and extinction procedures and tested for renewal of conditioned behavior in an ABBA design (i.e., acquisition in context A, extinction in context B, and test in both contexts A and B). Preliminary results suggest that if female rats were in the high-estrogen P phase during extinction, they show significantly higher renewal of behavior in the original training context as compared to the females that were in low-estrogen M/D phase during extinction. Male rats did not significantly differ from either group. Our results suggest that estrogen levels might modulate contextual information processing during extinction.

[88] The role of Reelin and mGluR in processes associated with Alzheimer's disease

Murat S. Durakoglugil*, Florian Plattner, Catherine Wasser, Courtney Lane, Xunde Xian, Joachim Herz
Center for Translational Neurodegeneration Research, Department of Molecular Genetics, UT Southwestern Medical Center, Dallas, TX 75390
*murat.durakoglugil@utsouthwestern.edu

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of amyloid plaques and neurofibrillary tangles. The main component of amyloid plaques is amyloid-beta (Aβ) that has been implicated in synaptic dysfunction by enhancing long-term depression (LTD) through activation of mGluR-dependent Striatal-Enriched Tyrosine Phosphatase (STEP). Carriers of the ε4 allele of ApoE (ApoE4) are at increased risk for AD compared with those carrying the more common ε3 allele (ApoE3). Reelin is a specific ligand for ApoER2- and VLDL receptors that also bind ApoE. Our previous results showed that ApoE4 may promote AD by impairing Reelin signaling, which in turn interferes with the trafficking of ApoER2- and glutamate receptors. Whether Reelin affects mGluR-LTD or expression of STEP is not known.

Our results show that Reelin application reduces DHPG-induced increase in STEP levels, regulates surface AMPA receptor trafficking and concomitantly blocks mGluR-dependent LTD in hippocampal area CA1. In a Reelin conditional knock-out mouse model the expression of calcium permeable GluA2-lacking AMPA receptors is enhanced resulting in a paradoxical reduction of DHPG-induced LTD as well as impairing the rapid synaptic scaling that occurs after NMDA receptor block. These data suggest that secreted Reelin is a modulator of mGluR-dependent LTD via AMPA receptor trafficking.

[89] Identification and manipulation of fear extinction engrams in the hippocampus

Anthony F Lacagnina*, Meredith McCarty, Chelsea Crovetti,
Christine A Denny, Michael R Drew
The University of Texas at Austin
*aflacagnina@gmail.com

Extinction is an exposure-based therapy in which repeated exposure to a fearful stimulus in the absence of threat gradually reduces fearful behavior. Instead of erasing the original memory, extinction appears to create a parallel memory trace that inhibits or competes with the original memory. While the notion that extinction creates a unique memory trace is the predominant view, direct evidence for this claim is lacking. To investigate the mechanisms responsible for extinction, we utilized ArcCreERT2 transgenic mice to indelibly tag and manipulate populations of neurons active during contextual fear acquisition or extinction. Recent studies using a similar technique have shown that hippocampal 'engram cells' of the dentate gyrus (DG) active during contextual fear acquisition are necessary and sufficient for driving fear memory recall. We found that extinction decreased the reactivation of DG 'acquisition cells' in the conditioning context, suggesting extinction recruits a unique population of neurons to represent the context. To test this directly, active neurons were tagged during either fear acquisition or extinction. Silencing 'acquisition cells' following extinction had no impact on behavior, while silencing 'extinction cells' caused an immediate return of fear in the extinguished context. Silencing 'extinction cells' after spontaneous recovery or following re-extinction had no effect. These findings support the DG encoding fear acquisition and extinction in unique populations of neurons, indicating the hippocampal representation of a context is modified by changes in emotional valence.

[90] Monocular deprivation in mice decreases binocular disparity selectivity

Jagruti J. Pattadkal[1]*, Ben Scholl[2], Nicholas Priebe[1]
[1]Center for Learning and Memory, University of Texas at Austin, [2]Max Planck Florida Institute, Jupiter, Florida
*jagrutipattadkal@gmail.com

Experience dependent plasticity plays a crucial role in shaping the responses of sensory neurons. Monocular deprivation (MD) during the visual critical period shifts the ocular preference of binocular neurons towards the open eye in the primary visual cortex. Normal mouse V1 neurons are dominated by inputs from the contralateral eye. MD of the contralateral eye causes the ocular inputs to become more balanced. Mice present a unique situation where contralateral eye deprivation causes neurons to become more binocular. It is not known how this shift in inputs alters the functional binocular responses of neurons. We measured the ocular dominance (OD) and disparity selectivity in mice following contralateral eye deprivation to study how the shift in OD affects disparity selectivity, a computation requiring binocular integration. The increase in binocularity as measured by OD decreased binocular disparity selectivity. The decrease in disparity selectivity was a result of disruption of existing tuning, as disparity selectivity in animals before MD was found to be similar to normal mature animals. Decreased disparity selectivity was most pronounced in binocular and ipsilaterally biased neurons, neurons that underwent largest changes in OD. We also observed the spatial resolution of the ipsilateral eye to have lowered following MD. These results suggest that suggest that new inputs following deprivation may not maintain the precise spatial relationship between the two eye inputs required for disparity selectivity.