

**Pavlovian Society Annual Meeting
September 22-24, 2011**



Hyatt Regency Milwaukee
333 West Kilbourn Avenue,
Milwaukee, Wisconsin, USA 53203

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- 2:40-3:05 Genetic control of active neural circuits
Mark Mayford, Scripps Research Institute-California
- 3:05-3:15 *Break*
- 3:15-3:25 Heroin-induced conditioned immunomodulation: Neural mechanisms [P44]
Jennifer Szczytkowski-Thompson, University of North Carolina
- 3:25-3:35 Communication between the prelimbic and infralimbic cortices is required for context-sensitive fear learning in the absence of the hippocampus [P39]
Moriel Zelikowsky, University of California, Los Angeles
- 3:35-3:45 NMDA receptors in retrosplenial cortex are necessary for the retrieval and extinction of recent and remote contextual fear memory [P22]
Kevin Corcoran, Northwestern University
- 3:45-3:55 Temporally graded increases in proteasome number and activity in the amygdala following fear conditioning [P31]
Timothy Jarome, University of Wisconsin-Milwaukee
- 3:55-4:30 Neural mechanisms of extinction learning and retrieval of cocaine-associated memories
Devin Mueller, University of Wisconsin-Milwaukee
- 4:30-5:05 Modulation of appetitive and consummatory behavior by food-related cues
Peter C. Holland, Johns Hopkins University

5:15-7:00PM **Poster session and cash bar** *[Atrium]*

Dinner (on your own)

Saturday September 24th

- 8:00-8:30 *Continental breakfast* *[Executive Ballroom/Atrium]*
- 8:30-9:05 Hippocampus-dependent learning: A smoking gun in understanding nicotine addiction
Thomas J Gould, Temple University
- 9:05-9:35 Neurogenesis and theta oscillations interact to keep the brain fit for learning
Tracey J. Shors, Rutgers University
- 9:35-10:10 Conditioning and extinction of fear: Different states of the same memory?
Jelena Radulovic, Northwestern University
- 10:10-10:30 *Break*
- 10:30-11:05 Ambiguous timing of aversive events enhances fear learning through hippocampal
prediction errors
Ki Goosens, Massachusetts Institute of Technology
- 11:05-11:40 Placing prediction into the fear circuit
Gavan McNally, University of New South Wales
- 11:40-12:00 Propranolol rescues poor active avoidance responding, suppresses freezing, and Induces
massive *c-fos* activation in the lateral division of central amygdala [P32]
Christopher Cain, New York University
- 12:00-1:30 *Lunch (on your own)*
- 1:30-1:40 Cytokine signaling in the brain in a mouse model of depression and PTSD after
myocardial infarction [P56]
Natalie Tronson, Northwestern University
- 1:40-1:50 Metaplasticity-like mechanism supporting the selection of fear memories [P55]
Ryan Parsons, Emory University
- 1:50-2:00 Npas 4 regulates a transcriptional program in CA3 required for contextual memory
formation [P36]
Kartik Ramamoorthi, Massachusetts Institute of Technology
- 2:00-2:35 Somatosensory cortex in trace eyeblink conditioning with whisker vibration CS
John Disterhoft, Northwestern University
- 2:35-3:00 Facilitated acquisition of delay and avoidance eyeblink conditioning in college-aged
females expressing inhibited temperament
Michael T. Allen, University of Northern Colorado
- 3:00-3:15 *Break*

- 3:15-3:50 Cellular mechanisms underlying aging-related deficits in extinction of trace fear conditioning.
James R. Moyer, Jr., University of Wisconsin-Milwaukee
- 3:50-4:25 Midbrain periaqueductal gray (PAG) mediates defensive behavior and aversive stimulus processing during fear conditioning
Hugh T. Blair, University of California, Los Angeles
- 4:25-5:00 Foraging in the face of fear: beyond Pavlovian fear conditioning
Jeansok J. Kim, University of Washington
- 6:00- 7:00 *Cash bar* *[Lakeshore ballroom]*
- 7:00 -9:30 Banquet and awards

Life in 3D and in the Dark: the Case of Zooplankton

J. Rudi Strickler, Shaw Distinguished Professor
Department of Biological Sciences, UW-Milwaukee
<http://www.planktonsafari.net/>

Friday oral presentations:

Note: Abstracts and author information for short talks can be found in the poster section by referring to the poster number next to the title in the schedule.

Delay cell contributions to trace conditioning

Michael Mauk, University of Texas at Austin

The cerebellum is necessary for both delay and trace eyelid conditioning, but only trace conditioning requires forebrain structures such as hippocampus and prefrontal cortex. I will present data demonstrating why the cerebellum requires input from forebrain during trace conditioning and that this input derives from a particular region of prefrontal cortex via a particular region of rostral pons. Recordings from these regions of prefrontal cortex and pons reveal that neurons in these regions show classic delay cell-like activity in trace-conditioned animals. These results demonstrate that delay cell activity, which was first recorded in primate dorso-lateral prefrontal cortex and that is widely regarded as being involved in working memory, provides the signal that bridges the temporal gap between CS and US and this is necessary to engage cerebellar learning in trace eyelid conditioning.

Aging and the development of CS-US awareness in classical eyeblink conditioning: Insights from human neuroimaging

John E. Desmond, Johns Hopkins University

When subjects view a movie while receiving paired presentations of tones (CS) and corneal airpuffs (US), but are only told that the tones and airpuffs are "distractors" of the movie, some subjects eventually become aware of the paired CS-US contingency while others do not. Our investigations of younger (20-30 year old) and older (60-70) subjects revealed that older subjects are less likely to become aware of the CS-US relationship. Analysis of brain activations for subjects who become aware versus those that do not reveal an interesting recruitment of regions that are associated with altered awareness (such as neglect) when they are damaged. These regions include parahippocampus, right parietal cortex, and basal ganglia. Changes in awareness-related activation patterns as a function of aging will be described, along with pilot investigations on altering the development of CS-US awareness using neuromodulation.

Neural Error Signals for Cerebellum-Dependent Learning

Jennifer Raymond, Stanford University

A key function of the cerebellum is motor learning. Results from my laboratory indicate that the cerebellum contains independent and molecularly-distinct building blocks from which motor memories can be constructed in a combinatorial fashion. We are now working to dissect cerebellum-dependent learning into its elemental components and understand the rules that determine which plasticity mechanisms are recruited during a given motor learning experience. To this end, we have been conducting recording and stimulation experiments to analyze the neural events controlling the recalibration of the vestibulo-ocular reflex by motor learning. Our results are consistent with the classic theory that the climbing fibers provide an error signal that can support learning. However, our results also suggest that climbing fiber activity supports only certain aspects of learning and not others. We find that learning can occur in the absence of error signals in the climbing fibers, and that the simple spike output of the Purkinje cells may provide an additional error signal guiding motor learning.

Learned together, extinguished apart: reducing fear to compound memories

Marie-H Monfils, University of Texas at Austin

When a neutral conditioned stimulus such as a light or a tone (CS) is paired with an aversive unconditioned stimulus (US) such as a mild foot-shock, associative learning develops such that the CS alone comes to elicit a conditioned response (e.g., freezing). After a few hours, this memory becomes consolidated into long-term storage. Reactivation of a previously consolidated memory, through the presentation of a single CS, opens a reconsolidation window, which allows updating or disruption of the memory before it is re-stored into an enduring representation (Nader et al., 2000). We have previously shown that fear conditioning to a tone+light compound stimulus (T+L) results in memories that are resistant to traditional extinction paradigms as evidenced by spontaneous recovery of freezing just 24 hours after extinction. Additionally, we found that sequential targeting of the individual components of the memory during the reconsolidation phase by presenting an extinction session 10 minutes after an isolated retrieval (ret+ext; Monfils et al., 2009) resulted in a significant reduction of fear expression. In the current study, in order to understand the role of reconsolidation-based techniques in compound fear memories, we investigated the neural regions activated after retrieval of the components of the compound CS. Our results provide insight into how compound memories are retrieved and which neural regions are activated after the partial retrieval of a complex fear memory.

Retrieval-induced enhancements in memory and performance

Matthew Lattal, Oregon Health & Science University

I will review the literature showing potentiation of performance as a function of the duration of the memory retrieval trial, with brief durations causing potentiation and long durations causing extinction. Much of this literature is open to different interpretations, depending on what one considers to be the appropriate behavioral comparison for making inferences about memory. I will review behavioral, pharmacological, and molecular data from our experiments examining performance as a function of the duration of the memory retrieval trial. We suggest a theoretical approach based on extinction processes and operant reinforcement to account for these potentiation effects.

A Deeper Understanding of Habituation From High-Throughput Behavioral Analyses of Mutations in 700+ Nervous System Genes

Catherine H. Rankin, University of British Columbia

We have recently developed a new high throughput behavioral system called the Multi-Worm Tracker (Swierczek et al, Nature Methods 2011) to study mechanosensory habituation in *C. elegans*. With very large sample sizes (over 32,000 wild-type worms and over 54,000 mutant worms for habituation at a 10s interstimulus interval;ISI) we have examined habituation in greater depth than any previous studies. In our studies we have been able to separate decrements in response probability, response size, response speed and latency to respond. We have found an interesting and surprising set of relationships among these variables. Response magnitude and response duration are highly correlated; however, to our surprise, response magnitude and response probability are not correlated. Mutations that altered response frequency did not necessarily alter response magnitude. Thus habituation of response frequency and response magnitude are regulated by different mechanisms. An earlier hypothesis from my lab was that habituation at 10 and 60 sec ISIs were mediated by different mechanisms. When we compared habituation to 10s and 60 s ISIs habituation of response frequency for both ISIs was very similar however there were significant differences in the kinetics of habituation of response probability for the two ISIs. Thus, the differences in habituation at short and long ISIs are primarily due to

differences in the habituation of response frequency. In contrast when we examined these measures for spontaneous recovery from habituation at 2, 10 and 60 s ISIs we found more rapid recovery of both response frequency and response magnitude at shorter ISIs than at longer ISIs. We have identified many genes that play a role in habituation of response magnitude, habituation of response frequency or of both measures. Taken together these data demonstrate that response habituation is composed of a number of different processes, each mediated by different genes and different mechanisms.

Imaging memory traces instilled by Pavlovian conditioning in flies.

Ron Davis, Scripps Research Institute-Florida

Recent studies have focused on using functional cellular imaging to define memory traces in *Drosophila* produced in response to olfactory classical conditioning. We have identified five different traces that form in different neurons in the olfactory nervous system with different temporal kinetics after acquisition. Three traces appear to correspond to short-term memory, one to the consolidation process, and two to long-term memory. The importance of these memory traces to learned behavior will be discussed.

Genetic Control of Active Neural Circuits

Mark Mayford, Scripps Research Institute, California

When we learn new information we use only a tiny fraction of the neurons in our brain for that particular memory trace. This sparse encoding makes it difficult to study the cellular and molecular changes associated with learning. In this lecture I will discuss recent results from our lab and others that seek to develop genetic tools to target the sparse subset of neurons associated with a particular specific memory trace. In one approach we combine elements of the Tet-system with a promoter that is stimulated by high level neural activity (the *cfos* promoter) to generate mice in which a genetic tag can be introduced into neurons based their activity at a given point in time. Using this approach we found that neurons activated during learning were reactivated during recall of the memory and that the behavioral performance was correlated with the strength of the reactivation. In a second set of studies we used this activity based approach to examine learning induced molecular and cellular changes specifically in neural circuits activated with learning. We found learning induced increased trafficking of glutamate receptors to the synapse in a manner and a structural decrease in dendritic spines specifically in activated neurons. These opposing mechanisms could work to store information while maintaining homeostasis on total synaptic drive. Finally, I will discuss studies that seek to determine the underlying circuit structure of a memory representation. Here we use the *cfos*-promoter based system to drive expression of a mutant **muscarinic** receptor hM3Dq (DREADD) into neurons activated by environmental stimuli. Neurons expressing the hM3Dq can be stimulated to fire action potentials by administration of a specific chemical ligand. We found that mice can incorporate anatomically dispersed artificial stimulation of neurons into a discrete memory trace. These results suggest a surprising degree of flexibility in the incorporation of neural activity into memory representations.

Neural mechanisms of extinction learning and retrieval of cocaine-associated memories

Devin Mueller, University of Wisconsin-Milwaukee

Drug addiction is a chronically relapsing disorder characterized by compulsive drug-seeking behavior, and is maintained by encounters with drug-associated cues. Presentation of these cues can elicit craving in humans and stimulate active drug seeking in rodents. Responses to these cues can be reduced through extinction learning or retrieval disruption. Currently, little is known about the neural mechanisms underlying extinction and retrieval of cocaine-associated memories. First, we demonstrate that consolidation of extinction requires NMDA receptor activation in the infralimbic prefrontal cortex. Second, we show that inhibition of β -adrenergic receptors induces a persistent deficit in retrieval of a cocaine-associated memory, providing protection against reinstatement. Moreover, we found that β -adrenergic signaling within the prelimbic prefrontal cortex and dorsal hippocampus, but not basolateral amygdala, is necessary for cocaine-associated memory retrieval. Pharmacological methods to facilitate extinction and impair memory retrieval are setting the stage for novel treatments for addiction.

Modulation of appetitive and consummatory behavior by food-related cues

Peter C. Holland, Johns Hopkins University

Associative learning processes play many important roles in the control of food consumption. Although these processes can complement regulatory mechanisms in the control of eating by providing opportunities for the anticipation of upcoming needs, they may also contribute to inappropriate or pathological consumption patterns by overriding internal regulatory signals. Food-sated rats and mice increase their food consumption after presentation of CSs that were previously paired with food delivery or the termination of food availability, while the rats were food-deprived. This cue-potentiated feeding is independent of conditioned approach responses and of the cue's ability to modulate or reinforce instrumental behavior, and is often highly specific to the foods associated with those CSs. Measures of taste reactivity and lick bursting suggest that transient, cue-induced changes of the food's palatability are important determinants of consumption. Lesion and immediate early gene data suggest that the modulation of food consumption by CSs is uniquely mediated by cortical and amygdalar neurons that directly target the lateral hypothalamus, and thus gain access to hypothalamic neuropeptide and other systems involved in the promotion and suppression of eating.

Saturday oral presentations:

Note: Abstracts and author information for short talks can be found in the poster section by referring to the poster number next to the title in the schedule.

Hippocampus-Dependent Learning: A Smoking Gun in Understanding Nicotine Addiction

Thomas J Gould, Temple University

Addiction is often associated with reward processes but addiction is more than that as it involves long-lasting changes in behavior. The ability of drugs of abuse to modify neural circuitry involved in learning and memory may facilitate the development and maintenance of addiction. We propose that with nicotine addiction there are at least three ways that nicotine-related changes in learning and the underlying neural substrates contribute to nicotine addiction: 1) initial precognitive effects may reinforce continued smoking while facilitating development of maladaptive drug-context associations; 2) changes in learning during periods of abstinence may facilitate relapse; 3) developmental exposure to nicotine may lead to future changes in learning processes that could contribute to nicotine use and abuse. Our work has examined the effects of nicotine on hippocampus-dependent learning and defined the cell signaling cascades involved in the acute effects of nicotine on learning, the neural substrates and changes associated with withdrawal-related impairments in learning, and the short-term and long-term effects of adolescent nicotine exposure on learning. Acute nicotine enhances cell signaling associated with long-term memory formation (PKA-ERK-CREB) but also leads to activation of JNK1 in the dorsal hippocampus, this kinase is necessary for the nicotine enhancement of learning. Nicotine withdrawal deficits in learning are associated with upregulation of hippocampal high-affinity nicotinic receptors. Finally, young mice are more sensitive to the acute effects of nicotine and less sensitive to withdrawal effect on learning than adult mice. In addition, nicotine exposure in young mice results in adult learning deficits while similar exposure in adults does not result in deficits. These effects may relate to changes in CREB signaling. Understanding how nicotine alters learning at different stages of developmental will contribute to our understanding of nicotine addiction and how to teach this illness.

Neurogenesis and Theta Oscillations Interact to Keep the Brain Fit for Learning

Tracey J. Shors, Rutgers University

New neurons are incorporated into the existing circuitry of the hippocampus each day, presumably to facilitate processes of learning and/or related thought processes. Their generation depends on a variety of factors ranging from age to aerobic exercise to sexual behavior to alcohol consumption. However, most of the cells will die unless the animal engages in some kind of effortful learning experience when the cells are about one week of age. The cells survive only if the learning process is successful, i.e. animals must learn well. Successful learning is also associated with the presence of endogenous theta activity in the hippocampus. Animals that have more endogenous theta activity learn better than animals with less activity and they also express more theta oscillations during the learning process. In this presentation, I will present data to suggest that theta oscillations and neurogenesis in the hippocampus interact with one another through learning to maintain a fit brain.

Conditioning and extinction of fear: Different states of the same memory?

Jelena Radulovic, Northwestern University

During associative learning, exposure to conditioned (CS) and unconditioned (US) stimuli triggers strong molecular responses in different parts of the brain. While sensory and affective properties of these stimuli determine which brain regions are activated, intricate networks of signaling complexes coordinate their processing. Ultimately, cascades of signaling events alter the cellular content and distribution of synaptic molecules along with neuronal excitability and firing patterns, which are viewed as a basis of memory.

Conditioning and extinction of fear have traditionally been viewed as two independent learning processes for encoding representations of contexts or cues (CS), aversive events (US), and their relationship. Based on the analysis of protein kinase signaling patterns in neurons of the fear circuit, however, fear and extinction are better conceptualized as emotional states triggered by a single CS representation with two opposing values: aversive and non-aversive. These values are conferred by the presence or absence of the US and encoded by distinct sets of kinases. Targeting specific protein kinases thus has the potential to modify emotional states and emerges as a promising treatment for anxiety disorders.

Ambiguous Timing of Aversive Events Enhances Fear Learning Through Hippocampal Prediction Errors **Ki Goosens**, Massachusetts Institute of Technology

Despite the ubiquitous use of Pavlovian fear conditioning as a model for fear learning, the highly predictable conditions used in the laboratory do not resemble real-world conditions, where the temporal relationship between a predictive cue and a subsequent aversive stimulus is highly variable. We found that unpredictable timing of aversive outcomes following a cue greatly enhances fear in rats. This effect was exacerbated by chronic stress prior to fear conditioning. Temporary inactivation of the dorsal hippocampus completely prevented the enhancement of fear by unpredictably timed aversive events. These results reveal that information about the timing of aversive events is rapidly acquired and that unexpectedly timed aversive events generate hippocampal “teaching signals” that enhance fear learning. We propose that hippocampal dysfunction following chronic stress increases the probability and magnitude of these temporal prediction errors, which may explain why individuals exposed to traumatic experiences are more likely to develop stress-related mental illnesses, such as post-traumatic stress disorder.

Placing prediction into the fear circuit

Gavan McNally, University of New South Wales

The acquisition and loss of conditioned fear depends on the actions of prediction error. Endogenous opioids regulate prediction error via psychologically and neuroanatomically distinct mechanisms. Opioid actions at Mu opioid receptors (MOR) in the PAG regulate fear learning by determining variations in the reinforcing effectiveness of the aversive US, and influencing a distributed neural circuit that includes the midline thalamus, medial prefrontal cortex, and basolateral amygdala. Opioid actions at MOR in the nucleus accumbens regulate fear learning by determining variations in the effectiveness of the CS as a signal for aversive reinforcement, an effect that also involves accumbens dopamine and ventral tegmental area. These two teaching signals may instruct amygdala-based synaptic plasticity during fear conditioning to enable the prediction of danger.

Somatosensory Cortex in Trace Eyeblink Conditioning with Whisker Vibration CS

John Disterhoft, Northwestern University

A series of studies investigating the role of somatosensory cortex in trace eyeblink conditioning when whisker vibration is used as the CS will be reviewed. Conditioning induces a learning-specific expansion of those barrels in SI somatosensory barrel cortex that mediate the CS in forebrain-dependent trace conditioning but not in delay conditioning. Our new findings support the hypothesis that SII cortex changes following SI lesions and is capable of supporting trace eyeblink conditioned responses after such lesions. Our lesion and single neuron recording data indicate that primary sensory cortex exhibits plastic changes during acquisition of forebrain dependent associative learning. But this plasticity is largely transient, and is reduced as the animals learn and become overtrained in the trace eyeblink conditioning task. Our data suggest that more central portions of the conditioned reflex arc must be mediating the plastic changes that underlie consolidated associations.

Facilitated Acquisition of Delay and Avoidance Eyeblink Conditioning in College-Aged Females Expressing Inhibited Temperament

Michael T. Allen, University of Northern Colorado

Facilitated acquisition of eyeblink conditioning has been reported for those expressing behavioral inhibition (BI), a temperamental disposition toward withdrawal in the face of novel social and nonsocial challenges. Whereas BI is a risk factor for anxiety disorders, and avoidance and its acquisition are core features of anxiety disorders, the question whether enhanced associative learning extends to avoidance learning is an open, albeit critical question. Previously, avoidance acquisition was assessed by comparing delay training (500 ms CS coterminating with a 50 ms air puff US) to delay training with an omission contingency (the presence of a CR during the CS prevented US delivery). Although acquisition of avoidance was not readily apparent, the proper comparison group would be a yoked control (an identical schedule of CS and US delivery as the omission group, but CR presence does not affect US delivery). In the current study, college students were randomly assigned to receive delay (D, n= 29), avoidance (A, n = 31) or yoked (Y, n=27) training. All students completed the Adult and Retrospective Measures of Behavioural inhibition (AMBI and RMBI) and the Spielberger State/Trait Anxiety Inventory (STAI). For Y training, subjects were matched on total AMBI and RMBI scores to a corresponding A subject, so that schedules corresponded with respect to BI. High BI individuals acquired CRs in the delay paradigm at a faster rate than low BI individuals. Avoidance was not apparent in either high or low BI, and acquisition rates with A or Y training were similar. For those expressing high RMBI, acquisition rates during D, A, and Y were greater than those with low RMBI scores. There was also an interaction between BI and gender such that females with high RMBI exhibited accelerated acquisition. Facilitated acquisition of eyeblink conditioning reinforces a learning-diathesis model for the development of anxiety disorders.

Cellular Mechanisms Underlying Aging-Related Deficits in Extinction of Trace Fear Conditioning.

James R. Moyer, Jr., University of Wisconsin-Milwaukee

Prefrontal cortex dysfunction is linked to aging-related impairments in executive function, such as cognitive flexibility. One example of cognitive flexibility is behavioral extinction, which is the learned inhibition of a former response tendency in light of a new set of rules. Extinction of conditioned fear in rats is a well-described model system for studying the neurobiological mechanisms underlying behavioral extinction, which critically depends upon ventromedial PFC (vmPFC). Likewise, studies in humans indicate that vmPFC plays an important role in extinction of conditioned fear, particularly the infralimbic (IL) and prelimbic (PL) subregions. Activity in IL facilitates extinction and is important for extinction memory whereas activity in PL impairs extinction. Unfortunately, little is known about how vmPFC changes during aging or how these changes contribute to deficits in behavioral flexibility. We have recently shown that intrinsic excitability of vmPFC neurons is altered during aging, and that these changes parallel aging-related deficits in extinction of trace fear conditioning (Kaczorowski, et al., 2011). Specifically, a decrease in the excitability of IL layer 2/3 regular spiking pyramidal neurons emerges in middle age. Conversely, excitability of burst spiking neurons within layer 2/3 of PL increases during aging. To further explore cellular and molecular changes in vmPFC that may contribute to extinction deficits, we also measured baseline expression of the IEG zif-268 (EGR-1) in adult, middle-aged, and aged F344 rats. Western blot analysis revealed a significant decrease in zif-268 expression in IL, but not PL, during aging. These data suggest that within vmPFC, normal aging is accompanied by region-specific changes in neuronal excitability and IEG expression that make it harder to drive IL activity, which may contribute to aging-related extinction deficits.

Midbrain periaqueductal gray (PAG) mediates defensive behavior and aversive stimulus processing during fear conditioning

Hugh T. Blair, University of California, Los Angeles

The midbrain PAG is an important relay center that mediates bidirectional communication between the central and peripheral nervous systems (CNS and PNS). Nociceptive sensory signals are transmitted through (and modulated by) PAG as they travel along ascending pathways from the PNS to the CNS. Likewise, behavioral motor signals are transmitted through (and modulated by) PAG as they travel along descending pathways from the CNS to PNS. In this talk, I will review several behavioral, neurophysiological, and pharmacological experiments that we have conducted in our lab to investigate the functional roles of bidirectional PAG pathways in the acquisition and expression of Pavlovian fear conditioning.

Foraging in the face of fear: beyond Pavlovian fear conditioning

Jeansok J. Kim, University of Washington

Pavlovian fear conditioning typically measures a "fractional" fear response and has been a crucial behavioral task for studying the basic mechanisms of learning and memory. I will present experiments where we investigated the rat's foraging behavior in a seminaturalistic environment when confronted with a LEGO mindstorms robot programmed to surge toward the animal seeking food, and how this predator-like threat reduces the distance the animal will travel to intercept food and alters the animal's foraging preference behavior.

Poster session:

Note: The formal poster session is scheduled for 5:15-7:00PM on Friday. However, posters should remain up through most of the meeting and be available during breaks and other unscheduled time. Please mount your poster on the board provided either Thursday PM or first thing Friday morning. All posters must be removed before 5:00PM on Saturday.

- P1. Facilitated acquisition of eyeblink conditioning in those at risk for anxiety disorders: Concordance among scales of inhibited temperament.** Caulfield, M. D., McAuley, J. D., Zhu, D. C., Servatius, R. J.
- P2. Effect of Perception of Emotional Valence on the Startle Response in Humans.** Reagh, Z. M., Knight, D. C.
- P3. Computerized Task for Studying Human Avoidance.** Sheynin, J., Shikari, S., Beck, K. D., Pang, K. C. H., Servatius, R. J., Gilbertson, M. W., Orr, S. P., Myers, C. E.
- P4. Non-spatial sequence memory in humans and rats.** Allen, T. A., Mattfeld, A., Fortin, N. J., Stark, C.
- P5. The Incremental Stimulus Intensity Effect in the habituation of the eyeblink response in humans.** Vogel, E. H., Ponce, F. P., Quintana, G. R., Wagner, A. R.
- P6. Acquisition and Extinction of Conditional Fear in Humans: Effect of Continuous and Partial Reinforcement.** Grady, A. K., Bowen, K. C., Knight, D. C.
- P7. Enhanced functional connectivity between amygdala and medial prefrontal cortex during awake rest after fear conditioning in humans.** Kanen, J. W., Hermans, E. J., Fernandez, G., Phelps, E. A.
- P8. Neuromagnetic amygdala responses during trace fear conditioning without awareness.** Balderston, N. L., Schultz, D. H., Baillet, S., Helmstetter, F. J.
- P9. Contributions of Primary Visual Cortex to Trace and Delay Eyeblink Conditioning.** Steinmetz, A. B., Harmon, T. C., Freeman, J. H.
- P10. The amygdala shows changes in functional connectivity following fear conditioning.** Schultz, D. H., Balderston, N. L., Helmstetter, F. J.
- P11. MEG study of associative learning using a streamed-trial procedure.** Maia, S. S., Jozefowicz, J., Green, G.
- P12. Hippocampal theta activity in the developing hippocampus during trace eyeblink conditioning.** Goldsberry, M. E., Freeman, J. H.
- P13. The development of the septohippocampal theta system and delay eyeblink conditioning.** Harmon, T. C., Freeman, J. H.

- P14. Aging-related changes in immediate early gene expression in rat medial prefrontal cortex and hippocampus.** Sehgal, M., Detert, J. A., Lambrecht, T. M., Moyer, J. R.
- P15. Developmental changes in medial auditory thalamic activity during eyeblink conditioning.** Ng, K. H., Freeman, J. H.
- P16. Fear-conditioning in adult zebrafish: A model for investigating the long term consequences of embryonic nicotine exposure.** Wolter, M. E., Udvardia, A. J., Svoboda, K. R.
- P17. Trace fear consolidation, but not extinction, may require the basolateral amygdala.** Kwapis, J. L., Jarome, T. J., Gilmartin, M. R., Helmstetter, F. J.
- P18. The role of mPFC subregions in context-induced reinstatement of extinguished alcoholic beer-seeking.** Willcocks, A. L., McNally, G. P.
- P19. Extinction of cocaine seeking reduces elevated bFGF expression and is enhanced by neutralizing bFGF in the medial prefrontal cortex.** Doncheck, E. M., Twining, R. C., Ruder, S. A., Hafenbreidel, M., Schneider, J. R., Mueller, D.
- P20. NMDA and β -adrenergic receptors are necessary for extinction of cocaine seeking.** Hafenbreidel, M. F., Twining, R. C., Schneider, J. R., Mueller, D. T.
- P21. N-methyl-D-aspartate Receptors in Fear Extinction after Continuous and Partial Reinforcement.** Leaderbrand, K. L., Radulovic, J.
- P22. NMDA receptors in retrosplenial cortex are necessary for the retrieval and extinction of recent and remote contextual fear memory.** Corcoran, K. A., Donnan, M. D., Tronson, N. C., Guzman, Y. F., Jovasevic, V., Leaderbrand, K., Guedea, A. L., Radulovic, J.
- P23. Behavioral and neurobiological evidence that short acquisition-extinction or retrieval-extinction intervals impair extinction and cause robust spontaneous recovery.** Stafford, J., Ilioi, E., Lattal, K. M.
- P24. Blunted stress reactivity predicts deficits in the extinction of conditioned fear.** Hill, J. E., Ehlenbach, C. E., Quinn, J. P., Stasic, N., Sanders, M. J., Gasser, P. J.
- P25. Different NMDA antagonists have opposite effects on fear extinction.** Padilla, E., Demis, J. D., Adkins, D. L., Oh, D., Monfils, M. H.
- P27. Epigenetic contributions of the amygdala to components of trace and delay fear conditioning in C57BL6 mice.** Raybuck, J. D., Lattal, K. M.
- P28. Trace Fear Conditioning Enhances Synaptic and Intrinsic Plasticity in Rat Hippocampus.** Song, C., Detert, J. A., Sehgal, M., Moyer, J. R.
- P29. Differential Effects of the Cannabinoid Receptor Agonist WIN5,212-2 on Delay, Long-Delay, and Trace Eyeblink Conditioning.** Steinmetz, A. B., Freeman, J. H.

- P30. Lateralized amygdala modulation of the eyeblink conditioned response in adult rats.** Kaercher, R. M., Goodfellow, M., Lindquist, D. H.
- P31. Temporally graded increases in proteasome number and activity in the amygdala following fear conditioning.** Jarome, T. J., Ruenzel, W. L., Kwapis, J. L., Helmstetter, F. J.
- P32. Propranolol Rescues Poor Active Avoidance Responding, Suppresses Freezing, and Induces Massive c-fos Activation in the Lateral Division of Central Amygdala.** Cain, C. K., Martinez, R. C., Sears, R., Lazaro-Munoz, G., LeDoux, J. E.
- P33. β -adrenergic receptors in the prelimbic cortex and dorsal hippocampus, but not basolateral amygdala, mediate the retrieval of a cocaine-associated memory.** Otis, J. M., Dashew, K. B., Schneider, J. R., Mueller, D.
- P34. Infusion of hippocampal BDNF slows acquisition of delay eyeblink conditioning in the Wistar-Kyoto but not Sprague Dawley rat.** Janke, K. L., Servatius, R. J., Pang, K. C.
- P35. The role of medial septaldiagonal band GABAergic neurons in proactive interference: effects of selective immunotoxic lesions in latent inhibition.** Sinha, S. P., Roland, J. J., Pang, K. C., Servatius, R. J.
- P36. Npas4 Regulates a Transcriptional Program in CA3 Required for Contextual Memory Formation.** Ramamoorthi, K., Fropf, R., Fitzmaurice, H. L., McKinney, R., Belfort, G. M., Neve, R. L., Otto, T., Lin, Y.
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- P55. Metaplasticity-like Mechanism Supporting the Selection of Fear Memories.** Parsons, R. G., Davis, M.
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P1. Facilitated acquisition of eyeblink conditioning in those at risk for anxiety disorders: Concordance among scales of inhibited temperament

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Behavioral inhibition (BI) is a risk factor for anxiety disorders typified by extreme withdrawal in the face of novel social and nonsocial challenges. To the extent that anxiety disorders have a core feature of avoidance, associative learning processes seem likely to play a central role in their development and expression. Previous work has shown that those classified as behaviorally inhibited by scales developed by Gladstone & Parker (Adult and Retrospective Measures Behavioural Inhibition, AMBI and RMBI, respectively) acquire an eyeblink conditioned response faster during delay-type conditioning (500ms, 1000-Hz tone conditioned stimulus (CS) coterminating with a 50-ms airpuff unconditional stimulus (US)). Here, we have two primary questions: 1) do published measures of BI differ in their sensitivity to differentiate facilitated acquisition? 2) are these individual differences also apparent in activity of the cerebellum and orbital frontal cortex in response to presentations of novel stimuli as measured during functional magnetic imaging (fMRI)? College students (ages 18-23 years old) participated for research credit or \$10.00 per hour. Of 111 students who thus far participated usable conditioning data was available for 73 (38 were excluded poor signal quality, inability to stay awake for the duration of the required 1 h, equipment difficulties, or lack of a UR). Training consisted of 45 paired CS-US trials immediately followed by an extinction period (15 CS alone trials). All participants completed the AMBI and RMBI, as well as the Reznick Concurrent and Retrospective Self-Report of Inhibition (CSRI and RSRI) and the Spielberger State/Trait Anxiety Inventory (STAI). Preliminary data show a strong concordance between the AMBI and CSRI ($r^2=.53$) as well as RMBI and RSRI ($r^2 = .73$). Replicating earlier work, facilitated acquisition is apparent at the extremes of the scales, representing those at risk for developing anxiety disorders. Analysis of imaging data awaits further participation. These preliminary data support a learning-diathesis model for the development of anxiety disorders.

P2. Effect of Perception of Emotional Valence on the Startle Response in Humans

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Prior work has demonstrated that the valence of emotional images modulates startle response magnitude. Existing studies have examined responses to startle probes presented during positive, negative, and neutral images. Negative images appear to potentiate the startle response. Other research has examined the effects of backward masking on emotion-modulated startle. Potentiated startle responses have been observed during the presentation of masked fear-relevant images. However, many prior masking studies have not rigorously assessed subjects' ability to perceive masked

stimuli. The present study investigated the effect of valence perception on emotion-modulated startle. Masked images of positive, negative, and neutral emotional valence were presented for either 1sec (perceived) or 17msec (unperceived). A startle probe (100dB whitenoise) was presented during 33% of each trial type while skin conductance response (SCR) was measured. We observed greater SCR to startle probes during both perceived and unperceived negative images compared to perceived and unperceived positive and neutral images. To assess perception, subjects rated the valence of each image. Participants accurately rated (compared to normative data) the valence of the 1sec images. In contrast, participants' ratings of the 17msec images fell at chance levels. Following the startle procedure, an independent forced-choice recognition task was completed using 17msec masked negative images. Participants performed at chance-levels on this task. These data indicate that subjects were unable to perceive the emotional valence and content of 17msec masked images. The current findings suggest that images of negative emotional valence can potentiate the startle response in the absence of conscious stimulus perception.

P3. Computerized Task for Studying Human Avoidance

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Although avoidance behavior is studied extensively in animals and is a common feature of anxiety disorders, including post-traumatic stress disorder (PTSD), there are few studies investigating avoidance learning in humans. In this project, we use a computerized task to study conditioned avoidance learning in human subjects, based on a previously published task by Molet et al. (2006). In this task, subjects learn to destroy enemy spaceships with the goal of increasing their score. Some cues are associated with the launching of a bomb that will hit the participant's spaceship and produce a significant reduction in the score (warning cues), while other cues predict the bomb will not appear ("safety" cues). In order to receive a high score, subjects learn to avoid the aversive bomb hit by hiding the spaceship during the warning cue presentation, before the bomb's appearance. The task also includes an extinction phase, where the warning cue is not followed by a bomb. Preliminary results replicate those of Molet et al. (2006) and show that healthy young adults are able to discriminate between the warning cue and the "safety" cue, acquire an avoidant behavior in response to the warning cue and exhibit a temporal discrimination with higher avoidance response towards the end of the warning signal. Currently, we are collecting data from older healthy individuals, as well as from individuals who self-report PTSD symptoms. Preliminary results suggest that different populations adapt different degrees of avoidance

behavior in response to the same cues. In addition, we are studying correlations between patterns of avoidance behavior and self-assessed personality measures, such as the State/Trait Anxiety Inventory (STAI), Adult and Retrospective Measures of Behavioral Inhibition (AMBI and RMBI, respectively), Tridimensional Personality Questionnaire (TPQ), Beck Depression Inventory (BDI) and the PTSD checklist (PCL). Seeking these correlations will help us understand which measures are associated with avoidance behavior and hence, might represent risk factors for developing anxiety disorders. In future work, we plan to expand the current task to further test additional aspects of avoidance behavior including contextual learning, escape-avoidance behavior pattern and the influence of safety signals on avoidance learning. Such design will parallel the animal avoidance work (e.g., Beck et al. 2010, 2011) and hence, promote translational research in the field of vulnerability factors in anxiety.

P4. Non-spatial sequence memory in humans and rats

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Episodic memory is the capacity to remember specific events with a spatial and/or temporal context. It has been proposed that the ability to encode and retrieve a sequence of events is an essential feature of episodic memory. Here, we present a novel cross-species sequential memory task. The task consists of a sequence-sampling phase and a test phase in which subjects indicate whether items were presented in or out of sequence. In humans, the sampling phase consists of button presses that initiate a series of fractal images. In rats, the sample phase consists of nose pokes that initiate a series of odors. Human sequences contain 6 items, whereas rat sequences contain 4 items to match error rate. During the test phase, the task is to hold the response (button press or nose poke) for more than 1 s, when items are presented in sequence. If an item is presented out of sequence the response must be released prior to 1 s. Sequential memory is demonstrated when subjects correctly respond to both in and out of sequence trials. Both humans and rats perform the sequence task well (>80% accuracy), with similar response latencies. When items are presented in sequence, humans hold the button for ~1250 ms and rats poke for ~1150 ms. When items are presented out of sequence, humans release the button within ~600 ms, and rats withdraw from poking within ~700 ms. The long-term goal is to run parallel cognitive and behavioral neuroscience physiology experiments to study the underlying neurobiology of sequence memory. Sequence memory relies on the hippocampus and medial prefrontal cortex (Kesner, 1998; DeVito et al., 2010). The complimentary neuroscience techniques used in rats and humans, and the strong behavioral equivalents, will allow an integration of different levels of analysis from neurons to systems.

P5. The Incremental Stimulus Intensity Effect in the habituation of the eyeblink response in humans

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The purpose of this study was to examine whether the greater decrement in responding that is commonly obtained with repeated presentation of a stimulus of gradually increasing as compared to constant intensities is due to greater habituation or less sensitization in the incremental condition. In one experiment, three groups of human participants were exposed to 100 tones of 100-ms duration. Participants in the constant group received the tones at a fixed 90-dB intensity. For the participants in the incremental group the tones increased from 60- to 87-dB in 3-dB steps, whereas participants in group random received tones of the same intensity as group incremental but in a pseudorandom order. In a subsequent testing block, the results indicated that there were less eyeblink responses to a 90-dB tone in the incremental than in the constant and random groups, which replicates the so called incremental stimulus intensity effect. However, it was also observed less responding in the incremental than in the other two groups to a novel tactile stimulus. Since, there has been demonstrated that there is little generalization of habituation from auditory to tactile cues, the results of this experiment suggest that the differences between the conditions may be due to a generalized factor, such a differential sensitization.

P6. Acquisition and Extinction of Conditional Fear in Humans: Effect of Continuous and Partial Reinforcement

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Previous research has demonstrated the partial reinforcement extinction effect (PREE) in a variety of animal model systems. However, relatively few studies have investigated the PREE in human Pavlovian Fear Conditioning. The present study investigated the effect of partial reinforcement on the extinction of the conditioned skin conductance response (SCR) and unconditioned stimulus (UCS) expectancies. Volunteers participated in a two tone discrimination procedure in which one tone (CS+) was paired with a loud (100dB) white noise (UCS) and a second tone (CS-) was presented alone during acquisition. During extinction, both conditioned stimuli were presented without the UCS. Participants were randomly assigned to one of four groups that received different CS-UCS pairing ratios. One group (C-C) received continuous (100%) pairing of the CS+ with the UCS throughout acquisition. A second group (P-P) received partially (50%) paired presentations of the CS+ and UCS during acquisition. A third group (C-P) received the CS+ paired with the UCS continuously (100%) during the first half of acquisition and partially paired (50%) during the last half of acquisition. The fourth group (P-C) received partial (50%), then continuous (100%) CS-UCS pairings during acquisition. SCR and UCS expectancy were monitored continuously throughout the conditioning procedure. A PREE in SCR and UCS expectancy was observed during conditioning. However, this effect may be due, in part, to the increased response to the CS- following the change in stimulus contingency (acquisition to extinction) instead of a simple resistance to extinction effect to the CS+ within partially reinforced groups.

P7. Enhanced functional connectivity between amygdala and medial prefrontal cortex during awake rest after fear conditioning in humans

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After encoding, newly formed memories undergo a process of consolidation that determines their long term retention. Animal models suggest a key role in this process for medial temporal-cortical interactions during off-line periods such as sleep or awake resting. For consolidation of conditioned fear, such interactions have been shown to include synchronized theta oscillations between the amygdala, hippocampus, and medial prefrontal cortex. However, no studies to date have investigated such processes in humans. Here, we used functional MRI in humans to identify changes in functional connectivity of the amygdala after fear conditioning.

Healthy participants were scanned using functional MRI during a differential fear conditioning paradigm with 2 conditioned stimuli (CS), one of which was paired with mild electrical shock (US). Participants underwent one habituation block, two acquisition blocks (with 50% reinforcement), and two extinction blocks on the first day, and two extinction blocks on the next day. These CS blocks alternated with 4.5 min resting state blocks. Skin conductance and pupil dilation responses to CSs were measured to assess conditioned fear. Functional connectivity of the amygdala was calculated for each resting state block using the first eigenvariate of the time courses extracted from the amygdala after correction for movement-related, cardiac, and respiratory nuisance signals.

As expected, we found robust differential fear conditioning effects in both skin conductance and pupil dilation responses. Brain imaging data showed that connectivity between the amygdala and medial PFC following acquisition blocks increased relative to the two resting blocks preceding fear acquisition.

Our findings demonstrate that interactions within the neural circuitry that is crucial for fear conditioning and extinction learning persist after acquisition of conditioned fear. Extending previous findings from animal studies, our data moreover suggest that such processes may not be restricted to sleep. Finally, our findings converge with a number of recent human studies that have shown alterations in intrinsic activity in the human brain following different types of learning. Although some of these studies have suggested a functional role for such activity in memory consolidation, it remains to be determined whether the intrinsic activity in the amygdala-medial prefrontal circuit plays a functional role in consolidation of fear memories.

P8. Neuromagnetic amygdala responses during trace fear conditioning without awareness

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After fear conditioning humans can generally state the experimental contingencies. CR expression depends on this conscious awareness only during trace conditioning. However, it may possible to show trace conditioning without awareness if a prepared stimulus is used as the CS. Given that the amygdala

is sensitive to face stimuli, we hypothesized that the amygdala may be capable of maintaining a representation of a face CS during a brief trace interval.

Subjects underwent 60 trials of differential trace conditioning with masked face CSs, while we recorded their brain activity using magnetoencephalography (MEG). We monitored UCS expectancy during the 900ms trace interval. Subjects showed similar patterns of UCS expectancy across trials for the CS+ and CS-, suggesting that they were unable to explicitly learn the experimental contingencies. One group of subjects saw broad spectrum face CSs, while another group saw highpass filtered faces, which have been shown not to drive amygdala activity.

We used source imaging to model the MEG signal. First, we collected structural MRI scans for each individual and generated 3d surface models of each individual's cortex, amygdala, and hippocampus. We then modeled the MEG signal by uniformly distributing current dipoles across the surfaces of these 3d models. Finally, we sampled the timecourse of amygdala activity during the 900ms trace interval and averaged the signal across subjects.

Although subjects were unaware of the contingencies during training, those shown the broad spectrum faces had larger magnitude amygdala responses during trace interval than those shown the filtered faces. These results suggest that the amygdala may be capable of maintaining a representation of a face CS during a brief trace interval, which may be sufficient to support trace conditioning in the absence of awareness. These results also suggest that source imaging can be used to localize MEG signals that originate from subcortical structures.

P9. Contributions of Primary Visual Cortex to Trace and Delay Eyeblink Conditioning

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Eyeblink conditioning (EBC) is a form of Pavlovian conditioning in which repeated pairings of a conditioned stimulus (CS) with an blink inducing unconditioned stimulus (US) lead to the emergence of an eyeblink conditioned response (CR). CS information is carried along parallel pathways to the pontine nucleus, whose projections converge with US information in the cerebellum. Past research has demonstrated that LGN projections to the medial pontine nucleus are necessary for delay EBC with a visual CS (Halverson and Freeman, 2009, *Learning and Memory*, 17, 80-85). However, other lines of research indicate that sensory cortical inputs may be required for more temporally complex forms of EBC. Learning-related changes in BOLD response have been observed in primary visual cortex (V1) during trace and delay EBC with an interstimulus interval (ISI) outside the optimal range (Miller et al., 2008, *J. Neuroscience*, 28, 19). Further, whisker cortical barrels undergo learning-related plasticity during trace EBC with a whisker-deflection CS (Galvez et al., 2006, *J. Neuroscience*, 26, 22), and lesioning this area prevents trace conditioning (Galvez et al., 2006, *Learning and Memory*, 26, 22). In the current study, V1 was infused with muscimol during acquisition and retention of delay EBC with an optimal ISI (short-delay EBC), delay EBC with a longer-than-optimal ISI (long-delay EBC), and trace EBC. Inactivation of V1 impaired acquisition and retention of long-delay and trace EBC, but had no effect on short-delay EBC. These results support the hypothesis that primary sensory cortex makes facilitative contributions to delay EBC that are necessary with longer ISIs. They also support the general model of trace EBC, in which forebrain structures maintain CS activity in the pontine nucleus over the trace interval (Woodruff-Pak &

Disterhoft,2008, Trends in Neuroscience, 31,2). Overall, the findings of this study require that contributions made by sensory cortex to EBC be reconsidered.

P10. The amygdala shows changes in functional connectivity following fear conditioning

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In differential fear conditioning, one stimulus (CS+) repeatedly predicts an aversive outcome (UCS) while another stimulus (CS-) serves as a safety signal. Eventually, the CS+ can elicit a learned fear response (CR). Fear conditioning has been used in various organisms to investigate learning, memory, and emotion. Recent studies have measured slow fluctuations (<0.1 Hz) in the BOLD response during resting conditions to identify functional networks. We hypothesized that fear conditioning would modify functional connectivity in networks including the amygdala.

The study consisted of three fMRI runs. The first run was an 8 minute resting-state scan. The second run was the fear conditioning task which consisted of 20 visual stimulus presentations (10 CS+ and 10 CS- presentations) in a pseudorandom order. The third run was another 8 minute resting-state scan. Skin conductance response (SCR) was used as a measure of implicit (autonomic) learning and continuous UCS expectancy was used as a measure of explicit knowledge about CS-UCS relationships.

Participants demonstrated learning related changes in UCS expectancy and skin conductance response during the course of conditioning. Consistent with previous studies, a whole-brain ANOVA identified several brain regions that demonstrated differential responses characterized by larger responses evoked by the CS+ than the CS-. These regions included areas of visual cortex, the caudate and the insula. We found that the amygdala showed a larger response evoked by the CS+ relative to the CS-. We correlated the mean low frequency amygdala signal with all of the other voxels in the brain both prior to and following the fear conditioning task. We found that functional connectivity between the amygdala and the superior frontal gyrus increased following conditioning. These findings suggest that fear conditioning can modify the functional connectivity profile of the amygdala and this change is evident in regions implicated in fear responses and anxiety.

P11. MEG study of associative learning using a streamed-trial procedure

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We used magnetoencephalographic recording techniques to investigate brain areas involved in associative learning. Participants were exposed to a variant of Allan et al. (2005)'s streamed trial

procedure: They were presented with 100-ms stimuli and had to judge the contingency between a target cue and an outcome, while their brain activity was recorded. The contingency between the cue and the outcome was manipulated by changing the probability between them while keeping constant the probability between a companion cue and the outcome. Behavioral results show that despite the difficulty of the task and the short duration of the stimuli, subjects' ratings were sensitive to the contingencies. Preliminary analysis of the MEG data revealed brain areas specifically sensitive to the manipulation of the contingency between the cue and the outcome.

P12. Hippocampal theta activity in the developing hippocampus during trace eyeblink conditioning

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Trace eyeblink conditioning (EBC) differs from delay EBC in that it involves the inclusion of a stimulus-free trace interval between the conditioned stimulus (CS) and the unconditioned stimulus (US). The neural circuitry of trace EBC has been shown to depend on the hippocampus in addition to the structures involved in delay EBC. Previous work in adult rats suggests that hippocampal theta (3-12Hz) activity may play a key role in both attention and learning. The goal of the current research was to examine the development of hippocampal theta activity during trace EBC in postnatal day (P) 21-23, 24-26, and 31-33 rat pups. Work from our laboratory has shown that learning-related hippocampal pyramidal cell activity emerges during these ages; therefore theta activity may be undergoing similar developmental changes. Prior to training pups were implanted with a miniaturized four-tetrode drive targeting the CA1 pyramidal cell layer of the dorsal hippocampus. Training consisted of two sessions daily for three days of either paired or unpaired training. Theta analyses showed substantial differences between paired and unpaired pups. Whereas unpaired pups had a low peak frequency that remained unchanged throughout training, the theta activity of pups that received paired training showed an increase in peak frequency as training continued. This increase was most evident during the session of initial acquisition. Age differences in peak frequency were not observed. However, all age groups showed increases in theta power levels following CS presentation, with age-related differences in theta power during the session of initial acquisition. Together, these findings suggest that hippocampal theta in developing animals may play an important role in acquisition of trace eyeblink conditioning.

P13. The development of the septohippocampal theta system and delay eyeblink conditioning

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The current experiment investigated the effects of disrupting the septohippocampal theta system on the developmental emergence of delay eyeblink conditioning (EBC). Theta oscillations are defined as electroencephalographic (EEG) waveforms with a frequency between 3-12 Hz. Hippocampal theta oscillations are generated by opposing inputs from the entorhinal cortex and the medial septum (Partlo and Sainsberry, 1995). These oscillations have been shown to support learning in a variety of paradigms, including EBC. For instance, lesions to the septohippocampal system disrupt theta oscillations and slow the rate at which EBC is learned (Berry and Thompson, 1979). Few studies have examined theta

oscillations in correspondence with the ontogeny of EBC, which emerges during the third postnatal week in rats. In the current study, infant rats received an electrolytic lesion of the medial septum at postnatal day (P)12. Rats were later given behavioral eyeblink surgeries and trained for six sessions with auditory delay EBC on P17-P19 or P24-P26. There was no significant difference between lesioned rats and rats that received sham surgery at P17-19. Conversely, lesioned rats were impaired at P24-26 relative to aged-matched sham controls. These preliminary results suggest that the septohippocampal system necessary for the production of theta oscillations comes online to facilitate acquisition of EBC after P19.

P14. Aging-related changes in immediate early gene expression in rat medial prefrontal cortex and hippocampus.

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Immediate early gene (IEG) expression is critical for memory acquisition and consolidation. Normal aging is associated with a variety of learning and memory impairments, particularly in those tasks that depend upon a functioning medial temporal lobe or prefrontal cortex (PFC). Using extinction of conditioned fear in rats as a measure of cognitive flexibility, we recently demonstrated that deficits in the extinction of trace fear conditioning emerge in middle age and are accompanied by a parallel redistribution of intrinsic excitability within sub-regions of medial PFC (mPFC; Kaczorowski, 2011). Specifically, within mPFC, the intrinsic excitability of layer II/III pyramidal neurons was significantly decreased in infralimbic (IL) and increased in prelimbic (PL) in both middle-aged and aged rats. Since IL and PL play opposite roles in fear extinction (IL activity favors extinction while PL activity favors fear expression), these physiological changes may underlie our observed aging-related extinction deficits. To further explore cellular and molecular changes in mPFC that may contribute to aging-related extinction deficits, the present study measured baseline expression of the IEG, zif-268 (EGR-1) in adult (3-5 mo.), middle aged (15-18 mo.), and aged (24-31 mo.) male F344 rats. Western blot analysis revealed a significant decline in zif-268 expression in IL as a function of aging [F (2,15) = 5.060, p = 0.021; 52.3% decrease in middle aged; 49.5% decrease in aged]. Although the expression of zif-268 in PL did decrease during aging (20% decrease in middle aged; 23.3% decrease in aged), this effect was not significant [F (2,20) = 1.06, ns]. No change was observed in zif-268 expression in either dorsal or ventral hippocampus as a function of aging. These data suggest that within mPFC, normal aging is accompanied by region-specific changes in IEG expression that make it harder to drive IL activity, which may contribute to an aging-related extinction deficit.

P15. Developmental changes in medial auditory thalamic activity during eyeblink conditioning

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The ontogeny of eyeblink conditioning depends on the development of conditioned stimulus (CS) input to the basilar pontine nuclei. A previous study found sensory-elicited and learning-related activity in the medial auditory thalamus during eyeblink conditioning in adult rats (Halverson et al., 2010, *J Neurosci*, 36, 8787). The current study examined sensory-elicited and learning-related activity in the medial auditory thalamus during eyeblink conditioning in developing rats. Rat pups were given an unpaired session followed by five paired sessions of delay eyeblink conditioning with a tone conditioned stimulus (CS) on postnatal days (P)17-19, 24-26, and 31-33. During these sessions, activity in the medial auditory thalamus was recorded using multiple tetrodes. The percentage of eyeblink conditioned responses was significantly lower for the P17-19 pups relative to the P24-26 and P31-33 pups. In the MGm, there was a developmental decrease in the percentage of neurons that showed exclusively short-latency responses to the CS, and a developmental increase in the percentage of neurons that showed learning-related activity. In the SG, there was an increase in the percentage of neurons that showed learning-related activity, and a decrease in percentage of neurons that showed short-latency activity. A developmental increase in the magnitude of sensory-elicited and learning-related activity in the MGm was observed. In the SG, a developmental increase in the magnitude of sensory-elicited activity was observed, but not the magnitude of long latency learning-related activity. The results demonstrate developmental changes in sensory- and learning-related activity in the medial auditory thalamus during eyeblink conditioning. Developmental changes in medial auditory thalamic responsiveness and plasticity may influence the ontogenetic emergence of cerebellar learning.

P16. Fear-conditioning in adult zebrafish: A model for investigating the long term consequences of embryonic nicotine exposure

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The prevalence of learning disabilities is rapidly increasing in the population at large. We are interested in the consequences of embryonic exposure to environmental toxicants on CNS development and how these could contribute to learning disabilities in adolescence. One toxicant of interest to us is nicotine. While there is a vast amount of information pertaining to the effects of cigarette smoking on developing humans, there is far less information on the effects of nicotine exposure itself on the developing vertebrate nervous system. Our previous work has shown that embryonic nicotine exposure results in changes in locomotor behavior of adult zebrafish. These changes are most likely related to changes in spinal neuron anatomy and/or physiology. We are extending those studies to determine if nicotine exposure, as well as other embryonic manipulations, affects learning and memory in adult fish. To facilitate this endeavor, we have developed a fear-conditioning assay in adult zebrafish which will allow us to evaluate the consequences of embryonic nicotine exposure on learning and memory. In an effort

to optimize this fear-conditioning assay, we have tested the effects of age, sex, and time of day on learning and memory in wild-type fish. The results thus far indicate that the experimental design is robust and suitable for the evaluation of long term changes in learning and memory which may arise from embryonic exposure to nicotine.

P17. Trace fear consolidation, but not extinction, may require the basolateral amygdala.

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The amygdala is known to play a key role in the acquisition and extinction of delay fear. Inhibiting protein or mRNA synthesis in the basolateral amygdala (BLA) prevents the consolidation of delay fear conditioning (see Helmstetter et al., 2008). Similarly, blocking NMDA receptors in the BLA disrupts delay fear extinction (eg Falls et al., 1992). Currently, it is unclear whether the BLA plays a similar role in the acquisition and extinction of trace fear conditioning, in which additional brain structures, such as the hippocampus and prefrontal cortex, are required for successful learning. It is possible that the involvement of additional structures changes the role of the BLA in either trace consolidation or extinction. In our initial study, rats were conditioned with delay or trace fear followed by an intra-BLA infusion of the protein synthesis inhibitor anisomycin. Both delay and trace animals given anisomycin showed disrupted memory to the CS and context the following day, indicating that protein synthesis in the BLA is a key requirement for both delay and trace fear consolidation. We then investigated the role of the BLA in trace fear extinction. Animals trained with delay or trace fear were extinguished the following day in the presence of an antagonist of AMPA or NMDA receptors. Blockade of either receptor type disrupted delay extinction without affecting trace extinction, suggesting that the amygdala is differentially involved in delay and trace fear extinction. Consistent with this finding, preliminary protein expression studies show upregulation of extinction-related plasticity proteins in the amygdala, including phosphorylated ERK and calcineurin, following extinction of delay, but not trace fear. Together, our results suggest that the BLA is required for trace fear consolidation but is not necessary for normal trace fear extinction.

P18. The role of mPFC subregions in context-induced reinstatement of extinguished alcoholic beer-seeking

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It is commonly proposed that dorsal regions of the mPFC are important for the initiation of drug-seeking behaviour whereas ventral regions are necessary for the inhibition of drug-seeking. At present there has been no systematic investigation of the role of the prelimbic (PL), infralimbic (IL), and dorsal peduncular (DP) mPFC subregions in context-induced reinstatement. In the current experiments rats were trained to nose-poke for alcoholic beer (4% v/v) in context A, extinguished in context B, and then tested under extinction conditions in either context B or context A. The PL, IL and DP were temporarily inactivated using infusions of GABA agonists baclofen/muscimol prior to test in either the alcohol-associated context (ABA renewal) or the extinction context (ABB control). The role of IL was also examined using

animals that were trained, extinguished, and tested in one context (AAA control). Each of the mPFC subregions were examined in terms of their role in the onset of drug-seeking (measured as latency to the first active nose-poke) and overall levels of drug-seeking in each context (total responses on the active and inactive nose-poke). The results show that, in the absence of IL, responding was more dependent upon the associative history of the test context, whereas in the absence of PL, responding on the active nose-poke in the alcohol-associated context was attenuated. Evidence for the proposed prelimbic – reinstatement/infralimbic – extinction dichotomy was only obtained in test context with a mixed history of reinforcement.

P19. Extinction of cocaine seeking reduces elevated bFGF expression and is enhanced by neutralizing bFGF in the medial prefrontal cortex.

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Emerging evidence implicates neurotrophic factors in the development and maintenance of compulsive drug-seeking. Cocaine or amphetamine increase expression of basic fibroblast growth factor (bFGF) in putative brain reward sites such as the ventral tegmental area (VTA), nucleus accumbens (NAc), and medial prefrontal cortex (mPFC) - possibly promoting a drug-addicted state (Fumagalli, 2006). In fact, endogenous bFGF in the VTA is required for the induction of locomotor sensitization by amphetamine (Flores et al., 2000). Although bFGF is increased by psychostimulants, whether this expression is regulated by drug-associated cues is not yet known. Experiment 1: Therefore, we determined whether extinction from a cocaine- induced conditioned place preference (CPP) would decrease elevated bFGF expression in the mPFC. Rats were first trained to express a preference for a cocaine-paired chamber and then a subset had their preference extinguished. bFGF immunoreactivity was examined in the infralimbic (IL) and prelimbic (PL) mPFC. Results indicate that increased bFGF expression in the ILmPFC exhibited by the cocaine “no extinction” group is reversed by extinction training ($F(1, 10) = 6.16$; $p < 0.03$). A similar effect was observed in the PL ($F(1, 10) = 4.77$; $p < 0.054$). These results suggest that increased prefrontal bFGF promotes drug-seeking and that extinction training effectively reduces abnormally maintained bFGF levels. Experiment 2: To determine whether endogenous bFGF promotes cocaine-seeking behavior cocaine self-administering rats were infused with a neutralizing antibody to bFGF into the ILmPFC ($0.35 \mu\text{g}/0.35 \mu\text{l}/\text{side}$) 1 hr before extinction training. When tested drug- and infusion-free, only the vehicle-treated rats exhibited robust drug seeking; by contrast, the anti-bFGF infusions reduced cocaine-seeking behavior ($F(9, 108) = 7.11$, $p < 0.0001$; Fisher LSD, $p < 0.05$). Taken together, these data suggest that increased endogenous bFGF in the mPFC maintains neuroadaptations that promote compulsive drug seeking. Normalizing these levels, either directly or through extinction training, may provide a novel strategy for therapeutic intervention.

P20. NMDA and β -adrenergic receptors are necessary for extinction of cocaine seeking

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Relapse is highly prevalent among recovering addicts and can be triggered by cues associated with the drug. Responding to these cues can be extinguished through repeated exposure to the cues in the absence of the drug. Extinction in other paradigms has been shown to be dependent on NMDA receptors (Santini et al., 2001), but it remains unknown whether this is true for extinction of drug seeking. In addition, beta-adrenergic receptors appear to contribute to extinction (LaLumiere et al., 2010) and retrieval of drug memories (Otis and Mueller, 2011). Thus, we investigated the role of NMDA and beta-adrenergic receptors in extinction of cocaine self-administration. Rats self-administered cocaine (0.25 mg/inf) in 90-minute daily sessions before undergoing four daily shortened extinction sessions of 45 minutes each. Prior to these sessions rats were injected with either the NMDA receptor antagonist CPP (10 mg/kg, i.p.), the beta-adrenergic receptor antagonist propranolol (10 mg/kg, s.c.), or a saline vehicle. Rats then underwent four longer drug-free extinction sessions of 90 minutes to determine what was retained from the previous shortened sessions. During the shortened extinction sessions, both CPP and propranolol treatment tended to reduce drug seeking as compared to saline treatment. When given longer drug-free extinction sessions, CPP pretreated rats significantly increased drug seeking compared to their behavior during the previous shortened sessions and to saline controls. Propranolol pretreated rats also significantly increased drug seeking compared to their behavior during the previous shortened sessions, whereas saline controls did not. These results indicate that NMDA and beta-adrenergic receptors have a role in extinction of cocaine seeking. Neither CPP nor propranolol pretreatment had any effect on subsequent cocaine-induced reinstatement of drug seeking. Finally, to test if beta-adrenergic receptor blockade could disrupt reinstatement, propranolol was administered prior to a reinstatement test. Results indicated a transient decrease in cocaine-induced reinstatement and a transient increase in stress-induced reinstatement. Overall, our findings indicate that extinction of cocaine seeking in a self-administration model is dependent on NMDA and beta-adrenergic receptor activation.

P21. N-methyl-D-aspartate Receptors in Fear Extinction after Continuous and Partial Reinforcement

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Anxiety disorders are a prevalent set of psychiatric illnesses characterized by intense and persistent fear. Fear conditioning in rodents is a model with which we can study the molecular correlates of fear memory acquisition and extinction to discover potential treatment targets for these disorders. N-methyl-D-aspartate receptors (NMDAR) in the hippocampus have been shown by our lab and others to play a critical role in fear conditioning and extinction. These receptors typically contain NR2 subunits, of which the NR2A and NR2B subtypes are known to play differential roles in contextual fear conditioning. The current work expands on this finding by examining the roles of NR2 subunits in fear extinction. Mice were trained in one of three fear conditioning paradigms—continuous reinforcement, partial reinforcement, or one reinforcement—followed by at least six extinction trials. Immediately after each

extinction trial, an NR2A- or NR2B-specific antagonist (NVP-AAM077 and Ro25-6981, respectively) was injected into the dorsal hippocampus. The NR2-subunit specific antagonism differentially regulated fear extinction in the three paradigms. We therefore examined differences in NMDAR signaling complexes formed after conditioning paradigms which lent either susceptibility or resistance to extinction (continuous reinforcement or partial reinforcement, respectively). Western blot and immunoprecipitation studies indicate that NR2 subunits and related scaffolding proteins are differentially expressed after continuous or partial reinforcement, and these subunits form complexes with important molecules in fear extinction, including extracellular-signal related kinase (ERK) and calcium/calmodulin-dependent protein kinase (CaMKII). Together, these data suggest that differential NR2 subunit expression and signaling complex composition after fear conditioning play an important role in facilitating or impairing fear extinction, and these pathways may therefore pose a potential target for treatments of anxiety disorders.

P22. NMDA receptors in retrosplenial cortex are necessary for the retrieval and extinction of recent and remote contextual fear memory

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The hippocampus is necessary for the retrieval of recently acquired context fear memories, but over time, this role for the hippocampus diminishes. It is thus thought that remotely acquired memory traces are stored and retrieved in the cerebral cortex (e.g., anterior cingulate cortex; ACd). Retrosplenial cortex (RSC) is one of the earliest brain regions to exhibit metabolic declines in Alzheimer's disease, and RSC lesions lead to deficits in retrieval of recently acquired context fear memory. In the present study, we examined the role of RSC in the retrieval of remotely acquired context fear memory. On day 1, mice were placed in a novel context, where they received a 30s tone followed by a 2s footshock. On days 2, 3, 36, and 37, they were returned to the conditioning chambers to test for context fear memory. Prior to the tests on days 3 and 27, either the NMDA receptor antagonist APV or aCSF was infused into RSC, hippocampus, or ACd. NMDAR blockade in RSC disrupted memory retrieval (i.e., decreased freezing) at both the recent (day 3) and remote (day 37) memory tests. In comparison, APV infused into hippocampus only disrupted recent memory retrieval, whereas APV infused into ACd had no effect at either time. Additionally, APV infused immediately after daily testing sessions prevented the extinction of both recently and remotely acquired context fear. It is unclear whether RSC serves as a site for storage and retrieval of recently and remotely acquired memories, or whether it serves to coordinate retrieval of memories stored in hippocampus and/or other cortical regions.

P23. Behavioral and neurobiological evidence that short acquisition-extinction or retrieval-extinction intervals impair extinction and cause robust spontaneous recovery.

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A great deal of interest has been given to some recent findings that a short interval between either fear acquisition and extinction or fear memory retrieval and extinction produces robust attenuation of fear expression. However, there is conflicting data with some studies failing to show these effects and others showing the opposite. The current study examines how the timing of extinction relative to fear acquisition and retrieval affects subsequent behavior under similar conditions in a contextual fear paradigm. Our results show that, under a variety of conditions, a short interval between contextual fear acquisition and extinction produces poor behavioral extinction while a long delay robustly attenuates fear and spontaneous recovery on subsequent tests. Similarly, a short interval between retrieval and extinction produced poor behavioral extinction while a longer interval produced robust attenuation of conditioned fear and spontaneous recovery on subsequent tests. Immunohistochemistry for the immediate early gene c-Fos indicated that c-Fos expression in sub regions of medial prefrontal cortex and amygdala predicts fear expression following long or short extinction delays, respectively. Together, our results are inconsistent with theories which predict that fear extinction training during the “consolidation” or “reconsolidation” window decreases subsequent fear expression by effectively “re-writing” the fearful memory (e.g., CS-shock) with an extinction memory (CS- no shock). We instead discuss our findings in terms of associative learning theory grounded in neurobiological evidence.

P24. Blunted stress reactivity predicts deficits in the extinction of conditioned fear

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The pathogenesis of post-traumatic stress disorder (PTSD) is thought to involve a deficit in consolidation mechanisms underlying the extinction of fear memory, but the mechanisms underlying this deficit have not been elucidated. PTSD patients also display heightened sensitivity of the hypothalamic pituitary adrenocortical (HPA) axis to negative feedback. As glucocorticoids play important roles in memory consolidation, increased sensitivity to HPA negative feedback, by blunting glucocorticoid responses, may interfere with the consolidation of extinction memory in PTSD patients. Evidence suggests that heightened negative feedback sensitivity represents a marker of susceptibility to developing PTSD, rather than an effect of trauma, but this hypothesis has not been tested in animal studies. To begin testing this hypothesis, we examined the extinction of fear memory in rodents with high (HR) and low (LR) locomotor responses to novelty. LR rats display smaller stress-induced increases in corticosterone than do HR rats, suggesting greater HPA axis sensitivity to negative feedback. Rats were separated into three groups: high-, low- and middle-responders, based on their locomotor response to a novel open

field. HR and LR rats were subjected to restraint stress, with repeated blood sampling from the tail vein. LR rats displayed significantly smaller stress-induced increases in corticosterone than did HR rats. A separate group of rats was subjected to contextual fear conditioning. Consolidation of fear memory was tested on D2 by measuring context freezing. There was no difference in freezing time on D2 between HR and LR rats. During extinction, rats were exposed to the training context for 10 minutes per day on D5-D9. Freezing behavior decreased over D5-D9 in HR, but not in LR rats, so that on D4 and D5, LR rats spent significantly more time freezing than did HR rats. These results suggest that increased HPA sensitivity to negative feedback represents a marker of PTSD susceptibility.

P25. Different NMDA antagonists have opposite effects on fear extinction.

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Ketamine and phencyclidine (PCP) are hallucinogenic, NMDA antagonists. They are interchangeably used on the assumption that they produce analogous effects on a variety of behaviors; however, these drugs have distinct biochemical profiles. Previous studies report that ketamine and PCP can disrupt extinction learning; however, the mechanism by which they affect the fear memory after conditioning is not readily understood. In the first experiment, we compared ketamine and vehicle groups in a fear conditioning paradigm. In a subsequent experiment, the effects of PCP and vehicle were analyzed using a similar paradigm. Rats were fear conditioned by pairing a tone with a footshock. One day after fear conditioning, they received systemic injections of ketamine, PCP or vehicle. The rats then received an extinction session either 1 day or 1 week following ketamine/PCP/vehicle injection. Our results indicated an effect of ketamine in the 1-day group, in which ketamine impaired fear extinction (more freezing behavior) compared to vehicle. There was also a trial by treatment interaction in the 1-week extinction group, in which the ketamine subjects showed retardation of extinction compared to the vehicle controls. The opposite was observed when PCP was compared to vehicle. Initially, there were no differences between PCP and vehicle in the 1-day extinction session. In the 1-week extinction group, PCP facilitated fear extinction (less freezing behavior) compared to vehicle. The current study provides preliminary evidence that ketamine and PCP produce opposite effects on fear extinction learning. We hypothesize that ketamine leads to a intrinsically-triggered memory retrieval among subjects that were fear conditioned, which strengthens the memory trace, and retards extinction. PCP may not interfere with the early fear memory trace, but may impair long-term memory consolidation through an unknown mechanism. The goal of ongoing studies is to identify the behavioral and neural mechanisms underlying these opposite effects.

P27. Epigenetic contributions of the amygdala to components of trace and delay fear conditioning in C57BL6 mice.

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Trace and delay fear conditioning differ in multiple ways. Primarily, in trace CS and US are separated by a stimulus free interval. As a result of this “trace-interval” subjects may assign different predictive value

to cues other than the CS. For instance in trace conditioning contextual learning tends to be stronger than in delay conditioning. This has been primarily attributed to the relative predictive value of the context vs the CS with different stimulus administration timings, resulting in more salience assigned to the context in trace conditioning. However, little is known of the substrates of plasticity that may underlie these differences in learning. Formation of long-term memory depends on gene transcription and translation of new proteins. A first step in this process is the epigenetic modification of histone cores that comprise the chromatin-formation that contains DNA. Acetylation of lysine residues in these histones facilitates transcription by easing the structure of chromatin allowing transcription factors to bind DNA. Inhibition of histone-deacetylase (HDAC) increases histone acetylation, enhancing gene transcription. To examine how learning could be enhanced through this mechanism we administered the HDAC inhibitor sodium butyrate (NaBut) in conjunction with trace and delay fear conditioning in male C57Bl6 mice. Systemic administration of NaBut enhanced both contextual and cued components of trace conditioning, but had no effects on delay conditioning. To further examine these effects we infused NaBut into the amygdala following trace and delay conditioning. Surprisingly in trace conditioning amygdala NaBut infusion enhanced contextual learning, but produced deficits in cued learning, whereas in delay conditioning amygdala NaBut infusion produced deficits in contextual learning and enhanced cued learning. These findings suggest that enhancing histone acetylation through HDAC inhibition has varied effects on learning depending upon the learning task and administration target. We hypothesize that these effects are due to relative contributions of the amygdala to these different learning tasks. In trace conditioning, the context may be more predictive of US onset than the CS, thus the amygdala contributes to learning a context-shock association at the cost of learning a CS-US association. During delay conditioning on the other hand, the CS is more predictive of shock onset, thus amygdala supported plasticity can facilitate CS-US learning at the cost of context-US learning.

P28. Trace Fear Conditioning Enhances Synaptic and Intrinsic Plasticity in Rat Hippocampus

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Experience-dependent synaptic and intrinsic plasticity are thought to be important substrates for learning-related changes in behavior. The present study combined trace fear conditioning with both extracellular and intracellular hippocampal recordings to study learning-related synaptic and intrinsic plasticity. Rats received one session of trace fear conditioning, followed by a brief CS test the next day. In order to relate behavioral performance (e.g., freezing during CS test) with measures of hippocampal CA1 physiology, brain slices were prepared within 1 hour of the CS test. Synaptic plasticity was evaluated by inducing long-term potentiation (LTP) at Schafer collateral-CA1 synapses and measuring dendritic field responses in stratum radiatum of CA1. Intrinsic plasticity was evaluated by using intracellular recordings to study changes to neuronal intrinsic excitability as a function of trace fear conditioning. Rats that were classified as good-learners had significantly enhanced LTP and intrinsic excitability compared to those of poor learners, pseudoconditioned, naïve, and chamber control rats. Moreover, in trace fear conditioned rats, both synaptic plasticity and intrinsic excitability were significantly correlated with behavior such that better learning corresponded with enhanced LTP ($r = 0.64$, $p < 0.05$) and a smaller post-burst afterhyperpolarization (AHP; $r = -.62$, $p < 0.05$). In contrast,

neither synaptic plasticity nor intrinsic excitability was correlated with behavior in the pseudoconditioned rats, whose electrophysiological data were comparable to those of the various control rats. These data illustrate that within the hippocampus both synaptic and intrinsic mechanisms are involved in the acquisition of trace fear conditioning.

P29. Differential Effects of the Cannabinoid Receptor Agonist WIN55,212-2 on Delay, Long-Delay, and Trace Eyeblink Conditioning

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Eyeblink conditioning is established by paired presentations of a conditioned stimulus (CS) such as a tone or light and an unconditioned stimulus (US) that elicits the blink reflex. Delay eyeblink conditioning involves the CS terminating with the US, whereas trace conditioning involves a temporal gap between the CS and US. Delay and trace conditioning both require intact cerebellar circuitry; however, trace conditioning also requires the hippocampus and prefrontal cortex. CS information is projected from the basilar pontine nuclei to the cerebellar interpositus nucleus and cortex. The cerebellar cortex, particularly the molecular layer, contains a high density of cannabinoid receptors (CB1R). The CB1Rs are located on the axon terminals of parallel fibers, stellate cells, basket cells, and climbing fibers where they inhibit neurotransmitter release. A previous study showed that subcutaneous administration of the CB1R agonist WIN55,212-2 impaired acquisition of delay eyeblink conditioning with a 400 ms inter-stimulus interval (ISI). (Steinmetz & Freeman, 2010, *Learn Mem*, 17, 571). The present study examined the effects of WIN55,212-2 on acquisition of delay eyeblink conditioning with a 250 ms (delay) or 750 ms (long-delay) ISI and trace conditioning with a 250 ms CS and a 500 ms trace interval (750 ms ISI). Rats were given subcutaneous administration of 3 mg/kg of WIN55,212-2 prior to each of 10 daily training sessions. Acquisition of delay and long-delay conditioning was impaired, although long-delay conditioning was more impaired than delay conditioning. In contrast, trace conditioning was unimpaired. The findings indicate that central cannabinoids modulate delay conditioning but do not play a role in trace conditioning.

P30. Lateralized amygdala modulation of the eyeblink conditioned response in adult rats

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Two process accounts of associative conditioning—as applied to cerebellar-dependent eyeblink classical conditioning—posit the rapid acquisition of emotional (fear) CRs, which influence or enhance acquisition of the more slowly acquired motor (eyeblink) CR (Lennartz and Weinberger, 1992; Mintz and Wang-Ninio, 2001). Multiple studies support the two process account, with retarded motor CR acquisition following lesions or pharmacological inactivation of the amygdala (Blankenship et al., 2005; Lee and Kim, 2004; Weisz et al., 1992). The amygdala, particularly the central nucleus (CEA), is proposed to amplify reactivity to the CS and US (Burhans and Schreurs, 2008; Taub and Mintz, 2010), leading to enhanced cerebellar plasticity and learning. To our knowledge, eyeblink conditioning studies that have assessed amygdala modulation, to date, have done so bilaterally. The current study investigates the effects of

pre-training bilateral, contralateral, or ipsilateral electrolytic CEA lesions on acquisition of the eyeblink CR.

Preliminary data replicates previous findings of slowed eyeblink CR acquisition following bilateral lesions relative to sham-operated controls. Freezing and the eyeblink UR amplitude, metrics of amygdala-dependent output, are similarly reduced with bilateral lesions. Eyeblink CR production is also partially retarded by amygdala lesions in either hemisphere alone. The decrease in CR acquisition appears more pronounced following contralateral than ipsilateral CEA lesions. The data suggests that the contralateral amygdala may play a primary role in modulating eyeblink CR acquisition (cf., Blair et al., 2005), but it does not rule out a lesser contribution by the ipsilateral amygdala. The results will contribute to our understanding of how emotion regulates motor learning and the rat eyeblink conditioning neural circuit, which may be more bilaterally distributed within the cerebellum than reported for the rabbit (e.g., Horiuchi and Kawahara, 2010).

P31. Temporally graded increases in proteasome number and activity in the amygdala following fear conditioning

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Pavlovian fear conditioning is a widely used paradigm to study the molecular neurobiology of learning and memory. Once acquired, these memories go through a time-dependent stabilization process at the molecular level referred to as memory “consolidation” (McGaugh, 2000). This consolidation process involves a number of intracellular signaling cascades and new protein synthesis in the amygdala and inhibiting any of these processes results in long-term memory impairments (Helmstetter et al., 2008). Recently, we have shown that this consolidation process also requires increased ubiquitin-proteasome mediated protein degradation at amygdala synapses (Jarome et al., in press). Fear conditioning increased the amount of degradation-specific polyubiquitination in the amygdala in a NMDA receptor-dependent manner, and blocking the degradation of these proteins impaired long-term memory. While increases in polyubiquitination have been reported in other brain structures important for fear memory consolidation (Lee et al., 2008; Lopez-Salon et al., 2001), very little is known about how the proteasome is regulated during the consolidation process. Some evidence suggests that proteasomes undergo changes in their cellular distribution and activity following NMDA stimulation in vitro (Bingol et al., 2006; 2010), so in the present study we tested the hypothesis that fear conditioning changes both proteasome number and activity in the amygdala. Rats were trained to an auditory fear conditioning paradigm and amygdala tissue was obtained various times later. Results indicate that the amount of the proteasome subunit Rpt6, an ATPase regulatory subunit on the 19S proteasome, is increased in the amygdala following fear conditioning, peaking at 60-min. This suggests that new proteasome components may be rapidly produced in response to fear conditioning to help regulate the increased demand for protein turnover. Supporting this, using an in vitro proteasome activity assay, we found that proteasome activity rapidly increased in the amygdala peaking at 4-hrs after fear conditioning. Collectively, these results suggest that both the ubiquitination process and proteasome number and activity undergo dramatic changes as a result of fear conditioning.

P32. Propranolol Rescues Poor Active Avoidance Responding, Suppresses Freezing, and Induces Massive c-fos Activation in the Lateral Division of Central Amygdala.

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In active avoidance (AA), rats learn to emit an instrumental response in the presence of threatening conditional stimuli (CSs) in order to prevent delivery of painful unconditional stimuli (USs). Early in AA training, CSs are paired with the US and subsequently trigger Pavlovian reactions such as freezing. To acquire AA, rats must suppress such responses. Although it is unknown how freezing suppression occurs during AA training, lesions of central amygdala that abolish freezing rescue poor AA.

Avoidance can be problematic in human anxiety, however, some therapists attempt to instill appropriate/adaptive active coping responses patients because this strategy: 1) gives the patients control in fearful situations, 2) reduces fearful reactions, and 3) likely produces a more lasting recovery than other treatments such as extinction-based exposure therapy. This may be ideally modeled by AA where subjects learn to suppress maladaptive Pavlovian reactions and perform adaptive instrumental actions when faced with threats.

We sought to evaluate a human treatment option in our rat model of active coping. Beta-adrenergic receptor blockers, like propranolol, alleviate performance anxiety in humans and impair freezing expression in rats. Thus, we hypothesized that propranolol would rescue poor AA performance. Rats received daily Sidman AA training and poor avoiders were injected with propranolol or saline prior to testing. Propranolol reduced freezing by 50% and increased AA responding 5-fold. This rescue was also associated with massive c-fos activation in one specific amygdala region: lateral division of central amygdala (CeL). Together, these findings suggest that beta blockers may facilitate AA and active coping in humans, perhaps via activation of CeL, a region very recently shown to gate Pavlovian fear and even select between reactive and active fear responses.

P33. β -adrenergic receptors in the prelimbic cortex and dorsal hippocampus, but not basolateral amygdala, mediate the retrieval of a cocaine-associated memory

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Compulsive drug-seeking behavior can be provoked by the presentation of drug-associated cues even following long periods of abstinence. Preventing the retrieval of these learned associations would therefore limit relapse susceptibility; however, little is known regarding the neural mechanisms of drug-associated memory retrieval. Recent evidence indicates that retrieval of a cocaine-associated memory is dependent on β -adrenergic receptor activation in the central nervous system. However, the locus or loci at which these receptors mediate retrieval is unknown. To identify this, we used a conditioned place preference (CPP) procedure in which rats were trained to associate one chamber, but not another, with cocaine. Following training, rats were subjected to daily CPP retrieval trials, with local microinfusions of β -adrenergic receptor antagonists prior to a trial. Microinfusions of the β -adrenergic

receptor antagonists propranolol or nadolol into the prelimbic medial prefrontal cortex (PL-mPFC) or dorsal hippocampus (dHipp) prevented memory retrieval during this trial and during subsequent drug-free trials, as indicated by no CPP expression. In contrast, microinfusions of propranolol or nadolol into the basolateral amygdala (BLA) had no effect on retrieval during that trial, but prevented CPP expression during subsequent trials. Thus, β -adrenergic receptor activation within the PL-mPFC and dHipp, but not BLA, is necessary for the retrieval of a CPP memory, and disruption of this activity induces a persistent deficit in retrieval. In contrast, β -adrenergic receptor activation within the BLA is necessary for the reconsolidation of a CPP memory, which is consistent with previous findings. These findings implicate two distinct β -adrenergic receptor dependent memory processes which are necessary for the expression and maintenance of drug-associated memories.

P34. Infusion of hippocampal BDNF slows acquisition of delay eyeblink conditioning in the Wistar-Kyoto but not Sprague Dawley rat.

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Brain-derived neurotrophic factor (BDNF) and its high affinity receptor, trkB, are extensively expressed in the mammalian hippocampus, and are necessary for neuronal development, survival, and synaptic plasticity associated with learning and memory. Mood disorders, including anxiety and post-traumatic stress disorder (PTSD), have been linked to reductions in hippocampal BDNF, hippocampal size, and impairments in hippocampal-dependent learning. Conversely, individuals with anxiety disorders exhibit accelerated learning in a classically conditioned eyeblink response using a delay paradigm (DEBC). While the hippocampus is not necessary to acquire DEBC, lesions accelerate learning in this task. Given that accelerated learning of DEBC may signal anxiety vulnerability and hippocampal dysfunction, we have been investigating the role of hippocampal BDNF on DEBC acquisition in an animal model of anxiety vulnerability. Wistar–Kyoto rat (WKY), is stress sensitive, demonstrates behavioral inhibition, has reduced hippocampal BDNF, and exhibits accelerated acquisition of DEBC compared to a control strain, the Sprague Dawley rat (SD). In the present study, WKY and SD rats were tested in the open-field to assess anxiety-like behavior and divided into BDNF or saline infusion groups. Infusions were given bilaterally into the dentate gyrus of the hippocampus one hour prior to training on days one and two of conditioning. The conditioning consisted of 100 trials per day with a 500ms conditioned stimulus (CS, 82dB white noise) co-terminating with a 10ms unconditioned stimulus (US, 10V stimulation) and an average inter-trial interval (ITI) of 30s. A third day was used to evaluate extinction in which the US was removed after the first 40 trials. Twenty-four hours after extinction training animals were sacrificed and brain tissue excised and stored for BDNF protein quantification. BDNF infusion significantly dampened the learning of the WKY rats. These results suggest that hippocampal dysfunction may play a role in the learning bias seen in the WKY rat.

P35. The role of medial septal/diagonal band GABAergic neurons in proactive interference: effects of selective immunotoxic lesions in latent inhibition

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The medial septum/diagonal band (MSDB) is a critical structure for learning and memory, yet the functional contributions of its individual neuronal populations are still being characterized. Recent studies have implicated a role for the GABAergic MSDB neuronal population, as selective immunotoxic GABAergic lesions of the MSDB (with GAT1-saporin) produce behavioral impairments in spatial and instrumental tasks. Compared to controls, rats with GABAergic MSDB lesions are impaired in learning new locations in a delayed match to position procedure and exhibit a slower rate of extinguishing a previously acquired avoidance response – behaviors that are consistent with an exacerbation of proactive interference. This study examined the effects of selective GABAergic MSDB lesions in latent inhibition (LI) of the classically conditioned eyeblink response. LI in delayed eyeblink conditioning is a phenomenon in which pre-exposure to the conditioned stimulus (CS) interferes with the subjects' ability to subsequently associate the CS with an unconditioned stimulus (US), resulting in slower acquisition of the conditioned response (CR). If damaging GABAergic MSDB neurons increases proactive interference, then rats with selective lesions may show facilitated LI. Male Sprague-Dawley rats were administered either phosphate-buffered saline or GAT1-saporin directly into the MSDB. After recovery, electrodes were implanted into the upper eyelids of the rats for delivery of US and EMG recording. Conditioning began after another 5-7 days of recovery, with Day 1 consisting of 30 minutes of acclimation to the conditioning context. Day 2 began with either 30 presentations of the CS or context pre-exposure of equal duration, followed immediately by 100 paired CS-US trials. In preliminary results, intraseptal GAT1-saporin did not alter CR acquisition in context pre-exposed rats. Rats with GABAergic MSDB lesions continued to exhibit latent inhibition. These preliminary results do not support the idea that damage of GABAergic MSDB neurons increase proactive interference of the classically conditioned eyeblink response.

P36. Npas4 Regulates a Transcriptional Program in CA3 Required for Contextual Memory Formation

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The rapid encoding of contextual memory requires the CA3 region of hippocampus, but the necessary genetic pathways remain unclear. We found that the activity-dependent transcription factor Npas4 regulates a transcriptional program in CA3 that is necessary for contextual memory formation. Npas4 was specifically expressed in CA3 after contextual learning. Global knockout or selective deletion of

Npas4 in CA3 both resulted in impaired contextual memory, and restoration of Npas4 in CA3 was sufficient to reverse the deficit in global knockout mice. By recruiting RNA Polymerase II to promoters and enhancers of target genes, Npas4 regulates a learning-specific transcriptional program in CA3 that includes many well-known activity-regulated genes, suggesting that Npas4 is a critical regulator of activity-regulated gene programs and central to memory formation.

P37. Classical estrogen receptors are localized to caveolar fractions in the mouse hippocampus

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It is now well established that estradiol can influence neuronal function via rapid, membrane-initiated events in addition to its classical, transcriptional-dependent effects. Although these rapid actions of estradiol require membrane localization of some type of estrogen binding protein/receptor, the identity of such receptor(s) remains subject to debate. In endothelial cells, the classical intracellular estrogen receptors, ER α and ER β , have been demonstrated to exist within specialized membrane microdomains known as caveolae. In the rat hippocampus, both ER α and ER β have been observed at extranuclear sites, and caveolin-1 (CAV1), the major structural and functional unit of caveolae, is essential for rapid, estradiol-induced CREB phosphorylation in hippocampal pyramidal neurons. As such, ER α and ER β may be localized to caveolae in the hippocampus. Here, we investigated estrogen receptor expression within caveolar fractions isolated from the dorsal hippocampus of young adult ovariectomized mice. Preliminary data suggest that ER α and ER β are present within dorsal hippocampal caveolar fractions and that members of distinct signaling cascades known to be estrogen sensitive also reside in hippocampal caveolae. Although preliminary, these data support previous findings localizing ER α and ER β to the neuronal membrane surface and data suggesting ER/caveolin interactions in non-neuronal cells. These results also suggest that hippocampal membrane localization and clustering of estrogen receptors and other signaling molecules may be critically dependent on CAV1 expression.

P38. Prelimbic inactivation blocks avoidance without reducing freezing: resolving the conflict

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In auditory fear conditioning, prefrontal cortex (PL) inactivation reduces tone-induced freezing (Sierra-Mercado et al. 2011) suggesting that PL mediates fear. In signaled avoidance conditioning, rats respond to the tone by moving to a safe place, escaping the shock. As avoidance responses are learned, freezing to the tone diminishes, suggesting a reduction in fear. Does PL play a role in avoidance, even though freezing is diminished? To address this question, rats previously trained to press a bar for food were trained to avoid a conditioned tone by stepping onto a nearby platform. Remaining on the platform for the duration of the tone protected them from the shock, but also prevented their access to food. After 10 days of training, avoidance responses gradually increased (from 45% to 70% of trials: $p < 0.001$), while tone-induced freezing gradually decreased (from 66% to 33%, $p < 0.001$). After conditioning, rats were

infused with saline (SAL) or GABAA agonist muscimol (MUS) in PL, and tested for avoidance. PL inactivation blocked avoidance responses (SAL 70%, MUS 20%, $p=0.005$). Surprisingly, however, PL inactivation did not reduce freezing to the tone (SAL 47%, MUS 54%, $p=0.48$), even though it blocked avoidance. Both groups increased their freezing at tone onset (SAL from 12% to 42%, $p=0.03$; MUS from 1% to 52%, $P<0.001$). These findings suggest a more complex role for PL than simply mediating freezing. In threatening situations, PL may resolve conflicts between behaviors so that the most advantageous behavior is favored; in fear conditioning “freezing over pressing” whereas in avoidance conditioning “avoidance over freezing”. This interpretation of PL function is consistent with the conflict monitoring function of the dorsal anterior cingulate cortex, a human homologue of PL.

P39. Communication between the prelimbic and infralimbic cortices is required for context-sensitive fear learning in the absence of the hippocampus

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Contextual factors powerfully impact learning and memory processes across species. In Pavlovian fear conditioning, contexts can be learned about directly, (e.g. contextual fear conditioning), or they can serve to modulate learning about discrete cues (e.g. fear extinction and renewal). The dorsal hippocampus (DH) has been implicated in both of these roles for context, as post-training damage to the DH results in a deficit for context fear and renewal (Kim & Fanselow, 1992; Zelikowsky, et. al, 2011). However, when DH lesions are made pre-training, context fear and fear renewal can remain intact (Wiltgen et al., 2006; Zelikowsky, et al., 2011), suggesting that in the absence of the DH, alternate brain structures are recruited to compensate. The identity of these compensatory regions and how they operate remains an open question. We tested the hypothesis that the prelimbic (PL) and infralimbic (IL) cortices are sites of hippocampal compensation. By combining double-lesions (DH+IL or DH+PL) with behavioral testing, retrograde tracing, and immediate early gene analyses, we found that in contrast to DH lesioned rats, double lesioned animals failed to show compensatory context-sensitive fear. Furthermore, compensation in DH lesioned animals correlated with an increase in activation of amygdala-projecting PL cells coupled with a decrease in activation of amygdala-projecting IL cells. To test whether this compensation required direct communication between the PL and IL, we performed a disconnection experiment wherein ipsilateral or contralateral lesions of the PL and IL were made in DH-lesioned rats. We found that only contralateral lesioned animals failed to express context fear and renewal. Collectively, these findings suggest that compensation in the absence of the DH requires interplay between the PL and IL cortex and corresponds to a re-balancing of neuronal activity within these areas.

P40. Selective serotonergic lesions of the insular cortex (IC) and ondansetron infusions into the visceral region of the IC, but not the gustatory region of the IC, attenuates LiCl-induced conditioned gaping, but not conditioned taste avoidance, in rats.

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Conditioned gaping in rats is selectively produced by emetic drugs, unlike conditioned taste avoidance (CTA). Drugs that elevate serotonin (5-HT) produce nausea in humans and conditioned gaping in rats and 5-HT₃ antagonists, such as ondansetron (OND), reduce nausea and gaping. Depletion of forebrain 5-HT and ablation of the insular cortex (IC) both block LiCl-induced conditioned gaping in rats. Experiment 1 evaluated the potential of selective depletion of 5-HT (by 5,7-Dihydroxytryptamine) in the IC to interfere with this nausea-like behavior. A 76% depletion of 5-HT in the IC, but not in control regions, suppressed LiCl-induced conditioned gaping, but not CTA. Experiment 2 determined the effect of intracranial administration of OND into the gustatory region of the IC (GIC) or the viscerosensitive (granular) region of the IC (VIC) on the establishment of LiCl-induced conditioned gaping and CTA in rats. The results revealed a double dissociation between the regional effects of OND on gaping and CTA. Bilateral infusions of OND (0.1 and 1 μ g) into the VIC interfered with gaping, but not CTA, but bilateral infusions of OND (1 μ g) into the GIC interfered with CTA, but not gaping. These results suggest that activation of 5-HT₃ receptors in the VIC by 5-HT may be responsible for the sensation of nausea necessary for the production of conditioned gaping reactions, but not CTA.

P41. CS-US Interval Determines the Transition from Overshadowing to Potentiation with an Odor + Taste Compound

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Taste-aversion conditioning regimen and CS-US interval (0, 30, 60, 120, and 240 min) were manipulated in two experiments with rat subjects. In Experiment 1, rats received either an odor solution or a taste + odor solution prior to toxicosis at one of the aforementioned trace intervals. Subsequent odor aversion testing confirmed taste-mediated odor potentiation across short and long intervals (0, 30, 60, and 120 min). In Experiment 2, the conditioning solutions were taste or the odor + taste compound, followed by illness at the same increasing trace intervals. In contrast with the odor results of Experiment 1, taste testing in Experiment 2 revealed a significantly weaker taste aversion (overshadowing) at the immediate interval, but a significantly stronger taste aversion (odor-mediated taste potentiation) at the 60- and 120-min intervals. Notably, the demonstration of reciprocal potentiation at the 120-min interval and the differential changes to taste and odor cues across the trace interval has implications for current theories of compound aversion conditioning. Furthermore these results are consistent with similar demonstrations from taste + taste conditioning that suggest a common mechanism for overshadowing and potentiation in flavor-aversion conditioning.

P42. Neural correlates of Appetitive and Aversive Interactions.

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The ability to learn about cues that predict reward and danger is a fundamental to survival. However the nature of interaction between appetitive and aversive learning, and the neural correlates of these interactions remain poorly understood. We used Pavlovian appetitive to aversive counterconditioning and superconditioning to study these. We first demonstrated that a CS established as a predictor of reward was retarded in the rate at which it could be transformed into a fear CS. We then used transreinforcer superconditioning to show that these appetitive – aversive interactions altered prediction error during fear learning. Finally we investigated the neural correlates of appetitive to aversive counterconditioning through mapping expression of phosphorylated mitogen-activated protein kinase (pMAPK) in the amygdala, prefrontal cortex (PFC) and periaqueductal gray (PAG). Increased levels of pMAPK were found in the lateral amygdala (LA) and the rostral agranular insular cortex (RAIC) whilst decreased levels of pMAPK were seen in the ventrolateral periaqueductal gray (vlPAG) during counterconditioning relative to fear and reward controls. These results show opponent interactions between appetitive – aversive motivational systems and suggest these interactions occur, at least in part, in amygdala, PFC and PAG.

P43. Rats are sensitive to ambiguity: Prior learning influences behavior in the presence of partial cues.

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In a series of experiments we investigated the role of prior learning on discriminations involving ambiguous situations. Experiment 1 found that covering a light cue (B) that previously served in a Negative Patterning discrimination (A+, B+, AB-) caused rats to respond significantly different than if B was uncovered and unlit (explicitly absent). Specifically, when B was covered (ambiguously absent), rats responded as if they were unable to determine if the trial constituted an elemental or compound trial from training. This same difference was not demonstrated by rats for which B had served in a Positive Patterning discrimination (A-, B-, AB+). Experiment 2 tested the hypothesis that the comparatively more complex task of Negative Patterning engages representational processing capacities necessary for sensitivity to ambiguity that are otherwise not engaged by Positive Patterning. To do this, rats were trained concurrently on both Positive and Negative Patterning discriminations (with different stimuli). In support of our hypothesis, rats tested on A in the Positive Patterning discrimination did indeed show sensitivity to covering B at test when they had also learned a Negative Patterning discrimination. Experiment 3 ruled out the potential contribution of reinforcement amount in the results of Experiments 1 and 2. Taken together, these results have interesting implications for representational processes engaged in problem solving.

P44. Heroin-Induced Conditioned Immunomodulation: Neural Mechanisms

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Administration of heroin has been shown to suppress a number of basic immune parameters. Remarkably, the suppressive effects of heroin on the immune system can be conditioned to environmental stimuli paired with drug administration. Recent studies in our laboratory have indicated that a circuit exists between the ventral tegmental area (VTA) basolateral amygdala (BLA) and nucleus accumbens (NAC) which mediates the expression of heroin-induced conditioned immunomodulation. The current investigation sought to expand upon these findings by determining the role of the hippocampus, a key brain region known to be involved in contextual recall. The hippocampal formation likely provides the VTA-BLA-NAC circuit with crucial information about drug-associated environmental stimuli and facilitates conditioned immunomodulation. Rats were given five conditioning trials in which they received an injection of heroin immediately upon placement into a distinctive environment. Rats then received bilateral microinfusions of a combination of GABA agonists aimed at the dorsal hippocampus (DH) to temporarily inactivate this brain region prior to testing of the conditioned response. Analyses indicate that lipopolysaccharide (LPS)-induced production of proinflammatory mediators was markedly suppressed following exposure to the heroin-paired environment relative to a control environment. Most importantly, inactivation of the DH attenuated this conditioned effect demonstrating a role for this brain region in the neural circuitry of heroin-induced conditioned immunomodulation. Furthermore, optimal IL-1 levels within the hippocampus have been shown to be necessary for associative learning processes. An siRNA-induced reduction in hippocampal IL-1 resulted in attenuation of the conditioned response indicating that IL-1 within the hippocampus is necessary for the expression of the conditioned effects of heroin on immune functioning. These results are the first to demonstrate the functional significance of CNS IL-1 expression in heroin-conditioned alterations in peripheral immune responses.

P45. Evidence for Place Responding with Rats in an Appetitive Spatial Task

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Animals navigating to a hidden goal use a variety of search strategies. Previous research on cue-dependent navigation with rats in the aversive situations encouraged the view that while the absolute place location of a goal may be learned early in training, response strategies often emerge following additional trials (Hamilton et al., 2008). Dry land studies indicated a similar pattern (Skinner et al., 2003). Hamilton et al. (2009) suggested the use of a “full pool” variant of the Morris task that was structured to reduce subjects’ reliance on inter-maze cues. The present study aimed to test for true place learning in a dry land maze that was surrounded by static extra-maze cues. We attempted minimize all intra-maze cues. In experiment one, rats exploration strategies were tested in either a shifted location, or a non-shifted control location. This shift allowed us to evaluate which of two strategies were controlling

previous search behavior. Rats employing place responding would search more often at the original place of the hidden cup (i.e., based on extra-maze cues), whereas, rats using directional responding would search at a location relative to intra-maze cues. In experiment two, rats were tested either early or late in open-field training. Probe trials with the maze repositioned revealed a preference for place learning regardless of the shift. Rats tested late in training continued to show a preference for place navigation. The results indicate that in a complex open-field maze, it may be possible to encourage place learning in rats across training and reduce the emergence of response strategies later in training. The results are discussed in terms of how behavioral options and spatial information provided by extra-maze cues influence the type of search strategy employed.

P46. Timing and Dopamine D1 versus D2 receptor affinity

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Motivation and timing in rat appetitive conditioning were assessed after intraperitoneal injections of the selective dopamine D1-family antagonist, SCH 23390 (vehicle, 0.05, and 0.1 mg/kg), and the D2-family antagonist, raclopride (vehicle, 0.4, and 0.8 mg/kg). During conditioning, a single food pellet was delivered 10 s after the termination of a 120-s white noise conditioned stimulus in the presence or absence of random intertrial pellets. During testing, timed head-entries into the food magazine were suppressed by both drugs in a dose-dependent manner; however, there was also a rightward shift in the peak time (delayed responding) under the high but not low dose of raclopride. Our results are consistent with a role for D2 receptors in both energizing and releasing a well conditioned behavior.

P47. Effects of lipopolysaccharides (Lps) treatment on cerebellar volume in an animal model of behavioral inhibition

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Autism is associated with pathophysiological changes in the cerebellum, particularly an increase volume and decreased numbers of Purkinje cells (PC). The cerebellum comprises an essential neuronal circuitry for the acquisition, expression and retention of conditioned responses (CR) in the delay eyeblink conditioning. Accordingly, faster acquisition of conditioned eyeblink responses is reported in autistics. Toward the development of an animal model of autism, we previously reported that LPS-induced proinflammatory cytokine production during the 2nd trimester of pregnancy induced faster acquisition of eyeblink conditioning in the offspring of Wistar-Kyoto (WKY), but not Sprague-Dawley (SD) rats. Here, we investigate cerebellar neuroanatomy of those male and female SD and WKY rats. Specifically, we determined whether LPS treated WKY rats would exhibit larger cerebellar cortical volumes compared to WKY controls. The granular layer was also included in the analysis since it is the major source of input to PCs and a possible underlying cause of faster acquisition of eyeblink responses.

The volume estimation analysis was carried out through the entire left cerebellar cortex of WKY (n=24) and SD (n=26) rats, except for the paraflocculus region to minimize the variability between and within the rats. To analyze the volume, tissue was mounted in gelatin and cut in a coronal plane with a freezing stage microtome. Every 6th section was mounted on gelatin coated slides and then stained with cresyl violet dye. Using computerized assisted stereology, volumes of the tissue sections were estimated using the Cavalieri principle. Granular cell layer-cerebellum ratio was also calculated. Our analysis of tissue revealed that SD rats have significantly larger cerebellar cortex and granular layer volumes compare to WKY rats. Prenatal LPS treatment showed a trend for larger cerebellar cortex and granule cell layer compared to vehicle treatment rats. These data highlight the difficulty in relating structural and functional abnormalities with a direct examination of the interaction of genetic and environmental influences in an animal model of Autism.

P48. The Utility of the Eyblink Conditioning Paradigm as a Diagnostic Tool for Traumatic Brain Injury.

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Investigations of traumatic brain injury (TBI) in humans and animal models of TBI demonstrate cerebellar damage even when the initial mechanical insult is indirect (for a review see Pots, Adwanikar, & Noble-Haeusslein, 2009). The consequences of TBI including ataxia, impairments in balance and fine motor skills, and even cognitive deficits, may be attributed in part to cerebellar damage, specifically Purkinje cell injury or loss. However, few studies of TBI, if any, have utilized the extensively studied cerebellar task of eyeblink conditioning (EBC). Importantly, the cerebellar circuit involved in EBC has been well identified. The cerebellar interpositus nucleus (IP) is known to be the critical site for learning and executing the conditioned eyeblink response (CR). The overlying cerebellar cortex (CTX) is also known to be important, particularly inhibitory Purkinje cells, for learning and proper timing of the CR. For example, Vogel et al. (2009) demonstrated that pharmacologically disengaging CTX with infusions of the non-competitive GABA-A antagonist picrotoxin impairs acquisition of the CR in rabbits trained with a long, non-optimal (750-ms) interstimulus interval (ISI). Notably, no impairment was observed in rabbits trained with a short, optimal (250-ms) ISI. The procedure of EBC in both humans and nonhuman species is identical and relies on the cerebellar circuitry. Thus, EBC can serve as an excellent translational approach to understanding cerebellar deficits related to TBI. In particular, because Purkinje cells are involved in the timing of the conditioned eyeblink response, a short and long delay EBC procedure potentially could be used to investigate timing abnormalities caused by TBI. Initial expectations are impaired acquisition and timing of the long delay CR in individuals who currently or historically have TBI. Such timing deficits potentially can serve as markers for the sustained effects of insults resulting from TBI and subsequently facilitate diagnosis.

P49. Escape and avoidance learning in the earthworm?

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The earthworm can serve as an inexpensive preparation for behavioral neuroscience research. For investigators interested in learning, the earthworm is capable of Pavlovian conditioning (CS: light, vibration, or "odor;" US: light, touch, "odor;" UR: contraction or locomotor change). Instrumental learning is less well documented: early demonstrations of T-maze learning were confounded by pheromone secretion in response to electric shock. We present data bearing on escape/avoidance learning in the earthworm. Earthworms were exposed to a vibratory CS that preceded an aversive light/thermal US. Locomotion by the earthworm during the US would cause US offset; locomotion during the CS would prevent the subsequent US. Experiments were conducted in Duplo open fields in a dimly lighted room. Work is currently in preliminary stages; results and perhaps variations on the procedure will be presented at the meeting.

P50. Oxytocin and glutamatergic systems differentially mediate fear conditioning and social modulation of fear.

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Social interactions are known to ameliorate anxiety disorders in a variety of species including humans. However the neurobiology and molecular mechanisms by which social interactions attenuate fear are not known. Previous studies done in our laboratory have demonstrated proactive social modulation of contextual fear conditioning in mice. Specifically we showed that when naïve animals are exposed to non-fearful conspecifics in the training context there is a marked reduction of freezing behavior tested 24 hrs after conditioning. Pharmacological studies in this novel mouse model have demonstrated an important role for oxytocin signaling in social modulation of fear. Oxytocin receptor blockade in the lateral septum prevented the reduction in freezing seen after interactions with non-fearful conspecifics. In addition, administration of oxytocin into the lateral septum enhances social modulation of fear by reducing the amount of time needed for the social interaction to mediate their modulatory effect. In the present work we expand upon this network by studying the role of oxytocin and glutamatergic transmission in the hippocampus. We show that blockade of glutamatergic NMDA receptors, with APV, disrupts social modulation of fear. Furthermore, blockade of oxytocin receptors in the hippocampus blocks social modulation of fear without having any effects on fear conditioning alone. This data suggests that oxytocin and glutamate signaling in the lateral septum and hippocampus are important for social modulation of fear by non-fearful conspecific.

P51. Modulation of threat response by multi-modal stimulus concordance

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Previous research has shown that hermit crabs (*Coenobita clypeatus*) react more slowly to a looming visual predator in the presence of an anthropogenic noise than in a silent condition (Chan et al., 2010). We measured the crabs' latencies to respond to a visual predator across three unique conditions: a white noise positioned next to the visual predator (Concordant Condition), a white noise away from the visual predator (Discordant Condition), and a Silent Condition. As attentional processes modulate reactivity to visual stimuli, we hypothesized that the crabs would be slower to react in the Discordant Condition as compared to the Concordant Condition. We found that crabs were more likely to freeze prior to hiding in the Silent and Concordant Conditions than in the Discordant Conditions. In addition, we discovered differences in the crabs' latencies to react to the visual predator in a fearful manner. We discuss these differences in terms of attentional processes and predator imminence.

P52. Destabilizing memories to disrupt them: Coupling D-cycloserine administration with blockade of reconsolidation to potentiate the attenuation of strong aversive fear memories.

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A central challenge for anxiety disorder research is to develop clinically effective methods to therapeutically attenuate maladaptive fear memories. When fear memories are retrieved (reactivated), they appear to enter a transiently destabilized state which is believed to require re-stabilization via a process referred to as reconsolidation. Targeting the reconsolidation process has been proposed to be a potential treatment for many psychopathologies (i.e. post-traumatic stress disorder, phobias, drug seeking cues). However targeting the reconsolidation process is only effective for memories that enter a destabilized state following memory reactivation and recent studies suggest that not all reactivated memories become destabilized, consequently making these memories resistant to modification/attenuation. For example, recent data demonstrate that the strength of fear conditioning training can limit the ability of a memory to enter a destabilized state upon reactivation and render these memories resistant to treatments that block the reconsolidation process. One mechanism that may be useful in directing resistant memories into a destabilized state following memory reactivation is activation of N-methyl D-aspartate receptors (NMDAR) within the lateral nucleus of the amygdala (LA). Therefore we hypothesized that by pharmacologically enhancing calcium influx through the NMDAR with the NR1 partial agonist D-cycloserine(DCS), we might induce destabilization during reactivation of

a strong fear memory and render it susceptible to disruption. We determined that intra-LA infusions of DCS prior to memory reactivation coupled with immediate post-reactivation infusion of anisomycin attenuated the strong fear memory as measured during a post-reactivation long term memory test (PR-LTM). Notably DCS infusion without post-reactivation infusion of anisomycin or saline pre-reactivation infusion with immediate post-reactivation infusion of anisomycin had no effect on the strength of the memory as measured during a PR-LTM test. Further experiments demonstrated that our findings were dependent on memory reactivation and the timing of DCS administration.

P53. Fear conditioning by-proxy in female sibling rats

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Pairing a previously neutral conditioned stimulus (CS; e.g., a tone) to an aversive unconditioned stimulus (US; e.g., a foot-shock) leads to associative learning such that the tone alone will elicit a conditioned response (e.g., freezing). In humans and primates, individuals can infer fear from a social context, such as observing fear acquisition in a conspecific. This may represent an important means of learning about potential dangers without having experienced that danger personally (Olsson and Phelps, 2007), a model that is only just beginning to be applied to rodents.

In the current study, we applied a social learning paradigm to female sibling rats. Rats were housed in triads with either sisters or non-related females. One rat from each cage was fear conditioned to a tone CS. The next day, the conditioned rat was returned to the chamber accompanied by a second cage-mate. Both rats were allowed to behave freely while the tone was played in the absence of the foot-shock. The previously untrained rat is referred to as the fear conditioning by-proxy (FCbP) animal, as she would freeze based on observations of her cage-mate's response rather than due to personal experience with the foot-shock. The following day, during the presentation of the CS, long-term memory tests (LTM) were performed. Consistent with our previous application of this paradigm in males (Bruchey et al., 2010), our results revealed that a portion of FCbP rats (FCbP+) froze significantly more than the others in the group. In this experiment, LTM freezing did not differ between the FCbP+ and fear-conditioned rats in sisters, but was significantly different in non-sisters. Additionally, c-Fos protein expression in the lateral amygdala after LTM was not significantly different between sister rats that were fear-conditioned and the FCbP rats. These results suggest that when female rats are raised together as sisters, social transmission of fear can produce fear expression that is equivalent to fear that is learned through personal experience.

P54. Latent Inhibition in a Rat Model of Anxiety: Fos-Related Activation in the Entorhinal Cortex and Cerebellum

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In associative learning, latent inhibition (LI) occurs when pre-exposure to a conditioned stimulus (CS) slows acquisition during subsequent conditioning with that CS. Reduced LI (comparable learning with and without CS pre-exposures) is observed in schizophrenia and anxiety disorders. Wistar-Kyoto (WKY) rats, a model for anxiety vulnerability, also fail to demonstrate LI, while non-anxious controls (Sprague-Dawley, SD), exhibit the expected delay in acquisition of the conditioned response (CR) during eyeblink conditioning. Simple delay eyeblink conditioning is often associated exclusively with the established cerebellar circuit, but a recent dissociation has been found in this lab wherein LI of delay conditioning is abolished in SD rats following lesions of the entorhinal cortex (EC), but not the hippocampus. One interpretation of this finding is that pre-exposures reduce CS saliency through alteration of activity in the EC as well as the cerebellum. Accordingly, it is predicted that CS pre-exposure would alter stimulus-elicited activation in the EC and/or cerebellum of SD but not WKY rats, modifying the subsequent eyeblink acquisition. Conversely, EC and cerebellar activation, and therefore CS saliency, may remain unchanged in WKY rats throughout the pre-exposure period. To test this hypothesis, WKY and SD rats were exposed to 0, 1, or 30 auditory CS (82 dB, 500-ms white noise) pre-exposures followed by delay eyeblink conditioning (100 CS-US pairings; 30-40 s ITI). Following either pre-exposure or pre-exposure and paired conditioning, neuronal activation in the EC, hippocampus, and cerebellum will be assessed using c-Fos immunoreactivity. For SD rats, CS pre-exposures are expected to modify activation in the EC and cerebellum, whereas no change in activation is expected in WKY rats. The predicted finding would support the hypothesis that sustained CS-related activation to potentially irrelevant cues may underlie the anxious phenotype. Funding provided by VA BLR&D Grant I01BX007080 & I01BX000218, NIH Grant NS44373, and the SMBI.

P55. Metaplasticity-like Mechanism Supporting the Selection of Fear Memories

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As we go about our daily lives most information is retained only briefly, while some things are stored long-term, perhaps even lasting a lifetime. How the brain goes about determining which memories are selected for long-term storage and which are not is critical for a full understanding of memory. One attractive possibility is that memories are selected for long-term storage based on the “neural state” of

the cells in a circuit responsible for any given memory. The history of neural activity and the current state of these neurons then determines the ability of those cells to undergo synaptic plasticity at some time in the future. This observation has been termed metaplasticity, and many in vitro studies have demonstrated metaplasticity-like effects in a variety of preparations. However, behavioral correlates of this idea are more limited. We show that a single pairing of a light with footshock, which does not result in an overt fear memory, primes future learning such that another trial delivered within a circumscribed time window results in the formation of a fear memory. The memory formed by two properly spaced trials lasts at least 1 month, and is only seen when both shocks are signaled by the same cue. A single pairing also results in the activation of several targets of protein kinase A (PKA) in the amygdala, and accordingly the priming effect can be blocked by a PKA inhibitor delivered to the amygdala prior to the first trial. We argue that these findings give insight into how memories are selected for long-term storage.

P56. Cytokine signaling in the brain in a mouse model of depression and PTSD after myocardial infarction

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Systemic activation of the innate immune system by chronic illness or injury is correlated with subsequent depression, anxiety and PTSD. After a heart attack (myocardial infarction, MI), for example, patients are three times more likely to develop PTSD, and twice as likely to develop major depression. Similar to other studies, post-heart attack incidence of PTSD and depression are correlated with increased levels of circulating pro-inflammatory cytokines. How circulating cytokines affect behavior and signaling in the brain remains unknown.

Here, we use a surgical model of myocardial infarction in mice to investigate the role of sustained peripheral inflammation on (1) the emergence of depression-like behaviors and enhanced fear, (2) cytokine release and signaling in the brain, and (3) sex differences in these phenomena.

After MI, but not sham surgery, mice exhibited increased depression-like behavior in the forced swim test. In addition, males, but not females showed robust enhancement of contextual fear conditioning. Importantly, MI did not affect locomotor activity, reaction to shock, or unconditioned freezing.

In mice with MI, cytokine-dependent signaling was upregulated in the hippocampus and prefrontal cortex. Notably, suppressors of cytokines-1 and 3 (SOCS1 and SOCS3) expression, and tyrosine phosphorylation of signal transduction and transcription factor-3 (STAT3) were significantly increased after MI. In addition, in female mice, but not males, serine phosphorylation of STAT3 was also significantly increased, suggesting qualitative differences in post-MI alterations in signaling. Levels of cytokines including TNF- α , IL-6, IL-2, and IL-10 in the brain after MI are currently under investigation.

These findings validate MI as a valid model for investigating the role of systemic inflammation in alterations of behavioral and neural signaling, and suggest cytokine-dependent signaling as a candidate mechanism for susceptibility to depression and PTSD after MI.

P57. Network-level examination of MAPK signaling in trace and delay fear conditioning

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We have recently shown that the acquisition of trace conditioning (TFC) is sensitive to unilateral disruption of ventral hippocampus, but full bilateral disruption of prelimbic (PL) mPFC (Gilmartin et al, 2010). The acquisition of trace, delay, and contextual fear responses is also sensitive to unilateral disruption of the amygdala (Gilmartin et al., 2011). These findings suggest that hippocampus, mPFC, and amygdala interact to form the trace fear memory. This study examines MAPK expression in each structure important for trace fear conditioning and investigates the functional contribution of the network on MAPK expression. In Experiment 1, phosphorylated ERK (pERK) expression is measured in prefrontal and temporal lobe structures following trace or delay fear conditioning. In Experiment 2, changes in trace-conditioning related pERK expression patterns are measured following targeted inactivation of PL, amygdala, or ventral hippocampus. For each structure, the GABA_A agonist muscimol was infused unilaterally in one hemisphere. Thirty minutes following infusion, rats were trained with trace or delay fear conditioning and euthanized after training. In all experiments, coronal slices were probed with pERK antibody using immunohistochemistry and pERK-expressing cells were counted in each region of interest. Initial findings are consistent with a network model of trace fear conditioning in which mPFC receives hippocampal input.
