Program for the 2010 Annual Meeting of the Pavlovian Society

Tremont Plaza Hotel, 222 St. Paul Place
Baltimore, MD 21202 1-800-TREMONT (800-873-6668)

Thursday, October 14 **Roman Strada (2nd floor)**
6:00-9:00 PM Reception and Registration

Friday, October 15 **All Paper Sessions in Mirror Room (5th floor)**
Breakfast, snack breaks and posters in Edinburgh Hall (5th floor)

7:30-8:25 **Light breakfast, registration and poster setup** (**Edinburgh Hall**)

8:25-8:30 **Peter Holland**, Johns Hopkins University. *Opening remarks*

8:30-9:00 Peter M. Jones and **Mark Haselgrove**, University of Nottingham. *Overshadowing and associability changes*

9:00-10:30 **Symposium: Epigenetics of memory formation.** Chair: **Glen Schafe**, Yale Univ.
Glenn Schafe, Yale Univ. *Epigenetic alterations underlying amygdala-dependent memory consolidation and synaptic plasticity*
Karyn Frick, Univ. Wisconsin-Milwaukee. *The role of epigenetic alterations in estrogenic modulation of hippocampal memory consolidation*
Marcelo Wood, Univ. California-Irvine. *Focal deletion of chromatin modifying enzymes: Effects on histone modification patterns and long-term memory*

10:30-10:45 **Coffee break and poster setup (Edinburgh Hall)**

10:45-11:30 **Tom Beckers**, Universities of Leuven and Amsterdam. *Effects of additivity and maximality on blocking: Formal models, their relative strengths, and their limitations*

11:30-12:00 **Rick Servatius,** New Jersey Medical School and DVA NJ Health Care System**.** *Faster acquisition of eyeblink conditioning in adolescents with inhibited temperament*

12:00-1:30 **Lunch break** (on your own)

1:30-3:30 **Symposium: Time and conditioning.** Chair: **Peter Balsam**, Barnard College/Columbia Univ.
Peter Balsam, Barnard College/Columbia Univ. *Time and the acquisition of conditioned responses*
Douglas A. Williams, Univ. of Winnepeg. *Some effects of random intertrial USs on CR timing*
Ralph R. Miller, Binghamton Univ.. *Timing in conditioned inhibition: Exactly when does an event not happen?*
E. James Kehoe, Univ. of New South Wales, Elliot A. Ludvig, Univ. of Alberta, and Richard S. Sutton, Univ. of Alberta. *Which comes first: Association or timing?*
Russell M. Church, Brown Univ. *Timing is everything*
Mark Bouton, Univ. of Vermont. *Discussant*

Friday, October 15 (continued) **All Paper Sessions in Mirror Room (5th floor)**

3:30-3:45 **Snack break (Edinburgh Hall)**

3:45-4:30 **Michael Fanselow**, Univ. California-Los Angeles. *Stress-enhanced fear learning as a model of post-traumatic stress disorder*

4:30-5:00 **Norbert Fortin,** Univ. of California-Irvine**.** *The hippocampus and the memory for sequences of non-spatial events*

5:00-5:30 **Betsy Murray**, National Institute of Mental Health. *What's it worth? Orbital prefrontal cortex contributions to reward-based decision making*

5:30-6:30 **Posters** (**Edinburgh Hall)**

6:30- **Dinner** (on your own)

Saturday, October 16 **All Paper Sessions in Mirror Room (5th floor)**
Breakfast, snack breaks and posters in Edinburgh Hall (5th floor)

7:30-8:30 **light breakfast (Edinburgh Hall)**

8:30-9:15 **Howard Eichenbaum**, Boston Univ. *Towards a comparative neurobiology of episodic memory*

9:15-10:00 **Mark Bouton**, Univ. of Vermont . *Timing and associative learning: does one explain the other?*

10:00-10:15 **Coffee break (Edinburgh Hall)**

10:15-11:45 **Symposium: Computational models of extinction.** Chair: **Nestor Schmajuk,** Duke Univ.

Sam Gershman, David Blei, and Yale Niv, Princeton Univ. *A normative statistical perspective on learning and extinction*
Mario A. Laborda, Cody W. Polack, Gonzolo Miguez, and Ralph R. Miller, Binghamton Univ. *Extinction, renewal, and the comparator model*
Munir G. Kutlu and Nestor Schmajuk , Duke Univ. *An attentional-associative model of extinction*

11:45-1:00 **Lunch Break** (on your own)

1:00-3:00 **Symposium: Systems consolidation in the hippocampus and neocortex.** Chair: Brian Wiltgen, Univ. of Virginia

Brian Wiltgen, Univ. of Virginia. *The hippocampus plays a selective role in the retrieval of precise contextual memories*
Courtney Miller, Scripps Florida. *DNA methylation and systems consolidation*
Kaori Takehara-Nishiuchi, Univ. Toronto. *Spontaneous changes of neocortical code for associative memory during consolidation*
Leonardo Restivo and Paul Frankland. Univ. Toronto/Hospital for Sick Children. C*onsolidation of fear memories in the neocortex*

Saturday, October 16 (continued) **All Paper Sessions in Mirror Room (5th floor)**

3:00-3:15 **Snack break (Edinburgh Hall)**

3:15-5:15 **Symposium: Hope, fear and the amygdala.** Chairs: **Joanne Lee** and **Marie Monfils**, Univ. Texas-Austin

Gorica Petrovich, Boston College. *Control of feeding by learned cues: Amygdala circuits*

Joanne Lee, Univ. of Texas, Austin. *Updating during retrieval of appetitive memory*

Susan Sangha, Univ. of California-San Francisco. *The role of GAD65 in extinguishing fear*

Tanja Jovanovic , Emory University. *Fear acquisition and inhibition in posttraumatic stress disorder*

5:15-6:30 **Posters (Edinburgh Hall)**

7:00-10:00 **Banquet (Doric Room – 4th floor)**

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Speaker and Symposium Abstracts (in program order)

Friday, October 15

Peter M. Jones and **Mark Haselgrove**, University of Nottingham. *Overshadowing and associability changes*

Three appetitive Pavlovian conditioning experiments with rats examined the associability of stimuli A and B that had a history of compound conditioning (AB+), relative to stimuli X and Y that had a history of conditioning in isolation (X+, Y+). Following this training, Experiment 1 revealed that conditioned responding was higher to X and Y than to A and B (overshadowing). In a subsequent AY+, AX-, BY- test discrimination, the AY/BY discrimination was solved more readily than the AY/AX discrimination. Experiment 2 revealed that following AB+, X+, Y+ training, A and B served as more effective discriminative stimuli than X and Y. In Experiment 3, following AB+, X+, Y+ training, A was able to acquire greater control of instrumental responding than Y when a compound of the two stimuli was used as a discriminative stimulus. These results imply that the associability of stimuli conditioned in compound is higher than stimuli conditioned in isolation. These results constitute a challenge to traditional theories of learning and attention (e.g. Pearce & Hall, 1980; Mackintosh, 1975), but can be explained by a contemporary hybrid model (Pearce & Mackintosh, 2010).

Symposium: Epigenetics of memory formation. Chair: **Glen Schafe**, Yale University
Traditional views of memory formation have emphasized the importance of NMDA receptor-driven alterations in protein kinase signaling cascades, the activation of transcription factors, and associated changes in gene expression that are thought to be critical for long-term memory and synaptic plasticity. Recent evidence indicates that an additional level of transcriptional regulation, including DNA methylation and modifications of chromatin structure, may also be critical for memory formation. Such 'epigenetic' mechanisms, long studied in the context of cellular differentiation and development in a variety of cell types, have in neurons recently been hypothesized to play an essential role in promoting enduring changes in synaptic plasticity and memory consolidation. In this symposium, we will examine the role of these epigenetic processes in both hippocampal and amygdala-dependent forms of learning and memory.

Glenn Schafe , Yale University. *Epigenetic alterations underlying amygdala-dependent memory consolidation and synaptic plasticity*
Epigenetic mechanisms including histone acetylation and DNA methylation have been widely implicated in hippocampal-dependent learning paradigms, but little is known about the role of these processes in amygdala-dependent learning and memory. Here, we have examined the role of epigenetic alterations in amygdala-dependent auditory Pavlovian fear conditioning and associated synaptic plasticity in the lateral nucleus of the amygdala (LA). We show that auditory fear conditioning is associated with changes in histone acetylation in the LA. Further, we show that pharmacological manipulation of DNA methyltransferase (DNMT) or histone deacetylase (HDAC) activity in the LA impairs or enhances, respectively, memory consolidation of auditory fear conditioning and long-term potentiation in the LA.

Karyn Frick, Univ. Wisconsin-Milwaukee. *The role of epigenetic alterations in estrogenic modulation of hippocampal memory consolidation*
Recent studies have demonstrated that histone acetylation and DNA methylation in the hippocampus are critical to the consolidation of long-term contextual fear memories. These epigenetic processes appear to be regulated by hippocampal ERK/MAPK activation. We recently demonstrated that dorsal hippocampal ERK activation is necessary for the potent estrogen, 17β-estradiol, to enhance the consolidation of object recognition memories in female mice. Therefore, we wondered if epigenetic mechanisms might be involved in this estradiol-induced memory facilitation. This talk will discuss our recent findings showing that histone acetylation and DNA methyltransferase activity are critical for the beneficial effects of estradiol on object memory consolidation in females.

Marcelo Wood, Univ. California-Irvine. *Focal deletion of chromatin modifying enzymes:Effects on histone modification patterns and long-term memory*
Gene expression is dynamically regulated by chromatin modifications on histone tails, such as acetylation. In general, histone acetylation promotes transcription, whereas histone deacetylation negatively regulates transcription. The interplay between histone acetyltranserases (HATs) and histone deacetylases (HDACs) is pivotal for the regulation of gene expression required for long-term memory processes. Currently, very little is known about the role of individual HDACs in learning and memory. We examined the role of HDAC3 in long-term memory using a combined genetic and pharmacologic approach. Our findings demonstrate that HDAC3 is a critical negative regulator of long-term memory formation.

Tom Beckers, Universities of Leuven and Amsterdam. *Effects of additivity and maximality on blocking: Formal models, their relative strengths, and their limitations*
Both in causal learning in humans and in Pavlovian conditioning in humans and rats, evidence suggests that forward blocking is absent (or at least strongly reduced) if subjects had learned previously that the predictions of other cues combine in a non-linear, sub-additive fashion (e.g., Beckers et al., 2005, 2006; Lovibond et al., 2003; Mitchell & Lovibond, 2002; Wheeler et al., 2008) or if the outcome presented during training is of a maximal intensity (e.g., Beckers et al., 2005, 2006; De Houwer & Beckers, 2002). Over the past few years, a number of formal accounts for these findings have been proposed. I will first present an non-formal, heuristic analysis of blocking that may illuminate why effects of additivity and maximality occur. I will then critically discuss several formal accounts for such effects, including associative (e.g., Haselgrove, 2010; Livesey & Boakes, 2004), connectionist (e.g., Schmajuk & Kutlu, 2009; Schmajuk & Larrauri, 2008) and Bayesian models (e.g., Lu et al., 2008; Lucas & Griffiths, 2010). I will point out the basic tenets of these models, their relative merits, as well as their major shortcomings.

Rick Servatius, New Jersey Medical School and DVA New Jersey Health Care System**.** *Faster acquisition of eyeblink conditioning in adolescents with inhibited temperament*
Converging evidence supports a *Diathesis-Learning* model in the etiology of anxiety disorders. The final common path appears to be the development and expression of avoidance. The prevailing view is that the development and persistence of avoidance stems from heightened responses to stress or trauma -- vulnerability modulates stress responsiveness. An alternative view is that vulnerability directly modifies associativity -- enhanced acquisition of avoidance reflects biases either in the form of cue-outcome or response-outcome learning. If so, such learning biases should be apparent in those at risk, prior to expressions of anxiety psychopathology. Acquisition of the classically conditioned eyeblink response was assessed in male and female adolescents (14-18 years of age) in one of two protocols: standard delay, in which a 500-ms conditioned stimulus coterminated with an airpuff, or delay with the additional imposition of a response contingency in which a conditioned response (CR) prevented delivery of the airpuff unconditional stimulus (US). Behaviorally inhibited (BI) temperament, a vulnerability for anxiety disorders, was assessed with self-report scales; the upper 1/3 was characterized as HIGH (BI-HIGH), the lower 2/3 third as LOW (BI-LOW). Acquisition of the eyeblink CR was faster in BI-HIGH compared to BI-LOW; unconditional response magnitudes were similar. For BI-HIGH, faster acquisition was more apparent in simple delay than in delay with the imposition of a response contingency. Thus, avoidance was not apparent to a great degree in BI-HIGH. To facilitate acquisition of avoidance, a subsequent study additionally provided a response-contingent change in the CS, that is, for half the subjects a CR resulted in the change in the CS for the final 60 ms of the 500 ms CS. Again, BI-HIGH acquired an eyeblink CR faster than BI-LOW.
Unexpectedly, the response-contingent change in the CS facilitated acquisition in delay-type training regardless of BI, but not delay-type training in the presence of an omission-contingency. Facilitated associative learning represents an expression of vulnerability, evident in adolescents and a likely accelerant to avoidance acquisition and expression in the face of adverse events.

Symposium: Time and conditioning. Chair: **Peter Balsam**, Barnard College/Columbia University

Peter Balsam, Barnard College/Columbia University. *Time and the acquisition of conditioned responses*

Temporal relations between CS and US play important roles in the acquisition of CR's by affecting the speed with which acquisition occurs, the form of the CR and the time at which the CR occurs during the CS. In delay conditioning with a fixed CS-US interval animals learn the exact times from CS onset to the US. This determines the pattern of responding within the CS but acquisition speed seems to depend only on the rate of reinforcement in a cue relative to the overall reinforcement rate and is not affected by fixing the CS-US interval.

Douglas A. Williams, Univ. of Winnepeg. *Some effects of random intertrial USs on CR timing*

When an unconditioned stimulus (US) is delivered at a fixed time after the onset of a conditioned stimulus (CS), an anticipatory response is normally acquired at the arrival time of the US. Contrary to previously accepted research and thinking, we find random intertrial USs do not undermine timed conditioned responding. In appetitive conditioning, rats display well timed conditioned responses (CRs) even when the probability of the US during the CS is much lower than during its absence. However, the nature of the conditioned CR can be subtlety or greatly altered in the presence of intertrial USs. Some examples include a) slowed rates of acquisition, b) rightward shifts in peak times, c) less than expected variability, d) greater contextual control, and e) susceptibility to behaviorally-silent learning. Results are discussed in relation to real-time models of conditioning, such as the componential extension of Wagner his colleague's SOP memory model and Sutton and his colleague's real-time microstimulus TD model.

Ralph R. Miller, SUNY-Binghamton. *Timing in conditioned inhibition: Exactly when does an event not happen?*

A multitude of studies have demonstrated that an excitatory CS can signal both whether and when an outcome is going to occur. The question I will address is whether an inhibitory CS communicates equivalent information about the absence of an outcome. Conceptually, organisms appear to encode 'temporal maps' depicting the temporal relationship between a conditioned inhibitor and the conditioned excitor with which it was trained, as well as the temporal relationship between the conditioned excitor used in inhibitory training and the outcome. Using a summation test, I will show how this information might be expected to interact with the temporal relationship between a transfer CS and its outcome, as well as the temporal relationship between the inhibitory CS and the transfer CS. Moreover, I will show how an inhibitory CS's temporal maps may interact with the temporal relationship between the inhibitory CS and the outcome on a retardation test. Data will then be presented showing that these expectations are largely fulfilled behaviorally. Thus, through higher-order conditioning, a conditioned inhibitor often conveys information about when the outcome will be omitted, analogous to the temporal information conveyed by an excitatory CS. More generally, these results are consistent with organisms' learning whether and when [as well as where, but that is another story] an outcome happened relative to a CS, and consequently is apt to happen again with the same relationship when presented with the CS.

E. James Kehoe, Univ. of New South Wales, Elliot A. Ludvig, Univ. of Alberta, and Richard S. Sutton, Univ. of Alberta.

Which comes first: Association or timing?

There have been three alternative approaches to CR timing in classical eyeblink conditioning: (1) operant avoidance hypotheses contend that the CR is shaped by the degree to which the eyelid closure overlaps the US; (2) scalar timing models contend that, as learning progresses, CR timing will become proportional to the CS-US interval and intertrial interval, and (3) Pavlovian timing models presume that the CS is encoded as a sequence of microstimuli, each of which gains associative strength according to its proximity to the US. Fine-grain analyses of individual movements in delay

and trace conditioning of the rabbit nictitating membrane preparation have revealed that movements as small as .10 mm, well below the conventional .50-mm criterion for a CR, are aligned with the US from their earliest appearance. The results are most consistent with Pavlovian timing models, only partly with scalar timing models, and not all with operant avoidance hypotheses.

Russell M. Church, Brown University. *Timing is everything*
Pavlov (1927) provided an explanation of temporal factors in conditioning. This has been used as a basis for computational models of temporal perception, memory, and decision processes, classical and instrumental conditioning, and response choice. A modular theory of learning and performance will be applied to several types of behavioral experiments with rats, and the adequacy of the theory will be evaluated.

Michael Fanselow, Univ. California-Los Angeles. *Stress-enhanced fear learning as a model of post-traumatic stress disorder*
Experience with events perceived as life threatening can lead to Post-Traumatic Stress Disorder (PTSD) a potentially life-long debilitating anxiety disorder. Such events can associatively condition fear to stimuli present at the time of trauma. However, there are also PTSD symptoms that are not easily explained by associative learning, such as a propensity to develop new fears, resistance to cognitive behavior therapy and increased substance abuse. I will describe an animal model that captures some of these symptoms. Rats exposed to a series of electric footshocks in one environment show a long lasting sensitization of fear circuitry that results in dramatically enhanced acquisition of new fears to novel stimuli that we call stress-enhanced fear learning (SEFL). SEFL is accompanied by long-lasting changes in gene expression within the amygdala. Pharmacological inactivation of the amygdala prior to stress prevents the development of SEFL. SEFL occurs even when associatively learning is blocked by NMDA-receptor antagonists or eliminated by extinction (exposure therapy). Like PTSD patients, SEFL rats show exaggerated responses to sudden stimuli and develop increased voluntary ethanol consumption. Pharmacologically, SEFL and fear conditioning can be dissociated. Thus successful treatment of PTSD will require different modalities to treat both the associative (fear conditioning) and nonassociative (SEFL) components of PTSD.

Norbert Fortin, University of California-Irvine**.** *The hippocampus and the memory for sequences of non-spatial events*
Our earlier work has shown that the hippocampus is critical to remember specific sequences of events, a defining feature of episodic memory. However, the fundamental neuronal mechanisms underlying this capacity remain unclear. Recent studies have reported that hippocampal neurons can represent temporal relations among sequences of locations. It remains to be determined whether this sequence coding is specific to spatial information, or reflects fundamental mechanisms by which the hippocampus encodes sequences of events.

To address this issue, we recorded from hippocampal neurons as animals performed a non-spatial sequence memory task. In this new paradigm, multiple series of five odors were either presented "*in sequence*" (i.e., A→B→C→D→E), or "*out of sequence*" (e.g., A→B→<u>D</u>→D→E). Animals were rewarded for correctly determining whether each odor was *in* or *out* of sequence.

Hippocampal neurons were classified into three main types that were consistent with the flow of information that occurred during each odor presentation. First, approximately 300ms after odor onset, a large proportion of neurons showed odor specificity, suggesting the animal had identified the odor being presented. Then, 300ms later, a second group of neurons showed distinct firing patterns if the odor was presented "*in sequence*" compared to "*out of sequence*". Subsequently, the activity of a third group of cells predicted whether the animal's impending choice would be correct or incorrect. These findings indicate that sequence coding in hippocampal neurons is not limited to the spatial domain, suggesting a fundamental role of the hippocampus in representing the temporal relations among events that constitute individual episodic memories.

Betsy Murray, National Institute of Mental Health. *What's it worth? Orbital prefrontal cortex contributions to reward-based decision making.*
Research in rats, monkeys and humans has provided compelling evidence for a role for orbital frontal cortex in representing reward expectancies. Our research in macaque monkeys has shown that the amygdala and the orbital prefrontal cortex (PFo), operate as part of a network involved in reward-based decision making. These circuits contribute to emotional responses, choice of objects associated with foods, and the valuation of choices based on a current biological state. The amygdala and PFo function cooperatively in some situations but they function in opposition in others. The specializations of different sectors of PFo will be discussed, with an emphasis on the relationship between affective processing and choice of actions.

Saturday, October 16

Howard Eichenbaum, Boston University. *Towards a comparative neurobiology of episodic memory*
There is currently major controversy about whether fundamental properties of episodic memory, our capacity to recollect past events, can be understood from studies in comparative neurobiology. This controversy centers on four key questions: (1) What is episodic memory and do animals have this capacity? (2) Is episodic recollection supported by a process that is distinct from a sense of familiarity, and does the hippocampus selectively support recollection? (3) Can we understand the role of the hippocampus in recollection as representing events in the spatial and temporal context in which they occurred? (4) How do components of the medial temporal lobe interact in support of the capacity for recollection in animals and humans? Evidence from our studies using an animal model of episodic memory will be discussed to provide a preliminary answer to these questions

Mark Bouton, Univ. of Vermont . *Timing and associative learning: does one explain the other?*
Temporal variables are clearly important in associative learning, and recent theorists have considered the possibility that timing processes may explain associative learning. Two lines of research using appetitive conditioning methods in rats shed light on this issue. In the first line, we examined the idea that the development of conditioned responding fundamentally depends on the animal's perception of time in the CS (T) and time in the intertrial interval (I). According to Gallistel and Gibbon (2000), conditioned responding emerges when the animal decides that the rate of reinforcement is higher in the CS than in the background, which occurs more quickly with higher I/T ratios. However, a number of experiments revealed large differences in the acquisition of conditioned responding in groups that had identical I/T ratios. The results of these experiments, which generally investigated the effects of intertrial interval on the rate of conditioning, are instead consistent with a trial-based model that emphasizes the role of short-term memory and surprise (e.g., Wagner, 1981, 2008). The second line of research studied the effect of intertrial interval as a discriminative stimulus signaling whether the next presentation of a 10-s CS will be reinforced or not reinforced. In one condition (Long+/Short-), a long ITI (e.g., 16 min) signaled that the next CS would be reinforced, and a shorter ITI (e.g., 4 min) signaled that the CS would not be reinforced. Animals readily learned this discrimination, but had trouble learning the opposite arrangement (Short+/Long-), where the short ITI signaled that the next tone would be reinforced and the long ITI signaled that it would not. The asymmetry is highly replicable, and does not seem to be anticipated by the major models of interval timing. It is instead consistent with the idea that time may be coded as a series of hypothetical "temporal elements," in which element A occurs and then B is added if additional time elapses. Elements A and B then enter into associations with the US according to the principles of compound conditioning. In such a scheme, the easy Long+/Short- discrimination is analogous to a feature-positive discrimination (AB+/A-) and the difficult Short+/Long- discrimination is analogous to a feature-negative discrimination (A+/AB-). The asymmetry is thus an example of the well-known Feature-Positive Effect. Ironically, and contrary to the idea that timing explains associative learning, the evidence may suggest that timing is well conceptualized as an associative learning process.

Symposium: Computational models of extinction. Chair: **Nestor Schmajuk,** Duke University.

Sam Gershman, David Blei, and Yale Niv, Princeton University. *A normative statistical perspective on learning and extinction*

I describe a normative statistical model of classical conditioning in which animals make inferences about the latent causes of cues and outcomes. In this model, cues and outcomes are associated by virtue of being generated by the same latent cause, rather than having direct associations with one another. Conditioned responses are conceptualized as predictions about reinforcement, conditional on the animal's beliefs about the currently active latent cause and its statistical relationship to reinforcement. I show how application of this idea can explain several rather perplexing phenomena in learning and extinction. Along the way, I suggest possible roles for dopamine and the hippocampus in these computations. For example, when acquisition and extinction occur in different contexts, conditioned responding is renewed upon return to the acquisition context (ABA renewal), a finding that is difficult to reconcile with associative learning theories in which extinction is modeled as unlearning of the association between cue and outcome. A different way to think about this finding is that the animal has inferred two different latent causes, one that generated its observations (cue, outcome and context) during the acquisition phase, and one that generated its observations during the extinction phase. Upon returning to the acquisition context, the animal infers that the acquisition cause is once again active, and therefore increases its prediction of reinforcement, which in turn renews its conditioned response. Hippocampal lesions attenuate the renewal effect, suggesting that it may play an important role in making inferences about latent causes.

Mario A. Laborda, Cody W. Polack, Gonzolo Miguez, and Ralph R. Miller, SUNY Binghamton. *Extinction, renewal, and the comparator model*

According to the mathematical implementation of the extended comparator hypothesis (SOCR; Stout & Miller, 2007), responding is determined by direct activation of the US representation by a CS, which is down modulated by the indirect activation of the US representation retrieved through associations with other stimuli present during acquisition (e.g., the training context). Extinction trials, in addition to weakening the CS-US association, increase the within-compound association between the target and the training context. This allows the CS to better retrieve a representation of the context, and consequently to activate a stronger indirect representation of the US at test, thereby producing a decrease in conditioned responding. Thus, SOCR emphasizes the role of contextual associations in extinction. We present two sets of experiments that evaluated SOCR's predictions about the role of contextual associations in extinction. Despite the success of SOCR in predicting extinction and the effect of context manipulations during extinction, in its current form, SOCR does not anticipate recovery from extinction when testing occurs outside the context of extinction (i.e., renewal effects: ABB<ABC; ABB<ABA; AAA<AAC). Here we introduce a critical modification to the model that addresses compound testing, thereby allowing SOCR to predict basic renewal effects. Finally, some assumptions from the adapted model about inhibitory learning are delineated and data supporting them presented.

Munir G. Kutlu and Nestor Schmajuk , Duke University. *An attentional-associative model of extinction.*

Larrauri and Schmajuk (2008) showed that an attentional-associative (SLG) model of classical conditioning was able to describe most of the properties of extinction, including spontaneous recovery, renewal, reinstatement, and reacquisition. According to the model, those properties result from the context becoming inhibitory and protecting the excitor from extinction. Because during the time spent in the context following extinction, attention to the inhibitory context decreases, summation tests do not reveal the inhibitory power of the context (Bouton & King, 1983). In a predictive learning experiment with humans, Kutlu and Schmajuk confirmed the model's prediction that prolonged non-reinforced presentations of an inhibitor conceal its inhibitory power, reflected in

both summation and retardation tests. However, this power is restored after the inhibitor is presented with a novel stimulus. Furthermore, computer simulations indicate that the SLG model also describes related phenomena showing that (1) extinction of the excitor decreases retardation of conditioning of the inhibitor (Lysle and Fowler, 1985), (2) but has no effect on the power of the inhibitor in a summation test (Rescorla and Holland, 1977), (3) conditioning of the excitor increases power of the inhibitor in summation and retardation tests (Amundson et al., 2005), and (4) relatively short extinction of the inhibitor increases retardation but has no effect on a summation test (Pearce et al.,1982).

Symposium: Systems consolidation in the hippocampus and neocortex. Chair: **Brian Wiltgen**, Univ. of Virginia

Brian Wiltgen, Univ. of Virginia. *The hippocampus plays a selective role in the retrieval of precise contextual memories*

It is widely believed that the hippocampus plays a temporary role in the retrieval of episodic and contextual memories. Initial research indicated that damage to this structure produced amnesia for newly acquired memories but did not affect those formed in the distant past. A number of recent studies, however, have found that the hippocampus is required for the retrieval of episodic and contextual memories regardless of their age. These findings are currently the subject of intense debate and a satisfying resolution has yet to be identified. The current experiments address this issue by demonstrating that detailed memories require the hippocampus while memories that lose precision become independent of this structure. First, we show that the dorsal hippocampus is preferentially activated by the retrieval of detailed context fear memories. We then establish that the hippocampus is necessary for the retrieval of detailed memories using a context generalization procedure. Mice that exhibit high levels of generalization to a novel environment show no memory loss when the hippocampus is subsequently inactivated. In contrast, mice that discriminate between contexts are significantly impaired by hippocampus inactivation. These data suggest that detailed context memories require the hippocampus while memories that lose precision can be retrieved without this structure. These findings can account for discrepancies in the literature - memories of our distant past can be *either* lost or retained after hippocampus damage depending on their quality – and provide a new framework for understanding memory consolidation.

Courtney Miller, Scripps Florida. *DNA methylation and systems consolidation*

A behavioral memory's lifetime represents multiple molecular lifetimes, suggesting the necessity for a self-perpetuating signal. One candidate is DNA methylation, a transcriptional repression mechanism that maintains cellular memory throughout development. Initially, we discovered an important, but transient transcriptional role for DNA methylation in the hippocampus with contextual fear conditioning. According to the system consolidation theory of memory, memories such as hippocampus-dependent fear memories continue to consolidate over time as control shifts from the hippocampus to the cortex. Therefore, we shifted our investigation to the prefrontal cortex. Here we found that persistent, gene-specific cortical hypermethylation is induced in rats by a single, hippocampus-dependent associative learning experience. Further, pharmacologic inhibition of methylation within the cortex one month after learning disrupted remote memory. We propose that the adult brain utilizes DNA methylation to preserve long-lasting memories.

Kaori Takehara-Nishiuchi, Univ. Toronto. *Spontaneous changes of neocortical code for associative memory during consolidation*

After learning, the medial prefrontal cortex (mPFC) gradually comes to modulate the expression of memories that initially depended on the hippocampus. We show that during this consolidation period, neural firing in the mPFC becomes selective for the acquired memories. After acquisition of memory associations, neuron populations in the mPFC of rats developed sustained activity during the

interval between two paired stimuli, but reduced activity during the corresponding interval between two unpaired stimuli. These new patterns developed over a period of several weeks after learning, with and without continued conditioning trials. Thus, in agreement with a central tenet of consolidation theory, acquired associations initiate subsequent, gradual processes that result in lasting changes of the mPFC's code, without continued training.

Leonardo Restivo and Paul Frankland. Univ. Toronto/Hospital for Sick Children. C*onsolidation of fear memories in the neocortex*
While the hippocampus may play an essential role in the expression of memories soon after encoding, expression of the same (or at least equivalent) memory may become independent of the hippocampus at later time points. One predominant view is that the transition of the memory from a hippocampus-dependent to hippocampus-independent form reflects a time-dependent process of reorganization, leading to the permanent storage of the memory in cortical networks. Our lab uses molecular and behavioral approaches to understand this consolidation process, and, in my talk, I will highlight two new studies aimed at 1) identifying the broad network of cortical regions supporting remote contextual fear memories, and 2) understanding the role of myocyte enhancer factor 2 (MEF2) in this process.

Symposium: Hope, fear and the amygdala. Chairs: **Joanne Lee** and **Marie Monfils**

Gorica Petrovich, Boston College. *Control of feeding by learned cues: Amygdala circuits.*
Appetite and eating are not only regulated by energy needs, but also by environmental factors unrelated to energy balance. Environmental signals such as learned cues can override homeostatic signals to stimulate eating in sated states, or inhibit eating in states of hunger. Nevertheless, the underlying brain mechanisms are poorly understood. We developed two rodent models to study how environmental cues are integrated with homeostatic signals within functional forebrain networks, and how these networks are modulated by experience. Our behavioral models rely on learning, Pavlovian conditioning, to enable initially neutral environmental signals to modulate food intake based on prior associations with either rewarding or aversive events. In one model, a cue previously paired with food when an animal was hungry induces eating in sated rats. In the other model, food-deprived rats inhibit feeding when presented with a cue that signals danger, such as a tone previously paired with footshocks. Here, I will provide an overview of the two behavioral models and the critical amygdalar circuitries mapped thus far. The network formed by the basolateral amygdala, lateral hypothalamus and medial prefrontal cortex mediates cue-driven feeding, while a parallel amygdalar circuitry formed by the central nucleus mediates suppression of eating by the aversive cue. Findings from these animal models will be informative for understanding aspects of motivational control of appetite and eating in humans, including maladaptive mechanisms that contribute to overeating and anorexia.

Joanne Lee, Univ. of Texas, Austin. *Updating during retrieval of appetitive memory*
Evidence suggests that previously consolidated memories may enter a labile state upon retrieval and may be reconsolidated as new memories. Monfils et. al. (2009) have recently shown that extinction training introduced during this window results in more persistent attenuation of fear expression (freezing). Here we demonstrate memory updating during the reconsolidation period in appetitive Pavlovian conditioning. First, we used the retrieval-extinction paradigm and tested for spontaneous recovery. Rats underwent an acquisition phase in which a light was followed by presentation of a food pellet. After the rats fully learned the light-food association, they received a single retrieval trial (light only) and underwent extinction trials one hour after the isolated retrieval. Twenty-one days later, they were tested for spontaneous recovery and underwent reacquisition training in which the same light that had been used in the initial conditioning signaled delivery of a food pellet anew. Rats exposed to a single retrieval trial prior to extinction showed no spontaneous recovery and also

showed attenuated conditioned responding during reacquisition training. In the second study, during the reconsolidation window we introduced novel conditioning to a previously learned appetitive association. Rats were initially conditioned to pair a light with food. Subsequently, after a single isolated retrieval trial, they received fear conditioning in which the same light was paired with a shock. Rats in this condition displayed stunted recovery of appetitive behaviors during extinction and reacquisition trials. Together, our data suggest that the retrieval manipulation may facilitate persistent updating of the original memory trace. This work may allow us to better understand learning as a dynamic and fluid memory process.

Susan Sangha, Univ. of California-San Francisco. *The role of GAD65 in extinguishing fear*
Extinction procedures are clinically relevant for reducing pathological fear, and the mechanisms of fear regulation are a subject of intense research. The amygdala, hippocampus and prefrontal cortex (PFC) have all been suggested to be key brain areas in extinction of conditioned fear. GABA has particularly been implicated in extinction learning. GABA production is mediated by the enzyme GAD which exists in 2 isoforms: GAD65 and GAD67. GAD67 maintains basal GABA levels whereas GAD65 is rapidly activated in times of high GABA demand and is thought to be essential for regulating responses to environmental signals, such as those encountered during learning. We hypothesized GAD65 to be important in both fear learning and extinction of fear.

Gad67-/- mice are lethal but *Gad65-/-* mice are viable and thus it was possible to investigate extinction learning in *Gad65* knock-out mice. Extinction of conditioned fear was examined in *Gad65-/-* mice while recording local field potentials from the amygdala, hippocampus, and PFC. *Gad65-/-* mice showed generalization of cued fear and impaired extinction of cued fear, such that fear remained high across extinction training and recall. This endurance in cued fear was associated with theta frequency synchronization between the amygdala and hippocampus. Extinction of contextual fear, however, was unaltered in *Gad65-/-* mice when compared to wild-type littermates. These data imply that GAD65 plays a critical role in regulating cued fear responses during extinction learning, and that during this process, GABAergic signaling is involved in modulating synchronized activity between the amygdala and hippocampus. In view of the more pronounced effect on cued versus contextual fear extinction, these influences may rely more on GABAergic mechanisms in the amygdala.

Tanja Jovanovic , Emory University. *Fear acquisition and inhibition in posttraumatic stress disorder*
The symptoms of Posttraumatic Stress Disorder (PTSD) can be explained, at least in part, as an inability to inhibit learned fear during conditions of safety. Our group has shown that fear inhibition is impaired in both combat and civilian PTSD populations. We used a differential conditioning protocol in which fear responses were first acquired through the presentation of one colored shape (reinforced conditioned stimulus, CS+) that was paired with an aversive airblast to the larynx (unconditioned stimulus, US) and a different colored shape that was not paired to the airblast (nonreinforced conditioned stimulus, CS-). Fear was extinguished 10 minutes later through repeated presentations of the CSs without reinforcement. We measured potentiation of the acoustic startle response from the eyeblink muscle and US expectancy ratings on each trial.

Both groups demonstrated successful fear conditioning based on startle and US-expectancy ratings, however, participants with PTSD displayed greater fear-potentiated startle responses to the CS+ and CS- compared to the group without PTSD. During fear extinction, the PTSD group showed elevated fear-potentiated startle responses to the previously reinforced CS+ during the early and middle stages of extinction. Startle potentiation to the CS- during acquisition predicted slower extinction, indicating a common fear inhibition deficit. These results suggest that PTSD is associated with enhanced fear learning and a greater “fear load” to extinguish after conditioned fear is acquired.

Poster abstracts

P1. Multiple Interval Generalization in Rats

Jennifer A. Chuchmuch, Mickey D. Stein, Douglas A. Williams. University of Winnipeg.

Temporal generalization was assessed to novel compounds derived from conditioned stimuli (CSs) signaling the arrival of an unconditioned stimulus (US) at different time intervals. Anticipatory responding into the food niche by rats served as the conditioned response. For all subjects, the onsets of the elements A, B, and C (white noise, clicker, and tone CSs, counterbalanced) signaled the delivery of a food pellet US at intervals of 8, 16, or 32 s, respectively. One subset of the rats also experienced a visual CS that signaled food delivery at 8 s (A visual), whereas the other subset received food delivery at 32 s (C visual). Following acquisition, test trials of AB, AC, BC, and ABC were introduced for both groups. Timed responding generalized to the test compounds but did not summate to a level above the individual elements. The rats appeared to be timing multiple intervals simultaneously rather than a single mean interval.

P2. The time between USs critically affects the magnitude of the US preexposure effect.

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The effects of variable versus fixed inter-US intervals during a preexposure phase were examined in a conditioned magazine approach paradigm with rats. In Experiment 1 one group of animals received preexposure to the US on a 30s variable time schedule (group VT), a second group on a 30s fixed time schedule (group FT), and a third group received only very limited US preexposures (group CTRL). Following preexposure all groups were trained with a 30s CS-US interval. The data revealed that compared to group CTRL group FT was only slightly impaired, while group VT was severely impaired in their acquisition of magazine approach responding. In Experiment 2 a 60s CS-US interval was used during training. The same general pattern of results were obtained in this study, however, early in training group FT exhibited more approach responses during the early portion of the CS than did group CTRL, while the reverse was true for responding during the late portion of the CS. These data suggest that subjects learn the temporal intervals between USs during the preexposure phase, and use this information during conditioning.

P3. Timing of the CS-US Interval Before Emergence of Conditioned Responding

Ryan D. Ward, Elizabeth Yohe Moore, Nastajjia Krementz, Daniela Cannizzaro, Kathleen Taylor & Peter D. Balsam. Columbia University

The temporal relationship between events in a conditioning protocol is learned very rapidly, perhaps even before the emergence of conditioned responding. The present study investigated whether temporal learning occurred prior to CR acquisition in appetitive conditioning. Separate groups of rats were trained on an appetitive conditioning protocol in which the onset of a tone CS preceded delivery of a food pellet US. During Phase 1, rats were given three conditioning sessions (20 trials each) with relatively long CS durations (50 s). Acquisition of conditioned head poking did not occur during this phase. During Phase 2, all rats were exposed to conditioning sessions with a 10 s CS until conditioned responding was substantial (6 sessions). Then rats were given one test session which consisted of 20 trials with CS durations of 200 s. During this session, the rate of responding was highest at around 10 s, but there was also an increase in the rate of responding at around 50 s, suggesting that rats had learned the CS duration in Phase 1 in the absence of manifest conditioned responding. These results provide further evidence that learning the times of events in a conditioning protocol precedes the emergence of conditioned responding.

P4. Ontogeny of timing behavior and neural structures: Emergence of CS-US timing

Elizabeth A. Londen[1], Jessica L. Ahern[1], Regina M. Sullivan, Anne-Marie Mouly[2], Bruce L. Brown[3], and Valérie Doyère[4]

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Knowledge about temporal relationships between significant events and memory for durations underlie the development of adaptive anticipatory behavior. For example, in fear conditioning CS-US pairings, the CS comes to elicit conditioned responses, but also predicts when the US is expected to arrive. The present experiment investigated the age at which rat pups can learn the interval separating the CS and US. To assess the behavioral neurobiology of the ontogeny of timing, we used an olfactory fear conditioning paradigm in infancy (postnatal (PN) day; 14-15, 16-18, 21-23 weaning). Pups were conditioned in a 45-min session: Paired (30s peppermint odor paired with 0.5mA 1s shock that overlapped at 29s, 4-min ITI), Unpaired, Odor-only. We observed behavior during the odor presentation over 10-trials, as well as during a final 11th CS-only trial. In parallel, 14C 2-DG autoradiography assessed neural activity (prefrontal cortex-PFC subareas: OFC-orbitofrontal cortex; IL-infralimbic; PL-prelimbic; ACC-anterior cingulate cortex - amygdala nuclei: CoA-cortical; LA-lateral; BLA-basolateral; MeA-medial; CeA-central - striatum). Results suggest that PN14 pups show no signs of CS-US timing. However, PN16 pups showed changes in behavior near the expected time of US arrival in the CS presence. Assessment of 2-DG autoradiography suggests that emergence of timing at PN16 is associated with PL and ACC activation. Amygdala nuclei were functionally activated at all ages. The results suggest that timing of CS-US interval emerges in parallel with functional activation of associative prefrontal networks.

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P5. Temporal map in odor fear conditioning: Ontogeny of ITI timing and neural networks.

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The elaboration of temporal maps permits the proper evaluation of ongoing and past events, and underlies the building of a general knowledge base. Here we begin to assess the development of timing using infant rats (postnatal (PN) ages 14-15, 17-18, weaning 21-23) and focus on pups' ability to time the intertrial interval (ITI). We used an olfactory fear conditioning paradigm - conditioned olfactory stimulus (CS) paired with an unconditioned stimulus (US) shock. Three conditions were compared: Paired (30s peppermint odor - 1s 0.5mA hindlimb shock), Unpaired and Odor-only. A fixed 4 min intertrial interval (ITI) was used. The ontogeny of ITI timing was assessed through behavioral observations during a final virtual trial when no CS or US was presented. We also assessed neural activity (14C 2-DG - prefrontal cortex (PFC) subareas: OFC–orbitofrontal cortex; IL-infralimbic; PL-prelimbic; ACC-anterior cingulate cortex - amygdala nuclei: CoA-cortical; LA-lateral; BLA-basolateral; MeA-medial; CeA-central - striatum). Results suggest that only the weanling aged pups showed signs of ITI timing, in association with activation of all PFC subareas during the acquisition. Amygdala nuclei were activated at all ages. These results suggest that ITI timing abilities emerge by weaning and are correlated with PFC areas engagement during acquisition. These results suggest that the capacity for timing ITIs, which is critical for the elaboration of temporal maps of the whole experience, emerges last when all PFC networks are functional.

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P6. Plasticity in striatal and amygdala networks associated with changes in the temporal structure of fear conditioning

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In Pavlovian conditioning, what is learned is not only that the conditioned stimulus (CS) predicts the arrival of the unconditioned stimulus (US), but also when the US is expected to arrive. While the amygdala is known to play a critical role in emotional learning, the dorsal striatum may be involved in interval timing. Using immunohistochemistry against Arc/Arg3.1 protein, we tested whether a change in the CS-US interval triggers plasticity processes in amygdala and striatal networks. Compared to animals for which the CS-US interval remained unchanged, animals which learned a new CS-US interval showed a differential activation of Arc/Arg3.1 in both structures, with an increase in the lateral amygdala and a reduction in the dorsomedial striatum. Surprisingly, infusion of a ERK/MAPK inhibitor in the dorsal striatum tended to facilitate learning of the new CS-US interval. On the other hand, using a reconsolidation procedure as a tool, we show that a change in the CS-US interval in a single trial triggers a protein synthesis dependent reconsolidation process in the lateral amygdala. However, the pattern of fear behavior suggests that while the initial fear memory is disrupted, the single trial learning of the new CS-US interval may be intact. In all, our data suggest that both dorsal striatum and amygdala networks are involved in the processing of temporal aspects of fear memories. While plasticity mechanisms in the lateral amygdala may serve to update fear memories when temporal mismatches are detected, plasticity in the dorsal striatum may help to maintain habitual temporal behavior.

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P7. Hippocampal Processing of Temporal Ambiguity Exacerbates Fear

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Despite the ubiquitous use of Pavlovian fear conditioning as a model for fear learning, the highly predictable conditions used to study fear learning in the laboratory do not resemble real-world conditions. For example, in a natural setting, the temporal relationship between a predictive cue and a subsequent aversive stimulus exhibits considerable variability. Here, we show in rodents that unpredictable timing of an aversive event following a predictive cue greatly enhances associative fear to the predictive cue. This effect is exacerbated if animals are chronically stressed prior to fear conditioning. Temporary inactivation of the dorsal hippocampus prior to fear conditioning completely and selectively prevents 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 may generate teaching signals to enhance fear learning. We propose that the hippocampus is essential for this form of temporal error prediction, and that chronic stress, which is known to alter hippocampal function, increases the occurrence of such predictions, thus enhancing fear learning. This may explain why individuals who have been exposed to traumatic experiences show increased susceptibility to earned fear.

P8. Chronic stress Impairs appetitive Pavlovian reward learning.

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In humans, chronic stress exacerbates affective mental illness, and influences both reward learning and fear disorders (Goeders, 2003; Heim and Nemeroff, 2009). In rodents, chronic stress facilitates the acquisition, but impairs the extinction, of Pavlovian fear conditioning (unpublished data; Baran et al., 2009), however little is known about the effects of chronic stress on appetitive tasks. Interestingly, the amygdala, which plays a role in fear and reward learning (Goosens and Maren, 2001; Morrison and Salzman, 2010), is stress-responsive, showing increased dendritic branching and spine density following chronic stress (Vyas, et al., 2006). In the present study, we examined the influence of chronic stress on an appetitive, amygdala-dependent Pavlovian task. Rats were exposed to either chronic immobilization stress (CIS) 3h/day for 21d or daily handling. One day following the final stress or handling session, animals were trained on a simple discriminative, associative task where one auditory stimulus (CS+) signaled delivery of a sucrose reward, while another auditory stimulus (CS-) signaled nothing. Twenty-five pseudorandom CS+ and CS- trials were presented each day for four days, followed by extinction training over two days, in which no reward was given following CS+ trials. The latency to port entry following CS onset and number of port entries were measured throughout all sessions. Contrasting with a fear conditioning task, chronic stress impaired reward learning. Chronic stress also impaired reward extinction over multiple days. Though the mechanisms underlying these findings remain unknown, reward and value processing in the amygdala likely contribute.

P9. The Influence of Stressor Controllability on Conditioned Fear Expression in Humans

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Controllability, the degree of behavioral control a person can exert over a stressor, may determine the impact of an aversive event. Previous research in rodents has shown that prior experience of control modulates the expression of conditioned fear. The present study investigates the influence of controllability on subsequent conditioned fear expression in humans. Participants took part in a three-day study consisting of an avoidance task followed by fear conditioning. On day 1, participants were randomly assigned to an escapable task, in which a learned avoidance response terminated shocks; a yoked inescapable task, in which shocks were administered regardless of performance; or to a control condition involving no shock exposure or experience of control. On day 2, one week after the avoidance session, participants took part in a partial reinforcement fear conditioning session in a visual conditioned stimulus was paired with shock. This was immediately followed by extinction, during which the conditioned stimulus is not reinforced and the fear response typically diminishes. On day 3, twenty-four hours later, extinction retention was tested to examine whether the fear response returned after a delay. Preliminary results showed that participants in the escapable group showed reduced fear expression during acquisition, extinction, and extinction retrieval, while participants in the inescapable group showed potentiated fear across all phases. These results suggest that prior experiences of behavioral control may be an important factor underlying resilience formation or vulnerability in humans.

P10. Activation of the Medial Prefrontal Cortex is Necessary but Not Sufficient to Impair Associative Learning after Stress in Females

Lisa Y. Maeng and Tracey J. Shors, Rutgers University

Acute stress exposure enhances classical eyeblink conditioning in male rats and profoundly impairs performance in females (Wood & Shors, 1998; Wood et al., 2001). Here we examined the role of the medial prefrontal cortex (mPFC) in this phenomenon. In a previous study, mPFC inactivation prevented the stress-induced learning impairment in females but not the facilitation of learning in male rats (Maeng, Waddell and Shors, submitted). Thus, neural activity within the mPFC is necessary for the stress effect on learning in females but not in males. To determine whether

activation of the mPFC alone is responsible for the modulation of learning after stress, both males and female were bilaterally infused with picrotoxin, a GABA-A antagonist, or vehicle. Following infusions, animals were loosely restrained for 30 minutes in a dark chamber in a separate room, either stressed or left unstressed, and then returned to their home cages. Twenty-four hours later, animals were trained with delay eyeblink conditioning (100 trials/day for 4 days) in a different context. Stressed males emitted more conditioned responses (CR) than unstressed males regardless of drug treatment ($p<0.05$). Stressed females emitted fewer CRs than the unstressed females that received picrotoxin or vehicle infusions ($p<0.05$). Thus, mPFC activation via picrotoxin infusions had no effect on eyeblink conditioning performance after and in the absence of stress in either sex. Together, these data suggest that neural activity within the mPFC is necessary, but activation of the mPFC alone is not sufficient to retard learning in females after an acute stressful experience.

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P11. Assessing anxiety- and reward-related behaviours following alcohol administration or chronic stress.

Harinder Aujla, Craig Hutton, and Ben Rogala. University of Winnipeg.

Dysregulation of stress- and reward-related neurocircuitry that results from experience with alcohol or chronic stress may underlie vulnerability to initiate or relapse to alcohol use. Related changes in behaviours associated with such dysregulation may provide insight into factors that increase or decrease vulnerability to alcohol dependence in humans. In the present study, anxiety-like behaviour and the acquisition of conditioned place preference were assessed in male Wistar rats with differing histories of exposure to stress or alcohol. Thus, time spent on the open arms of the elevated plus maze as well as the number of days required to acquire alcohol-based place conditioning were evaluated in control animals vs. those with a history of exposure to chronic unpredictable stress, experimenter-administered intragstric alcohol, or self administered alcohol. No difference in open arm exploration was observed between the control group and experimental groups. However, animals with a history of intragastric ethanol administration or chronic unpredictable stress acquired alcohol-based placed conditioning after 3 alcohol-context pairings while control animals and animals with a history of alcohol self-administration required 4 alcohol-context pairings to acquire a significant preference for the alcohol-paired compartment. Results reveal that 1) a history of alcohol contributes to the acquistion of conditioned place preference but is dependent on the administration regimen and 2) chronic unpredictable stress enhances the acquisition of alcohol-based conditioned place preference. These findings suggest overlap in the neuroadaptive changes that result from chronic exposure to alcohol or stress which may contribute to vulnerability to alcohol use.

P12. The effects of galantamine on nicotine-withdrawal induced deficits in contextual fear conditioning in C57BL/6 mice

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Nicotine binding to nicotinic acetylcholine receptors (nAChRs) modulates various types of learning and memory, including contextual fear conditioning. While acute nicotine enhances, nicotine withdrawal disrupts contextual fear conditioning. Acetylcholine, the endogenous ligand for nAChRs, has also been implicated in learning and memory with enhanced acetylcholinergic activity corresponding to enhanced learning and memory. It is unknown however whether enhanced acetylcholinergic activity will reverse the cognitive deficits produced by nicotine withdrawal. The present study examined the use of galantamine, an inhibitor of the enzyme that degrades acetylcholine, on nicotine-withdrawal induced deficits in contextual fear conditioning in C57BL/6 mice. An acute dose-response experiment revealed that 0.5 and 1 mg/kg galantamine had no effect on fear conditioning while 2 mg/kg galantamine enhanced contextual, but not cued, fear conditioning. To determine if galantamine was able to reverse nicotine-withdrawal related deficits in

contextual fear conditioning, mice were implanted with osmotic mini-pumps that delivered chronic saline or 6.3 mg/kg/d nicotine for 12 days then pumps were removed. Training and testing for fear conditioning occurred 24 and 48 hours later, respectively. Nicotine withdrawal disrupted contextual fear conditioning, which was reversed with 1 but not 0.5 mg/kg galantamine. In addition, 2 mg/kg galantamine not only reversed nicotine-withdrawal deficits but also enhanced contextual fear conditioning. These results show that treatments that enhance acetylcholinergic activity reverse cognitive deficits produce by nicotine withdrawal and might represent a pharmacological strategy for aiding in smoking cessation.

P13. JNK1 knockout mice do not show enhancement of contextual fear conditioning by nicotine.
P.T. Leach, J.W. Kenney, T.J. Gould. Psychology/Neuroscience: Temple University, Philadelphia, PA 19122

Mitogen activated protein kinases (MAPKs) are molecules known to be involved in learning and memory. Recently, levels of c-jun N terminal kinase 1 (JNK1; MAPK8) mRNA were shown to rapidly increase in response to fear conditioning in the presence of nicotine administration. Furthermore, administration of a broad spectrum JNK inhibitor prevented the nicotine induced enhancement of fear conditioning. In order to determine if JNK1 specifically is necessary for the nicotine induced enhancement of contextual fear conditioning, the present study examined the effects of nicotine in JNK1 knockout and wildtype mice. JNK1 knockout and wildtype mice maintained on a C57/129 background were bred at Temple University from heterozygous mice originally obtained from Jackson Laboratories. Knockout and wildtype mice received treatment of nicotine (0 or 0.09mg/kg, IP) 5 minutes prior to both training and testing sessions. The fear conditioning paradigm consisted of exposure to a single 15 second white noise conditioned stimulus, two second 0.57mA shock unconditioned stimulus pairing. 24 hours after training, mice were returned to the conditioning chamber and scored for freezing to context. Next, mice were tested for freezing to a novel context for three minutes and were subsequently assessed for freezing in response to the auditory cue. Nicotine administration resulted in enhancement of fear conditioning in the WT mice, but had no effect in the KO mice. This suggests JNK1 is critical for the enhancing effects of nicotine on contextual fear conditioning.

P14. Sex Differences in Adult Sequential Learning Impairments Caused by Adolescent Nicotine Exposure
Jeremy D. Meduri (Kent State University), Laura R. G. Pickens (Kent State University), James D. Rowan (Wesleyan College), Rick A. Bevins (University of Nebraska Lincoln) & Stephen B. Fountain (Kent State University)

Adolescent nicotine exposure produces neurophysiological changes (Trauth et al., 1999) and cognitive deficits (Trauth et al., 2000; Fountain et al., 2008) in adult rats. We examined the effects of adolescent nicotine exposure on adult sequential learning in both male and female rats over a longer period of acquisition than previously studied to examine asymptotic levels of acquisition (cf. Fountain et al., 2008). Adolescent Long Evans rats (12 per group) were exposed to either vehicle or 1.0 mg/kg nicotine via daily i.p. injections on postnatal days 25-59 (P25-P59), but not thereafter. Beginning on P95, adult rats were trained to perform a highly structured sequence of responses in an 8-position circular array of nose poke receptacles for water reinforcement. The 24-element serial pattern of responses was 123-234-345-456-567-678-781-818, where digits indicate the clockwise positions of correct receptacles on successive trials. Rats experienced 10 repetitions of this response sequence for 49 days. The sequence is composed of eight 3-element chunks, as in Fountain et al. (2008), but with the addition of an element at the end of the sequence that violated the otherwise simple pattern structure. The current study indicated that adolescent nicotine exposure caused retardation of learning for some aspects of serial patterns, namely, for chunk boundaries and the violation, but did not cause differences in asymptotic performance. In addition, the results revealed sex differences in pattern acquisition and in response to adolescent nicotine exposure. The results add to the evidence that adolescent nicotine exposure is a threat to adult cognitive capacity.

P15. Exposure to Adolescent Nicotine Results in an Increase in the Forgetting of Contextual Cues in Adult Rats

Patrick K. Cullen, Luke Stewart, Kimberly K. Gos, Laura R.G. Pickens, Stephen B. Fountain, & David C. Riccio

Two experiments examined the effects of adolescent nicotine exposure on adult memory for contextual cues. In experiment 1, adolescent rats received daily i.p. injections of nicotine at 0mg/kg (1.0 mg/kg saline), 0.03mg/kg, 0.1 mg/kg, 0.3 mg/kg, or 1.0mg/kg on postnatal days (PD) 25 through 59. At age PD 170, animals were trained on a passive avoidance task in one distinct context and then tested for fear 5 days later in either the same or a novel context. Males exposed to 1.0mg/kg of nicotine showed significantly higher generalization (i.e., more forgetting of contextual cues) between the two different contexts than the 0mg/kg group. No differences were observed between females receiving adolescent nicotine exposure and female controls. In experiment 2, all animals were tested for generalization of contextual fear at a much shorter retention interval following training. Adolescent rats received daily injections of either 1.0 mg/kg nicotine or 1.0 mg/kg saline on postnatal days (PD) 25 through 59. All animals were trained at PD 170 and tested for fear retention 24 hours later in either the same or a novel context. Both males and females exposed to 1.0mg/kg of nicotine showed significantly more generalization of fear between the two different contexts than nicotine controls. In other words, nicotine animals exhibited more forgetting of the contextual cues that distinguish the two contexts, and therefore treated the two contexts as the same. Our results indicate that exposure to nicotine during adolescence results in long lasting changes in adult memory for contextual cues.

P16. Scopolamine Retards Acquisition of Rat Serial Pattern Reversal Learning

Amber M. Chenoweth (Hiram College) & Stephen B. Fountain (Kent State University)

In serial pattern learning, “phrasing cues” positioned at chunk boundaries can facilitate learning transitions between chunks which are harder to learn than elements within chunks. We have shown before that disruptions in chunk boundary performance occur when phrasing cues are removed or when scopolamine, a muscarinic cholinergic antagonist, is administered. The present study examined the effects of both manipulations concurrently. Rats were initially trained to nose poke one of two patterns in a circular array: Perfect (123-234-345-456-567-678-781-812) and Violation (123-234-345-456-567678-781-818), where digits indicate positions of correct responses, dashes indicate 3-s phrasing cues, intertrial intervals (ITI) were 1 s, and the last element of the Violation sequence violated pattern structure. During this initial training, rats were given daily injections of either scopolamine (0.6 mg/kg) or saline. Once rats reached a high level of performance on their respective patterns, in the transfer phase phrasing cues were removed, leaving a 1 s ITI throughout each pattern. Rats were also assigned to the same or different drug condition in the transfer phase. Scopolamine produced differential deficits in acquisition of the reversal learning task depending upon pattern element type, with violation element performance showing the greatest difficulty in reacquisition compared to chunk-boundary and within-chunk elements. In all three elements, rats that received scopolamine in initial training and/or transfer showed greater impairment than rats that received saline in both acquisition and transfer. These results indicate that scopolamine dissociates the cognitive systems necessary to acquire, retain, and retrain sequential patterns.

P17. The Effects of Inactivation of the VTA on Heroin-Induced Conditioned Immunomodulation

Hutson LW, Szczytkowski JL, Saurer TB, Lysle DT

Heroin use has been shown to suppress several immune parameters that are important to the innate immune response, such as the production of nitric oxide and the expression of TNF-α and IL-6. Previous studies in our laboratory have shown that these effects of heroin on immune functioning can be conditioned to environmental stimuli. Recently, we have demonstrated that these conditioned responses are mediated via a circuit that exists between the nucleus accumbens and basolateral amygdala. Furthermore, stimulation of D1 dopamine receptors within these brain regions

is necessary to produce heroin-induced conditioned immunomodulation within these brain regions. The current study investigates the role of the ventral tegmental area (VTA), which is the source of dopaminergic projections within the mesolimbic system. The conditioning procedure consisted of repeated pairing of heroin administration with placement into a distinctive environment. On test day, animals received intra-VTA microinfusions of a mixture of GABA agonists to temporarily inactivate the VTA prior to re-exposure to the conditioned stimulus. Following removal from the chambers, animals received an injection of lipopolysaccharide to induce expression of nitric oxide, TNF-α and IL-6. Analyses using real-time RT-PCR indicate that inactivation of the VTA blocked the suppressive effects of the heroin-associated conditioned stimulus on iNOS induction and on the expression of proinflammatory cytokines, TNF-α and IL-6, in spleen tissue. This study is important because it is the first to identify the VTA as being involved in neural immune interactions.

P18. Neural Circuitry of HeroinInduced Conditioned Immunomodulation

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The high incidence of opportunistic infections among heroin users suggests that opioids may impair host defense against infectious disease. Remarkably, the suppressive effects of opioids on the immune system can be conditioned to environmental stimuli paired with drug administration; however, little is known about the brain circuitry responsible for the expression of these conditioned effects. Recent studies in our laboratory have indicated that the basolateral amygdala (BLA) and the nucleus accumbens (NAC) play critical roles in heroininduced conditioned immunomodulation. Consistent with this, antagonism of either D1 dopaminergic receptors in the BLA or glutamatergic NMDA receptors in the NAC inhibits classically conditioned decreases in the production of proinflammatory mediators. The present study was designed to determine whether the BLA and the NAC interact or independently contribute to this phenomenon, utilizing the functional disconnection procedure. Rats first received conditioning trials during which heroin administration was paired repeatedly with exposure to a distinctive environment. After conditioning, rats received unilateral dopamine D1 antagonist treatment into the BLA concomitantly with unilateral NMDA antagonist treatment into the contralateral or ipsilateral NAC shell. Subsequently, the rats were reexposed to the previously heroinpaired environment followed by immune challenge with lipopolysaccharide. Disconnection of the BLA from the NAC (contralateral manipulation) attenuated heroininduced conditioned suppression of proinflammatory mediators in response to lipopolysaccharide, whereas ipsilateral control manipulation had no effect. This suggests that sequential information processing by the BLA and NAC is necessary for heroininduced conditioned immunosuppression, defining for the first time a specific neural circuit involved in this phenomenon.

P19. Reinstatement of the extinguished eyeblink conditioned response in the rat: Creation of an excitatory context at test

John T. Green and Alexandra Thanellou. University of Vermont

Of the four most well-established experimental paradigms that produce recovery of the extinguished conditioned response, only two (spontaneous recovery; rapid reacquisition) have been demonstrated in eyeblink conditioning. We (Thanellou & Green, 2007) and others (Napier, Macrae, & Kehoe, 1992) have been unable to demonstrate reinstatement of the extinguished eyeblink CR. Generally, reinstatement requires an excitatory context at test that is established during US re-exposure after extinction. We hypothesized that: (1) The eye stimulation US used in eyeblink conditioning does not render the context excitatory after US re-exposure; and (2) Introduction of a foot shock between extinction and test would render the context excitatory during test and reinstate the extinguished eyeblink CR. Three groups of rats were tested. All three groups underwent 6 sessions of 280-ms delay eyeblink conditioning and 3 sessions of extinction. The day after the final session of extinction, Group 1 was given 100 eyelid stimulation presentations (the same number as in each session of conditioning), Group 2 was given 10 foot shock presentations (beginning at minute 3 and with the final presentation at approximately minute 55), and Group 3 received no stimuli. The

next day, animals were placed in the testing box, filmed for 6 minutes, and then received 100 tone CS presentations. Preliminary results show that Groups 1 and 3 both demonstrated equivalent spontaneous recovery during the test session, replicating our failure to find reinstatement of the extinguished eyeblink CR with re-exposure to the eye stimulation US. Supporting our first hypothesis, we could not detect context excitation (as indexed by contextual freezing) in Group 1. In contrast, context excitation was strong in Group 2. However, contrary to our second hypothesis, Group 2 demonstrated significantly less, not more, responding to the CS at the beginning of the test session compared to Groups 1 and 3.

P20. Effect of continuous and partial reinforcement on the acquisition and extinction of conditional fear in humans.

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Previous studies have examined the partial reinforcement extinction effect (PREE) in a variety of animal model systems. However, relatively few studies have investigated the PREE in humans. Research on the PREE indicates that continuous reinforcement results in quicker extinction than partial reinforcement. The present study was designed to investigate the effect of partial reinforcement on the extinction of the conditioned skin conductance response (SCR) and unconditioned stimulus (UCS) expectancies. Volunteers were randomly assigned to continuous or partial reinforcement groups. Participants were exposed to a two tone discrimination procedure in which one tone (CS+) was paired with a loud (100dB) white noise (UCS) and the second tone (CS-) was presented without the UCS during acquisition. During extinction, both conditioned stimuli were presented without the UCS. SCR and UCS expectancy were monitored continuously throughout the conditioning procedure. The reinforcement procedure influenced SCR and UCS expectancy response magnitudes during acquisition and extinction. During acquisition, continuous reinforcement produced larger amplitude responses than partial reinforcement. The reinforcement procedure also affected extinction, such that the continuously reinforced group's CR extinguished at a faster rate than the partially reinforced group's CR. However, partial reinforcement did not result in a larger CR than continuous reinforcement. Interestingly, we also observed a transient increase in SCR and UCS expectancy to the CS- following the change in stimulus contingencies during extinction. These data indicate that partial and continuous reinforcement schedules have differing behavioral and physiological effects on humans during CR acquisition and extinction.

P21. Differential contribution of amygdala kinase and phosphatase pathways to extinction of auditory fear memory

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The current study examined the contribution of phosphodiesterase, kinase and phosphatase pathways to the extinction of auditory fear conditioning within the mouse amygdala. Both the PKA and PKG pathways are engaged during learning and memory formation and may be involved in fear extinction. The cAMP and cGMP cyclic nucleotides trigger PKA and PKG activation and multiple downstream regulatory pathways, including the phosphorylation of the cAMP response element binding protein. Together many of these intracellular signaling cascades have been implicated in amygdala-dependent memory processing. The activity of both cAMP and cGMP signaling pathways are modulated by a variety of phosphodiesterases and phosphatases. Analysis of gene expression microarrays demonstrated that many genes in the regulatory phosphodiesterase and phosphatase pathways were increased in the amygdala two hours after extinction, suggesting negative regulation of PKA or PKG may be important for extinction of fear. A follow up experiment using real-time PCR replicated the above finding by showing increased phosphodiesterase and phosphatase mRNA two hours after extinction. Direct infusion of a PKA or PKG antagonist into the amygdala immediately following extinction showed that PKG, but not necessarily PKA, inactivation enhanced extinction of conditioned fear. Together, our mRNA expression and pharmacological manipulations suggest that

decreases in cyclic nucleotide mediated protein kinase function during the consolidation period may enhance extinction learning.

P22. Pavlovian conditioning and extinction in rhesus monkeys: the role of the infralimbic cortex

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The infralimbic cortex (IL) in rats is critical for recall of extinction learning in both appetitive and aversive Pavlovian conditioning paradigms. Little is known about the function of the IL in monkeys (Walker's area 25), although preliminary reports suggest that it is not required for extinction of a previously rewarded instrumental response. In both rodents and primates the IL is anatomically connected to nuclei that regulate autonomic functioning, such as portions of hypothalamus, amygdala and periacqueductal grey. We hypothesize that lesions of the IL in monkeys, like those in rats, will lead to spontaneous recovery of an extinguished autonomic response.

Rhesus monkeys with bilateral lesions of the IL (N=2) and unoperated controls (N=4) were trained in a Pavlovian conditioning task which was subsequently carried out under extinction conditions. Changes in pupil diameter (PD), a measure of autonomic responding, were monitored throughout. Presentation of the CS+ led to the delivery of a fluid reward whereas presentation of the CS- did not. Initially, both groups of monkeys showed PD responses to the reward delivery and over a number of sessions this response transferred to the CS+ but not the CS-. Once monkeys showed a robust difference in PD responses between CS+ and CS- they entered the extinction phase where reward no longer followed presentation of the CS+. Over four sessions, controls showed progressively diminishing responses to the CS+. Extinction testing of monkeys with IL lesions is ongoing.

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P23. Effects of D-Cycloserine on operant extinction learning

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There has been a surge of interest among clinicians in the drug d-cycloserine (DCS), a partial agonist of the NMDA receptor, which is known to facilitate context-dependent extinction of conditioned fear in rats. Studies with human subjects have further supported the idea that DCS can enhance exposure therapies for anxiety disorders, and have encouraged speculation that DCS might also boost the efficacy of extinction-like treatments for drug-seeking and other maladaptive operant behaviors. However, there have been few positive reports of DCS effects on extinction of operant behavior in the laboratory. In each of three experiments, we examined the effect of DCS on extinction of operant behavior in rats. Subjects were first trained to lever press for food pellets over a series of sessions in one context (A). They were then extinguished in a second context (B) 15 mins after administration of one of four doses of DCS (0.0 mg/kg, 5.0 mg/kg, 15.0 mg/kg, or 30.0 mg/kg). On the next day, the rats were tested for lever pressing in both contexts in a counterbalanced order. Experiments 1 and 2 examined extinction of free operant behavior trained on a VI 30-s schedule. Rats in Experiment 2 were additionally given noncontingent pellets during extinction and were tested both with and without noncontingent pellets in each context. In Experiment 3, rats were trained on a discriminated operant task in which lever pressing was reinforced only during 30-s trials with a visual stimulus. We found no evidence that DCS facilitated extinction as examined with any of these methods. Furthermore, DCS had no effect on the level of renewed responding that occurred in each experiment when testing occurred in Context A after extinction in Context B. The latter is consistent with previous findings in experiments with Pavlovian fear conditioning.

P24. Renewal and Spontaneous Recovery in Pavlovian Retroactive Cue Interference

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Retroactive cue interference refers to the observation that A→C followed by B→C weakens responding to A relative to A→C followed by B / C. Two experiments in conditioned suppression with rats were conducted to determine if recovery effects, typically observed in retroactive outcome interference, can be also observed in retroactive cue interference. Experiment 1 found that a delay between Phase 2 (the interfering phase) and testing produces a recovery from the reduction observed in responding due to cue interference, which is analogous to the spontaneous recovery effect observed following extinction treatments found in retroactive outcome interference. Experiment 2 found that after Phase 1 (the target phase) in one context and Phase 2 (the interfering phase) in a second context, testing in a neutral context also produces a recovery from the reduction in responding observed due to cue interference, which is an analogous to the ABC renewal effect. The results are discussed in terms of the possibility that similar associative mechanisms underlie cue and outcome interference. This suggests a unified theory explaining interference between stimuli that share associations with a common element. It does not matter whether the common element is an outcome with interfering cues or a cue with interfering outcomes; recovery effects appear in both situations.

P25. Parallel effects of NMDA receptor antagonism and blockade of ARC protein expression in trace fear conditioning.

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Recent data from our laboratory have shown that neither lesions nor temporary inactivation of the dorsal hippocampus result in an observable impairment in the acquisition of trace fear conditioning. By contrast, the results of previous studies suggest that infusion of compounds designed to block NMDA receptor-dependent plasticity within dorsal hippocampus may have the opposite effect, that is, impair acquisition of trace fear conditioning. Moreover, the expression of the immediate-early gene ARC and its protein product have been implicated in both synaptic plasticity and some forms of learning. We have recently begun examining the extent to which administration of the NMDA receptor antagonist APV or ARC anti-sense oligodeoxynucleotides prior to training blocks acquisition in this paradigm. We have found that infusions of the NMDA receptor antagonist APV or ARC anti-sense oligodeoxynucleotides in the dorsal hippocampus dramatically attenuates the acquisition of trace fear conditioning. Consistent with these behavioral observations, the expression of both the immediate-early gene ARC and its protein product are robustly enhanced in the dorsal hippocampus in normal animals following training. These data suggest that while neither lesions nor inactivation of dorsal hippocampus have a significant effect on the acquisition of trace fear conditioning, NMDA receptor- and ARC-dependent plasticity within this region are critically important if the dorsal hippocampus is intact during learning.

P26. Bilateral activation of the ventral hippocampus is necessary for trace and contextual fear conditioning

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Trace fear conditioning (TFC) requires rats to associate an auditory conditional stimulus (CS) and a fear-producing shock unconditional stimulus (UCS) that are separated by an empty trace interval. Unlike standard delay fear conditioning (DFC), trace fear conditioning is dependent upon an intact hippocampus (McEchron et al., 1998, 2000; Quinn et al., 2002). We have recently shown that the prelimbic area of the medial prefrontal cortex (mPFC) is also necessary for the acquisition of trace, but not delay, fear memories (Gilmartin & Helmstetter, 2010). Specifically, inactivating prelimbic mPFC with the $GABA_A$ agonist muscimol or blocking NMDA receptor-mediated neurotransmission with APV impairs the formation of trace and contextual fear responses (Gilmartin & Helmstetter, 2010). Previous work using single neuron recording in rats and fMRI BOLD in humans

suggest that hippocampal and prefrontal regions may serve distinct but complementary roles in TFC (Gilmartin & McEchron, 2005a,b; Knight et al., 2004). These lines of evidence suggest that learning the CS-UCS association across a trace interval in TFC requires a functional interaction between the ventral hippocampus and prelimbic mPFC. This study attempted to address this question using a "disconnection" design: targeted unilateral inactivation of ventral hippocampus and the contralateral or ipsilateral prelimbic mPFC prior to TFC, using infusions of muscimol. We found that simultaneous unilateral inactivation of the ventral hippocampus and mPFC impaired the formation of memory for the CS and context measured 24 hours later, compared with saline-infused control rats. A follow-up experiment revealed that unilateral VH inactivation but not unilateral mPFC inactivation impaired trace and contextual fear conditioning. These results suggest that the acquisition of trace and contextual memories requires bilateral activation of the VH, but only unilateral activation of the mPFC.

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P27. Temporary inactivation of dorsal hippocampus impairs the acquisition of explicitly discriminative contextual fear conditioning in a novel paradigm

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Studies examining the role of the dorsal hippocampus in the acquisition of contextual fear conditioning have yielded conflicting results; lesions or temporary inactivation of the dorsal subregion sometimes attenuates acquisition, while other times elicits no effect. Although the vast majority of these studies have examined the effects of manipulations of the hippocampus on the acquisition of nondiscriminative forms of contextual learning, emerging evidence suggests that the dorsal hippocampus may play a particularly prominent role in contextual conditioning procedures requiring a discrimination between multiple contexts. Thus, the purpose of the present studies was to examine the role of the dorsal hippocampus in explicitly discriminative contextual fear conditioning using a novel, discriminative contextual conditioning paradigm. Prior to training, subjects received bilateral infusions of either the GABA-agonist muscimol or saline into the dorsal subregion. The extent of contextual conditioning was assessed 24 hours later. Conditioning to an explicit auditory CS in a novel context was also assessed. As predicted, animals receiving pre-training infusions of saline demonstrated robust post-training contextual discrimination, while animals receiving pre-training infusions of muscimol demonstrated dramatically impaired discrimination. By contrast, all animals acquired the association between an explicit auditory CS and footshock. Collectively these data suggest that the dorsal hippocampus contributes importantly to the acquisition of fear in explicitly discriminative contextual conditioning.

P28. Computational Model of Cortico-Hippocampal Network: Implications for Hippocampal Atrophy

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Hippocampal atrophy (HA) has been shown to correlate with cognitive impairments and future development of Alzheimer's disease. In a previous study of acquired equivalence, non-demented elderly individuals with mild HA visible on MRI, could learn new associations, but showed a significant impairment in transfer performance when the same stimulus features were presented in novel recombinations (Myers et al., 2003).

Several causes might underlie the impairments seen among HA subjects, e.g., neuron or synaptic loss, or reduced synaptic plasticity. By using computational modeling, we explored which of these could produce deficits in the model similar to what is observed in HA subjects. A model for

simulating the acquired equivalence task on the cortico-hippocampal network was developed, based on an existing model (Gluck & Myers, 1993). Different parameters in the model were modified (e.g., learning rate and number of nodes) and the resulting outcomes were compared to the empirical data.

In the model, reducing the learning rate was sufficient to produce the same outcome seen in humans with HA. Eliminating nodes and connections between nodes impaired learning of new associations, whereas in HA individuals this learning is spared. These findings suggest that reduced synaptic plasticity may be sufficient to account for the impairments observed among HA subjects. Therefore, upregulating different aspects of plasticity might be a potential intervention to consider in remediating subjects with HA.

P29. Voluntary exercise followed by environmental complexity reverses deficits in trace eyeblink conditioning and adult hippocampal neurogenesis in a rat model of Fetal Alcohol Spectrum Disorder

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Exposure to alcohol on postnatal days (PD) 4-9 impairs learning and disrupts dentate gyrus granule cell neurogenesis in adult rats. The present studies examined whether exercise (wheel running, WR) followed by rearing in environmental complexity (EC) during adolescence increased survival of newly generated cells in dentate gyrus and reversed learning impairments in alcohol exposed rats. On PD4-9, pups were intubated with alcohol in a binge-like manner (5.25g/kg/day, EtOH), sham-intubated (SI), or reared normally. On PD30 animals were randomly assigned to WR+EC or were socially housed (SH) for the duration of the experiment. All animals were injected with 200 mg/kg BrdU on PD41. As demonstrated by neuroanatomy study, survival of newly generated DG cells (BrdU+) was significantly enhanced in the alcohol and sham-intubated WR+EC animals in comparison with SH littermates. Littermates of rats from the neuroanatomy study received trace eyeblink conditioning on ~PD77-79 using a 3 (EtOH, SI, Normal Rearing) x 2 (WR+EC vs SH) x 6 (training session) mixed factorial design. In SH controls, EtOH impaired trace eyeblink conditioning relative to the two control groups. In the WR+EC condition, some evidence for the amelioration of the alcohol-induced deficit was found. Post-weaning environmental manipulations promote cell survival and reverse learning deficits in rats that were exposed to alcohol during development. These manipulations may provide a basis for developing interventions that mitigate learning impairments associated with human fetal alcohol spectrum disorders.

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P30. Reducing Neurogenesis Disrupts Trace Conditioning: A Possible Link to Theta Rhythm

Miriam S. Nokia & Tracey J. Shors, Rutgers University

Hippocampal theta (4-12 Hz) activity predicts subsequent learning rate during classical eyeblink conditioning (Berry & Thompson, 1978, Nokia et al., 2008; 2009), and synchronizes with theta in the cerebellum (Wikgren et al., 2010), where the memory trace of the conditioned eyeblink resides (Thompson & Steinmetz, 2009). At the structural level, thousands of new neural cells are generated daily in the adult mammalian hippocampus, but only a fraction of them survive to become mature neurons. However, survival rate is greatly increased by learning an eyeblink conditioning task that is dependent on the hippocampus (Gould et al., 1999; Shors 2009). Vice versa, blocking neurogenesis in the hippocampus is detrimental to learning certain types of conditioning tasks (Shors et al., 2001). In order to elucidate the role of adult-born new neurons in learning and related hippocampal oscillatory activity, we administered an antimitotic drug (Temozolomide) to adult male Sprague-Dawley rats mimicking chemotherapy in humans. After the cessation of treatment (3 days a week for 4 weeks), we trained the rats on trace and delay eyeblink conditioning, while recording local-field potentials in the dentate gyrus. Reducing adult neurogenesis disrupted learning during hippocampus-dependent trace conditioning. However, the rats readily learned the delay response,

which does not depend on the hippocampus. Preliminary results suggest that hippocampal theta band responses to the conditioned stimulus are compromised by the preceding antimitotic treatment. Our current results confirm that reducing adult neurogenesis disrupts learning in some but not all tasks. In addition, the effect might be mediated via disruptions in hippocampal oscillatory activity.

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P31. Neurogenesis in the Adult Hippocampus: Maintaining Equilibrium in Response to Learning and Memory.

Anderson, ML, Sisti, HM, Curlik, DM, and Shors, TJ

Learning increases the number of immature neurons that survive and mature in the adult hippocampus (Gould et al., 1999). One week old cells are more likely to survive in response to learning than cells in animals that are exposed to training but don't learn (Shors, 2009). Because neurogenesis is an ongoing and overlapping process, it is possible that learning differentially affects new cells, as a function of cell maturity. To address this issue, we examined the effects of associative learning on the survival of cells at different stages of their development. The number of cells produced was not affected by training. However, the number of surviving neurons was increased after learning an associative trace task when the cells were 1-2 weeks of age at the time of training but not when the cells were younger or older. In contrast, cells that were produced during training were less likely to survive when compared to cells in untrained animals. Additionally, cells that were generated after the learning were not more likely to survive than cells within untrained animals. Finally, survival was not increased if the association was reacquired and expressed when the cells were about 1 week old. Together, these results indicate that new neurons are rescued from death by initial acquisition, not the expression or reacquisition, of an associative memory only during a critical period. Overall, these results suggest the presence of a feedback system, which controls how many new neurons become incorporated into the adult brain in response to learning.

P32. Learning Increases the Survival of Newborn Neurons Provided that Learning is Difficult to Achieve and Successful.

Daniel M. Curlik II and Tracey J. Shors, Ph.D.; Rutgers University

Learning increases neurogenesis by increasing the survival of new cells generated in the adult hippocampal formation (Gould et al., 1999; Shors, 2009). However, only some types of learning are effective. Recent studies demonstrate that animals that learn the conditioned response (CR), but require more trials to do so, retain more new neurons than animals that quickly acquire the CR, or that fail to acquire the CR (Waddell and Shors, 2008). In these studies task parameters were altered to modify the number of trials required to learn a CR. Here we asked whether pharmacological manipulations that prevent or facilitate learning would decrease or increase, respectively, the number of cells that remain in the hippocampus after training. To answer this question, we first prevented learning with the competitive NMDA receptor antagonist (RS)-3-(2-Carboxypiperazin-4-yl) propyl-1-phosphonic acid (CPP). As a consequence, training did not increase cell survival. Second, we facilitated learning with the cognitive enhancer D-cycloserine (DCS), which increases NMDA receptor activity via its actions at the glycine-binding site. Administration of DCS each day before training increased the number of learned responses and the number of cells that survived. All animals that learned the CR retained more of the new cells, but those that learned very quickly retained fewer than those that required more training trials to learn. Together, these results demonstrate that NMDA receptor activation modifies learning and as a consequence, alters the number of surviving cells in the adult hippocampus.

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P33. Hippocampal Fos protein expression and the context preexposure facilitation effect.

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The context preexposure facilitation effect (CPFE) describes contextual fear conditioning to an immediate shock in rats preexposed to the training context relative to those preexposed to an alternate context, who demonstrate an immediate shock deficit (ISD). Although conditioning is disrupted by hippocampal lesions or inactivation during each of the three phases of the CPFE paradigm (preexposure, training, and testing; Rudy & O'Reilly, 2001,*Cogn Affect Behav Neurosci*, 1, 66-82), little is known about the nature of hippocampal activity or the cellular processes supporting the CPFE. Here we examine Fos protein expression in the hippocampus following different phases of the CPFE paradigm. Juvenile rats preexposed to the training context (Pre) show the CPFE whereas those preexposed to an alternate context (No Pre) show the ISD. Rats from both Pre and No Pre groups sacrificed 2h following the preexposure or immediate shock (1.5 mA, 2s) phase show elevated Fos expression in CA1 and CA3 relative to home-caged controls (CTL). CA1 Fos expression following testing was highest in No Pre, lowest in CTL, and intermediate in Pre. Fos expression in the dentate gyrus was generally moderate, neither differing between exposure groups nor by training phase. Fos is a general marker of neuronal activity and our results agree with inactivation studies indicating hippocampal activity is necessary during each of the three phase of the CPFE. Cellular and molecular activity in the hippocampus in relation to behavioral studies and theoretical constructs of the CPFE are discussed.

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P34. Selective entorhinal, but not hippocampal, lesion abolishes latent inhibition in eyeblink conditioning paradigm in rats but spares a hippocampal dependent spatial learning task

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The brain structures of the medial temporal lobe, the hippocampal region and the adjacent cortices, are greatly interconnected and their respective contribution to sensory processing, learning, and memory is difficult to differentiate. Entorhinal cortex (EC) is the primary source of polymodal sensory input to the hippocampus and receives highly convergent projections from a wide range of association cortices. An important issue to consider is whether EC is an essential contributor to learning processes separate from that contributed by the hippocampus or whether it serves as a passive relay of information to the hippocampus.

The present study aimed to examine the effects of selective ibotenic acid lesions of EC and hippocampus on delay eyeblink conditioning paradigm of latent inhibition (LI) as well as spatial learning in the Morris water maze. LI refers to the retardation in learning of a conditioned stimulus (CS)-unconditioned stimulus association following the repeated non-reinforced presentations of the CS alone. Based on prior computational modeling and studies of selective EC lesions in rabbits, a double dissociation is expected whereby EC lesions impair LI but not spatial learning, whereas hippocampal lesions disrupt spatial learning but not LI.

Preliminary findings indicate that EC lesioned rats have impaired LI while hippocampal lesions and shams demonstrate no deficit in LI. In addition, EC lesions did not hinder performance in the Morris water maze to the same extent that hippocampal lesions did.

Results demonstrate a double dissociation between hippocampal and entorhinal functions in LI as well as the Morris water maze. This suggests that EC is not just a gateway between sensory association cortices and hippocampus but is rather involved in learning and memory processes with distinct functionality from hippocampus.

P35. The role of the dorsal hippocampus in appetitive renewal of magazine approach using physical and temporal contexts

Vincent Campese and Andrew R. Delamater - Brooklyn College

Destruction or inactivation of the dorsal hippocampus (DH) has been shown to eliminate certain forms of renewal of extinguished fear (Corcoran & Maren 2001; 2004; Ji & Maren 2005; Maren & Hobin, 2007). However, appetitive magazine approach conditioning studies from our lab found that the contextual control over responding to extinguished stimuli is not disrupted when the DH is inactivated (Campese & Delamater, 2009 SfN). In two new experiments we provide further support for the hippocampal independence of context-dependent recall. In particular, we here show that neither ABA nor ABC renewal of conditioned magazine approach responses were disrupted by post-training excitotoxic lesions of the DH. However, our prior research demonstrated that spontaneous recovery of magazine approach was eliminated by DH inactivation at the time of test. Since this phenomenon has been interpreted as a form of renewal by temporal contexts, in a third experiment we examined DH inactivation effects on ABA renewal when time of day served as a contextual cue. Early results suggest that DH inactivation impairs temporally modulated memory retrieval in this task supporting a role for DH in temporal conditional control processes.

P36. Double dissociation of amygdala and hippocampal contributions to trace and delay fear conditioning

JD Raybuck & KM Lattal, OHSU

Trace fear conditioning, where the CS and US are separated by a trace interval, requires the hippocampus and prefrontal cortex to form a CS-US association. However, the role of the amygdala in trace conditioning has yet to be examined. It is possible that recruitment of cortical structures by trace conditioning alters the role of the amygdala in this task compared to delay fear conditioning, where the CS and US co-terminate. To investigate this question, we deactivated the amygdala of male C57BL/6 mice with muscimol infusion prior to trace or delay fear conditioning; with 2 CS-US pairings either separated by a 30s trace interval, or co-terminating. Amygdala inactivation produced deficits in contextual and delay conditioning, but had no effect on trace conditioning. Alternately, dorsal hippocampal inactivation produced deficits in trace and contextual, but not delay fear conditioning. These findings support previous reports that the dorsal hippocampus is critical for trace and contextual fear learning and that the amygdala is critical to delay and contextual conditioning. However, lack of effect of amygdala inactivation on trace fear conditioning suggests that this task may be supported by novel circuitry.

P37. Visualizing contextual fear: differential activation of neuronal ensembles in the hippocampus, amygdala and medial prefrontal cortex

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The ability to recognize contexts and the significant events that occur within them is vital to the survival of any species. Contextual fear conditioning provides an excellent model of this ability, as it requires an animal to form a contextual representation and associate that representation with an aversive event. Activity within the brain regions implicated in contextual fear can be assessed using catFISH (cellular compartment analysis of temporal activity using fluorescent *in situ* hybridization), which provides a footprint of the neuronal populations involved in two, temporally distinct events (indexed by Arc mRNA expression). We investigated how context-activated neuronal ensembles change when a context has been fear conditioned. Rats were exposed to a context and shocked either following a delay or immediately (Event 1). They were then re-exposed to the context (Event 2) and brains were subsequently processed for Arc. Contextual fear (freezing) was seen in delay but not immediately-shocked rats. CatFISH analyses revealed that in the dorsal hippocampus (DH), cells that were activated by Event 1 were reactivated during Event 2, suggesting that the DH is not

sensitive to the emotional valence of an environment. Conversely, shock alone was not enough to bias amygdala neurons used in Event 1 to be reactivated during Event 2, as only fearful (delay) animals exhibited this effect. Lastly, neurons in the infralimbic cortex remained relatively quiet, while a significant increase in neurons in the prelimbic cortex were activated by Event 1 and re-activated during Event 2, regardless of training condition. Collectively, these data provide initial insight into the region-specific behavior of neuronal ensembles during contextual fear conditioning.

P38. Categorical representations in human fear learning

Joseph E. Dunsmoor, Alex Martin, Kevin S. LaBar

In a typical fear conditioning experiment, subjects learn that a neutral conditioned stimulus (CS; e.g. a tone) predicts an aversive unconditioned stimulus (US; e.g. an electric shock), and display fear behaviors in the presence of the CS. In many real world situations, however, it is important for individuals to extrapolate beyond a specific CS exemplar and extend learned behaviors to related stimuli that portend the same outcome. In the present study, we examined fear conditioning across categorically related stimuli that varied considerably in perceptual features. Subjects were presented with CSs composed of eighty different images from two object categories-- tools and animals. Objects from one category (CS+) were partially reinforced by an electrical shock US, whereas the other category (CS-) was never paired with the US. We show evidence for categorical representations in fear learning across three indices: higher US expectancy ratings (online subjective report), heightened physiological arousal (skin conductance responses), and more accurate long-term declarative memory (24 hour surprise recognition memory test) for the CS+ category than the CS- category. Combined, these results provide new evidence that humans make inferences during fear learning on the basis of the conceptual qualities of conditioned stimuli, and suggests that fear expression is mediated in part by conceptual knowledge systems. In addition, these findings shed light on the persistent nature of fear memories following an aversive experience, as subjects preferentially remembered categorically related items that predicted an aversive outcome relative to related items that were “safe.”

P39. Evidence for trace conditioning without awareness using "biologically-relevant" CSs.

Balderston, N. L., Schultz, D. H., & Helmstetter, F. J.

Pavlovian fear conditioning in humans leads to implicit autonomic CRs and explicit awareness of the CS-UCS contingency. It is unclear whether these two behaviors are mediated by independent learning processes. If so, then it should be possible to manipulate the learning process mediating one behavior without affecting the other. Experimental manipulation of awareness tends to affect trace but not delay conditioning. However, research using backward masking to control awareness has shown that trace conditioning without awareness is possible when “fear-relevant” stimuli are used, suggesting that awareness is needed to maintain a representation of fear-irrelevant but not fear-relevant stimuli during the trace interval.

To test this hypothesis we trained subjects using masked fearful and emotionally neutral faces as CSs paired with a shock UCS that was presented immediately upon CS offset or delayed by 500 msec. We measured the effects of this training on performance during a subsequent unmasked differential conditioning session, where novel CSs were paired with a previously masked stimulus in a sequential blocking paradigm.

Even though participants couldn’t identify the CSs during the masking phase, they acquired the novel CS-UCS contingencies more slowly if the novel CSs were paired with a previously reinforced stimulus, relative to a previously unpaired stimulus, which suggest that participants were able to implicitly associate the masked fearful and emotionally neutral faces with the UCS, even with a trace interval. Surprisingly, these results suggest that a representation of a face, whether fearful or neutral, can be maintained without awareness during a brief trace interval.

P40. Human learning of outcome identity and outcome value in a transreinforcer blocking paradigm

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Learning is thought to be driven by prediction errors, that is, the difference between the value of what one expects and what one receives. Here we ask what happens when the value of an outcome is exactly as expected, however, the identity of the outcome is different. We replicate in humans a Pavlovian blocking task that has found, in rats, dissociable roles for the ventral striatum and the orbitofrontal cortex in learning driven by value versus identity-based prediction errors (McDannald, Lucantonio, Burke, Niv & Schoenbaum, under review). In the blocking paradigm, a novel stimulus is blocked from learning when it is paired with a stimulus that has previously predicted the same outcome; presumably, this results from the occurrence of the outcome failing to produce a prediction error for the novel stimulus. Using visual stimuli and different colored M&M's as rewards, we compare learning of a stimulus associated with an already predicted reward, a stimulus that predicts a change in the color but not amount of reward, and one which is associated with a change in the amount of the reward. Behavioral results show that human participants indeed exhibit blocking in this task. Our aim in future work is to use fMRI to elucidate the characteristics of neural activity in response to identity-based prediction errors.

P41. The activity-regulated cytoskeletal-associated protein (Arc/Arg3.1) is required for reconsolidation of auditory Pavlovian fear memories in the lateral amygdala.

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The immediate-early gene Arc/Arg3.1 has been implicated in synaptic plasticity and in a variety of memory tasks, including spatial memory formation in the hippocampus (Guzowski et al 2001) and in the consolidation of auditory fear memories within the lateral amygdala (LA; Ploski et al 2008). The functional role of Arc/Arg3.1 in memory reconsolidation processes, however, has never been systematically examined. Here, we show using Western blotting and immunohistochemistry that Arc/Arg3.1 protein is regulated in the LA by retrieval of a previously acquired auditory fear memory. In behavioral experiments, we next examined the effect of Arc/Arg3.1 knockdown in the LA on auditory fear memory reconsolidation. Rats were trained with two tone-shock pairings consisting of a 5kHz, 75dB, 30s tone which co-terminated with a 1s, 2.0mA footshock (ITI=120s). Twenty-four hrs later, they were given intra-LA infusion of Arc/Arg3.1 antisense or scrambled oligodeoxynucleotides (ODNs; 200pmol; 1 µl/side) 90min prior to a tone reactivation trial administered in a distinct context. Post-reactivation STM (PR-STM) was assessed 3hrs later and post-reactivation LTM (PR-LTM) was assessed ~24hrs later. Arc/Arg3.1 knockdown via local ODN infusions in the LA prior to memory reactivation left PR-STM intact, while PR-LTM was significantly impaired. Furthermore, additional controls suggested that in the absence of tone reactivation there is no effect of Arc/Arg3.1 knockdown on PR-LTM, and that the effect of Arc/Arg3.1 knockdown occurs within a relatively narrow time window (e.g. 6hrs) following memory reactivation. These findings indicate that retrieval-induced expression of Arc/Arg3.1 within the LA is required for auditory fear memory reconsolidation.

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P42. Disrupting the Reconsolidation of Alcohol based Conditioned Place Preference

Lorena M. Novel, Harinder Aujla. University of Winnipeg

During reconsolidation memories are susceptible to disruption. The present experiment sought to determine if post-test administration of the N-methyl-D-aspartate (NMDA) receptor antagonist (MK-801) or a dopamine D1 receptor antagonist (SCH23390) would disrupt the reconsolidation of alcohol-based conditioned place preference (CPP). Male Wistar or Sprague-Dawley rats underwent four CPP sessions with ethanol (1g/kg intraperitoneal) or saline solution. Following a

15-minute test session, vehicle, a D1 antagonist, or MK-801 was administered and a second test session was conducted later to evaluate reconsolidation. Subsequent reconditioning of CPP was assessed. Rats that received vehicle exhibited ethanol-based place conditioning. SCH23390 dose dependently (2.0 but not 0.1 or 1.0 mg/kg) and MK-801 (0.2 mg/kg) disrupted place conditioning during the reconsolidation and reacquisition session. Results suggest a potential for D1 receptors as pharmacotherapeutic target in treatment of cue-related relapse to alcohol use.

P43. Compound Extinction with Multiple Excitors: A Nonlinear Relationship

Bridget L. McConnell & Ralph R. Miller. SUNY Binghamton

In three experiments with rats, we investigated the effect of conducting extinction treatment of target cue X in the presence of zero, one, or two additional excitors. According to total error reduction theories (e.g., Rescorla-Wagner, 1972), increasing the number of compound excitors should monotonically deepen extinction. In contrast to this prediction, Experiment 1 demonstrated more responding (i.e., less extinction) following extinction in the presence of two additional excitors relative to extinction in the presence of one additional excitors. Deepened extinction was observed following extinction with one additional excitor relative to no additional excitors. Thus, a nonlinear relationship was observed regarding extinction in the presence of multiple excitors. This was not due to differential generalization decrement. The results are inconsistent with a total error reduction approach but are explainable within a comparator hypothesis framework. Experiments 2 and 3 demonstrated the emergence of deepened extinction following extinction with two additional excitors when the association between one of the additional excitors and the target cue or the association between one of the additional excitors and the US was weakened. These results are also consistent with a performance-focused account of extinction in the presence of a concurrent excitor.

P44. Retrospective revaluation of Pavlovian retroactive cue interference

Gonzalo Miguez, Mario A. Laborda, & Ralph R. Miller. State University of New York - Binghamton

Pavlovian retroactive cue interference refers to the reduction in responding to the target cue (X) at test when pairings of another cue with the outcome (e.g., A-O) is interposed between the target cue-outcome pairings (e.g., X-O) and testing. Two experiments using a sensory preconditioning paradigm in conditioned lick suppression with rats were conducted. The experiments endeavored to determine if the associative status of the interfering cue (A) at test differentially determines the reduction in behavior to the target (X) in Pavlovian retroactive cue interference. Experiment 1 found that more A→O pairings in Phase 2 produced greater interference (12 > 4 > 3 > 2 > 0) in responding to X (which received 4 X-O pairings during Phase 1). Experiment 2 found that extinction of the interfering cue after the A-O pairing phase attenuated the reduction in responding to X produced by interference. The results are discussed in terms of the possibility that similar associative mechanisms underlie both cue interference and cue competition.

P45. Associative learning from replayed experience

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We introduce an extension to the Rescorla-Wagner model of associative learning. In addition to learning from the current trial, our model postulates that animals continuously replay previous experiences and learn from those replays using the same learning rule. This one simple idea provides a unifying explanation for diverse phenomena that are difficult to reconcile with the original Rescorla-Wagner model, including spontaneous recovery, latent inhibition, and retrospective revaluation. For example, spontaneous recovery is explained by supposing that the animal replays its previous experience during the interval between extinction and test. This experience includes replays of both extinction trials and acquisition trials. As a result, there is a gradual re-acquisition of the conditioned response. Similarly, latent inhibition is caused by the replay of the initial CS-alone trials during the course of acquisition. The model is informed by reinforcement learning algorithms that

interleave learning and planning in the same architecture and evidence that spatial experience is replayed in the hippocampus. Finally, our model provides both testable predictions as well as a computational mechanism for understanding the process of consolidation and the interaction of episodic memory with associative learning.

P46. What's mediated about mediated extinction in human causal learning?

Tom Beckers. Department of Psychology, University of Leuven, Belgium, Department of Psychology, University of Amsterdam, the Netherlands

Recently, Liljeholm and Balleine (2009) presented evidence to suggest that physical and functional similarity critically modulate the occurrence of mediated extinction versus retrospective revaluation in human causal learning. I will present evidence to suggest that the mediated extinction effects that they obtained do not originate from a within-compound association between mediated and mediator cue, and in that sense do not represent mediated extinction proper.

P47. Effects of Self-Generated Priming of the Conditioned Stimulus on the Acquisition of Conditioned Responding

Travis P. Todd, Neil E. Winterbauer, and Mark E. Bouton. University of Vermont

An appetitive conditioning experiment with rat subjects further examined the effect of "priming" the conditioned stimulus by presenting it briefly before each conditioning trial (e.g., Bouton & Sunsay, 2003; Sunsay, Stetson, & Bouton, 2004). During each daily session, a 10-s target CS was paired with a food pellet US eight times. Either 30 or 60 s prior to the target CS, a nonreinforced presentation of the same CS occurred. This nonreinforced presentation was either 2 or 20 s in duration. The design was thus a 2 x 2 factorial, with prime duration (2 vs. 20 s) and prime-target interval (30 or 60 s) as factors. The ratio of reinforcement rate in the CS and in the background was equated across groups. The results indicated that rats trained with a 2 s nonreinforced CS prior to the target CS acquired conditioned responding more rapidly than rats trained with a 20 s prime. This was evident in both a rate of response measure and in the number of reinforcers required to reach several acquisition criteria. Application of the Gallistel, Fairhurst, and Balsam (2004) change-point algorithm indicated that conditioned responding first emerged at a similar point in all groups. Results are discussed in terms of time-based models of learning (Gallistel & Gibbon, 2000) and associative, trial-based models of learning that emphasize the effects of dynamic short-term memory processes on learning and performance (e.g., Wagner, 1981).

P48. Appetitive to aversive counterconditioning

Helen M. Nasser and Gavan P. McNally

Appetitive and aversive motivational states are frequently viewed as independent and mutually inhibitory. We examined this using appetitive to aversive counterconditioning, where fear learning to a previously established appetitive CS is retarded relative to a novel control. Experiment 1 replicated counterconditioning as demonstrated by Bouton and Peck (1992). Experiment 2 studied whether this effect was dependent on appetitive properties of the CS or if it could be attributed to the history of CS exposure. Thus an additional control was included, involving unpaired presentations of the CS and reward. Retardation of freezing during Stage II aversive conditioning was seen for both of these groups relative to the control whereas these groups differed on expression of the appetitive CR. Further experiments determined whether retardation of fear learning during counterconditioning was due to low levels of attention allocated to the CS on its first pairing with the aversive CS in Stage II or whether this effect was due to motivational conflict. These results will be discussed in terms of associative and motivational learning theories.

P49. Functional MRI of children during eyeblink classical conditioning

Dominic T. Cheng, Ernesta M. Meintjes, Mark E. Stanton, John E. Desmond, Mariska Pienaar, Neil C. Dodge, John M. Power, Christopher D. Molteno, John F. Disterhoft, Joseph L. Jacobson, Sandra W. Jacobson

Functional magnetic resonance imaging (fMRI) studies have demonstrated cerebellar and hippocampal involvement in adults during human eyeblink classical conditioning. The present fMRI study is the first to use similar methodologies to examine conditioning-related neural activity in normal, healthy children (M=11.5 yr, range=9.3-13.8, n=11). This study is part of a larger effort to characterize the neural bases of eyeblink conditioning in children with fetal alcohol syndrome (FAS). Brain imaging was performed on a Siemens 3T Magnetom Allegra in Cape Town, South Africa. Functional images were collected using an echo planar imaging pulse sequence (3 mm axial slices; TR: 2000 ms; TE: 30.0 ms; flip angle: 90°), while structural imaging was acquired using a T1-weighted magnetization-prepared rapid acquisition gradient echo sequence. Single-cue delay conditioning trials were presented during fMRI scanning. Delay (750 ms) CSs were 1000 Hz tones (95 dB) delivered binaurally; the US was a 100 ms corneal airpuff (10 psi). Trials were grouped into blocks: 9 trials per block, 2 s per trial, 3 s ITI. Pseudoconditioning (4 tone alone and 4 airpuff alone blocks) was followed by acquisition (8 tone-airpuff pairing blocks). Children showed more CRs during acquisition relative to pseudoconditioning indicating that they successfully learned the CS-US association. Greater activation in cerebellar lobule VI and deep nuclei was also detected during acquisition relative to pseudoconditioning. These results suggest that the neural circuitry supporting delay eyeblink conditioning in children, adults, and laboratory animals are functionally similar. Future fMRI studies will examine conditioning-related brain activity in children diagnosed with FAS.

P50. Delay and trace eyeblink conditioning deficits in children with fetal alcohol syndrome

Sandra W. Jacobson, Mark E. Stanton, Neil C. Dodge, Mariska Pienaar, Ernesta M. Meintjes, Christopher D. Molteno, Joseph L. Jacobson

Developmental alcohol exposure impairs eyeblink conditioning (EBC) in rodent models of fetal alcohol spectrum disorder. We have recently identified impaired EBC to be a remarkably consistent deficit associated with fetal alcohol exposure in young children. In the 5-year follow-up of heavily alcohol-exposed children in Cape Town, South Africa, not a single child with fetal alcohol syndrome (FAS) met criterion for conditioning, as contrasted with 75.0% of controls. Delay EBC was examined in a new sample of 63 children at 11.3 years, and trace conditioning in 32 of the same children at 12.8 years. At each age, two sessions of 50 trials each were administered on the same day; two more sessions the next day. Only 33.3% of the children with FAS met criterion for delay, compared with 79.3% of controls. Trace conditioning was also highly sensitive to exposure. Only 16.7% of the FAS group met criterion for trace, compared with 66.7% of controls. Magnitude of effect of diagnostic group on trace was not greater than on delay conditioning, findings consistent with recent rat studies. Longer latency to onset and to peak eyeblink CR in exposed children indicated poor timing. Extended training resulted in some but not all exposed children reaching criterion. These data extend our findings of impaired EBC at 5 years to school-age. Alcohol-related impairment in cerebellar circuitry may be sufficient to account for the deficit in both tasks. EBC provides a well-characterized model system for assessment of cerebellar-related learning and memory dysfunction in fetal alcohol exposed children.

P51. Developmental Emergence of Delay and Trace Eyeblink Conditioning with a Vibration Conditioned Stimulus

Mary E. Goldsberry, Thomas C. Harmon, Magdalyn E. Elkin, and John H. Freeman. University of Iowa, Iowa City, IA

Delay eyeblink conditioning (EBC) with an auditory CS emerges ontogenetically after postnatal day (P) 19 in rats and precedes trace EBC (Ivkovich et al., 2000). Trace EBC differs from delay EBC in that it contains a stimulus-free trace period between the CS and US. A sufficiently long trace interval recruits late-developing forebrain structures including the hippocampus and prefrontal cortex.

Findings from our laboratory suggest that a rate-limiting factor in the ontogeny of delay EBC is the development of CS input to the basilar pontine nuclei. Therefore, the ontogenetic emergence of trace EBC may be also be attributable to development of CS input to the pontine nuclei or to development of forebrain structures. The current study used a vibration CS to activate an early-developing sensory system during delay and trace eyeblink conditioning to determine whether bypassing the limitations of the later-developing auditory and visual CS pathways would result in earlier emergence of forebrain-dependent and forebrain-independent forms of cerebellar learning. In Experiment 1, rat pups were given delay EBC with a vibration CS on P14-15, 17-18, 21-22, or 24-25. All but the youngest age group showed high levels of conditioning. In Experiment 2, rats pups were given trace EBC on P17-18, P21-22, or P24-25. There was an age-related increase in trace conditioning, with even the youngest age group showing low levels of conditioning. The results suggest that the ontogeny of EBC depends on the development of sensory input to the pontine nuclei and trace EBC may also require development of forebrain structures.

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P52. Inactivation of the Ventral Lateral Geniculate Impairs Retention of Visual Eyeblink Conditioning

Adam B. Steinmetz, Eric W. Buss, and John H. Freeeman. University of Iowa, Iowa City, IA

The conditioned stimulus (CS) pathway necessary for visual delay eyeblink conditioning was investigated using muscimol inactivation in rats. Visual delay eyeblink conditioning is established by pairing a light conditioned stimulus (CS) with an unconditioned stimulus (US) that elicits the eyeblink reflex. Previous research has shown that stimulation of the ventral lateral geniculate (LGNv) as a CS produces rapid CR acquisition in rats (Halverson, Hubbard, & Freeman, 2009, Learn Mem, 16, 300). The LGNv projects ipsilaterally to the medial basilar pontine nuclei and inactivation of the medial pons impairs retention of visual eyeblink conditioning (Halverson & Freeman, 2010, Learn Mem, 17, 80). In addition, retrograde labeling with fluorogold was used to identify ipsilateral projections from the nucleus of the optic tract (OT) and LGNv to the medial pontine nuclei (Halverson & Freeman, 2010). In the present experiment, rats were implanted with infusion cannulae in the right (contralateral to the conditioned eye) LGNv and then given delay eyeblink conditioning with a light CS for five days. Muscimol was infused into the LGNv on day 6 to examine the effect of inactivation on CR retention with the light CS. Vehicle infusions were given the following day (day 7). Muscimol infusions into the LGNv severely impaired retention of CRs to the light CS. The extent of muscimol spread in the LGNv was assessed with fluorescent muscimol. The findings indicate that inputs from the LGNv to the medial pontine nuclei are part of the visual CS pathway necessary for visual eyeblink conditioning.

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P53. Central Cannabinoid Receptors Modulate Acquisition, Retention, and Extinction of Eyeblink Conditioning

Adam B. Steinmetz and John H. Freeman. University of Iowa, Iowa City, IA

The cerebellar cortex, particularly the molecular layer, contains the highest density of cannabinoid receptors (CBR1) in the mammalian brain. The CBR1s are located on the axon terminals of parallel fibers, stellate cells, and basket cells where they inhibit neurotransmitter release. Cerebellar long-term depression is impaired in CBR1 knockout mice and with pharmacological antagonists. Past research in humans and mice has indicated a role for these receptors in the acquisition of delay eyeblink conditioning. The present study examined the effects of a CBR1 agonist, WIN55,212-2, and antagonist, SR141716A, on acquisition, retention, and extinction of delay eyeblink conditioning in rats. In Experiment 1, rats were given subcutaneous administration of 1, 2, or 3 mg/kg of WIN55,212-2 or 1, 3, or 5 mg/kg SR141716A during 10 days of acquisition training. There was a dose-dependent impairment in acquisition, with no effect on spontaneous or non-associative blinking with both drugs. In Experiment 2, 3 mg/kg of WIN55,212-2 or 5 mg/kg of SR141716A was given after 5 days of training with no infusions, followed by a day of training with a vehicle injection.

Extinction training with WIN55,212-2, SR141716A or vehicle injections was then administered for 2 days. Injection of WIN55,212-2 after learning produced an impairment in retention. Extinction of the eyeblink CR was also slower in the rats that were given WIN55,212-2. However, retention and extinction were not impaired for rats adminstered with SR141716A. The findings support the hypothesis that CBR1s in the cerebellar cortex play important roles in acquisition, retention, and extinction of eyeblink conditioning.

Grant support: NIHM MH080005

P54. Worms in a Wheel: Developing a New Procedure

W. Jeffrey Wilson, Albion College

Earthworms have been the focus of behavioral and neurophysiological studies for almost a century, starting with the comparative studies of Yerkes in 1912. Over the course of this time Pavlovian and instrumental learning have been studied, as have circadian changes in locomotion, and both surgical and pharmacological manipulations have been employed. Several studies have reported that worms will crawl in a "running wheel" at speeds up to 30 cm/min. I report progress in developing a running wheel that provides accurate information about small movements. The behavior of two different species (European nightcrawlers [Eisenia Hortensis] and African nightcrawlers [Eudrilus eugeniae]) of worms is compared (both species are easily raised in the laboratory). The wheel will provide the basis for several escape and avoidance studies, and might also prove useful in studies of classically conditioned responses. Video of worms in a wheel will be shown.

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P55. A new paradigm to investigate reward, fear and safety learning

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Reliably recognizing rewards, danger and safety present in the environment is an important survival trait. Also essential is learning to react quickly to cues that predict these situations. Fear and reward conditioning have been well studied independently. However, few studies have investigated them side by side. Even less is known about how the mechanisms of learning reward, fear and safety may overlap because the three are rarely studied concurrently in the same animal.

We have developed a paradigm to investigate fear, reward and safety learning in parallel. Rats (n=8) were conditioned to three distinct cues: Cue A (reward) predicted sucrose, Cue B (fear) ended in a footshock, and Cue B in conjunction with Cue C predicted **no** footshock. Cue C acted as the safety signal. Safety conditioning is a form of inhibitory conditioning. The safety signal in our paradigm satisfies both tests that a valid inhibitory cue should pass (Rescorla, 1969):

1) *Summation test*. The safety cue inhibited the fear response elicited by the fear cue.

2) *Retardation of the development of the conditioned response*. After safety training, the safety cue was then paired with the footshock. The fear response did not develop as quickly as compared to when the footshock was paired with an originally neutral stimulus.

Our paradigm reliably elicits fear, reward seeking and safety behavior to specific cues within the same observation session, making it a useful paradigm in investigating overlapping mechanisms underlying the learning of these three behaviors.

P56. 2-trial fear conditioning produces optimal fear-potentiated startle using proper trial spacing.

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One of the most consistent observations in the field of learning and memory is that spaced training results in a more robust memory than does massed training. Most of the prior experiments examining the effect of trial spacing on learning have used several training trials. In the current set of experiments we studied the effect of trial spacing using 2-trial fear potentiated startle. Rats were

trained using a 4-sec light that terminated with a footshock, and memory was tested 2 days after the final trial. Several different ITIs were examined ranging from 4 min to 30 days. We found that spacing the trials by 60 min to 3 days resulted in optimal conditioning, whereas spacing the trials by shorter or longer periods of time outside of this window resulted in very little long-term memory. A separate study demonstrated that the memory formed by spacing the trials by 60 min or 24 hrs lasts at least 2 weeks. While the mechanism behind our results is unknown, it is likely to involve the signaling pathway mediated by cyclic AMP. Several studies (Yin et al., 1994; Josselyn et al., 2001; Phillips et al., 2007) have implicated this pathway in mediating trial spacing effects. The time course of our effect may suggest a modification of intrinsic neuronal properties induced by the first training trial that last for several days and allows for facilitation of subsequent learning. Studies are underway designed to understand the mechanism that supports the trial spacing effect in our experiments.

P57. Introducing a novel human pain-related fear conditioning paradigm: acquisition and generalization of pain-related fear of movement

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Pain-related fear (PRF) is considered a key factor in the development of chronic pain. Presumably, PRF is acquired through classical conditioning, i.e., neutral stimuli (movements) start to elicit defensive fear responses (avoidance) due to acquired propositional knowledge or formed associations between these stimuli and pain. First, this assumption has never been investigated experimentally. Second, generalization of acquisition to four novel CSs was tested to examine whether PRF of movement transfers to movements that were never followed by pain. Third, little is known about effects of unpredictable pain versus predictable pain [3].

We developed a pain-relevant fear conditioning paradigm using a proprioceptive conditioned stimulus (CS) and a painful shock-US to examine the effects of (un)predictable shocks on PRF and pain intensity. Participants moved a joystick to the left/right in the predictable condition (PC), and upwards/downwards in the unpredictable conditions (UC). In the PC, the CS+ movement, but not the CS- movement, was followed by shock; in the UC, shocks were delivered during the intertrial interval.

Both PRF ratings and startle measures showed more PRF to the CS+ than CS-, whereas no differences occurred between both unpredictable CSs. Preliminary results show that –at least in the verbal ratings– PRF transferred more to the movements having a common feature with the original CS+ than to the movements having a common feature with the original CS-. Identical shocks were rated as more painful when presented unpredictably. These data support this pain-relevant fear conditioning paradigm as a promising tool to study learning of (un)predictable PRF.

P58. Incubation of conditioned fear in the conditioned suppression model in rats: role of cue-shock interval, food-restriction conditions, length of conditioned cue, and generality to conditioned freezing

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We recently adapted the conditioned suppression of operant responding model to study fear incubation. We found that food-restricted rats show low fear 2 days after extended (10 d; 100 30-sec tone-shock pairings) fear training and high fear after 1-2 months. Here, we studied two potential mechanisms of fear incubation: interval between shock-exposure and fear testing, and extended food-restriction stress. We also studied whether fear incubation is observed after fear training with prolonged-duration (6-min) cues and using the conditioned freezing measure. Conditioned fear was assessed 2 days and 1 month after training.

In the conditioned suppression model, non-contingent shock exposure 2 days prior to testing 1 month after training (100 30-sec tone—0.5-sec footshock pairings over 10 daily sessions) had no

effect on fear incubation. In this model, fear incubation was reliably observed in rats given moderate food-restriction conditions (18-20 g food/day) that allowed for weight gain, and after extended (10 d), but not limited (1 d), fear training with 6-min cues. Incubation of conditioned freezing was observed after extended fear training in rats lever-pressing for food and rats not lever-pressing for food.
Results indicate that neither prolonged hunger-related stress nor the interval between shock exposure and fear testing can account for fear incubation in the conditioned suppression model, and that fear incubation generalizes to longer-duration (6-min) fear cues. Extended training also leads to fear incubation of conditioned freezing in rats with or without an operant task.

P59. Fear is an inverted-U function of US intensity

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The purpose of the present experiments was twofold. First, we sought to document that suppression in fear-conditioning is an inverted-U function of footshock intensity as suggested in cross-publication comparisons of prior research. Second, we tested the sometimes competing retrieval (SOCR; Stout & Miller, 2007) model's predictions concerning the effect of US intensity on conditioned suppression and the role of the context in determining the relationship between US intensity and suppression. Experiment 1a measured suppression after training with 0.4-, 0.6-, 0.8-, 1.0-, 1.2-, or 1.4-mA footshocks. Suppression to the CS was an inverted-U function of shock intensity: suppression was weaker (albeit marginally) after training with 1.4-mA shocks than with 1.0- or 1.2-mA shocks. The results demonstrated that responding after training with the most intense shock was less than with moderate intensity shock. Experiment 1b replicated the inverted-U pattern with larger effect sizes using a wider range of shock intensities (0.3 to 1.8 mA in 0.5 mA increments). Experiment 2 replicated the critical result of Experiment 1, demonstrating that high intensity footshocks produce less suppression than moderate footshocks. Compound conditioning attenuated suppression following the moderate footshock; the opposite occurred when high intensity footshocks were used. Additionally, posttraining extinction of the context increased responding in the high intensity footshock condition. These results confirmed SOCR's predictions concerning the effect of US intensity and were inconsistent with several other accounts of associative learning.

P60. Generalization of acquisition and extinction in C57bl/6 mice

Yannick Boddez*,Tom Beckers, Zsuzsanna Callaerts- Vegh, Dirk Hermans, & Frank Baeyens

In the study at hand we addressed the issue of generalization in the most commonly used mouse strain of behavioural genetics, C57Bl/6. Generalization occurs when the conditioned response is elicited by a stimulus different from the one that underwent training. We compared the generalization of acquisition with the generalization of extinction in a fear conditioning paradigm. We hypothesised that the generalization gradient of acquisition would be broader than the generalization gradient of extinction. Results confirm this hypothesis.

List of posters, alphabetically by first author (number indicates poster and abstract location).

Temporal map in odor fear conditioning: Ontogeny of ITI timing and neural networks (P5)
Jessica L. Ahern[1], Elizabeth A. Londen[1], Valérie Doyère[2], Bruce L. Brown[3], Anne-Marie Mouly[4], and Regina M. Sullivan[1]

Neurogenesis in the adult hippocampus: maintaining equilibrium in response to learning and memory.
Anderson, ML, Sisti, HM, Curlik, DM, Shors, TJ **(P31)**

Assessing anxiety- and reward-related behaviours following alcohol administration or chronic stress.
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