Program for the 2009 Annual Meeting of the Pavlovian Society
Hilton Burlington, 60 Battery Street
Burlington, Vermont 05401 (802) 658-6500

Thursday, October 29 Seasons on the Lake

6:00-9:00 *Reception and Registration*

Friday, October 30 Lake Champlain Salon (except as noted)

8:00 Continental Breakfast

8:30-8:35 Mark Bouton, University of Vermont, *Opening remarks*

8:35-9:05 Ralph R. Miller & Mario Laborda, SUNY-Binghamton, *Minimizing Recovery from Extinction*

9:05-9:35 K. Matthew Lattal, Oregon Health & Science University, *What is enhanced in enhanced extinction effects?*

9:35-10:05 Jeansok Kim, University of Washington , *Little Albert (fear conditioning) cells in the amygdala*

10:05-10:20 Coffee Break

10:20-10:50 Glenn Schafe, Yale University, *Fear Memory Consolidation: A View From Both Sides of the Thalamo-Amygdala Synapse*

10:50-11:20 Bruce McNaughton, University of Lethbridge, *Hippocampal Granule Cells Opt for Early Retirement*

11:20-11:35 Jeff Wilson, Albion College, *50 Years of DMTS: The Semicentennial of Seminal Papers by Konorski and Blough*

11:35-1:00 Lunch Break

1:00-3:00 Symposium: Amnesia and Reconsolidation, Karim Nader, McGill University, *Chair*. *Participants*: Karim Nader; Jonathan Lee, University of Birmingham; Amy Milton, University of Cambridge; Merel Kindt, University of Amsterdam.

3:00-4:30 Snack Break and Poster Session **Green Mountain BC**
(Posters to be available from 12:00-7:00 PM)

4:30-5:00 John Pearce & Murray Horne, Cardiff University, *Evaluation of a Pavlovian analysis of spatial learning*

5:00-5:30 Allan Wagner, Yale University, *Relative validity effects in Pavlovian conditioning and human causal learning*

5:30-7:00 Reception (posters still available) **Green Mountain Ballroom**

Saturday, October 31 Lake Champlain Salon

8:00 Continental Breakfast

8:30-10:30 Symposium: Neural Systems in Habit Learning, Barbara Knowlton, UCLA, *Chair*.
Participants: Christina Gremel & Rui Costa, NIAAA/NIH; Norman White & Elia Nahas, McGill University; Veronique Bohbot , McGill University; Barbara Knowlton.

10:30-10:45 Coffee Break

10:45-11:15 Anthony Dickinson, University of Cambridge, *Actions, Habits and Conflict: Reflections on the Castaway's Dilemma*

11:15-11:45 Craig Weiss, Northwestern University Medical School, *Roles of the Cerebral Cortex During Trace Eyeblink Conditioning*

11:45-12:00 Nestor Schmajuk, Duke University, *Computational Models of Pavlovian Conditioning: The State of the Art*

12:00-1:30 Lunch Break

1:30-3:30 Symposium: New Frontiers in Studying the Effects of Repeated Stimulation, Catharine Rankin, University of British Columbia, *Chair*.
Participants: Susanne Schmid, University of Western Ontario; Brian Smith, Arizona State University; Catharine Rankin.

3:30-3:50 Coffee Break

3:50-4:05 Shepard Siegel, Lorraine Allen, & Samuel D. Hannah, McMaster University, *The Fate of the Blocked Stimulus in Contingency Assessment*

4:05-4:20 Cheryl L. Limebeer, Kiran Vimuri***, Holly Bedard, Klaus-Peter Ossenkopp**, Alexandros Makriyannis*** and Linda A. Parker**,** University of Guelph, *Nausea is Produced by Peripheral Inverse Agonism of Cannabinoid$_1$ Receptors: Evidence from the Conditioned Gaping Model in Rats*
** University of Western Ontario, *** Northeastern University

4:20-6:20 Symposium, Pavlovian Influences on Intake and Energy Regulation. Terry Davidson, Purdue University, *Chair*. *Participants*: Stephen C. Woods, University of Cincinnati; Anthony Sclafani, Brooklyn College of CUNY; Peter C. Holland, Johns Hopkins University; Terry L. Davidson.

7:30 **Reception and Awards Dinner Green Mountain Ballroom**

Posters:

P1. Protection from and Reemergence of Extinction

Bridget L. McConnell & Ralph R. Miller (SUNY-Binghamton)

Three conditioned suppression experiments with rats investigated the influence of a Pavlovian conditioned inhibitor on extinction of a target conditioned stimulus. In Experiment 1, a target CS that was extinguished elementally exhibited normal extinction (i.e., weak behavioral control), and similarly a target that was extinguished with an associatively neutral stimulus showed little effect of the added stimulus. However, strong behavioral control was observed to the target cue that was given extinction treatment in the presence of a conditioned inhibitor, which suggests that the conditioned inhibitor was able to protect the target from the normal response attenuating effects of extinction treatment. This effect was replicated in a sensory preconditioning preparation in Experiment 2, and in Experiment 3, in a sensory preconditioning preparation, this protection effect was retroactively attenuated when the conditioned excitor used to train the conditioned inhibitor was extinguished following extinction of the target. That is, following extinction of the excitor used in inhibitory training, responding to the target decreased, representing an emergence of the target extinction treatment. This provides evidence that stimuli that are only indirectly associated with the target cue (e.g., the excitor used to train the conditioned inhibitor) can contribute to the response potential of the target. Moreover, this shows that the response potential of a stimulus is fluid in that it continues to be affected throughout training by changes in associative strength of other cues, even in its absence.

P2. Modeling conditioned fears without recall of causes: Stimulus-response associations, their extinction, and recovery

Mario A. Laborda, James E. Witnauer, & Ralph R. Miller (SUNY–Binghamton)

Associative accounts of the etiology of phobias have been criticized because of numerous cases in which clients do not remember a traumatic event with the phobic object. In three lick suppression experiments with rats, we modeled an associative account for such fears. Experiment 1 demonstrated stimulus-responses associations in first-order fear conditioning. After behaviorally complete devaluation of the unconditioned stimulus, the target cue still produced strong conditioned responses, suggesting that a target cue-response association had been formed (in addition to a target cue-unconditioned stimulus association). Experiment 2 demonstrated extinction of stimulus-response associations and showed that extinguished stimulus-response associations were restored when testing occurs outside of the extinction context (i.e., renewal). Experiment 3 found that a delay between extinction and testing also produced a restoration of extinguished stimulus-response associations (i.e., spontaneous recovery). The results suggest that conditioned fears for which people can not recall conditioning events can be explained in an associative framework, and that those fears are susceptible to recovery after extinction.

P3. Secondary Extinction of Pavlovian Conditioned Fear Requires Intermixed Conditioning Trials.

Drina Vurbic and Mark E. Bouton (University of Vermont)

Pavlov (1927) first reported that following appetitive conditioning of multiple stimuli, extinction of one CS attenuated responding to others which had not undergone any simple extinction (so-called “secondary extinction”). In three conditioned suppression experiments we investigated potential mechanisms of secondary extinction. Experiment 1 assessed whether secondary extinction would be more likely to occur

with target CSs that have themselves undergone some prior extinction. Such an effect might be expected if the extinction context acquired features of a negative occasion setter. We fear conditioned two stimuli and subsequently extinguished one CS before a test of the second CS. Rats were tested with either a CS that had previously undergone some extinction or one that had not. A robust secondary extinction effect was obtained with the non-extinguished target CS, which suggests that the context had not become an occasion setter. Experiment 2 investigated the role of inhibition conditioned to the extinction context by testing the target CS in a neutral context following extinction training. Despite the context switch secondary extinction was clearly observed, indicating that this effect is not mediated by the extinction context. Experiment 3 examined whether the intermixing of the two stimuli during conditioning is necessary for secondary extinction to occur. Rats were either conditioned with intermixed trials as in Experiments 1 and 2, or with blocked trials of each CS presented in separate conditioning sessions. Secondary extinction was observed only in the former condition, suggesting that this effect is mediated by the initial encoding of the associations formed during conditioning.

P4. The interesting effect of extinction on the transfer of non-extinguished CSs to new contexts in appetitive conditioning with rats.

James Byron Nelson (University of the Basque Country), Sebastian Lombas (University of the Basque Country), Samuel P. Leon (University of Jaen)

Previous work is reviewed, and two experiments are presented, to assess the hypothesis that extinction arouses attention to contextual cues, resulting in subsequent learning becoming context specific (Rosas, Callejas-Aguilera, 2006). In Experiment 1, rats received appetitive conditioning with a flasher CS followed by conditioning of a tone in Context A. Throughout, the rats received an equivalent treatment in another context, Context B. Conditioning of the tone occurred alone during the sessions (Group No Extinction) or while the flasher was undergoing extinction (Group Extinction). The groups did not differ in their rate of conditioning to the tone. On the critical test, all rats were subsequently tested with the tone in Context B. Contrary to the hypothesis, responding to T was greater in Group Extinction than in Group No Extinction. The design of Experiment 2 was a 2 x 2 between-subjects factorial that replicated the training of the two groups just discussed and tested half of each group in the context where training occurred (Context A) or in the new context (Context B). The test produced a three-way interaction (Trials x Context x Conditioning Treatment). Compared to Group No Extinction, the general trend was for rats in Group Extinction to show more responding (better transfer) when tested in Context B and less responding when tested in Context A.

P5. Different mechanisms in two kinds of resurgence following the extinction of an operant response

Neil Winterbauer and Mark E. Bouton (University of Vermont)

Extinction of an operant response, such as leverpressing, during the concurrent acquisition of a second, novel operant, sets the stage for a return to the initial response upon extinction of that second operant (this return to responding is resurgence). Importantly, resurgence has also been observed when extinction of the first response and acquisition of the second one occur in separate phases. Leitenberg and Rawson (e.g. Leitenberg, Rawson, and Bath, 1970; Leitenberg, Rawson, and Mulick, 1975) explored a number of explanations for the return to responding observed with the concurrent extinction and acquisition resurgence procedure, ultimately concluding that the primary mechanism was incomplete extinction that occurred because emission of the first response was partially prevented during acquisition of the second (Rawson, Leitenberg, Mulick, and Lefebvre, 1979). We show that this "response prevention" mechanism

is insufficient to account for resurgence in the concurrent training procedure, and advance an alternative contextual account of the phenomenon. That account, however, is less obviously applicable to resurgence in the separate phases procedure; the mechanism of which has received little empirical scrutiny. We examine the role of pellet delivery following extinction in supporting the separate phases form of resurgence, because in paradigms where that delivery is not a consequence of operant behavior, free pellets produce a return to responding (via reinstatement).

P6. Predictability of the temporal relationship between CS and US affects the distribution of conditioned responding

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

As an online measure of unconditioned stimulus (US) expectancy, magazine entries in appetitive Pavlovian conditioning present the experimenter with a fundamental choice. Entries may not only be characterized as occurring with a certain frequency, but also tend to show distinctive patterns in their persistence over the course of conditioning; hence one might plausibly employ rate of entry as an index of US expectancy, or one might equally plausibly employ duration of entry as such an index. Although both choices are well represented in the learning literature, their equivalence is not obvious, as in the limits they must necessarily provide opposite conclusions (i.e. high durations of entry certainly translate into low rates of behavior). Additionally, the nature of the expectation that drives behavior might well be expected to affect the validity of the different measures of that expectation, in that animals might be expected to utilize fundamentally different strategies of magazine checking in different conditioning situations. We contrasted the effect of delivering a pellet US to rats at predictable, deterministic time points in the conditioned stimulus (CS) with the effect of delivering the US at unpredictable, uniformly random time points in the CS using several measures of conditioned responding (CR). We found that group momentary averages of rate and duration of magazine entry were clearly affected by the predictability of the US, and that the use of different methods of averaging and visualizing CRs greatly facilitated interpretation of the role of momentary US expectancy in performance.

P7. Contrasting Asymmetries in Within Trial Temporal Discrimination Learning

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

Three experiments examined temporal discriminations within Pavlovian conditioning trials. In all experiments, the duration of a feature stimulus (white noise) signaled whether or not a 10-s target tone would be reinforced. In Experiment 1, the feature stimulus durations were 4 and 1 min. For one group of rats (Group 4+/1-), 4 minutes of noise signaled the tone would be reinforced and 1 minute of noise signaled the tone would not be reinforced. A second group (Group 1+/4-) was trained with the reverse contingency. The results showed a clear asymmetry in temporal discrimination learning: Rats trained with 4+/1- (Long+/Short-) learned the discrimination readily, whereas rats trained with 1+/4- (Short+/Long) did not. In Experiment 2, the feature durations were shortened to 60 and 15 s. At these intervals, the feature acquired strong excitatory conditioning, which was especially true for the 15-s feature. Conditioning to the feature resulted in the reverse asymmetry, with the Short+/Long- discrimination learned more readily than the Long+/Short- discrimination. However, Experiment 3 demonstrated that the original Long+/Short- advantage could be recovered while using short feature durations if excitatory conditioning of the feature was reduced by including nonreinforced feature trials. The results supported previous research involving the timing of intertrial intervals, and are consistent with the temporal element hypothesis which holds that the passage of time is encoded as a series of hypothetical stimulus elements.

P8. Good Contiguity Predicts Overshadowing

Douglas A. Williams (University of Winnipeg)

Two experiments assessed whether a shorter CS2 whose termination signalled the delivery of an appetitive US would more effectively overshadow a longer CS1 than would a completely overlapping CS2. Three groups of rats received appetitive conditioning in which a single food pellet US occurred at a fixed time either 90 (Experiment 1) or 110 s (Experiment 2) after the onset of a 120-s auditory CS1 (tone or white noise, counterbalanced). Groups differed in the duration of CS2, which terminated before (30 or 10 s before, Experiments 1 and 2 respectively), upon, or after (30 or 10 s after, Experiments 1 and 2 respectively) the delivery of the US in separate groups. Only in Group After did CS1 and CS2 overlap from beginning to end. Random USs occurred in the intertrial interval to slow acquisition of the head-entry CR, and increase the likelihood of finding group differences. Responding on CS1 probe trials was least overshadowed in the Group After in both experiments. Other probe trials revealed that CS2 termination controlled responding in Groups Before and Upon, whereas CS2 onset and not offset caused increased responding in Group After. Our results suggest that good contiguity between CS2 termination and US delivery was more important in this instance than either the degree of overlap or temporal encoding.

P9. Physical and Temporal Contexts Can Disambiguate Conflicting Temporal Information

Gonzalo Miguez, Mikael Molet, & Ralph R. Miller (SUNY-Binghamton)

Three conditioned lick suppression experiments with rats examined the role of the context in the selection and integration of independently acquired interval relationships. In Experiment 1, rats were exposed to separate CS1-CS2 pairings with two different interval relationships (no gap and a 5-s gap), each in its own distinctive context, X or Y. The resultant integration was determined by the context (X or Y) in which US-CS2 backward pairings (with a 4.5-s gap) occurred, as assessed in a third neutral context (Z). In Experiment 2, rats experienced CS1-CS2 pairings with two different interval relationships as in Experiment 1, and then received US-CS2 pairings in both contexts X and Y. The testing context (i.e., X or Y) determined the resultant integration. In Experiment 3, rats were exposed to CS1-CS2 pairings with two different interval relationships each in different phases (i.e., Phases 1 and 2), and then in Phase 3 received US-CS2 pairings. The temporal context of testing (i.e., short or long retention interval) determined the resultant integration. Specifically, responding soon after Phase 3 was consistent with the most recently trained CS1-CS2 relationship, but a shift from recency to primacy was observed with a long retention interval. To explain these results, the temporal coding hypothesis (Savastano & Miller, 1998) was combined with Miller and Escobar's (2002) extension of Bouton's (1993) retrieval model. Thus, physical and temporal contexts can be used to disambiguate conflicting temporal information.

P10. Temporally specific recovery from conditioned inhibition

Kimble, WL (Auburn University), Suits, WT (Seminole Community College), & Escobar, M (Auburn University)

In two experiments with rat subjects, we used a Pavlovian conditioned inhibition procedure (i.e., A-US / AC-no US) to determine whether conditioned inhibition to CS C was dependent upon the excitatory value of its training excitor (CS A), and whether this dependence is temporally specific. CS A was trained as a predictor of the US at both its initial and final segments. Then, excitation was extinguished at either the

initial (Experiment 1) or final (Experiment 2) segment of CS A. Using a retardation test, slower acquisition of responding to CS C was observed in the temporal location that matched the segment of CS A that remained excitatory, but no retardation was observed in the segment that matched the extinguished segment.

P11. Scalar Timing and Adaptive Responding in Trace and Delay Conditioning

Elliot A. Ludvig, & Richard S. Sutton (University of Alberta), & E. James Kehoe (University of New South Wales)

The present experiments characterized conditioned nictitating membrane (NM) movements as a function of the interstimulus interval (ISI) between CS onset and US onset. Most important, the full range of discernible movements (> .06 mm), rather than movements exceeding a conventional criterion (> .50 mm), were examined. Across ISIs, onset latency and peak latency were approximately, but not strictly, scalar for all but the smallest movements (<.10 mm). That is, both the mean and standard deviation of the timing measures increased in proportion to the ISI. In addition, the duration of individual responses grew in proportion to the ISI. Thus, despite the increasing inaccuracy in the timing of the movements, the eye was largely closed during the period the US was presented, thereby protecting the eye during the period of threat. The results are discussed with respect to a real-time, temporal-difference (TD) model that we are developing.

P12. Paradoxal timing in fear conditioning

Jeremie Jozefowiez, James E. Witnauer, & Ralph R. Miller
Universidade do Minho & SUNY - Binghamton

In an appetitive delay conditioning procedure, animals usually temporally regulate their behavior with respect to the CS-US interval, a property of responding sometimes labeled inhibition of delay and usually attributed to interval timing, the ability of animals to perceive durations in the range of several seconds to several minutes. Despite the claim that interval timing is essential to Pavlovian conditioning (e.g. Gallistel & Gibbon, 2000), inhibition of delay is notoriously more difficult to obtain in fear conditioning preparations: more CS-US pairings are necessary and it seems almost impossible to get it with CS durations of less than a minute. In a previous report, we documented an "anti-inhibition-of-delay" pattern in rats trained in a lick suppression procedure: licking was more suppressed at the beginning of the CS, when the probability of the shock US was at its lowest, than at the end of the CS, when the delivery of the shock US was imminent. Moreover, the timescale invariance signature property of interval timing was absent. In the present report, we showed that training aimed at establishing the beginning of the CS as a conditioned inhibitor did not disrupt the anti-inhibition-of-delay pattern and that it was not observed in a bar-press suppression procedure unless the rats were tested in an associatively neutral context. Conclusions about the temporal control of fear-induced responses are drawn from these results.

P13. Inhibition of delay in rat eyeblink conditioning

Alexandra Thanellou and John T. Green (University of Vermont)

We examined whether inhibition of delay (IOD; defined as an increase in CR latency as learning progresses) is seen in 750-ms delay eyeblink conditioning in rats and, if so, whether it can be explained by the development of conditioned inhibition in the first 250-ms of the long-delay CS. In Experiment 1 (Retardation 1), three groups (Delay 750 Tone; Tone only; No Stimuli) were trained. Rats in the Delay 750 Tone group exhibited IOD. Subsequently, all groups underwent a retardation test in which each trial

consisted of a 765-ms tone with the US delivered 250-ms after CS onset. The Delay 750 Tone group exhibited faster (rather than retarded) acquisition to the shortened CS-US interval. In Experiment 2 (Retardation 2), three groups were trained (Delay 750 Tone; Delay 750 Light; No Stimuli). Subsequently, all groups underwent a retardation test in which they were tested as in Experiment 1. The Delay 750 Tone group again exhibited faster (rather than retarded) acquisition to the shortened CS-US interval. In Experiment 3 (Summation), two groups were trained (Delay 750 Tone; Delay 250 Tone). Both groups also had intermixed Delay 250 Light trials in preparation for summation testing. Subsequently, both groups underwent a summation test with three trial types (trial type 1: 750-ms Tone/250-ms Light compound with light during the first 250-ms of the tone; trial type 2: 250-ms Light; trial type 3: 750-ms Tone/250-ms Light compound with light during the last 250-ms of the tone). The Delay 750 Tone group showed more (not fewer) CRs on trial type 1 compared to trial type 2. Failure of both the retardation and the summation tests suggests that IOD does not involve conditioned inhibition. The results of the retardation test suggest that CRs present early in conditioning during the early part of a long CS may be subject to rapid reacquisition later, making IOD more like an extinction phenomenon.

P14. Functional MRI of human eyeblink conditioning using long and short interstimulus intervals

D. T. Cheng[1], A. M. Katzenelson[2], M.L. Faulkner[1], J. F. Disterhoft[3], & J. E. Desmond[1]

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Previous work from our laboratory used functional MRI to study the neural substrates underlying human eyeblink conditioning. We continue this line of work by investigating the effects of different interstimulus intervals (ISI) during delay conditioning. Since an MRI environment introduces unique challenges (e.g. RF pulses, subject in a supine position) not typically encountered in traditional behavioral studies, shorter ISIs may be one technique that can be used to optimize conditioning. Furthermore, it has been reported that shorter ISIs produce greater learning than longer ISIs in young adults. However, it is unclear whether short and long ISIs elicit distinct functional brain activity. The present study used event-related fMRI to study single-cue delay conditioning using two different ISIs (750 and 1250 msec). In a between groups design, subjects received either a short (850 msec) or long (1350 msec) CS (1000 Hz tones) coterminating with a 100 ms corneal airpuff (US; 5 psi). Behavioral findings showed similar levels of conditioning over the course of the experiment between both groups although more short ISIs subjects showed early learning. Neuroimaging data showed robust auditory cortex activation common to both ISIs, indicating that subjects could hear both tones over the scanner noise. Differential patterns of activation in the basal ganglia and cerebellum were also observed between ISIs. These findings suggest that, although similar levels of behavioral CRs were measured, unique brain regions may be differentially engaged as a function of interstimulus intervals.

P15. Cerebellar Theta Oscillations Are Synchronized During Hippocampal Theta-Contingent Trace Conditioning

Loren C. Hoffmann and Stephen D. Berry

The hippocampus and cerebellum are critically involved in trace eyeblink classical conditioning (EBCC). The mechanisms underlying the hippocampal-cerebellar interaction during this task are not well understood, although hippocampal theta (3-7 Hz) oscillations are known to reflect a favorable state for

EBCC. Two groups of rabbits received trace EBCC in which a brain-computer interface administered trials in either the explicit presence or absence of naturally occurring hippocampal theta. A high percentage of robust theta led to a striking enhancement of learning accompanied by rhythmic theta-band (6-7 Hz) oscillations in the interpositus nucleus (IPN) and cerebellar cortex that were time-locked both to hippocampal rhythms and sensory stimuli during training. Rhythmic activity was absent in the cerebellum of the non-theta group. Here, we present findings characterizing the theta-contingent dichotomy in physiological responses of the hippocampus and cerebellum. These data strongly suggest a beneficial impact of theta-based coordination of hippocampus and cerebellum and, importantly, demonstrate that hippocampal theta oscillations can be used to regulate the functional properties of the cerebellum.

P16. Single-unit activity in the developing hippocampus during trace eyeblink conditioning.

M. E. Levillain[1], M. M. Campolattaro[1], A. Kashef[1], K.H. Ng[1], & J. H. Freeman[1] [1]Department of Psychology, University of Iowa, Iowa City, IA 52242

Trace eyeblink conditioning involves the association of a conditioned stimulus (CS) with an unconditioned stimulus (US) over a stimulus-free trace interval. In contrast to delay conditioning, trace conditioning requires the hippocampus. While a number of studies have investigated the role of hippocampal neuronal activity during trace eyeblink conditioning in adult animals, its role has yet to be studied in younger animals. The goal of the current research was to examine the activity of CA1 hippocampal pyramidal cells during acquisition of trace eyeblink conditioning in 21-22, 24-26 and 31-33 day old rat pups. These ages were chosen because data from our laboratory indicates that reliable trace eyeblink conditioning begins to emerge at approximately postnatal day (P) 24. In order to increase the quality of neuronal recording in rat pups, we developed a miniaturized three-tetrode drive for rat pups. Implantation of the drive occurred on either P19, 22 or 29. Pups then received two sessions per day of trace eyeblink conditioning on P21-22, 24-26 or 31-33. Pyramidal cell recordings demonstrated a number of different firing profiles, with increased activity during the CS, trace interval, US, or a combination of trial events. Furthermore, these units had an increased level of firing during conditioned response (CR) trials when compared to non-CR trials. These findings demonstrate that pyramidal cells in the developing hippocampus not only encode the different trial events during trace eyeblink conditioning, but show learning-related changes in activity.

P17. Neuronal Activity in the Interpositus and Pontine Nuclei During Cross-Modal Eyeblink Conditioning in Rats

Matthew M. Campolattaro & John H. Freeman (University of Iowa)

This experiment examined neurobiological components underlying cross-modal savings of eyeblink conditioning in rats. Cross-modal savings occurs when training with one modality CS enhances subsequent conditioning with a different modality CS. This type of learning results from the general transfer information from one sensory modality to another. This experiment was designed to assess activity within the interpositus nucleus (IPN) and pontine nucleus (PN) during cross modal transfer training. In Phase 1, rats received pre-exposure training with separate presentations of a tone and light CS. In Phase 2, rats were given explicitly unpaired presentations of the tone, light and a periorbital shock US. In Phase 3, paired presentations of a CS (i.e., a tone; CS1+) and US were given to establish eyeblink CRs. In Phase 4, rats received cross-modal transfer training with the new modality CS (i.e., a light, CS2+). In Phase 5, separate CS1+ and CS2+ presentations were used to establish additional conditioning to the CSs. The results revealed that CS processing in the IPN and PN was primarily unimodal during Phases 1 and 2, whereas CS processing in the IPN and PN during Phase 4 cross-modal transfer training was mostly

multimodal. The findings also demonstrated that learning-related changes in IPN and PN activity developed during cross-modal transfer and these changes occurred more rapidly in the IPN than the PN, possibly due to feedback from the IPN to the PN. The findings support the hypothesis that coordination of multisensory processing within two these brain areas is important for establishing cross-modal savings.

P18. Cross-Modal Savings in the Contralateral Eyelid During Eyeblink Conditioning in Rats

Eric W. Buss, Matthew M. Campolattaro, and John H. Freeman (University of Iowa)

This experiment monitored bilateral eyelid responses during eyeblink conditioning in rats using unilateral US presentations. Three groups of rats were used to test the hypothesis that cross-modal savings occurs when the location of the US is switched from one eyelid to the other. Each group first received ten daily sessions of paired eyeblink conditioning with a CS (tone or light) and a periorbital shock US. The groups were then given five daily sessions of paired training but the US location (group 1), CS modality (group 2) or both US location and CS modality (group 3) were changed. All rats acquired high levels of CRs in both eyelids during initial training, but acquisition was faster, CR percentage was higher, and CR amplitude was larger in the eyelid that was ipsilateral to the US. Changing the location of the US alone resulted in an immediate transfer of conditioning in both eyelids (group 1). However, the CR amplitude in the newly reinforced eyelid increased whereas the previously reinforced eyelid decreased. Facilitated learning to the new modality CS was observed in both groups 2 and 3 indicating that cross-modal savings occurs whether or not the location of the US is changed. A similar shift in CR amplitude between the eyelids found in group 1 was also observed in group 3. The results are consistent with the ideas that conditioning is most dominant in the reinforced eyelid and that cross-modal savings occurs robustly in the eyelid that is initially contralateral to the US.

P19. The effect of septo-hippocampal lesions on the acquisition of the classically conditioned eyeblink response in rats.

J.J. Roland[1]*, K. Janke[5], M.A. Gluck[4], K.C.H. Pang[1,2,3] & R.J. Servatius[1,2,3]
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Both human and animal studies have demonstrated that the hippocampus is not essential for the acquisition of delay eyeblink conditioning that involves a simple discrimination. Data have shown that cholinergic lesions or acetylcholinesterase inhibitor administration do not result in learning deficits during delay eyeblink conditioning. However, studies that have examined total medial septal damage, in both rabbits and humans, have shown that acquisition as well as latent inhibition of delay eyeblink conditioning is impaired. These results suggest a possible involvement of non-cholinergic medial septal neurons in delay eyeblink conditioning. The major noncholinergic projection from the medial septum to the hippocampus comes from GABAergic neurons although recent studies also suggest a possible glutamatergic projection. Nevertheless, these studies did not differentiate between cholinergic and GABAergic medial septal damage. The question remains then, if medial septal damage disrupts eyeblink conditioning, is it a result of the GABAergic or cholinergic neurons alone or is total medial septal damaged needed before impairment is seen. The current study examined the effect of GABAergic and cholinergic medial septal lesions on the classically conditioned eye-blink response. Adult male Sprague Dawley rats with GABAergic medial septal/diagonal band (MS/DB) lesions will be compared to those with a sham surgery and those with a cholinergic MSDB lesion. . Two weeks after lesion surgery, all animals were implanted with stimulating and recording electrodes in the periorbital muscle. Two to three

days after surgery all animals received three consecutive days of delay eyeblink conditioning that consisted of 100 trials each day with an average intertrial interval (ITI) of 30 seconds. All trials consisted of a 500ms tone (CS) which co-terminated with a 10ms, 10mV periorbital stimulation (US). Our preliminary results show that both the cholinergic and GABAergic lesion groups impaired acquisition as compared to the sham-lesioned group. However, after three days of training all three groups reached the same asymptotic performance. Combined cholinergic and GABAergic lesions during the conditioned eyeblink response will also be examined.

P20. Physical activity and eyeblink classical conditioning in Wistar and Spontaneously Hypertensive rats

John T. Green, Montana Burns, Claire E. Bollinger, and Kira M. Schachinger (University of Vermont)

We examined the effects of two forms of physical activity on eyeblink conditioning in Wistar rats and in spontaneously hypertensive rats (SHRs), which have been proposed as an animal model of attention-deficit/hyperactivity disorder. In Experiment 1, exercising Wistars and SHRs were given 17 days of free access to a running wheel in their home cage prior to eyeblink conditioning. Sedentary control rats were housed in standard cages. Subsequently, all four groups underwent 750-ms delay eyeblink conditioning. Preliminary results revealed a trend for a faster rate of conditioning in exercising SHRs compared to sedentary SHRs and a trend for a greater asymptote of conditioning in exercising Wistars compared to sedentary Wistars. These effects may be due to the well-documented induction of hippocampal plasticity by exercise. In addition, as we have shown previously, SHRs showed shorter conditioned response (CR) onset latencies compared to Wistars, regardless of condition. In Experiment 2, acrobatic training Wistars and SHRs were given 15 days of motor skill training on an elevated obstacle course prior to eyeblink conditioning. Motor control rats underwent 15 days of running in an open field. Subsequent eyeblink conditioning was identical to Experiment 1. Preliminary results revealed no difference in percentage of CRs between acrobatic training SHRs and motor control SHRs or between acrobatic training Wistars and motor control Wistars. As in Experiment 1, SHRs showed shorter CR onset latencies compared to Wistars, regardless of condition. The well-documented cerebellar cortical plasticity induced by acrobatic training, at least as it was conducted here, may not influence the plasticity in the deep cerebellar nuclei that underlies eyeblink conditioning.

P21. Voluntary Exercise Enhances Learning And Consolidation But Not The Retrieval Of Cued Conditioned Fear In Mice.

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Exercise is associated with improved cognitive function in humans as well as improved learning across a range of learning tasks in rodents, including Pavlovian conditioned fear. We have shown, for example, that two weeks of voluntary exercise prior to tone and foot-shock pairings improves cued Pavlovian fear conditioning. However, in this experiment, as in most, exercise was initiated prior to conditioning and was continued through to testing for conditioned fear. Thus it was difficult to determine whether voluntary exercise improved the learning, consolidation or retrieval of conditioned fear. In an effort to isolate which of these processes were modulated by exercise, we ran experiments in which two weeks of voluntary exercise was restricted to time periods that would most likely affect learning, consolidation or retrieval of conditioned fear. Groups of exercising or sedentary mice were given 5 tone and foot-shock conditioning trials. Access to a running wheel was introduced either during the two weeks prior to fear conditioning, the 2 weeks immediately after fear conditioning (consolidation period) or 2 weeks after fear conditioning. In all groups conditioned fear was assessed after the two week exercise period using the

fear-potentiated startle procedure. Compared to sedentary mice, mice that exercised either prior to fear conditioning or immediately after fear conditioning showed enhanced conditioned fear. Fear conditioning was not enhanced in mice that began exercising 2 weeks after fear conditioning. These results suggest that exercise improves the learning and consolidation of fear memory but does not improve the retrieval or performance of conditioned fear.

P22. Anxiety vulnerability modulates learning in humans: The effect of trait anxiety on classical eyeblink conditioning

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Trait anxiety is a risk factor for the development of anxiety disorders, characterized by fearful responses to stressors and enhanced sensitivity to threat over various situations and for extended periods of time. Individuals with high trait anxiety demonstrate enhanced attention to, and processing of, fear- and threat-related stimuli. In addition, early work by Spence and colleagues revealed that high anxious subjects demonstrate faster conditioned response acquisition compared to low anxious subjects in classical eyeblink conditioning tasks. Considering the results of Spence's work, the progression from anxiety vulnerability to clinical anxiety may result from enhanced defensive learning and reactivity toward neutral or negative environmental cues, rather than to fear or threat stimuli exclusively. As avoidance is also central to anxiety psychopathology, it is possible that avoidant responses, or responses resulting in avoidance of an outcome, might likewise be enhanced. Therefore, the present study assessed associative learning as a function of anxiety vulnerability using classical conditioning of the eyeblink response in two paradigms: delay and omission. Participants first completed the Spielberger State/Trait Anxiety Inventory (STAI) as well as the adult and retrospective measures of behavioural inhibition (AMBI and RMBI, respectively). Acquisition was then measured in either a delay or an omission eyeblink conditioning paradigm. The delay paradigm consisted of 60 paired CS/US trials (500-ms, 1000-Hz tone conditioned stimulus (CS) co-terminating with a 50-ms, 5-psi airpuff unconditioned stimulus (US)), while the omission paradigm was identical to the delay paradigm, except that the emission of a conditioned response (CR) by the participant resulted in the US being omitted for that trial. Analysis of the data revealed that individuals with high trait anxiety had significantly faster CR acquisition than those with low or moderate levels of trait anxiety in the delay conditioning paradigm, recapitulating Spence's early work. Additionally, behavioral inhibition was similarly associated with facilitated acquisition in the delay conditioning task. The 'omission' paradigm did not result in distinguishing between anxiety vulnerable and non-vulnerable individuals with respect to CR acquisition. The results indicate that anxiety vulnerability is associated with faster associative learning in a delay conditioning task, although these phenotypes do not seem to be sensitive to US omission in this particular paradigm. In summary, there is a requisite need to identify how the learning capacity associated with anxiety vulnerability translates into frank psychopathology.

P23. Chronic stress increases PACAP/PAC1 receptor signaling in the bed nucleus of the stria terminalis (BNST) and facilitates anxiety-like behavior.

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The anterolateral bed nucleus of the stria terminalis (BNST) has been argued to mediate anxiety-like

responding to threatening and stressful stimuli. These stimuli activate the BNST, which coordinates many stress-related endocrine, autonomic and behavioral responses. Maladaptive BNST responding has been suggested to underlie some human anxiety disorders, and chronic stress has been shown to increase BNST neuroplasticity. Pituitary adenylate cyclase activating polypeptide (PACAP) and its cognate PAC1 receptor enhance neuronal excitability and neuroplasticity, and have been identified in stress-associated areas like the BNST. In order to determine whether chronic stress alters BNST PACAP expression, rats were exposed to a 7-day chronic variate stress paradigm prior to brain dissection and quantitative RT-PCR processing. Chronic variate stress selectively increased PACAP transcript levels nearly 10-fold in the anterolateral BNST. PACAP levels in other regions, including subregions of the amygdala, were not different from non-stressed control tissues. Chronic variate stress also increased PACAP immunoreactivity discretely in the oval nucleus of the BNST. The stress-induced increase in BNST PACAP transcripts was associated with a 2-fold increase in BNST PAC1 receptor mRNA expression, and chronic stress also increased anxiety-like behavior. Intra-BNST infusions of PACAP38 also increased anxiety-like behavior (baseline startle responding), and this increase in anxiety-like behavior was still pronounced one week after injection. The effects of inhibiting PACAP signaling on the behavioral consequences of chronic variate stress are currently being explored. These results in aggregate suggest that central PACAP receptor activation mediates some of the behavioral and physiological consequences of chronic stress.

P24. Chronic Variable Stress Enhances Conditional Fear But Also Accelerates Extinction

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Chronic stress alters fear acquisition and extinction. Exposure to a 7d chronic variable stress (CVS) protocol enhances subsequent tone conditioning in female but not male mice. The present experiment was designed to investigate 1) the role of ovarian hormones in the CVS effect and 2) the impact of CVS on extinction. Female mice received either ovariectomy or sham surgery, and then subjected to either CVS (a semi-random presentation of 7 stressors, 2 per d) or control handling for 7 d. Twenty-four h after the final stressor, mice were conditioned with 3 tone-shock pairings. Mice were returned to the conditioning chamber 24h later for a test of context fear. Mice were placed in a novel context 48h after conditioning for a test of tone fear. The tone test consisted of a 2-min baseline and an 8-min tone. Identical tone tests were conducted 1 and 7 d after the initial tone test. The unconditional response was quantified by the burst elicited by the shock, while the conditional response was quantified as the percentage of time spent freezing. The unconditional response was not altered by any experimental manipulation. Replicating prior observations, stress did not alter context fear but enhanced tone fear during the initial tone test. By the final day of tone testing, however, the effect had reversed: Stressed mice demonstrated significantly less tone fear than controls. Ovariectomy failed to alter the impact of CVS on fear conditioning and extinction.

P25. Effect of Scopolamine in contextual learning in an appetitive conditioning procedure

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The effect of muscarinic cholinergic antagonists agents has been widely demonstrated to produce deficits in contextual fear conditioning; but there is little evidence about the role of muscarinic cholinocepotrs in appetitive tasks. Twenty-four male rats were conditioned in an appetitive procedure. Rats were assigned to three groups and groups received either a systemic injection of 0.1 mg/kg scopolamine hydrobromide,

0.1 mg/kg scopolamine methylbromide or saline fifteen minutes before each session of training. During three days rats were exposed to a tone (CS) followed by the presentation of 20% sucrose solution (US) in a given context, (A). One week after training, rats were tested in a counterbalanced manner in the original training context (A) and in a novel context (B) for tone conditioning.

P26. The Role of the Dorsal Hippocampus in Renewal and Spontaneous Recovery of Extinguished Appetitive Learning

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We examined the role of the dorsal hippocampus (DH) in renewal and spontaneous recovery (SR) of extinguished appetitive magazine approach responding in rats. The DH was inactivated by infusing muscimol (a GABAa receptor agonist) before tests for renewal and SR. Subjects in Experiment 1 were trained to associate 2 stimuli with food in 2 contexts (i.e., Ctx 1: S1+, Ctx 2: S2+). Each stimulus was extinguished in the other cue's training context (i.e., Ctx 1: S2-, Ctx 2: S1-). Both cues were then tested in each context (i.e., Ctx 1: S1-, S2-; Ctx 2: S1-, S2-) to produce a within-subject assessment of ABA vs ABB renewal. Both control and muscimol treated rats showed the ABA renewal effect. However, these same subjects, were impaired on a non-matching to place task following DH inactivation. These results suggest that the DH is not involved in the expression of contextually gated conditional learning, at least in an ABA renewal design. Experiment 2, however, showed that SR, another phenomenon that has been interpreted in terms of conditional learning, was disrupted by muscimol infusions. SR has been interpreted as a case of ABC renewal where time cues function as contexts (Bouton, 2004). If this interpretation is correct, it suggests that DH inactivation affects ABC but not ABA renewal, which has been reported in aversive conditioning renewal designs (Corcoran and Maren, 2004; see also Zelikowsky, Pham and Fanselow, 2008). The results from an ABC renewal experiment using discrete context cues will also be reported.

P27. Neuronal Gap Junctions Control Dorsal Hippocampal Contribution to Fear Learning and Memory

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The amygdala-hippocampal network plays a crucial role in the generation of fear learning and memories. In the last decade key studies have demonstrated that such network can emerge from the synchronized firing of local GABAergic interneurons electrically coupled via Cx36 forming gap junctions. While our knowledge about neuronal gap junctions has clearly shed new light for their role in adult brain function, their contribution to fear learning and memory processes currently remains unknown. Using Pavlovian fear conditioning in rats, we found that blockade of gap junctions containing Cx36 in the dorsal hippocampus specifically disrupts the formation of contextual fear memories, accelerate fear extinction to a conditioned stimulus and prevents fear renewal.
The effects on context fear retrieval were corroborated by analyses of neuronal activity using *c-fos* expression as readout. Blocking gap junctions also prevented the benefits of context pre-exposure in an immediate shock deficit paradigm. Furthermore EEG recordings of theta activity within the dorsal hippocampus in freely moving rats revealed that blocking gap junction selectively disrupted type-1 and type-2 theta rhythms.
Our data suggest that gap junctions control dorsal hippocampal network and its resulting contribution to fear learning processes. Gap-junction mediated neuronal transmission might be as critical for the physiology of emotional memories as traditional chemical synapses.

P28. Hypothesized Role of Persistent Firing Neurons in Trace Fear Conditioning

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Transient memory is essential for cognition and behavior. The trace conditioning paradigm has been used to gain insights into the neurobiology of transient memory. Trace conditioning requires a transient representation of the conditional stimulus (CS) to persist during the time interval between the CS offset and the onset of the unconditional stimulus (US). In trace fear conditioning, the trace interval is typically tens of seconds. One emerging theory is that trace fear conditioning is supported by endogenous persistent firing, which was first described in entorhinal cortex (EC) and the lateral nucleus of the amygdala (LA). The sustained depolarization underlying persistent firing is thought to be mediated by a calcium-dependent, non-selective, cation conductance (G_{CAN}). Persistent firing is reliably and completely blocked by flufenamic acid, which is thought to inhibit G_{CAN}. Persistent firing is enabled by activation of muscarinic cholinergic receptors (mAChRs) and is blocked by mAChR antagonists. Three recent findings combine to suggest that persistent-firing neurons in perirhinal cortex (PR) may play a role in trace fear conditioning. First, PR is critically-important for trace but not delay fear conditioning. Second, endogenous persistent firing neurons are prevalent in PR, where the firing durations commonly last tens of seconds to minutes. Third, infusion of PR with a non-selective mAChR antagonist (scopolamine) profoundly impairs trace but not delay conditioning. Since PR is reciprocally and strongly connected to EC and LA, persistent-firing neurons in these three structures may sometimes cooperate in support of a regional memory buffer system.

P29. Hippocampus-independent context-sensitive fear requires the infralimbic cortex

Moriel Zelikowsky & Michael Fanselow (UCLA)

Mammals will invariably learn to fear an environment in which they have experienced an aversive event, so long as they have a good representation of that place. Environments or "contexts" may also set the occasion for a particular discrete cue to signal the presence or absence of an aversive event, as is the case after fear extinction. These "context-sensitive" forms of fear learning involve – to varying degrees – the dorsal hippocampus (DH), and fear extinction, in particular, involves the infralimbic cortex (IL). We investigated the respective and combined roles of the DH and IL in contextual fear and fear renewal after extinction. Rats underwent tone fear conditioning in one environment, "A". In Experiment 1, rats were then extinguished in a different environment "B" and tested for tone fear back in context "A" ("ABA" renewal and "AAA" controls). In Experiment 2, following acquisition, animals were simply tested for context fear in the "dangerous" environment ("A"), or in a completely "novel" environment ("B"). Animals received pre-training or post-extinction lesions of the DH, IL or both DH+IL. DH-lesioned animals demonstrated both context fear and "early" fear renewal – however, "late" or sustained renewal was attenuated. Conversely, IL lesions result in completely exaggerated levels of fear expression in either the extinction, non-extinction or "novel" environment. These data suggest that the IL cortex may be important for inhibiting, and the DH may be important for sustaining, context-sensitive fear. Interestingly, combined DH+IL lesions result in a complete loss of both fear recovery after extinction and context fear, suggesting that in the absence of the DH an animal uses its IL cortex to learn about an environment, and that an IL-DH circuit is vital for context-sensitive fear. Immunohistochemistry analyses looking at cfos expression in these regions were also performed.

P30. Dorsomedial prefrontal cortex contributes to blocking of fear learning

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There is a growing body of literature indicating that the medial prefrontal cortex (mPFC) is involved in emotional learning. Specifically, it has been suggested that the dorsal (anterior cingulate [AC] and prelimbic [PL]) and ventral (infralimbic [IL]) sub-divisions of the mPFC are critical for the expression and extinction of learned fear respectively. However, the exact function of the dmPFC in fear conditioning remains unclear. We used c-Fos immunohistochemistry and temporary inactivation techniques to examine the involvement of the dmPFC in predictive fear learning. During training rats in the expected group received multiple tone-shock pairings. Rats in the unexpected group were simply placed into the conditioning chamber for the same duration. At test, both groups received two tone-shock pairings. A control group received tone-alone presentations during both training and test. Two hours after test rats were perfused and the brains were processed for c-Fos, a marker of neuronal activity. Results demonstrated that animals in the unexpected group had significantly more c-Fos immunoreactive neurons in the dmPFC than rats in both the expected and control groups. This finding suggests rat dmPFC may be important in detecting and/or learning about the surprising conditioning trial. To further examine this possibility, the dmPFC was temporarily inactivated via infusion of baclofen/muscimol bilaterally prior to Stage II training in a within-subjects blocking design. dmPFC inactivation prevented the occurrence of blocking and had no effect on learning about a control (non-blocked) stimulus. Collectively these results provide converging lines of evidence for a role of dmPFC in determining the actions of prediction error on fear learning.

P31. A neurocomputational model of dopamine and prefrontalstriatal interactions during multi-cue category learning by Parkinson's patients

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Most existing models of dopamine and learning in Parkinson’s disease (PD) focus on simulating the role of basal ganglia dopamine in reinforcement learning. Much data argue, however, for a critical role for prefrontal cortex (PFC) dopamine in stimulus selection in attentional learning. Here, we present a new computational model that simulates performance in multi-cue category learning, such as the "weather prediction" task. The model addresses how PD and dopamine medications affect stimulus selection processes, which mediate reinforcement learning. In this model, PFC dopamine is key for attentional learning, while basal ganglia dopamine, consistent with other models, is key for reinforcement and motor learning. The model assumes that competitive dynamics among PFC neurons is the neural mechanism underlying stimulus selection with limited attentional resources, whereas competitive dynamics among striatal neurons is the neural mechanism underlying action selection. According to our model, PD is associated with decreased phasic and tonic dopamine levels in both the PFC and basal ganglia. We assume that dopamine medications increase dopamine levels in both the basal ganglia and PFC, which, in turn, increase tonic dopamine levels but decrease the magnitude of phasic dopamine signaling in these brain structures. Increase of tonic dopamine levels in the simulated PFC enhances attentional shifting performance. The model provides a mechanistic account for several phenomena, including (a) medicated PD patients are more impaired at multi-cue probabilistic category learning than unmedicated patients and (b) medicated PD patients opt out of reversal when there are alternative and redundant cue dimensions.

P32. Effects of extinction on classical conditioning and conditioning-specific reflex modification of rabbit heart rate

Lauren B. Burhans, Carrie Smith-Bell and Bernard G. Schreurs

Understanding mechanisms of fear extinction is important for treating fear- and stress- related disorders, particularly post-traumatic stress disorder (PTSD). Rabbit heart rate (HR) conditioning is an established model of fear conditioning yet little is known about extinction procedures other than repeated CS alone presentations. We examined the effects of CS alone, US alone, unpaired CS/US presentations, continued CS-US pairings, or no further stimulation following HR conditioning. We have shown previously that rabbit HR to the US can change dramatically as a function of learning when measured in the absence of the CS – conditioning-specific reflex modification (CRM). During HR CRM, reflexive HR responses to the US following conditioning exhibit dramatic deceleration that is reminiscent of the CR. The following study also examined effects of extinction treatments on CRM. Important findings were: (1) heart rate CRs were extinguished by CS alone and unpaired CS/US presentations – treatments successful in other fear conditioning models; (2) CRM diminished over time even without extinction treatments, indicating that extinction of HR CRs was not required for extinction of HR CRM; (3) a subset of rabbits receiving unpaired extinction continued to show robust CRM, suggesting a unique consequence of switching from paired to unpaired presentations in a select population. Taken together, the findings elucidate the parameters of HR extinction, the transient nature of HR CRM, and show that HR CRM is not simply a CR that has generalized from the CS to the US.

P33. Distribution and Characterization of Premotor Interpositus Neurons After Pseudo Rabies Virus Injections into *Orbicularis Oculi* Muscle of the Rabbit

Jimena Gonzalez-Joekes and Bernard G. Schreurs

Evidence suggests the Interpositus nucleus (IP) is important for the formation and expression of conditioned eyelid responses. Although there is some understanding of IP physiology and anatomy, our knowledge of the nature and involvement of different cells types in rabbit eye blink conditioning is limited. To explore the cells in the IP and their connectivity, we used PRV-152 (attenuated pseudo rabies virus) injections to retrogradely label neurons that project to the eyelid. PRV is a swine herpes virus that is transported retrogradely and acts as a trans-synaptic tracer that can label circuits. We injected PRV into each rabbit's eyelid and allowed the virus to replicate and spread retrogradely for three, four, or five days. We saw PRV antibody labeling in the ipsilateral facial nucleus and scant labeling in the contralateral red nucleus after three days. After four days, the red nucleus was more extensively labeled and sparse labeling of large excitatory neurons was seen in ipsilateral IP. By day five, numerous cells in ipsilateral IP were labeled and a few labeled cells were seen in contralateral IP. At this time we also found different classes of IP neurons labeled with PRV. A subset of smaller PRV-labeled neurons showed excitatory and inhibitory markers, suggesting these cells co-express GABA and glutamate and are synaptically connected to principal IP neurons. Taken together, these data begin to show the distribution and organization of IP neurons and to characterize cells in the premotor network involved in the eye blink.

P34. High dietary cholesterol modulates the excitability of rabbit hippocampal pyramidal neurons

Desheng Wang and Bernard G. Schreurs

Previous work has shown that high dietary cholesterol can affect learning and memory including rabbit eyeblink conditioning and this effect may be due to increased membrane cholesterol and enhanced production of amyloid beta in the hippocampus. These effects have included enhanced levels of

conditioning in the absence of beta amyloid plaques. The aim of this study was to investigate whether high dietary cholesterol could modulate the membrane properties of rabbit hippocampal pyramidal neurons – cells that have previously been shown to be involved in rabbit eyeblink conditioning. When compared to data from rabbits fed normal chow, whole-cell current clamp recordings in hippocampal CA1 pyramidal neurons from rabbits fed 2% cholesterol for 8 weeks revealed a number of significant differences. There was a significant decrease in the amplitude of action potential after-hyperpolarizations (1.76 ± 1.43mV vs 6.0 ± 1.39mV, $p < 0.05$) suggestive of increased excitability and a measure previously used to index higher levels of conditioning. However, there was also a reduction in the half-width of action potentials (1.66 ± 0.06 ms vs 1.93 ± 0.07 ms, $p < 0.05$) and an increased threshold for evoked action potential firing (0.31 ± 0.05 nA vs 0.13 ± 0.02nA, $p < 0.05$), both suggestive of a decrease in excitability. This is the first demonstration of dietary cholesterol-induced changes in membrane properties of rabbit hippocampal pyramidal neurons particularly membrane excitability, which may mediate the behavioral effects of dietary cholesterol on rabbit eyeblink conditioning.

P35. Proteasome-dependent protein degradation is critical for long-term memory formation in the amygdala.

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While there is abundant research demonstrating that protein synthesis is important for the formation of Pavlovian fear memories (Helmstetter et al., 2008), there is little evidence examining the role of protein destruction in this process. In the present study, we quantified the rate of ubiquitin-proteasome mediated protein degradation following the acquisition of auditory and context fear memories using an immobilized S5a fusion protein. Results indicated that protein degradation is rapidly enhanced in the amygdala following acquisition, where it peaks at 1-hr and is maintained for at least 2-hrs. Similar results were found in the dorsal hippocampus and auditory thalamus. Further experiments revealed that this increase of proteasome-dependent degradation within the amygdala occurs specifically in response to CS-UCS learning and returns to basal levels within 6-hrs. Interestingly, this pattern mirrors that of protein translation as indicated by the phosphorylation of P70S6 kinase. This increase in protein degradation was critical for the consolidation of both fear memories, as a proteasome inhibitor produced long-term memory impairments similar to that of the protein synthesis inhibitor anisomycin and simultaneous blockade of protein degradation and synthesis did not rescue these deficits as has been suggested in hippocampal LTP (Fonseca et al., 2006). Additionally, we found that protein degradation was transiently increased in the amygdala following auditory fear memory retrieval, suggesting that it may underlie the protein synthesis requirement in the reconsolidation process (Lee et al., 2008). These results indicate that proteasome-dependent protein degradation is a major regulator of long-term memory formation and stability at amygdala synapses.

P36. What does the retrosplenial cortex do? Insights from associative learning

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The retrosplenial cortex (RSP) provides a major source of cortical input to the postrhinal cortex (POR) and medial entorhinal cortex, which in turn project to the hippocampus. Yet, little is known about the unique contributions of RSP to medial temporal lobe-dependent memory despite evidence for a close functional and anatomical relationship between the hippocampus and RSP. To fill this gap in the literature, a recent series of studies in our laboratory has focused on elucidating the role of RSP in

associative learning. Our previous findings provide strong evidence that RSP, like POR, plays a critical role in contextual learning, which involves the integration of numerous static stimuli in the training environment. Consistent with our hypothesis that RSP has a particularly important role in processing co-occurring stimuli, we also found that damage to RSP impairs the ability to learn a conditional discrimination involving a light and tone that co-occur, manifest as impaired learning on both tone-alone reinforced trials and light+tone nonreinforced trials (compound feature negative discrimination, CFND). Experiment 1 in the present study examined the hypothesis that RSP damage would affect even simple forms of learning in which a compound stimulus (light+tone) was paired with food reward. Contrary to this hypothesis, RSP damage did not impact simple compound conditioning. However, an extinction test suggested that both lesioned and control rats solved the task primarily using one stimulus (i.e., the tone). Thus, in Experiment 2, we examined the effect of damage to RSP in a conditional discrimination similar to the previously-used CFND task, except that the trial outcomes were reversed such that tone-alone trials were now non-reinforced and the compound light+tone presentations were reinforced (ie, compound feature positive discrimination, CFPD). In contrast to the deficits exhibited in the CFND task, preliminary results suggest that rats with damage to RSP can successfully learn the CFPD task. These results suggest that RSP may contribute to the flexible use of stimulus associations or the formation of multiple associations for individual stimuli occurring together. A third experiment is underway involving another conditional discrimination using serial presentations of stimuli as opposed to compound stimulus presentations, in which we expect to find deficits similar to those found in the CFND task. Such an outcome would support the involvement of RSP in forming stimulus associations.

P37. Contributions of the rodent medial prefrontal cortex to negative occasion setting

Jill E. MacLeod & David J. Bucci (Dartmouth College)

The medial prefrontal cortex of rats has a role in many aspects of cognitive function, including forms of inhibitory learning. Recent research has revealed heterogeneous functions of the prelimbic (PL) and infralimbic (IL) regions of the medial prefrontal cortex in response inhibition. We tested the effects of separate neurotoxic lesions of the PL or IL in a serial feature negative discrimination paradigm (negative occasion setting). Rats received training sessions consisting of 16 trials: on 4 trials in each session, a tone was presented and followed by food reward; on the other 12 trials, the tone was preceded by a visual stimulus and not reinforced. Our results indicate that PL but not IL is necessary for learning the discrimination. Next we investigated the effects of these lesions on rats that were first extensively trained in this task. We found that rats that had been trained for 30 days prior to receiving PL or IL lesions were still able to perform the task as well as controls. We conclude that PL lesions disrupt acquisition but not performance of a serial feature negative discrimination.

P38. Learning-related modulation of unconditioned fMRI signal responses during Pavlovian fear conditioning

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The present study investigated human brain activation produced by unconditioned stimulus (UCS) presentations to determine the neural mechanisms that modulate unconditioned response (UCR) expression. Healthy volunteers participated in a conditioning study in which skin conductance response (SCR) and UCS expectancy were measured concurrently with functional magnetic resonance imaging (fMRI). Volunteers were exposed to a two tone discrimination procedure in which one tone (CS+) predicted a loud (100dB) white noise UCS, and the second tone (CS-) was presented alone during the

acquisition phase of the study. During a test phase, participants received UCS presentations that coterminated with the CS+ and CS-, as well as presentations of the UCS alone. UCRs within the medial and dorsolateral prefrontal cortex (PFC) were reduced when the UCS followed the CS+ compared to when it followed the CS- or UCS alone. These findings demonstrate diminution of the UCR within the medial and dorsolateral PFC, and suggest that learning-related changes within these brain regions may modulate UCR expression during Pavlovian fear conditioning.

P39. Oculomotor Learning and Conditioned Inhibition

Stephan König & Harald Lachnit

When participants saccade to a target in the visual periphery the trajectory of their eye movement typically does not follow a straight line but shows some curvature instead. If, for example, a participant is instructed to (1) perform a saccade to a visual target straight up from a central fixation point and at the same time to (2) ignore a visual distractor stimulus that is simultaneously presented to the left or right, the eye movement trajectory typically deviates away from the distractor location. In models of saccadic target selection inhibitory mechanisms have been included to account for deviation away: the motor map encoding saccades receives top-down inhibition at the distractor location because the participant is instructed to ignore (i.e. not to look at) the lateral distractor.
In an oculomotor conditioning paradigm we examined how saccadic curvature corresponds with the concept of conditioned inhibition. We used the standard paradigm of conditioned inhibition in which two central cues A and AX predicted two different peripheral target locations (left or right). At the end of training the central cues elicited differential anticipatory eye movements to the trained target locations. According to the Rescorla-Wagner model training of A+left, AX+right should lead to an inhibitory association between cue X and the left target position. In subsequent test trials with AX and X we analyzed how saccadic curvature is affected by inhibitory properties of X.

P40. A Medial Hypothalamus to Paraventricular thalamus pathway is associated with extinction of reward seeking

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We used an ABB model of contextual control over extinction to investigate the neural mechanism of extinction. Previous studies using lesions have identified paraventricular thalamus (PVT) as a critical structure in ABA renewal of alcohol seeking. We investigated the hypothalamic control over expression of extinction, and characterised a hypothalamic to PVT pathway recruited during test in the extinction context (ABB). To do this, we combined retrograde neuronal tract-tracing with Cholera Toxin subunit B (CTb) from PVT with the activation marker c-Fos. A separate experiment involved infusions of the neuropeptide CART into medial hypothalamus (MH). Prior to training rats received microinjections of CTb into PVT. A separate group of rats were implanted with bilateral guide cannula directed towards MH. After recovery rats were trained to respond for 4% beer in one context (A) and then extinguished in a different context (B). In the retrograde tracing experiment, three groups of rats were tested in either context A (ABA), B (ABB), or not tested (AB0), and then perfused 1 hour after test. In the MH infusion experiments, rats received infusions of either CART (2.5µg/side) or vehicle in an extinction test. The retrograde tracing experiments revealed a significant increase in the percentage of MH CTb-IR cells expressing c-Fos in ABB rats compared to both ABA and AB0. Infusion of CART into MH reinstated extinguished responding in the extinction context B compared to vehicle. These experiments provide the

first evidence for a role of the hypothalamus, and a MH to PVT pathway, in mediating extinction of reward seeking.

P41. Selective amygdala lesions facilitate acquisition of signaled leverpress avoidance in Wistar Kyoto and Sprague Dawley rats.

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Servatius et al. (*Behav. Brain Res*., 2008) demonstated that inbred Wistar Kyoto (WKY) rats acquired signaled avoidance responding more rapidly and were resistant to extinction compared to Sprague Dawley (SD) rats. Muscimol infusion into the central amygdalar region early in training retarded acquisition of signaled avoidance in both WKY and SD rats (Miller et al., *Pavlovian Society Abstracts*, 2008). To further delineate the role of the amygdala in avoidance learning between the two strains, we made large selective neurotoxic lesions in both the central and basolateral amygdala prior to nine days of signaled leverpress avoidance conditioning. In contrast to our central amygdala inactivation results, both WKY and SD rats showed more rapid acquisition of avoidance learning following amygdalar lesions. Specifically, sham WKY rats acquired avoidance responding more rapidly than sham SD rats, and amygdala lesioned SD rats appeared to acquire avoidance responding at an accelerated rate that was similar to WKY shams. Amygdala lesioned WKY rats appeared to have the fastest rate of avoidance acquisition overall. It has been suggested that the basolateral amygdala encodes sensory specific emotional events while the central amygdala encodes general affective significance in parallel with each other (Balleine and Killcross, *TRENDS in Neurosci*, 2006). Our present findings suggest that disrupting both of these systems allows other brain areas to more quickly establish associations critical for avoidance responding. Perhaps one of the basic differences that allows WKY rats to acquire avoidance responding more quickly than outbred strains is an inherant decrease in the functioning of both of these amygdalar systems.

P42. NMDA receptors in the basolateral amygdala are critical for the acquisition and extinction, but not consolidation, of second-order fear.

Shauna L. Parkes and R. F. Westbrook

Activation of *N*-methyl-D-aspartic acid receptors (NMDAr) in the basolateral complex of the amygdala (BLA) is necessary for the acquisition of fear responses to a stimulus (e.g., noise) which signals aversive stimulation (e.g., foot shock) and for the extinction of these responses when the auditory conditioned stimulus (CS) is presented in the absence of the foot shock unconditioned stimulus (US). The present experiments examined whether NMDAr activation is also necessary for the acquisition of fear responses to a stimulus (a light) which signals the dangerous noise and the extinction of these responses when the second-order conditioned light is presented in the absence of the first-order conditioned noise. In Experiment 1, rats received second-order conditioning under ifenprodil, a NR2B subunit selective NMDAr antagonist, or vehicle. Ifenprodil disrupted the acquisition of second-order fear responses. Activation of NMDAr was not necessary for consolidation of the second-order association as infusion of ifenprodil after second-order conditioning spared fear responding on test. However, BLA neuronal activity was required for consolidation as infusion of the $GABA_A$ agonist, muscimol, after second-order conditioning reduced fear responses on test. In Experiment 2, rats were extinguished to the second-order CS under ifenprodil or vehicle. Ifenprodil disrupted extinction of second-order fear responses. The present

results show that NMDAr activation is critical for acquisition of second-order conditioned fear and for the inhibition of this fear across extinction. Consolidation of second-order fear requires neuronal activity in the BLA but not NMDAr activation. These results parallel those obtained for acquisition and extinction of first-order conditioned fear.

P43. Neural correlates of objects and places in rodent postrhinal cortex during a visual object discrimination task.

Sharon C. Furtak and Rebecca D. Burwell

Previous research indicates that the rodent postrhinal cortex (POR) is involved in object recognition tasks when the spatial location or spatial arrangement of the object(s) is important for successful completion of the task. Based on these findings, we hypothesize that the firing properties of POR neurons may reflect the integration of an object's identity with its spatial location. To test this hypothesis, single units were recorded from the POR of Long-Evan rats while they performed a visual object discrimination task on two randomly-interleaved pairs of stimuli. Two-dimensional visual objects were displayed on the floor of a behavioral chamber by rear projection via a standard LCD projector. Visual objects consisted of varied patterns within equal-sized circles. Among stimulus pairs, the total area of black and the total area of white within the patterns were equivalent. Presentations rotated between two locations, such that each stimulus appeared in four spatial locations. Due to the high level of accuracy (75-80%) on the task, only correct trials were analyzed. The firing rate of well-isolated units was compared between baseline (spontaneous) activity during the intertrial interval and the 2 second period following the stimulus choice (outcome phase). Several POR units displayed a significant change in firing rate during the outcome phase of the task. Of those, several patterns were observed. For example, a number of POR single units increased firing rate when the correct stimulus was in a particular location. Preliminary findings suggest that POR neurons encode representations that link objects and places.

P44. Fibroblast Growth Factor-2 enhances long-term extinction of conditioned fear and reduces renewal in rats

Bronwyn M Graham & Rick Richardson

Fibroblast Growth Factor-2 (FGF2) is a potent mitogen that regulates brain development and adulthood neurogenesis. We recently proposed that FGF2 also regulates neural plasticity underlying long-term memory, and demonstrated that acute systemic administration of FGF2 enhances contextual fear conditioning and extinction of conditioned fear in rats (Graham & Richardson, 2009a, 2009b). The latter study also demonstrated that FGF2 significantly reduces stress-precipitated relapse following extinction (i.e., reinstatement). This series of experiments examined the effect of FGF2 on renewal, which refers to the recovery of fear to an extinguished cue when it is presented in a different context to that in which extinction training occurred (Bouton & Bolles 1979). It is possible that FGF2 enhances extinction by facilitating memory for the extinction context, making it a better retrieval cue for the extinction memory. If so, then FGF2-treated rats should show renewal of fear when tested in a different context. Experiment 1 replicated the finding that post-extinction training FGF2 administration enhances extinction, and furthermore, demonstrated that FGF2 must be administered at a dose of no less than 20ng/gm of body weight in order to be effective. Unexpectedly, Experiment 2 demonstrated that FGF2 significantly reduced renewal, even when vehicle rats were given double the amount of extinction to equate the "strength" of the extinction memory in FGF2 and vehicle-treated rats. These results suggest that FGF2 does not facilitate extinction by improving the inhibitory control of the context. Rather, they suggest that FGF2 changes the quality of the extinction memory, reducing its susceptibility to relapse.

P45. Activation of medial septal neurons in changing navigation strategies

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Ability to accurately navigate through space is known to require a functioning hippocampus. The medial septum/diagonal band of Broca (MSDB) provides a major input to the hippocampus with the primary projection from cholinergic and GABAergic neurons. While non-selective MSDB lesions impair spatial learning and memory, selective cholinergic or GABAergic lesions of the MSDB result in mild or no impairments. Recently we have reported that selective lesions of MSDB GABAergic neurons, but not the cholinergic neurons, impaired performance in a delayed non-match to position task. We speculated that this impairment was due to increased proactive interference. In the present study, we investigated whether switching between different spatial strategies activates different types of MSDB neurons.
Male Sprague Dawley rats were initially trained on an allocentric spatial task in a plus maze. For each trial, rats were randomly started from either the North or the South arm and the opposite arm was blocked to make a T-maze. During this stage, only the West arm was rewarded with food. Upon reaching the criteria animals were matched based on their performance, randomly assigned to one of the three groups, and run in a single test session (stage 2). In the first group, the goal arm remained the same and animals continued to receive reinforcement in the West arm (No Shift). The second group was reinforced for entering the East arm (Spatial Reversal). The third group was reinforced for making a left or right turn (Strategy Shift to Egocentric responding) regardless of the starting position. Ninety minutes after the end of the session, animals were sacrificed and perfused. Brain sections were prepared for immunocytochemical detection of parvalbumin and choline-acetyltransferase (for identification of GABAergic and cholinergic septohippocampal neurons respectively) as well as c-Fos immunoreactivity (to localize the activated neurons).
The preliminary data shows that performance during second stage was best for the No Shift group (95.7% correct, n=3) followed by the Spatial Reversal group (66.7% correct, n=3) and the Strategy Shift group (33.3% correct, n=3). The No Shift group had the lowest number of c-Fos immunoreactive MSDB neurons (28136 ± 2144) compared to the Spatial Reversal group (37596 ± 2787) and the Strategy Shift group (48768 ± 6573). The number of MSDB cholinergic cells was the lowest for the No Shift group (8,464 ± 495) and was similar for the Spatial Reversal (10336 ± 740) and the Strategy Shift group (10176 ± 804). The number of activated choline-acetyltransferase immunoreactive MSDB neurons (ChAT and c-Fos double labeled) was 1160 ± 242 for the No Shift group, 1240 ± 147 for the Spatial Reversal group, and 1640 ± 376 for the Strategy Shift group. The No Shift group had the lowest number of GABAergic MSDB neurons (3040 ± 79) compared to Spatial Reversal group (5000 ± 498) and the Strategy Shift group (3685 ± 188). The number of activated parvalbumin immunoreactive MSDB neurons (PV and c-Fos double labeled) was also the lowest in the No Shift group (208 ± 40cells) followed by the Spatial Reversal group (360 ± 60) and Strategy Shift group (416 ± 188). The preliminary results suggest that activation of septohippocampal neurons was enhanced most during shifts in navigation strategies and least during no strategy shifting. Future work will increase the number of animals in the analysis and further investigate the types of MSDB neurons activated during switching between different spatial strategies.

P46. Comparing the effect of histone deacetylase inhibitors on conditioning, extinction and recently retrieved memories

James M. Stafford & K. Matthew Lattal

Recent research indicates that histone deacetylase (HDAC) inhibition can enhance conditioning, extinction and recently retrieved conditioned fear memories. Few studies have directly compared the effects of pharmacologically enhancing new memory formation (e.g., conditioning) to enhancements in memories that follow retrieval (e.g., extinction, reactivation). This study attempted to compare these effects by closely matching the experiences of mice receiving HDAC inhibition during the initial formation or retrieval of contextual fear memories. Two groups received equal exposures to a conditioning context (CTX) over two days. On the second day, mice received subcutaneous HDAC inhibitor injections combined with either a context-shock trial (Conditioning group) or a memory retrieval trial (Retrieval group). Memory for the context-shock association was tested 1 and/or 14 d after the drug injections. When the HDAC inhibitor was given immediately prior to or after initial contextual fear conditioning no memory enhancement was seen during testing 1 and 14 d later. In contrast, HDAC inhibitor treatment both prior to and immediately after the memory retrieval session enhanced fear extinction during testing 1 d later. When tested 14 d later, systemic HDAC inhibitor treatment resulted in persistent enhancements in extinction only when mice were given pre-session HDAC inhibitor treatment and repeated testing. However, this persistent effect was complicated by drug-induced differences during the extinction session and by the effects of repeated testing. Overall, these experiments demonstrate that when experiences are matched, HDAC inhibition has greater effects on extinction and retrieval than it does on initial conditioning memory formation. Theoretical and translational implications of these results will be presented.

P47. Prenatal Choline does not Protect Against the Context Conditioning Deficits Induced by Neonatal Alcohol Exposure in the Juvenile Rat.

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Choline supplementation over postnatal days (PD) 4-20 protects against neonatal (PD4-9) ethanol-induced deficits in trace fear conditioning in juvenile rats(Wagner & Hunt, 2006, Behav Neurosci, 120, 482-7), while prenatal choline (gestational day [GD] 12-17) protects against acute NMDA antagonist-induced neurotoxicity in adolescent female rats (Guo-Ross, et al., 2002, J Neurosci, 22, RC195). Neonatal alcohol exposure disrupts the context preexposure facilitation effect (CPFE), a variant of context conditioning in which context exposure and (immediate) shock occur on separate occasions (Murawski & Stanton, submitted). We examined possible prophylactic effects of prenatal choline on this effect of neonatal alcohol exposure. Pregnant Long-Evans dams were given water supplemented with either 25 mM choline chloride + 50 mM saccharin or only saccharin over GD12-17. Offspring of treated dams were left undisturbed (UD), exposed to 5.25 g/kg/day of alcohol (EtOH), or sham intubated (SI) over PD4-9. UD and SI rats preexposed to the testing context on PD31 24h prior to immediate shock showed the CPFE, while controls preexposed to an alternate context showed an immediate shock deficit (ISD). All EtOH rats, regardless of preexposure, showed the ISD. Prenatal supplementation with choline or control did not affect conditioning in any group. These results demonstrate that neonatal ethanol exposure disrupts the CPFE, while prenatal choline treatment is ineffective in ameliorating these ethanol-induced deficits. [Supported by AA014288-01]

P48. Ontogeny and Neural Substrates of the Context Preexposure Facilitation Effect

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Contextual fear conditioning emerges around post-natal day (PND) 23 in the rat. This is thought to reflect maturation of a hippocampus-dependent configural associative system (CAS), which mediates the conjugation of the individual feature representations of the context into a unified conjunctive representation, which can then be associated with the reinforcer (Fanselow, 2000). However, context conditioning can also be supported by a hippocampus-independent, feature-based simple associative system (SAS) and this could operate on PND23-24 (Pugh & Rudy, 1996). To address this issue, we studied the ontogeny of a variant of contextual fear conditioning, termed the context-preexposure-facilitation-effect (CPFE), in which exposure to the context and (immediate) foot shock occur on successive occasions. This variant preferentially utilizes the CAS relative to the SAS (Rudy & O'Reilly, 2001). PND17, 24, and 31 rats were tested on the CPFE (Exp. 1); on the CPFE vs. conventional context conditioning (Exp. 2); and on the CPFE with stronger reinforcement (Exp. 3). The CPFE emerged on PND24 regardless of reinforcer strength and in parallel with context conditioning. Infusions of the NMDA antagonist, MK-801, into the dorsal hippocampus on the preexposure day eliminated the CPFE on PND24 (Exp. 4). This is the first conclusive demonstration that the ontogeny of contextual fear conditioning depends on CAS mechanisms and that these involve hippocampal NMDA receptors as early as PND24.

P49. A direct comparison of conditioned responding following US habituation and CS extinction

Andreas Berg Storsve, Gavan P. McNally, & Rick Richardson

The present series of experiments directly compared the effects of US habituation and CS extinction on learned fear. In Experiment 1, US habituation was found to reduce conditioned fear responses to a CS previously paired with that US. We then showed that the reduction in learned fear responses resulting from either US habituation or CS extinction was context specific (i.e., a change in context led to a renewal of the learned fear response; Experiment 2) and, furthermore, was attenuated when a pre-test shock was given (i.e., reinstatement of fear was observed in both cases; Experiment 3). Finally, Experiments 4A and 4B demonstrated that an injection of the NMDA antagonist MK-801 prior to either US habituation or CS extinction impaired long-term retention of the learning that takes place during both of these procedures. Together, these results suggest that the decrement in learned fear responses produced by US habituation and CS extinction is similar, and, furthermore, that current theories may provide an incomplete account of the processes that underlie the inhibition of fear.

P50. Antagonism of the serotonin 6 receptor disrupts the inhibition of fear in rats

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Studies suggest a role for the serotonin 6 receptor in emotional regulation. Here, we tested a highly specific $5HT_6$ receptor antagonist (Ro4368554 supplied by Roche Palo Alto LLC) using AX+, BX- discrimination learning to determine the effect of this receptor on the expression of aversive emotional learning. AX+, BX- discrimination learning is a fear-conditioning paradigm in which cue A, coupled with a foot-shock, comes to elicit fear, and cue B, presented in the absence of foot-shock, becomes a safety signal that inhibits fear. X is an additional cue presented in compound with A or B in order to reduce

unwanted effects like second-order conditioning and external inhibition and preventing a configural strategy to solve the discrimination. Inhibition of fear by B is evident behaviorally in test trials conducted following training in which animals exhibit robust fear-potentiated startle to A alone, little to no fear potentiated startle to B alone and low fear potentiated startle to a novel compound AB(because B inhibits fear elicited by A). Following a three day training period with 5 AX+ and BX- training trials per day, male and female rats were tested for their acoustic startle responses to cue A, cue B and the combination of cues A and B, following intraperitoneal injection of Ro4368554 or vehicle. Antagonism of the $5HT_6$ receptor during testing disrupted the inhibition of fear to the combined AB cue in both sexes. These data suggest that one function of the $5HT_6$ receptor is to actively inhibit the expression of fear.

P51. Positive and Negative Social Signals Elicit Different Firing Patterns in Rat Amygdala

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Rat ultrasonic vocalizations (USVs) are conspecific auditory social signals. Twenty-two kHz USVs and 50 kHz USVs are emitted, respectively, during affectively negative and positive emotional states. The present study examined single-unit responses to these two types of USVs in the lateral nucleus of the amygdala (LA), which is known to be critically-involved in emotional responses. Experimentally-naïve rats were exposed to randomized-presentations of a 22 kHz USV, a 50 kHz USV, and frequency-matched tones. Altogether, 127 well-discriminated units were analyzed. Conventionally, single-unit analysis of LA has focused on the maximum discharge rate in a selected group of neurons that fire with a transient increase in response to the stimulus onset. This is only one of many firing patterns. Here we analyzed the categories of firing patterns using a recently-developed scheme. The majority of units (82%) were significantly responsive to one or more of the stimuli. In addition, there was a significant difference in the proportion of firing patterns elicited by 20 kHz versus 50 kHz sounds (USVs or tones). The most obvious difference was that 22 kHz sounds most often elicited a sustained increase in the firing rate, relative to the baseline firing rate; whereas 50 kHz sounds most commonly elicited a sustained decrease in the firing rate, relative to baseline rate. All four stimuli also elicited other firing patterns. The categories of elicited firing patterns may offer richer insights into the neurophysiology of LA. Supported by NIH grant MH8045 to THB.

Abstracts for Talks:

Lorraine G. Allan, Shepard Siegel, and Samuel D. Hannah, McMaster University – The Fate of the Blocked Stimulus in Contingency Assessment

In studies of contingency assessment a participant is asked to judge the relationship between a cue and an outcome. Contingency assessment research was reinvigorated in the mid-1980s by suggestions that simple associative models could be applied to the contingency assessment situation. One strength of such associative models is that they can explain cue interaction effects, such as blocking. In a short time these cue-interaction effects were reported by contingency assessment researchers. That is, participants minimize the contingency between a target cue (C_T) and outcome if the C_T is presented in compound with a companion cue (C_C) that is highly predictive of the outcome. On the basis of most associative theories, blocking indicates that the participant learns little about a blocked C_T; thus, the blocking seen in contingency assessment typically has been attributed to the participant learning little about the C_T-outcome relationship.

We have suggested that psychophysics (and one psychophysical model in particular, signal detection theory, SDT) can profitably be applied to understanding contingency assessment. We present new findings demonstrating that an analysis of blocking in contingency assessment that incorporates SDT is better than one that does not -- The simultaneous presence of a C_C that is highly predictive of the outcome does not attenuate learning about C_T, but rather alters the participant's criterion for responding. We conclude that a SDT analysis of contingency assessment is not an alternative to associative models. Rather, it inspires an analysis of learning that incorporates psychophysical as well as associative principles

Anthony Dickinson, University of Cambridge -- Actions, Habits and Conflict: Reflections on the Castaway's Dilemma

There is an emerging consensus that instrumental behavior is controlled by two dissociable systems: a goal-directed system through which actions are controlled by representations of their outcomes, and a habitual system in which outcomes function, not as goals, but rather as reinforcers of stimulus-response habits. Within this theoretical framework, a critical issue concerns the factors that determine which of the two systems exerts behavioral control. In this talk I shall consider three factors. The first is developmental in that the capacity for goal-directed action by children does not appear to emerge until the third year of life, possibly due to the maturation of the prefrontal cortex. Secondly, overtraining favors habitual control unless the animal has the opportunity to choose between actions that yield different outcome. Finally, I shall argue that conflict within the goal-directed system can produce regression to habitual control.

Jeansok Kim, University of Washington -- Little Albert (fear conditioning) cells in the amygdala

A fundamental issue in Pavlovian fear conditioning regards the existence and location of neurons in the brain that receive convergent information about the CS and US during the acquisition of conditioned fear memory. Convergent activation of neurons is generally viewed as a key event for fear learning, yet there has been almost no direct evidence of this critical event in the mammalian brain. We employed Arc cellular *c*ompartment *a*nalysis of *t*emporal gene transcription by *f*luorescence *i*n *s*itu *h*ybridization (catFISH) to identify neurons activated during single trial contextual fear conditioning in rats. Analysis yielded clear evidence that a population of basolateral amygdalar neurons receives convergent CS and US information at the time of the learning, that this only occurs when the CS-US arrangement is supportive of the learning, and that this process requires NMDA receptor activation.

K. Matthew Lattal, Oregon Health & Science University – What is enhanced in enhanced extinction effects?

Many recent studies have examined pharmacological manipulations that may enhance extinction. These studies are informative about basic mechanisms that underlie the learning processes involved in extinction and about potential clinical treatments for disorders that involve failures in extinction. We have found that extinction of conditioned fear and cocaine-induced place preferences can by enhanced by histone deacetylase (HDAC) inhibitors, drugs that facilitate interaction between transcription factors and DNA, thereby promoting gene expression. Further, these HDAC inhibitors weaken spontaneous recovery, reconditioning, and reinstatement after extinction, suggesting that some aspect of the extinction experience is enhanced by HDAC inhibition. However, the persistence of these effects is often eliminated if extinction is not expressed in behavior during or soon after the extinction session. I will discuss implications of these HDAC inhibition data in the broader context of general challenges in interpreting pharmacological enhancements of extinction. At the molecular level, these challenges include questions about both the specificity of a given drug and the downstream effects of that drug. At the behavioral level, these challenges include determining how drugs affect the excitatory and inhibitory psychological processes that are involved in extinction. Because extinction involves multiple learning processes, it is important to consider the ways in which extinction may be enhanced by drugs that promote or inhibit cellular function.

Cheryl L. Limebeer*, Kiran Vimuri*, Holly Bedard*, Klaus-Peter Ossenkopp**, Alexandros Makriyannis*** and Linda A. Parker* -** Nausea is Produced by Peripheral Inverse Agonism of Cannabinoid$_1$ Receptors: Evidence from the Conditioned Gaping Model in Rats

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Introduction: Although rats are not capable of vomiting, they display characteristic conditioned gaping reactions when exposed to a flavor previously paired with a nausea-inducing treatment, such as Lithium Chloride (LiCl). Cannabinoid compounds modify conditioned gaping in rats in a manner that suggests they reduce nausea as well as vomiting. CB1 receptor agonists reduce LiCl-induced conditioned gaping reactions and the CB1 receptor antagonist/inverse agonist, SR141716, potentiates LiCl-induced conditioned gaping at a low dose that does not produce gaping on its own. Here we evaluated the potential of the CB1 antagonist/inverse agonist, AM251, and the silent CB1 antagonists, AM6527 (centrally and peripherally active) and AM6545 (peripherally active) to produce conditioned gaping and to potentiate LiCl-induced conditioned gaping.
Methods: All rats were surgically implanted with an intra-oral cannula to facilitate infusion of saccharin directly to the oral cavity. Rats in the centrally administered groups were implanted with a unilateral guide cannula directed at the lateral ventricle or the 4th ventricle. All AM compounds were prepared in a vehicle of 45% 2-hydroxypropyl-β-cyclodextrin at a concentration of 1 mg/ml. With the exception of microinfusion to the ventricals, all AM compounds were administered intraperitoneally (i.p). LiCl was prepared in a 0.15M solution with sterile water and administered i.p. at a volume of 20 ml/kg.
Results: At 8 mg/kg, only AM251 produced conditioned gaping reactions when paired with saccharin solution. Furthermore, at a dose that does not produce conditioned gaping on its own, systemically administered AM251 potentiated LiCl-induced conditioned gaping; however even doses as high as 8 mg/kg of AM6545 and AM6527 did not potentiate LiCl-induced conditioned gaping in rats.

Intracerbroventricular (icv) infusions of AM251 did not potentiate LiCl-induced conditioned gaping reactions, but both doses attenuated saccharin palatability.
Conclusions: These results suggest that the nausea producing effects of AM251 are mediated by its inverse agonist properties and may be peripherally mediated.

Bruce McNaughton, University of Lethbridge – Hippocampal Granule Cells Opt for Early Retirement

I will make the case from published and more recent data that the vast majority of dentate gyrus granule cells is functionally silent. Although not yet confirmed, based on available data, the small, excitable population probably corresponds to the most recently generated cells. It appears that, rather than contributing to the recollection of long-past events, most granule cells, possibly 95% or more, are effectively 'retired'. Activation of a new set of granule cells when old memories are reinstated would likely lead to multiple traces of these experiences in CA3 and may contribute to reconsolidation phenomena.

Ralph R. Miller & Mario Laborda, SUNY-Binghamton -- Minimizing Recovery from Extinction

With an eye to modeling relapse from exposure therapy, we will review techniques for reducing recovery from extinction, with an emphasis on the benefits of deepening extinction through manipulation of the extinction procedures. Among the ploys to be considered will be conducting extinction in multiple contexts, giving massive extinction (i.e., subzero extinction), spacing of the extinction trials, and administering extinction in the presence of a second excitor. There will be consideration of what each of these manipulations do during extinction treatment and how well the resultant extinction resists spontaneous recovery and renewal, as well as how readily the benefits of these different manipulations summate. With appropriate parameters, these manipulations complement the benefit of bringing the extinction context over to testing. Additionally, for each manipulation, attention will be given to the multiple potential roles of the extinction context. We will also discuss the role in fear conditioning and extinction of S-R associations as well as S-S associations.

John M. Pearce & Murray Horne, Cardiff University -- Evaluation of a Pavlovian analysis of spatial learning

Animals are able to locate a hidden goal by reference to cues provided by the shape of the environment, and learning about these cues does not appear to be overshadowed by the presence of a landmark that also indicates where the goal is located. To explain these failures of overshadowing, Miller and Shettleworth (2008) developed an associative model of geometry learning which is based on the Rescorla-Wagner (1972) theory. In order to test the Miller and Shettleworth model, rats were first trained to find a hidden goal in one corner of a rectangular arena when a landmark was absent, but not when it was present. They were then required to find the goal in the same corner of the arena but now in the presence of the landmark. Subsequent test trials revealed that the landmark resulted in superconditioning with the cues provided by the rectangular shape. Although, the results can be understood in terms of the Rescorla-Wagner (1972) theory, they do not follow from the modification to this theory proposed by Miller and Shettleworth.

Glenn Schafe, Yale University -- Fear Memory Consolidation: A View From Both Sides of the Thalamo-Amygdala Synapse

The consolidation of fear memories is thought to involve NMDAR-mediated alterations in synaptic transmission at lateral amygdala (LA) synapses. Most recent studies in the fear conditioning literature

have focused their efforts on examining the role of downstream effectors of NMDARs in LA cells. These have included protein kinase signaling cascades, such as the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK), that are thought to promote long-term plastic change and memory, in part, by engaging activators of transcription and translation in the nucleus (Schafe *et al.*, 2001). Growing evidence, however, indicates that fear memory consolidation is accompanied by both pre- and postsynaptic alterations at LA synapses. We have recently shown, for example, that ERK-driven gene expression in the auditory thalamus (MGm/PIN), is also required for memory consolidation of auditory Pavlovian fear conditioning and associated synaptic plasticity at LA synapses (Apergis-Schoute *et al.*, 2005). Together with our recent observations that nitric oxide (NO) signaling in the LA is critical for fear memory formation (Schafe et al, 2005; Ota et al, 2008), we have hypothesized that NO signaling in the LA at the time of fear learning coordinates ERK-driven transcriptional changes in both MGm/PIN and LA neurons that serve to promote pre- and postsynaptic alterations at thalamo-LA synapses, respectively. Here, I present findings from a series of studies that indicate that synaptic plasticity and NO signaling in the LA during auditory fear conditioning coordinately regulates alterations in ERK-driven gene expression in both the LA and the MGm/PIN that is required for both fear memory consolidation as well as corresponding changes in the expression of pre- and postsynaptically localized proteins at LA synapses. Our findings support the hypothesis that synaptic plasticity and NO signaling in the LA drives changes in gene expression in thalamic projection neurons that are critical for fear memory formation by promoting presynaptic aspects of plasticity at LA synapses, and support a more general role for NO-driven "retrograde signaling" in mammalian memory formation.

Nestor Schmajuk, Duke University – Computational Models of Pavlovian Conditioning: The State of the Art

A review of current models of classical conditioning seems to indicate that accurate descriptions of experimental results might require a higher level of complexity than that included in the old familiar models.

Allan R. Wagner, Yale University – Relative validity effects in Pavlovian conditioning and human causal learning

I will briefly rehearse a pattern of early findings concerning relative validity effects in Pavlovian conditioning, and, then, via some new data, reflect upon whether some related observations in human causal learning may or may not be produced by the same mechanism

Craig Weiss, Northwestern University Medical School -- Roles of the Cerebral Cortex During Trace Eyeblink Conditioning

The neural substrate that bridges the stimulus free trace interval during acquisition and consolidation of forebrain-dependent trace eyeblink conditioning is still unknown, but likely to involve the prefrontal cortex (PFC) and sensory cortex. This talk will review data from our lesion, recording, imaging, and tract tracing experiments in rabbits that reveal cortical involvement for the acquisition and retention of conditioned blinks. The goal of these experiments is to test the hypothesis that the PFC utilizes feedback from the hippocampus and cerebellum via the anteroventral and ventral anterior thalamus respectively, as well as projections with the dorsomedial thalamus to maintain neural activity during the trace interval. This prefrontal activity is hypothesized to be similar to that of "delay cells" in the dorsolateral PFC of non-human primates during delay matching to sample tasks. In this regard, the PFC would serve to orchestrate information between the sensory cortex and striatum, and to potentiate activity in pontine neurons that project to the cerebellar cortex. The potentiation would permit LTD to occur at parallel

fiber-Purkinje cell synapses even though the trace period is much longer than the typical timing used for LTD. We are currently taking advantage of the precise somatotopy of the whisker barrel system to examine the role of sensory cortex, and we are examining different subregions of the PFC to determine if acquisition and maintenance of learned responses can be attributed to specific regions. We propose that the PFC in conjunction with thalamus and cortex is one system that mediates consolidation and spanning of the trace interval.

Symposia Titles:

Terry Davidson – Symposium title: Pavlovian *Influences on Intake and Energy Regulation*

The role of conditioning in influencing food intake
Stephen C. Woods
University of Cincinnati

Flavor preference conditioning by nutrients in the gut
Anthony Sclafani
Brooklyn College of CUNY

Modulation of feeding by learned cues
Peter C. Holland
Johns Hopkins University

Energy Dysregulation and Learning
Terry L. Davidson
Purdue University

Barbara Knowlton – Symposium title: Neural Systems in Habit Learning

The role of orbital-striatal circuits in shifting between goal-directed actions and habitual performance
Christina Gremel & Rui Costa
NIAAA/NIH

The Neural Basis of the Win-Stay Radial Maze Task
Norman White & Elia Nahas
McGill University

Modulators of Spatial and Response Learning Strategies
Veronique Bohbot
McGill University

Competing systems for habit and declarative learning in humans
Barbara Knowlton
UCLA

Karim Nader – Symposium Title: Amnesia and Reconsolidation

A New paradigm to examine the Nature of amnesia
Karim Nader
McGill University

Is reconsolidation a mechanism for updating memories?
Jonathan Lee
University of Birmingham

Disruption of appetitive memories underlying addiction
Amy Milton
University of Cambridge

Reconsolidation versus Extinction: in search for boundary conditions
Merel Kindt
University of Amsterdam

Catharine Rankin – Symposium Title: New Frontiers in Studying the Effects of Repeated Stimulation

Mechanisms of habituation of the acoustic startle response in rats
Susanne Schmid
University of Western Ontario

Components of nonassociative and associative plasticity in early sensory processing
Brian Smith
Arizona State University

Associative and non-associative aspects of habituation in C. elegans
Catharine Rankin
University of British Columbia